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A review on pharmacokinetic modeling and the effects of environmental stressors on pharmacokinetics for operational medicine:

Operational pharmacokinetics

Henry Peng

Bob Cheung

Defence R&D Canada
Technical Report
DRDC Toronto TR 2009-037
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Abstract

In this report, we conducted a comprehensive literature review on the effects of a range of physiological and psychological stressors on drug absorption, distribution and elimination (pharmacokinetics), and current pharmacokinetic models (including computerized modeling tools and algorithms) used to predict pharmacokinetic changes. Although sophisticated computerized mathematical models have been widely used to quantitatively describe the pharmacokinetics of drugs in the human body, limited experimental data for both descriptive and predictive purposes were available. The effects of isolated physical activities on pharmacokinetics have been documented. However, some inconsistencies need to be addressed, such as the intensity and duration of each physical activity, and timing of drug administration. Other physiological stressors, such as temperature, hypoxic, hyperbaric and hyperoxic conditions have been studied to a lesser extent. There are only a few reports describing the psychological effects on drug pharmacokinetics. After carefully reviewing the literature, our goal is to develop a physiologically-based pharmacokinetic model to predict the absorption, distribution and elimination of drugs employed under various military physiological and psychological stressors.

Résumé

Dans le cadre de ce compte rendu, nous avons procédé à un vaste examen de la documentation portant sur les effets d'un ensemble d'agents stressants physiologiques et psychologiques, sur l'absorption des médicaments, la distribution et l'élimination (pharmacocinétique), ainsi que sur les modèles pharmacocinétiques actuels (notamment les outils de modélisation et les algorithmes informatisés), servant à prédire les changements pharmacocinétiques. Bien que des modèles mathématiques complexes aient été largement utilisées afin de décrire quantitativement la pharmacocinétique de divers médicaments dans l'organisme humain, les données expérimentales descriptives et prédictives étaient rares. Les effets de diverses activités physiques sur les paramètres pharmacocinétiques ont été étudiés. Cependant, certaines contradictions demeurent inexpliquées, notamment en ce qui a trait à l'intensité et à la durée de chaque activité physique ainsi qu'au moment de l'administration du médicament. Les effets d'autres agents stressants physiologiques tels que la température et les états hypoxique, hyperbare et hyperoxique, ont été étudiés mais, dans une moindre mesure. Peu de comptes rendus décrivent les effets des facteurs psychologiques sur la pharmacocinétique des médicaments. Après avoir révisé attentivement la documentation déjà disponible, nous nous sommes fixé comme objectif de développer un modèle de pharmacocinétique basé sur les paramètres physiologiques qui permettrait de prédire l'absorption, la distribution et l'élimination des médicaments consommés par les militaires alors qu'ils subissent l'influence d'agents stressants physiologiques et psychologiques.

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Executive summary

A review on pharmacokinetic modeling and the effects of environmental stressors on pharmacokinetics for operational medicine: Operational pharmacokinetics

Henry Peng; Bob Cheung; DRDC Toronto TR 2009-037; Defence R&D Canada – Toronto; September 2009.

Background: The current guidelines regarding drug dosage, routes of administration and contraindication employed by the Canadian Forces (CF) were developed by Health Canada for the civilian population in a controlled clinical laboratory setting that does not reflect military operational environments. Considering some of the extreme and hostile environmental conditions that the CF might encounter during operations, the pharmacokinetics and pharmacodynamics of the drugs are expected to be different from controlled clinical laboratory conditions. Therefore, we conducted a literature search into the effects of environmental stressors on the pharmacokinetics of commonly prescribed medications employed by the CF. This report is a comprehensive review of the subject matter in preparation for further experimental validation of an advanced pharmacological model to advise the CF on the modification of dosage and other related issues in operational pharmacokinetics.

Results: Our literature review of numerous experimental studies have demonstrated the effects of a number of physiological, psychological and environmental stressors on the pharmacokinetics of a broad spectrum of drugs, in particular the influence of isolated physical activity. To a lesser extent, psychological stressors were also shown to alter the pharmacokinetics as a result of psycho-somatic changes. In addition, our review suggested that various pharmacokinetic models, specifically a physiologically-based model, may be able to provide theoretical predictions for the interactions of military stressors with pharmacokinetics.

Significance: The review enables us to conduct further research toward the development of a system that will provide a guideline on dosage, route of administration, contraindications etc. to the CF especially, Director General of Health Services, Director of Medical Policy / Pharmacy Policy & Standards.

Future plans: Based on the literature review, pharmacokinetic models will be developed and laboratory studies simulating the operational environments will be conducted in order to provide recommendations on better use of the common pharmaceuticals employed by the CF.

Sommaire

A review on pharmacokinetic modeling and the effects of environmental stressors on pharmacokinetics for operational medicine: Operational pharmacokinetics

Henry Peng; Bob Cheung; DRDC Toronto TR 2009-037; R & D pour la défense Canada – Toronto; Septembre 2009.

Introduction ou contexte: Les directives actuellement en vigueur dans les Forces Canadiennes (FC) concernant la posologie, la voie d'administration et les contre-indications des médicaments ont été établies par Santé Canada, pour les civils, dans le cadre d'essais cliniques effectués en laboratoire en milieu contrôlé et elles ne tiennent pas compte du contexte militaire opérationnel. Compte tenu de certaines des conditions environnementales extrêmes et hostiles auxquelles les militaires des FC peuvent être exposés pendant les opérations, nous nous attendons à ce que la pharmacocinétique et la pharmacodynamique des médicaments diffèrent de celles observées dans le cadre des essais cliniques effectués en laboratoire en milieu contrôlé. Par conséquent, nous avons cherché dans la littérature existante des documents traitant des effets des agents stressants de l'environnement sur la pharmacocinétique de certains des médicaments souvent prescrits qui sont utilisés dans les FC. Ce rapport constitue un vaste examen du sujet en prélude à la validation expérimentale ultérieure d'un modèle pharmacologique plus évolué, qui permettra de guider les FC dans l'adaptation de la posologie ainsi que relativement à d'autres problèmes reliés à la pharmacocinétique opérationnelle.

Résultats: Notre examen de la documentation, basé sur de nombreuses études expérimentales, a mis en évidence les effets d'un certain nombre d'agents stressants physiologiques, psychologiques et environnementaux sur la pharmacocinétique d'un vaste ensemble de médicaments, en particulier l'influence de l'activité physique prise isolément sur la pharmacocinétique. Dans une moindre mesure, il a également été démontré que les agents stressants psychologiques modifient la pharmacocinétique en réponse aux changements psychosomatiques. De plus, notre examen a révélé que divers modèles pharmacocinétiques, particulièrement celui basé sur les paramètres physiologiques, pouvaient fournir des prévisions théoriques décrivant les interactions entre les agents stressants auxquels sont confrontés les militaires et la pharmacocinétique.

Importance: Cet examen nous permettra de poursuivre les recherches nécessaires à l'élaboration d'un système qui fournira des directives, particulièrement au DGS SAN D Pol San/Pol et Normes pharm des FC, concernant la posologie, la voie d'administration, les contre-indications, etc.

Perspectives: À la lumière de ce compte rendu, on mettra au point des modèles pharmacocinétiques et on effectuera des études en laboratoire dans des conditions simulant les différents environnements opérationnels, afin d'être en mesure de conseiller les FC sur la meilleure utilisation possible des médicaments couramment utilisés.

Table of contents

List of figures

List of tables

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1 Background

The relationship between drug dosage and the response of the drug is described by pharmacokinetics and pharmacodynamics. Pharmacokinetics can be defined as what the body does to the drug and pharmacodynamics as what the drug does to the body. In order to produce its characteristic effects, a drug must be present in an appropriate concentration at its site of action. Although the availability of the drug is a function of the amount of drug being administered, it also depends on the extent and rate of its absorption, distribution, binding and localisation in tissues, biotransformation and excretion, all of which can be affected by a number of physiological and psychological stressors. The current guidelines for prescribing medication to the Canadian Forces (CF) are provided by Health Canada. They are based on the safety, dosage, and efficacy data established by clinical trials in laboratory settings which can be different from the environmental, physiological and psychological conditions experienced during military operations. Specifically, military operations involve a broad spectrum of hostile factors or stressors such as environmental temperature extremes, hypoxia, noise, motion disturbance, sensory deprivation, physical exertion, physical trauma, sleep deprivation, disruption of circadian rhythms, fatigue, dehydration, irregular food intake, fear, anxiety and mental stress. These stressors can induce physiological and psychological changes that might result in the modification of the pharmacokinetics and pharmacodynamics of the drugs and reduce the intended efficacy. The importance of pharmacokinetics in the care of our soldiers in military operations rests on the improvement in efficacy that can only be attained by attention to the principles when dosage regimens are chosen and modified based on the operational environment.

The primary purpose of this report is to provide an extensive literature review on the known effects of various stressors on the pharmacokinetics of a number of pharmaceuticals, and current pharmacokinetics models and modeling tools. The secondary purpose is to provide a sound scientific background in designing appropriate human studies on the most commonly used drugs by the CF under simulated operational environments in the laboratory. The results of these studies will be used to validate chosen pharmacokinetic models in order to establish guidelines for field application.

Given the wide range of available pharmaceuticals and the complexity and cost for conducting human trials, we restricted our review to the following categories. This list was derived based on the initial Top 10 category of operational drugs identified through consultation with military physicians/consultants and a review of the Canadian Forces Drug Benefit list at http://hrapp.dnd.ca/benefitlist/engraph/home_e.asp>Lev1-2&Lev2=19.

i. Analgesics including non-steroidal anti-inflammatory drugs (e.g., fentanyl, morphine)

ii. Antibiotics including anti-malarials (e.g., mefloquine, vancomycin)

iii. Antihistamines (e.g., mizolastine, promethazine)

iv. Antihypertensives (e.g., Angiotensin-Converting Enzyme inhibitors, beta-blockers, calcium blockers, diuretics)

v. Asthma medications (e.g., inhaled short and long-acting beta-antagonists, anti-cholinergics, corticosteroids, oral leukotriene inhibitors)

vi. Antidepressants (e.g., venlafaxine, bupropion, sertraline, citalopram and escitalopram currently approved for aircrew)

vii. Antimotion sickness medications (e.g., promethazine, dextroamphetamine, scopolamine, dimenhydrinate, meclizine)

viii. Antilipemics (e.g., statins, fenofibrates, niacin, ezetimibe)

ix. Sedative/hypnotics – (e.g., zaleplon, zopiclone, temazepam, zolpidem)

x. Alertness management medications (e.g., modafinil, amphetamines, caffeine)

A PubMed search was completed using the search terms listed in Annex A, Table A-1. Specific drugs of interest (e.g., pyridostigmine) were also used as keywords in the search. Abstracts were used to determine the relevance and when appropriate further review of the original articles. Additional publications were selected from the cross references listed in the original articles. Furthermore, searches were made through Medline, Scopus and Institute of Scientific Information databases for those topics/drug categories with limited findings from PubMed. All the searches were focused on human studies only unless *in vitro* and animal studies were deemed to be very relevant. Drugs obtained from the search were further analyzed using the information which appeared in the Top 200 US Prescriptions Dispensed for 2007 list (RxList Inc.) and http://en.wikipedia.org.

This review is divided into the following sections: (1) an overview on various pharmacokinetic models; (2) available modeling tools; (3) a summary of existing pharmacokinetic models for relevant drugs; (4) a thorough review of the reported effects of a number of stressors on pharmacokinetics; (5) proposed methodology in developing a model to predict the pharmacokinetics of the drugs of interests in response to military stressors. A comprehensive reference list and some abstracts of relevant literature are provided for further information.

2 Overview of pharmacokinetic models

Pharmacokinetics is the dynamic processes that dictate bioavailability (the fraction of a drug absorbed into the systemic circulation), volume of distribution (a measure of apparent space in the body available to contain the drug), and clearance (a measure of the body's ability to eliminate the drug). Of lesser importance are the rates of bioavailability and distribution of the drug.

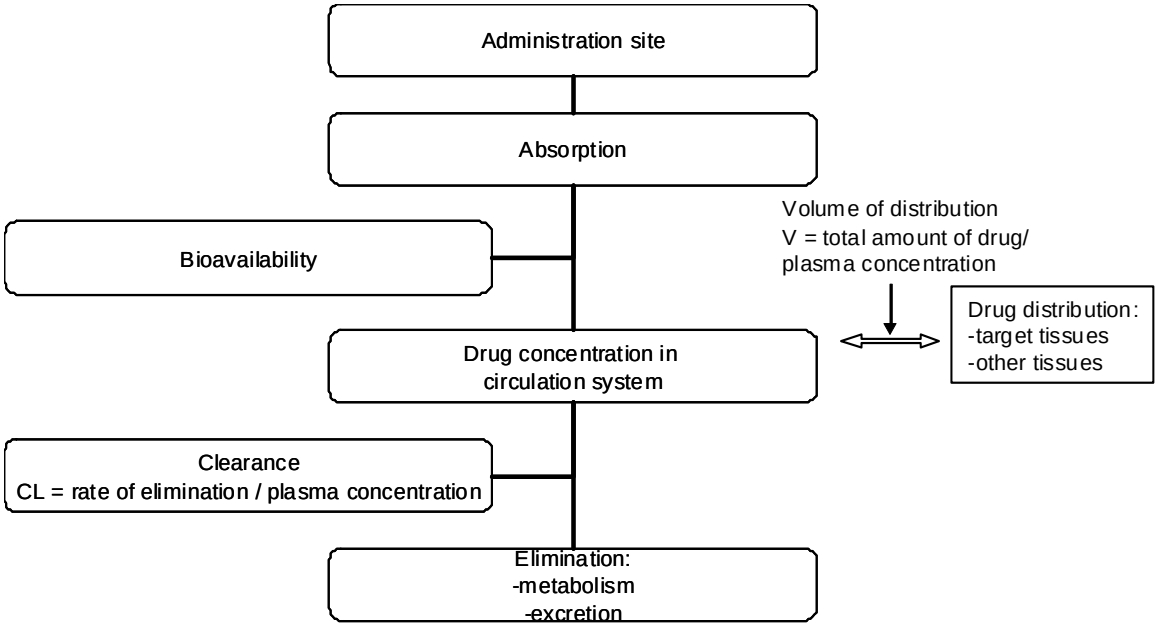


Figure 1: Factors determining the pharmacokinetics of a drug.

A fundamental hypothesis of pharmacokinetics is that a relationship exists between the pharmacologic or toxic response to a drug and the concentration of the drug in the blood (plasma). However, for some drugs there is no clear or simple relationship between pharmacologic effects and concentration in plasma. Nevertheless, pharmacokinetics plays a role in a dose-efficacy scheme by providing a quantitative relationship between dose and effect and the framework with which to interpret measurements of concentrations of drugs in biological fluids. In most cases, the concentration of drug in the systemic circulation is related to the concentration of drug at its sites of action. The various psychophysiological and pathophysiological variables that dictate adjustment of dosage are a direct result of modification of the pharmacokinetic parameters depicted in Figure 1.

Mathematics is widely used for the quantitative description of drug absorption, distribution, metabolism and excretion (ADME). Some typical pharmacokinetic parameters are defined by mathematic equations. For example, the rate of total elimination can be calculated as $Q(C_{arterial} - C_{venous})$, where Q, $C_{arterial}$, C_{venous} are cardiac output, drug concentration in the arterial and venous systems, respectively. Other parameters include bioavailability, peak plasma concentration, half-life in the plasma, volume of distribution, renal clearance, and hepatic clearance. They can be

obtained by direct measurement or through calculation using experimental data based on developed mathematical equations.

More complex mathematical manipulations called mathematical models have been used to describe pharmacokinetics (Bonate 2006). There are many classifications of pharmacokinetic models. Figure 2 presents a flow chart based on one type of classification that is used in this review. It demonstrates two general approaches to pharmacokinetic modeling: compartment-based modeling (Holz and Fahr 2001) and noncompartment-based modeling (Veng-Pedersen 2001). Both types of modeling take advantage of the quantitative structure-pharmacokinetic relationships that are described by empirical mathematical algorithms. They can be used to estimate the activity of a compound based on its chemical structure in a numeric format (referred to as molecular descriptors) (Krejsa, Horvath et al. 2003; Mager 2006).

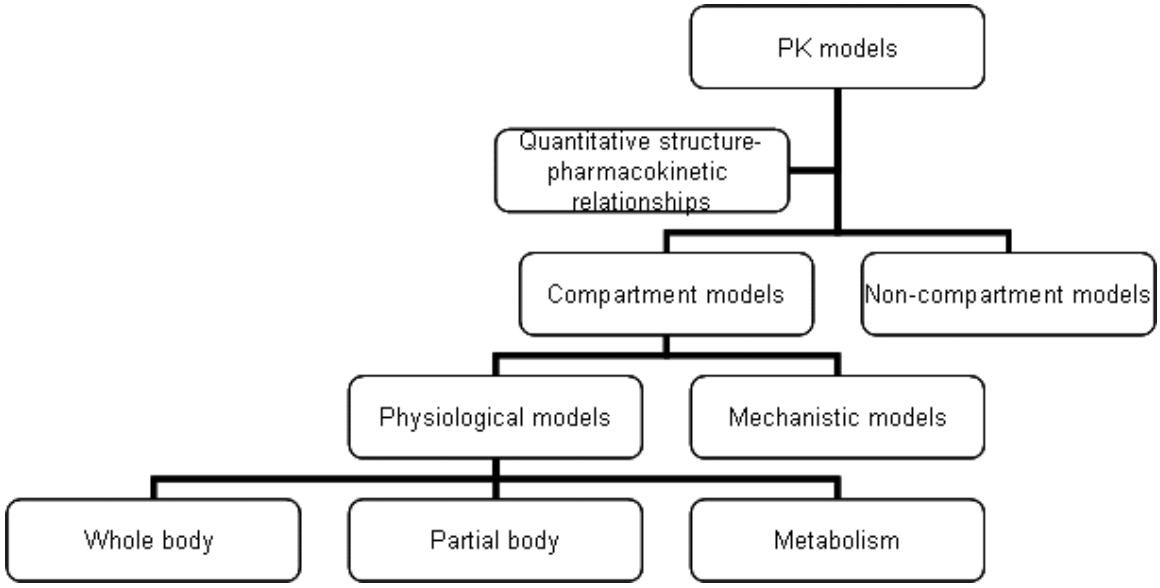


Figure 2: Classification of pharmacokinetic models.

2.1 Compartment models

Compartment models can be further classified into mechanistic models and physiological models. The former can relate its parameters to physiological processes, but does not necessarily reflect all the functional entities of the organism. On the other hand, physiological models are based on well-defined and structured compartments interconnected by blood flow, lymph flow or other biochemical fluxes, and are the most comprehensive models (Holz and Fahr 2001; Aarons 2005). Mechanistic models can be further subdivided into compartments; designated as mammillary and catenary compartment model (Figure 3). A mammillary model consists of a central compartment interacting with a number of peripheral compartments surrounding it while the catenary model comprises of a chain of interconnected compartments.

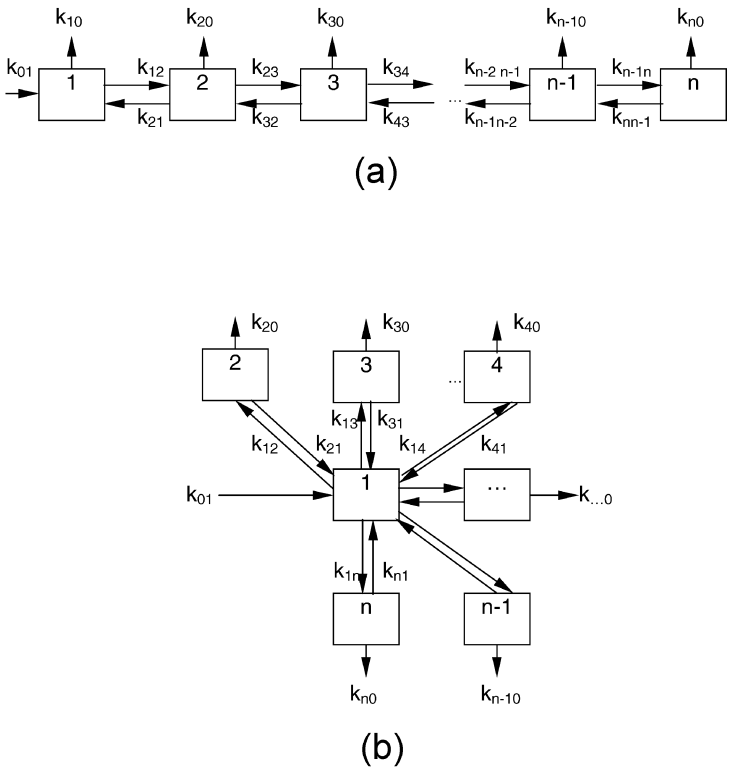


Figure 3: The general compartment model architecture: (a) The catenary compartment model; (b) the mammillary compartment model.

2.2 Non-compartment models

Non-compartment models are often based on linear system analysis principles rather than anatomical structures or physiological properties (Veng-Pedersen 2001). They have been mainly used to derive the following 3 properties: (1) estimation of pharmacokinetic parameters, e.g., area under plasma concentration curve (AUC) with mathematical integration of experimental data; (2) description of the relationship between the input rate and the resulting systemic drug concentration using a convolution integral equation; (3) description of a terminal phase in the drug concentration time-course using an exponential term. The representative equations for each property are listed as follows:

$$AUC = \int_0^\infty C_t dt \,, \tag{1}$$

$$C_t = \int_0^t C(t-\tau) \cdot R(\tau) dt \,, \text{ and} \tag{2}$$

$$C_t = A \cdot e^{-\lambda_i \cdot t}, \quad (3)$$

where $C_t, C, R, \tau, A, \lambda_i$ are drug concentration at time t, response function from an instantaneous input of a unit amount of drug, drug input rate and duration, coefficient and terminal rate constant, respectively.

Although useful for data description and interpolation, non-compartment models do not take much consideration for physiology and thus model parameters do not have any physiological interpretations. Therefore, it is difficult to predict and extrapolate pharmacokinetics with non-compartment models when physiological changes take place. However, they can be useful adjuncts to physiological pharmacokinetic models in the sense that they provide applicable general mathematical methods (Gillespie 1991).

Mathematical models can also be divided into two major categories based on their intended applications (Friberg and Karlsson 2003; Kreuer, Bruhn et al. 2007): (1) empirical or descriptive models; and (2) mechanistic or explanatory models. In general, empirical (descriptive) models provide quantitative summaries of pharmacokinetic parameters based on experimental data. The latter can be extrapolated beyond the condition where the model was estimated and used for predictions of pharmacokinetics/pharmacodynamics in clinical settings. Alternatively, some of the pharmacokinetic models may be associated with Bayesian formats (Lunn, Best et al. 2002) and Monte Carlo simulations (Bonate 2001) when these statistical methods are employed. The former takes previous knowledge into account for reference values on model parameters, while the latter treats the model parameters as random variables rather than as fixed values.

In addition, application-specific mathematical models have also been derived for each pharmacokinetic process (Boobis, Gundert-Remy et al. 2002; Ahmad 2007) such as oral absorption (Grass 1997; Yu and Amidon 1999; Agoram, Woltosz et al. 2001; Zhou 2003; Willmann, Schmitt et al. 2004), drug disposition (Lombardo, Obach et al. 2002; Gallo, Vicini et al. 2004; Fliszar, Hill et al. 2007), clearance (Lave, Coassolo et al. 1999; Liu and Pang 2006), drug concentrations in specific regions (Upton, Runciman et al. 1991), or through a specific route of administration, e.g., transdermal delivery (Williams and Riviere 1995; Mccarley and Bunge 2001) and antibody-targeted delivery (Strand, Zanzonico et al. 1993). Moreover, population pharmacokinetic models were used for the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest (Ette, Williams et al. 2004). More recent models employed linear time-invariant dynamic systems, artificial-neural networks, fuzzy logic and the concept of fractals (Durisova and Dedik 2005).

2.3 Physiologically-based pharmacokinetic (PBPK) models

The physiologically-based pharmacokinetic (PBPK) model was introduced by Haagard (1924). The concept was to divide the body into physiologically relevant compartments/major organs, and to formulate a mass balance differential equation for each compartment describing the fate of the substance within that compartment (Figure 4). The PBPK model is a compartmental model, but differs from classical compartmental models in that the compartments represent actual tissue and

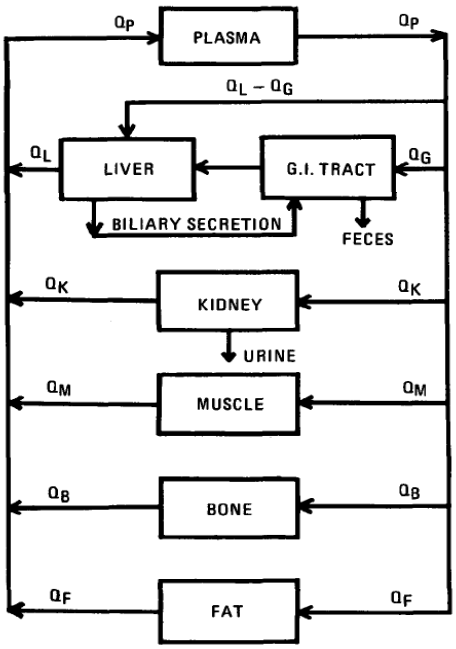
organ spaces and physical volumes where physiological, physiochemical and biochemical processes are described mathematically. The PBPK models include the following three types:

Whole body PBPK models using a closed-loop circulation concept (Nestorov 2003)

Partial PBPK models of isolated body systems (e.g., perfused hind limb, gastrointestinal tract etc.) (Willmann, Schmitt et al. 2004);

Metabolic PBPK models describing the hepatic elimination of drugs using physiological and biochemical parameters (e.g., liver blood flow, intrinsic clearance, protein binding, etc.) (Liu and Pang 2006).

The mathematical description of mass balance for each compartment (i.e., tissues or organs) may vary depending on the mechanisms of drug absorption, distribution, metabolism and excretion. For example, either linear or Michaelis-Menten equations can be used to describe liver metabolism.



$$V_i \frac{dC_i}{dt} = Q_i C_P - Q_i \frac{C_i}{R_i} - K_i \frac{C_i}{R_i}$$

$$V_P \frac{dC_P}{dt} = K_0 + Q_L \frac{C_L}{R_L} + Q_G \frac{C_G}{R_G} + Q_K \frac{C_K}{R_K} + Q_M \frac{C_M}{R_M} + Q_B \frac{C_B}{R_B} + Q_F \frac{C_F}{R_F} - Q_P C_P$$

Figure 4: An example of a PBPK model and representation of drug distribution in a compartment i. The compartments represent tissues and organs; connecting arrows represent blood supplies; G.I. is gastrointestine; Q, V, C, K, R are blood flow rate, compartment volume, concentration of drug, rate of drug elimination and partition coefficient where subscripts P, L, G, K, M, B and F denote plasma, liver, gastrointestine, kidney, muscle, bone, and fat, respectively. K_0 is the drug input function.

Figure 5 illustrates a general procedure to develop a PBPK model. In addition to the tissues of special interest with a particular drug, a typical PBPK model structure includes the monitoring of drug concentrations in core tissues/fluids/organs: arterial and venous blood, liver (the main metabolising organ), kidney (for renally excreted drugs) and adipose tissues (for lipothilic drugs). The inclusion or exclusion of tissues should be judged against their impact on the time course of the whole body mass balance and the applications of the model. Within each compartment,

mathematical equations are derived from the law of mass transfer. Linear ordinary differential equations (e.g., the equations in Figure 4) are the most common description of the pharmacokinetic processes in PBPK models with the assumption that each tissue or organ served as a single well-stirred compartment. Within these equations, there are a number of parameters that require specification and estimation. The PBPK models have two groups of parameters: drug-specific and physiological parameters. Typical drug-specific parameters include tissue-to-plasma partition coefficients, metabolism rate constants, and plasma protein binding constants. Their values can be estimated by either *in vitro* and *in vivo* experiments (Lin, Sugiyama et al. 1982; Naritomi, Terashita et al. 2001), or theoretic calculations based on quantitative structure-property relationships (Fouch´ecourt, B´eliveau et al. 2001), or allometric scaling (Tang and Mayersohn 2005). The physiological parameters include cardiac output, regional and tissue blood flow rates, volumes of blood and different tissues and other allometric parameters. Their values are drug-independent and have been documented in the literature (Williams and Leggett 1989; Price, Conolly et al. 2003).

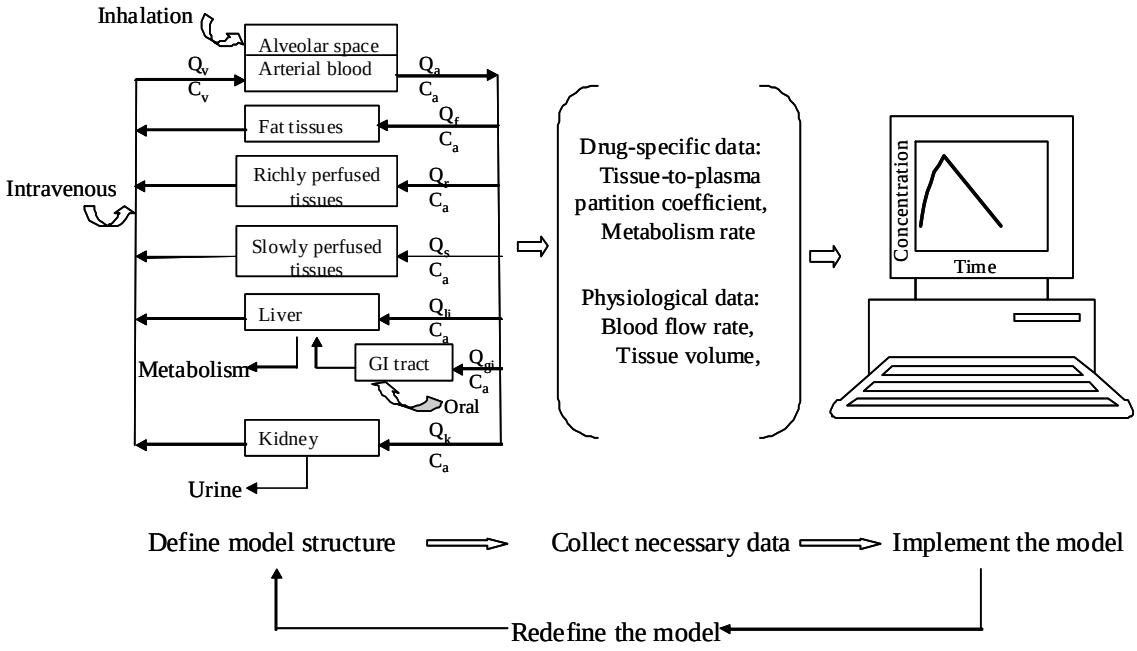


Figure 5: Development of a PBPK model. Q,,C represent blood flow rate and drug concentration, respectively. The subscripts v, a, f, r, s, li, gi, k denote venous, arterial, fat, richly perfused, slowly perfused, liver, gastrointestinal, kidney.

Once the equations and associated parameters are written and determined, they are coded in computer language for subsequent estimation or computer simulation. There is a wide variety of such software available which will be discussed in Section 3.

2.3.1 Applications and limitations

The PBPK modeling has attracted considerable attention in pharmacological and toxicological research (Grass and Sinko 2002). Its applications include early drug discovery and development (Lüpfert and Reichel 2005; Poulin and Theil 2002), dose estimation (Johnson 2005) and drug-drug interactions (Chien, Mohutsky et al. 2003). The model has been shown to be superior to the allometric approach at providing better extrapolation of animal pharmacokinetic data to humans (Lin 1995).

As stated in the Background, physiological (e.g., tissue volumes and blood flow rates), physicochemical (e.g., tissue to blood partition coefficients), and biochemical (e.g., metabolism rates, protein binding affinity) changes strongly influence pharmacokinetics. This has been demonstrated in the study of the effects of age-specific changes on pharmacokinetics (Price, Haddad et al. 2003) on drugs such as caffeine, theophyline (Ginsberg, Hattis et al. 2004), acetaminophen, alfentanil, morphine and levofloxacin (Edginton, Schmitt et al. 2006a). In addition to the age effects, the model has also been applied for predicting pharmacokinetic effects of various factors, such as food intake (Jones, Parrott et al. 2006a), and weightlessness (Srinivasan, Bourne et al. 1994). In addition, models have been developed taking into account the individual variation in physiological parameters (Price, Conolly et al. 2003), for example, in pregnant and lactating individuals (Byczkowski and Fisher 1995; Young 1998).

Although widely used, the physiologically-based pharmacokinetic approach requires intense resources to generate the data on the various parameters described in the models (Subramanian 2005). The use of quantitative calculations from commonly available physicochemical properties would enhance the widespread use of PBPK modeling. For example, an available software package called PK-Sim® developed by Bayer Technology Services (Willmann, Lippert et al. 2003) can be employed for such purpose.

2.3.2 Future developments

It has been suggested that there will be an increase in applying PBPK models for the predictions of human pharmacokinetics (Jones, Parrott et al. 2006b) since the key components required for the PBPK model, such as solubility, dissolution and partition coefficients, can now be easily measured or mathematically calculated (Poulin and Theil 2000). Model complexity will also increase with increasing applications. The majority of current PBPK models describe functions at a tissue/organ level. Further refinement of the physiological and anatomical description of the body (for example, at the cellular level) will lead to a more complex and detailed PBPK model in the future. Similarly, advanced models involving other biologic processes may be developed via a combined mathematic description of pharmacokinetic and biological processes in order to understand their interaction. An integrated approach has also been taken to correlate the pharmacokinetics, pharmacodynamics and disease aspects into mathematic models (Dingemanse and Appel-Dingemanse 2007). This would allow prediction of the potential changes in drug kinetics of differing biological make-up, changes caused by disease states or changes due to additional drugs. Furthermore, different statistical methods, such as Fuzzy Sets Theory, have been incorporated in PBPK models to take into account the high degree of variability and uncertainty in physiological pharmacokinetics (Seng, Nestorov et al. 2008). The PBPK modeling also offers a platform to integrate various pieces of information from different computer models,

in vitro and *in vivo* studies to evaluate the outcome under various assumptions (Boobis, Gundert-Remy et al. 2002). Lastly, with continuously increasing applications in drug discovery, development, clinical trials and risk assessment, new applications of PBPK models, such as interpretation of biomonitoring data (Clewell, Tan et al. 2008), are expected.

3 Overview of pharmacokinetic modeling tools

Computational tools are increasingly being used for pharmacokinetic modeling. Table 1 lists a variety of commercial software currently available for such purpose (Charles and Duffull 2001; Boobis, Gundert-Remy et al. 2002; Chiu, Barton et al. 2007). Some are designed for general modeling applications (MatLab) or for simple applications similar to Excel Spreadsheet (Haddad, Pelekis et al. 1996). These tools have evolved from programming languages, such as Fortran (Lewis, Luecke et al. 1988), and progress to simulation languages, such as advanced continuous simulation language (Thomas, Yang et al. 1996) and MatLab Simulink (Wada, Stanski et al. 1995). However, the majority are designed specifically for modeling pharmacokinetics (Levitt 2002) as well as pharmacodynamics (Aarons 1999). They may be further grouped into the software used for a specific parameter such as absorption rate (GastroPlus™ and iDEA™) and metabolism, as well as for the complete process within pharmacokinetics and pharmacodynamics (PK-Sim®).

Each modeling technology has its own strengths and weaknesses and may be employed for different purposes. The major advantage of the general modeling tools is their flexibility, but they require the user to possess a mathematical background and time-consuming programming skills. As a result, they are reserved for a small group of "modeling expert" users. Some of the pharmacokinetics-specific softwares are equipped with model structures and convenient graphical user interfaces which enable wider application and make them accessible for individuals that are not specialists in modeling. However, this type of software lacks flexibility.

In addition, *in silico* (computer simulation) predictions of absorption, distribution, metabolism and excretion (ADME) have been carried out based on molecular structure-property relationships using different software tools such as VolSurf, QikProp, Admensal Interactive, ADME Boxes, PhysChem, K-Pro, PreADME, C2 ADME, OraSpotter, Qmpr/Gastro Plus, Know-it-All, and truPK (Krejsa, Horvath et al. 2003; Subramanian 2005). Generally, the predictions are no worse than those made using *in vitro* tests, with the decisive advantage of decreased cost. However, there is still a lack of confidence in these approaches. It has been shown that different computer programs used to analyse the same data set resulted in different pharmacokinetic parameters due to the fact that these programs use different methods to analyze data (Pascual and Montoro 1997). The software needs to be standardized and adequately validated (Boobis, Gundert-Remy et al. 2002).

Table 1: Computer software used for pharmacokinetic modeling.

Software	**Developer/vendor**	**Salient features**	**References**
Fortran compiler with IMSL library packages, C, Pascal, Basic	Many vendors sell different compiler packages available on the market	Machine language compiler packages that require certain knowledge of computer programming; models can be customized to simulate specific condition.	Hoang 1995; Karba, Zupancic et al. 1990

Software	Developer/vendor	Salient features	References
ACSL, ACSL-Tox, or acslXtreme (Advance Continuous Simulation Language)	The Aegis Technologies Group, Inc., Huntsville, AL, USA	The most commonly used for PBPK modeling in the toxicology community. Language designed for modeling and evaluating the performance of continuous systems described by time-dependent, nonlinear differential equations.	Dong 1994; Thomas, Yang et al. 1996
SimuSolv	Dow Chemical Company, Midland, MI (no longer distributed outside the company), USA	Makes use of ACSL language to write the dynamic nonlinear systems that are translated into FORTRAN at run time.	Rey and Havranek 1996
MatLab	The MathWorks, Natick, MA, USA	Mathematical software with matrix-related computations, numerical integration algorithms capable of solving systems of ordinary differential equations, and graphical nonlinear simulation.	Wada, Stanski et al. 1995; Easterling, Evans et al. 2000
Simulink	The MathWorks, Natick, MA, USA	The blocks representing physiological structure can be linked together flexibly to form models for different drugs.	Wada, Stanski et al. 1995
Microsoft Excel	Microsoft Corporation, Redmond, WA, USA	Neither translation of the model nor the compilation into a program is required, but integration algorithm and interval should be specified by the user.	Johanson and Näslund 1988; Abdallah and Ludden 1995; Haddad, Pelekis et al. 1996
ScoP (Simulation Control Program)	Simulation Resources, Inc., Redlands, CA, USA	An interactive control program for constructing models; when used with a C compiler, SCoP greatly simplifies the construction of a simulation program.	Menzel, Wolpert et al. 1987
Stella	Isee Systems (formerly High Performance Systems Inc.), Lebanon, NH, USA	Macintosh, interactive graphical user interface software; enables the user to generate models with diagrams, where a minimal knowledge of computer programming is required.	Hoang 1995
Mathematica	Wolfram Research, Inc., Champaign, IL, USA	Mathematical software with matrix-related computations; numerical integration algorithms capable of solving systems of ordinary differential equations.	Burmaster and Murray 1998

Software	Developer/vendor	Salient features	References
Berkely Madonna	Robert Macey and George Oster, University of California at Berkeley, CA, USA	This program is a general-purpose differential equation solver. It is currently used by academic and commercial institutions for constructing mathematical models for research and teaching.	Reddy, Andersen et al. 2003
SONCHES (Simulation of Nonlinear Complex Hierarchical Ecological Systems)	Central institute of Cybernetics and Information Processes, Academy of Sciences of GDR, Berlin, Germany	A computer system where connections between various data libraries in the preparation and post-processing of simulation are executed by macro commands.	Wünscher, Kersting et al. 1991
BASICA	California Department of Pesticide Regulation, Sacramento, CA, USA	Numerical integration algorithms developed by the Department for PBPK modeling.	Dong 1994
AVS (Application Visualization System)	Advanced Visual Systems, Inc., Waltham, MA, USA	A visualization software package capable of importing processed resonance images and combining the use of ACSL to create three-dimensional representations of the PBPK of a chemical in an organism.	Nichols, Rheingans et al. 1994
MCSim	Drs. Bois and Maszle University of California at Berkeley, Berkeley, CA, USA	This software facilitates Bayesian analysis.	Jonsson and Johanson 2003
SAAM II	SAAM Institute, University of Washington, Seattle, WA, USA	It contains the compartmental and numerical modules to conceptualize biological processes, link the inputs, transfers between compartments, and fit data to different models.	Charles and Duffull 2001
CMATRIX	Drs. Ball and Schwartz Georgetown University, Washington DC, USA	It allows the user to create compartmental pharmacokinetic models based on personal biological knowledge, leaving the construction and numerical solution of the differential equations to the software.	Ball and Schwartz 1994
PKQuest	Dr. Levitt University of Minnesota, Minneapolis, MN, USA	A large set of data about kinetics in different organs and physiological parameters that can be called, and a simple graphical interface that provides a complete description of pharmacokinetics.	Levitt 2002
PANSYM	Dr. Thomaseth Institute of Systems Science and Biomedical Engineering, Padova, Italy	A symbolic equation generator	Thomaseth 1994

Software	Developer/vendor	Salient features	References
NONMEM	University of California, San Francisco, CA, USA	A widely used program for the analysis of population pharmacokinetic/pharmacodynamic data based on maximum likelihood method.	Aarons 1999
GastroPlus™	Simulation Plus, Inc., Lancaster, CA, USA	A software specific for intestinal absorption based on advanced compartmental absorption and transit model.	Yu and Amidon 1999; Wei and Lobenberg 2006
iDEA™	LionBioscience, Inc., Heidelberg, Germany	A software specific for intestinal absorption based on advanced compartmental absorption and transit model.	Yu and Amidon 1999; Parrott and Lavé 2002
SimCyp®	SimCyp Ltd., Sheffield, UK	A PBPK software specifically for metabolic process.	Johnson, Tucker et al. 2003
Spotfire®	TIBCO Spotfire, U.S., Somerville, MA, USA	Data mining from corporate Oracle databases.	Stoner, Gifford et al. 2004
PK-Sim®	Bayer Technology Services GmbH, D-51368 Leverkusen, Germany	Whole-body physiologically-based pharmacokinetic simulation software consists of a large numbers of differential equations, experimentally validated physiology-related parameters.	Willmann, Lippert et al. 2003

4 Overview of pharmacokinetic modeling for the drugs commonly used by Canadian Forces

This section focuses on reviewing literature of various models describing pharmacokinetics of the drugs under each drug category identified to be of potential interest to the CF (see Background section). The pharmacokinetic models of each drug and their uses are summarized in Table 2.

As previously indicated, compartment models have been used extensively to describe the pharmacokinetics of drugs. In a simple compartment model, a drug enters the compartments by means of arterial blood and is presumed to be eliminated in specific organs, such as liver and kidney. Another assumption is that the concentration of the drugs is homogeneous within the compartment. It is also commonly assumed that drug uptake, at least for lipophilic drugs, is blood-flow limited. The extent to which of compartment models can be used for predictive purposes remains to be determined. In contrast, the PBPK models have been used to investigate the effects of ages and pathophysiological states on the pharmacokinetics of methadone (Yang, Tong et al. 2006) and midazolam (Bjorkman, Wada et al. 2001), respectively. These models may be modified to predict pharmacokinetics under certain operational stresses through adjusting the values of model parameters to reflect corresponding physiological changes.

Given the tremendous efforts of modeling physiological responses to military scenarios (Yokota, Berglund et al. 2005), there is huge potential for PBPK modeling for operational stressors when the physiological and pharmacokinetic modeling approaches are combined. In addition, the PBPK approach can address pharmacokinetic changes in a specific organ/tissue of interest by designating it as a separate compartment to include drug transport processes within the compartment. For example, a brain tissue compartment can be included along with four transport processes between the brain blood and brain tissue (endothelial transport, transcytosis, passive diffusion and mediated transport) to study the effects of the brain-blood barrier permeability on drug disposition to the brain tissue (Watson 2001), which is likely to alter under extreme environmental conditions.

In contrast with the compartment models, there are only a few non-compartment models which may be not suitable for CF applications since they are based on mathematical integral equations for deriving various pharmacokinetic parameters from experimental data, such as: (1) area under the plasma concentration-time curve; (2) mean absorption time; (3) volume of distribution; (4) total plasma clearance. The models have no anatomical structures and as a result, physiological parameters are not included. Therefore, they do not have the capability to reasonably extrapolate beyond the generating limited time-concentration data. On the other hand, the advantage of non-compartmental modeling relates to the use of fewer restrictive assumptions than in the compartmental methods (Gillespie 1991). When the pharmacokinetic parameters change over time, such as in an autoinduction process that increases a drug's hepatic clearance with repeated administration involvement, or when human circadian rhythms have significant effects on the pharmacokinetics of exogenous substances, a non-compartmental analysis may be more appropriate than the compartmental models (Marzo, Rescigno et al. 1993).

No reports were found on any pharmacokinetic models for antimotion sickness medications (e.g., dextroamphetamine, dimenhydrinate, meclizine), antilipemics (e.g., fenofibrates, niacin),

sedatives (e.g., zaleplon, temazepam), and alertness management medications (e.g., modafinil). Preliminary models need to be constructed and validated for further development to study the pharmacokinetic effects of the stresses on these drugs.

Table 2: Summary of pharmacokinetic models for selected drugs.

Category	Drugs	Uses	PK models	References
Analgesics	Alfentanil	Anesthesia in surgery	PBPK model	Björkman, Wada et al. 1994; Bjorkman, Wada et al. 1998
	Fentanyl	Anesthesia and analgesia, most often in the operating room and intensive care unit	PBPK models and empirical polyexponential equations	Scott and Stanski 1987; Shafer, Varvel et al. 1990; Björkman, Wada et al. 1994; Bjorkman, Wada et al. 1998; Bjorkman 2003
	Ketamine	Treatment of pain associated with various pathological conditions and minor surgery; potential treatment of depression, alcoholism and heroin addiction	Two-compartment and PBPK models	Mason, Swinhoe et al. 1996; Hijazi, Bodonian et al. 2003; Levitt 2004
	Methadone	Narcotic analgesic and detoxification treatment of opioid dependence and maintenance therapy in narcotic addiction	PBPK model taking account of age-dependent physiological, physicochemical, biochemical varieties	Yang, Tong et al. 2006
	Methamphetamine	Psychostimulant and sympathomimetic drug	One-compartment model with first-order input and a lag time	Cook, Jeffcoat et al. 1992
	Rocuronium, propofol, thiopental, halothane	Muscle relaxant, general anesthesia,	Recirculatory models for flow-dependent and pulmonary uptaking drugs due to early-phase distribution	Reekers, Boer et al. 2003

Category	Drugs	Uses	PK models	References
Analgesics (continued)	Sufentanil	The main use of this medication is in operating suites and critical care where pain relief is required for a short period of time	Two- and three-compartment models with zero-order input and first-order elimination	Slepchenko, Simon et al. 2003
	Lidocaine	Local anaesthetic and antiarrhythmic	Three-compartment model	Williams and Riviere1993
	Morphine and Morphine-6-glucuronide	A highly-potent opiate analgesic drug for a variety of pain relief	PBPK model and two- or three-compartment models with exponential functions or constant infusion and first-order elimination	Stanski, Greenblatt et al. 1976; Persson, Wiklund et al. 1986; Lötsch, Skarke et al. 2002 ; Romberg, Olofsen et al. 2004
	Thiopental	General anesthesia through intravenous injection	PBPK model	Bischoff and Dedrick 1968
Non-steroidal anti-inflammatory drugs	Ibuprofen	Treatment of pain and inflammatory disorders	Open two-compartment model with first order absorption	Wagner, Albert et al. 1984
	Tenoxicam	Treatment of inflammation, swelling, stiffness, and pain	PBPK model	Kwon and Bourne 1987
Antibiotics including anti-malarials	Cefazolin	Skin infection	PBPK models under non-steady-state conditions	Tsuji, Nishide et al. 1985; Lagneau, Marty et al. 2005
	Ceftazidime	Treatment of infections caused by Pseudomonas aeruginosa	PBPK model and two-compartment model with first order elimination	Granero, Chesa-Jimenez et al. 1993; Conil, Georges et al. 2007
	Ceftriaxone: a third-generation cephalosporin antibiotic	Treatment of community-acquired pneumonia	Two-compartment model with constant infusion and first-order elimination	Simon, Dussol et al. 2006

Category	Drugs	Uses	PK models	References
Antibiotics including anti-malarials (continued)	Mefloquine	Treatment of Malaria infection during field deployment	One- two- and three-compartment models with first-order absorption and elimination	Svensson, Alin et al. 2002; Ashley, Stepniewska et al. 2006; Charles, Blomgren et al. 2007
	Malarone	Treatment of multi-drug resistant malaria	Two-compartment model with zero-order input and first-order elimination	Na-Bangchang, Manyando et al. 2005
	Tafenoquine	Prophylaxis against and potential treatment for malaria	One-compartment model with first-order absorption and elimination	Edstein, Kocisko et al. 2001; Charles, Miller et al. 2007
	Tetracycline	Use against many bacterial infections	PBPK model for constant release	Olanoff and Anderson 1979
	Vancomycin	Prophylaxis against and treatment of infections caused by Gram-positive bacteria	One-compartment model with zero-order infusion and first-order elimination	Anderson, Allegaert et al. 2007
	Artemisinin	Treatment of multi-drug resistant strains of falciparum malaria	Multi-compartment model with first-order absorption and elimination	Gordi, Xie et al. 2005
Antihistamines	Mizolastine	Treatment for allergies including hayfever and skin reactions	Two-compartment and noncompartmental models	Mesnil, Dubruc et al. 1997
	Promethazine	Multiple indications for motion sickness, postnarcotic nausea, hay fever	Three-compartment model with first-order absorption and elimination	Stavchansky, Wallace et al. 1987
Anti-hypertensives	Acebutolol: a cardioselective β blocker	Treatment of hypertension, angina, and arrhythmia	Three-compartment model	Scott, Meredith et al. 1995

Category	Drugs	Uses	PK models	References
Anti-hypertensives (continued)	Nitrendipine: a calcium-channel blocker	Treatment of mild or moderate hypertension	Multi-compartment models and artificial neural networks for modelling the relationship between nitrendipine plasma profiles and its effects after oral administration of the drug	Grabnar, Belic et al. 1998; Belic, Grabnar et al. 2005
	Moxonidine	Treatment of mild to moderate essential hypertension	One-compartment model with first-order absorption and elimination	Troconiz, de Alwis et al. 2000
	Propranolol	Treatment of hypertension, angina pectoris and cardiac arrhythmias	PBPK model	Kiriyama, Honbo et al. 2008
	Verapamil: an L-type calcium channel blocker	Treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches	PBPK model	Peters 2008
Asthma medications	Atropine	An anticholinergic drug	Two-compartment model linked by a first-order process	Scheinin, Helminen et al. 1999
	Corticosteroids	Inflammatory treatment	A large diversity of mathematical models	Czock, Keller et al. 2005; Semmar and Simon 2006
	Terbutaline β2-adrenergic receptor agonist	Short-term asthma treatment	Two-compartment model	Lima, Matsushima et al. 2004
	Theophylline	Treatment of respiratory diseases	Gamma generalized linear models	Salway and Wakefield 2007
Anti-depressants	Bupropion	Treatment of major depressive disorder	A two-compartment model with first-order absorption	Findlay, Van Wyck Fleet et al. 1981

Category	Drugs	Uses	PK models	References
Anti-depressants (continued)	Citalopram	Treatment of depression associated with mood disorders and occasionally for body dysmorphic disorder and anxiety	One-compartment model with first-order absorption and elimination	Friberg, Isbister et al. 2006
	Escitalopram	Treatment of major depressive disorder and generalized anxiety disorder	One- and two-compartment models with and without lag time	Areberg, Christophersen et al. 2006
	Imipramine	Treatment of clinical depression and enuresis	One-compartment model with linear kinetics	Gram 1988; Tamayo, Fernández de Gatta et al. 1992
	Reboxetine	Treatment of patients with depression	Linear pharmacokinetics best described by a one-compartment model following single and multiple oral dosage	Dostert, Benedetti et al. 1997; Fleishaker 2000
	Sertraline	Treatment of clinical depression in adult outpatients as well as obsessive-compulsive, panic and social anxiety disorders in both adults and children	One-compartment model with first-order input with no lag time	Wang, DeVane et al. 2006
	Venlafaxine	Treatment of mood disorders	PBPK model and one-compartment model described by a bi-exponential function	Taft, Iyer et al. 1997; Troy, Parker et al. 1997

Category	Drugs	Uses	PK models	References
Antimotion sickness medications	Scopolamine	Treatment of nausea and motion sickness	Non-compartment, two- and three-exponential models and two-compartment models linked by a first-order process	Scheinin, Helminen et al. 1999; Ebert, Grossmann et al. 2001; Renner, Oertel et al. 2005
Antilipemics	Adenosine receptor agonist	Reduction of free fatty acid production	Two-compartment model with first-order elimination	Zannikos, Rohatagi et al. 2001
	Ezetimibe	Treatment of hypercholesterolemia	Two-compartment model	Ezzet, Krishna et al. 2001
	Statins: simvastatin, rosuvastatin, atorvastatin	Treatment of hypercholesterolemia	PBPK model and an indirect-effect model with precursor and response compartments	Faltaos, Urien et al. 2006; Shitara and Sugiyama 2006
Sedatives	Diazepam	Treating anxiety, insomnia, seizures, alcohol withdrawal, and muscle spasms	PBPK model or two-compartment model described by exponential functions	Mould, DeFeo et al. 1995; Langdon, Gueorguieva et al. 2007; Seng, Nestorov et al. 2008
	Lorazepam	Short-term management of severe anxiety	One- and three-compartment models with linear or nonlinear input and output	Blin, Simon et al. 2001; Swart, Zuideveld et al. 2004
	Midazolam	Short term treatment of insomnia and acute management of aggressive or delirious patients	PBPK and two-compartment models	Bjorkman, Wada et al. 2001; Swart, Zuideveld et al. 2004
	Propofol	Induction and maintenance of general anesthesia	PBPK model or three-compartment mammilary model	Barr, Egan et al. 2001; Edginton, Schmitt et al. 2006b

Category	Drugs	Uses	PK models	References
Sedatives (continued)	Zolpidem	Short-term treatment of insomnia and some brain disorders	Two-compartment model described by exponential functions	Lau, Sun et al. 2002
	Zopiclone (imovane)	Treatment of insomnia	A linear one-compartment model	Luurila and Olkkola 1996
Alertness management medications	Amphetamines	Treatment of attention-deficit disorder and fatigue management	One- or two-compartment models with first order absorption and elimination	Watanalumlerd, Christensen et al. 2007
	Caffeine	Reduction of physical fatigue and restore mental alertness	PBPK models for adults and children; one-compartment model with first order absorption	Ginsberg, Hattis et al. 2004
	Melatonin	Treatment of cancer, immune disorders, cardiovascular diseases, depression, seasonal affective disorder, sleep disorders	Local polynomial regression model	Gamst, Wolfson et al. 2004
Nicotine replacement therapy	Nicotine patch	Smoking cessation	One-compartment model with zero-order absorption	Roberts 2006
	Nicotine gum		Non-compartmental input function models	Pitsiu, Gries et al. 2002
	Nicotine nasal spray		One-compartment model with zero-order absorption	Hutson, Fishbein et al. 2002
	Intravenous injection		PBPK model	Holmes, Ward et al. 2000
Other medications	Pyridostigmine: a cholinesterase inhibitor	Symptomatic treatment of myasthenia gravis; military use for prophylaxis against nerve gas attacks	Two-compartment model with first-order absorption and elimination	Marino, Schuster et al. 1998

PBPK = Physiologically-Based Pharmacokinetic

5 Pharmacokinetics of drugs potentially affected by operational stressors

The effects of various stressors on drug response were recognized decades ago with studies specifically limited to animals. For example, leg ligation in rats significantly decreased pharmacological actions of drugs, such as hexobarbital, meprobamate, and pentobarbital (Rupe, Bousquet et al. 1963). Nowadays, human studies have been performed and the stressors involved can range from life-threatening acute injuries to chronic physical effects or psychological/mental disorders. In general, any external factors affecting our normal functions can be considered as a stressor. Although well recognized, the true meaning of stress is often difficult to describe and pinpoint. Selye, who began his pioneering work in the early 20th century, defined stress as the 'nonspecific response of the body to any demand' and stressor is an event which threatens or is perceived to threaten homeostasis (Selye 1976). In this report, stress is used interchangeably with stressors and refers to subsequent changes in various processes (e.g., physiological and behavioural alterations) during a military operation. In the context of a military environment, the stressor is often called an operational stressor and can be both physiological and psychological.

The effects of stressors, such as exercise (Somani, Gupta et al. 1990; Lenz, Lenz et al. 2004), heat (Vanakoski and Seppala 1998) and disease state (De Paepe, Belpaire et al. 2002), and the associated changes in a drug's pharmacokinetics have been documented. They rely heavily on the mechanisms by which stress-induced pathophysiological changes may influence various pharmacological processes. However, many of these proposals have not been validated, particularly their clinical implications and relevance to the therapeutic effects (i.e., pharmacodynamics of drugs). Given the large individual pharmacodynamic variability, usually exceeding pharmacokinetic variability (Levy 1998), the stressful effects on the former may be more pronounced. However, it is beyond the scope of this report to review any possible effects that military operations might have on the pharmacological response of a drug. On the other hand, there were a number of studies evaluating the use of drugs to combat the effects of operational stressors in military settings (Caldwell and Caldwell 2005; Kautz, Thomas et al. 2007). The following section reviews reported human studies of any operational stresses affecting pharmacokinetics.

5.1 Physiological response to stressors

Stressors are known to exert a broad range of physiological effects on the human body. Some effects include cardiovascular changes and diseases (Selye 1970) and induced neuroimmunological functions (Friedman and Lawrence 2002). A number of physiological responses to environmental stressors and their resultant effects on pharmacokinetics have been investigated a few decades ago, mainly through animal studies (Buckley 1972). Table 3 is a summary of the stressors encountered during military operations which may affect physiological parameters and subsequently influence pharmacokinetic variables. For example, during intense exercise, changes in cardiovascular, renal and hepatic function, and fluctuations in plasma protein concentrations affect the absorption, distribution and elimination of the drugs. For example, exercise decreases blood flow into the splanchnic region (Rowell 1974), thus reducing drug absorption through gastrointestinal tract and drug elimination by the liver and the kidney. The

effect of the reduced absorption on plasma drug concentration is the opposite to that of the reduced elimination. On the other hand, the changes in blood flow can affect the pharmacokinetic processes in a concurrent manner, likely resulting in more profound pharmacokinetic effects. For example, exercise increases blood flow through skin, enhancing the absorption of transdermal drugs, and simultaneously reduces blood flow to liver and kidney, thereby impairing elimination. Both mechanisms would elevate the plasma drug concentration.

In addition to physiological stressors, military operation involves unique psychological stressors (Balson, Manning et al. 1986), which may cause physiological changes. For example, emotional distress may lead to elevated heart rate, blood pressure and glucocorticoid levels (Vig, Forsythe et al. 2006). The pharmacokinetic effects of these physiological changes need to be studied more thoroughly. In theory, pharmacokinetic models may be developed to incorporate those physiological variables that contribute to the pharmacokinetic changes during military operations. This may be achieved by modifying the models that have been developed based on individual variations in the physiological parameters (Price, Conolly et al. 2003).

Table 3: Effects of stressors on physiological and subsequent pharmacokinetic changes.

Stresses	**Physiological impact**	**Pharmacokinetic effects**	**References**
Physical activities	Alteration in blood flow and cardiac output	Absorption changes in either way depending on the site of drug administration and blood flow to the site; declined clearance of drugs that undergo extensive hepatic metabolism	Ciccone 1995
	Increased GI transit and emptying time especially during vigorous exercise	Prolonged absorption after oral administration	Persky, Eddington et al. 2003; Lenz, Lenz et al. 2004
	Lower GI pH and increased membrane permeability	Absorption changes depending on drug pK_a	Ryan, Chang et al. 1996; Khazaeinia, Ramsey et al. 2000
	Decreased plasma volume and increased plasma binding	Decreased volume of distribution and elimination especially for low-extraction (binding-sensitive) drugs	Martyn 1986; Somani, Gupta et al. 1990; Ciccone 1995; Khazaeinia, Ramsey et al. 2000
	Decreased renal glomerular filtration rate and increased tubular reabsorption	Renal clearance decreases for high-extraction drugs	Ciccone 1995; Khazaeinia, Ramsey et al. 2000

Stresses	Physiological impact	Pharmacokinetic effects	References
Physical activities (continued)	Increased the activity and content of hepatic microsomal enzymes by chronic exercise	Increased hepatic drug metabolism	Dossing 1985
	Increased biliary excretion	Increased drug clearance	Khazaeinia, Ramsey et al. 2000
Hyper-thermia (heat)	A 10- to 12-fold increase in skin blood flow and 2-fold increase in cardiac output; a 30-35% decrease in the blood flow to GI tract, liver and kidney	Increased drug absorption through skin	Vanakoski and Seppälä 1998
	Temporary haemodilution and thereafter haemoconcentration	Unknown	Kukkonen-Harjula, Oja et al. 1989; Vanakoski and Seppälä 1998
	Initial decrease followed by increases in plasma concentration	Decreased volume of distribution and elimination especially for low-extraction (binding-sensitive) drugs	Vanakoski and Seppälä 1998
	Generally increased enzyme bioactivities	Increased metabolism	Kukkonen-Harjula, Oja et al. 1989; Vanakoski and Seppälä 1998
Hypothermia (cold)	Increased oxygen consumption	Decreased clearance of cytochrome P_{450} metabolized drugs	Frank 2001; Tortorici, Kochanek et al. 2007
	Increased blood pressure and impaired blood coagulation	Unknown	Frank 2001

Stresses	Physiological impact	Pharmacokinetic effects	References
Hypothermia (continued)	Decreased brain volume, increased extracerebral space volume, increased respiratory rate	Increased effects of neuromuscular blockers, decreased minimum alveolar concentration of inhaled anaesthetics	Frank 2001
	Inhibited enzyme functions	Reduced metabolism	Tortorici, Kochanek et al. 2007
Altitude	Decreased body oxygen and plasma volume	Reduced hepatic clearance by cytochrome P_{450} enzymes	Ritschel, Paulos et al. 1996a,b; Ritschel, Paulos et al. 1998a; Streit, Göggelmann et al. 2005
	Increased blood flow to the brain	Drug distribution to the brain	Ritschel, Paulos et al. 1996a,b
	Increased blood pH	Unknown, but depending on pKa of the drug	
	Increased erythrocyte mass and plasma protein concentration	Increased protein binding and decreased V_{SS} for highly cleared drugs and increased CL for low CL drugs	Ritschel, Paulos et al. 1996a,b; Mehvar 2005
Hyperbaric oxygen	Reduction by 10-20% in cardiac output	All central pharmacokinetic parameters: bioavailability, distribution, metabolism and excretion.	Merritt and Slade 1993

V_{SS} = volume of distribution at steady state; CL = Clearance; GI= gastrointestinal

5.2 Physical activity

Exercise or extreme physical activity is the most significant operational stressor experienced in the military. Exercise can be acute or chronic. The former can be further defined as light, moderate or heavy exercise as based on heart rate measurements (Andersen 1968). Chronic

exercise, sometimes referred to as exercise training, has been defined as acute exercise repeated over time (> 3 times/week) (Persky, Eddington et al. 2003). Both types of physical activities are highly relevant to military training. Extensive research and reviews on the effects of acute exercise on drug pharmacokinetics has been addressed (Reents 2000).

5.2.1 Physiological changes affecting drug kinetics

Table 4 lists the most significant physiological changes associated with acute and chronic exercise (Persky, Eddington et al. 2003). Among these changes, cardiovascular responses to exercise are well documented to have a major effect on a drug's pharmacokinetics (Fagiolino, Eiraldi et al. 2006). This is consistent with the predictions from physiologically-based modeling (Wada, Bjorkman et al. 1997; Bjorkman, Wada et al. 1998). From a theoretic standpoint, these changes should affect the kinetics of flow-sensitive drugs (i.e., drugs not limited by plasma protein binding) more profoundly than capacity-limited drugs (i.e., drugs strongly bound to plasma proteins and poorly extracted by the liver and kidney) (Somani, Gupta et al. 1990).

Although pharmacokinetic changes in response to exercise have been mostly investigated by a number of researchers (Somani, Gupta et al. 1990; Somani 1996; Lenz, Lenz et al. 2004), their clinical significance remains unclear. Furthermore, the results can be inconsistent and conflicting. For example, one study demonstrated that exercise raised the maximal plasma caffeine concentrations and reduced both the half-life and the volume of distribution (Collomp, Anselme et al. 1991), while others reported that there were no effects (Vanakoski, Kosunen et al. 1998; Graham 2001).

Table 4: Physiological changes associated with acute and chronic exercise (Novosadová 1977; Dossing 1985; Persky, Eddington et al. 2003) .

Acute exercise	Chronic exercise
Reduced plasma volume with concomitant haemoconcentration and increased protein concentration	Increased blood volume
Decreased hepatic blood flow	Decreased resting heart rate and fat mass
Increase heart rate	Increased muscle capillary density
Increased systolic blood pressure	Morphological changes in the heart
Increased cardiac output	Increased maximum volume of oxygen uptake at rest
Increased pulmonary ventilation and volume of oxygen uptake	Increased oxidative enzymes, mitochondrial size and number.
	Thyroid function, hormones, lipoproteins metabolism

In general, the major underlying influence of acute exercise effects is a change in blood flow dynamics as shown in Figure 6. Circulating blood is shunted away from the splanchnic organs (e.g., liver) toward the relevant working muscles involved with that particular exercise. Furthermore, it has been demonstrated both theoretically and experimentally that cardiac output is a major influence and plays a major role in drug pharmacokinetics (Upton, Ludbrook et al. 1999; Upton 2000). Other mechanisms may be involved such as increased maximal oxygen uptake as a result of chronic exercise affecting biotransformation of drugs (Dossing 1985).

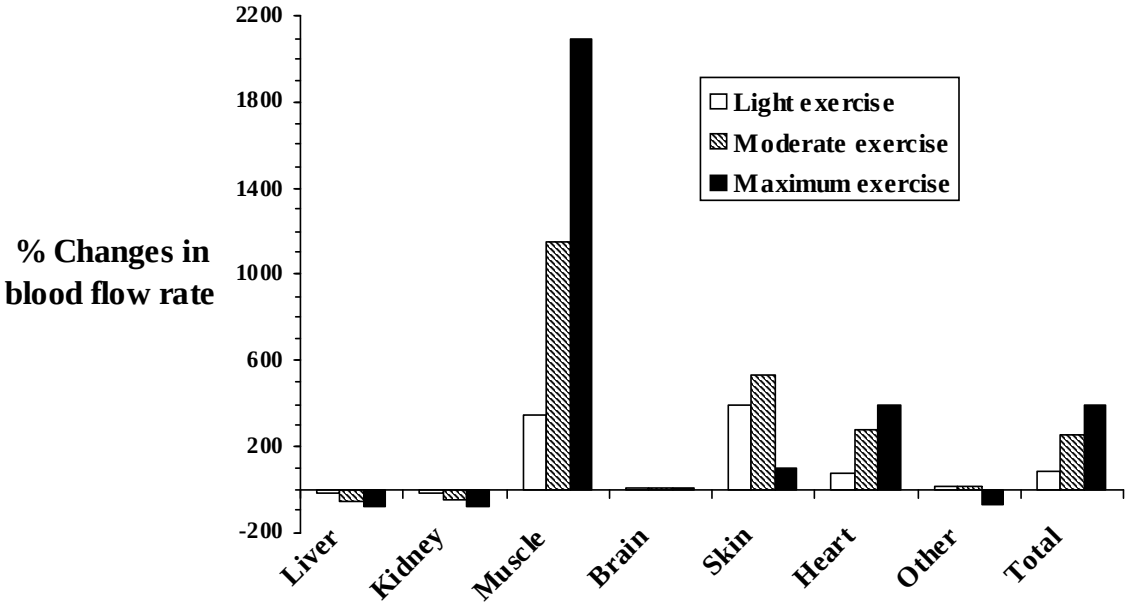


Figure 6: Changes in blood flow during exercise.

5.2.2 Pharmacokinetic studies: the effects of exercise(s)

Extensive studies on the effects of exercise on drug pharmacokinetics have been conducted in sports medicine (Reents 2000). Table 5 summarizes the effects on the pharmacokinetics of the drugs that fall under each category of interest. These drugs have been administered by various routes: oral, intravenous, intramuscular injection, and transdermal therapeutic delivery system. A variety of test conditions were reported in terms of the intensity, duration and timing of each physical activity. Readers may consult the citations for detailed discussions (Somani, Gupta et al. 1990; Ylitalo 1991; Khazaeinia, Ramsey et al. 2000; Lenz, Lenz et al. 2004).

Cardiovascular drugs have enormous potential therapeutic benefits and thus have been a popular category of drugs to investigate. For example, a number of studies have been conducted for propranolol, a non-selective beta blocker mainly used in the treatment of hypertension. These

studies confirmed that the route of administration (oral vs. intravenous) and exercise intensity induced the pharmacokinetic changes (Arends, Bohm et al. 1986; van Baak, Mooij et al. 1992).

On the other hand, there are contradicting results from studies conducted under similar conditions, which may be explained by different experimental protocols and population-specific parameters/variations such as gender, age, ethnicity and health habits. Gender differences in absorption, distribution, metabolism and excretion have been reported (Arbuckle 2006).

Different pharmacokinetics was reported between smokers and non-smokers. One study found that at an average daily dose of 281 mg clozapine (an antipsychotic medication used in the treatment of schizophrenia), the average plasma levels of smokers were 81.8% of those of non-smokers (Haling, Meise et al. 1989).

A variety of factors associated with exercise may alter a drug's pharmacokinetics (Ylitalo 1991). However, it has been difficult to predict quantitatively the exercise-induced pharmacokinetic effects (Stoschitzky, Zweiker et al. 2002). In addition, even for the same drug (e.g., propranolol), no effects were reported under exercise which is perhaps due to a different intensity and duration of the exercise (Panton, Guillen et al. 1995). Further studies are required to address these inconsistent reports in the literature. Different effects of exercise on plasma concentrations of the same class of drugs (e.g., beta-blockers) were also reported and ascribed to their behaviour of release from adrenergic nerves during exercise (Stoschitzky, Stoschitzky et al. 2004). Although most studies focused on the alterations in plasma concentration, some were conducted specifically for the effects on drug hepatic metabolism (Dossing 1985) and renal clearance (Villa, Bayon et al. 1999). Clearly, the impact of exercise on drug pharmacokinetics is influenced by a variety of physiological and physicochemical factors.

As summarized in Table 6, the effects of physical activities on the absorption, distribution, metabolism and excretion of a drug depend on the route of administration as well as the physiochemical properties of the drug. The route of administration plays a main role in the effects of exercise on absorption. For example, regardless of its type, the absorption of a drug from intramuscular, subcutaneous and transdermal sites is likely to be increased due to the increased blood flow through the sites, the augmented lymphatic drainage, and the pumping effects of contracting muscles (Rowell 1974). On the other hand, oral dose could have reduced absorption because of the reduction of splanchnic blood flow and the gastric emptying effect (Fordtran and Saltin 1967). The type of drug has a strong influence on its distribution, metabolism and elimination processes under exercise. Although different metabolic pathways are involved in drug metabolism, most drugs are metabolized by a system of enzymes, known as oxygenases or microsomal hydroxylases in liver. Therefore, the effects of exercise on drug metabolism may be mainly attributed to its modification of blood flow to the liver and enzyme activities. As for drug elimination, it may be more diverse than its metabolism. The hepatic or renal elimination of a capacity-limited drug is opposite to that of a flow-limited drug and is increased.

Table 5: The effects of exercise on pharmacokinetics. The type of exercise is noted under Exercise Intensity (acronyms are listed at the end of the table)

Category	**Drugs**	**Routes of administration**	**Exercise intensity**	**Effects**	**Author(s) & Year**
Analgesics	Acetaminophen	Oral ingestion of 1 g prior to exercise	Walking on a treadmill for 20 min each half hour for 3 h	No effects on plasma drug concentration, $t_{1/2}$ and CL	Sawrymowicz 1997
	Aminopyrine	Oral ingestion of 9 mg/kg	Gymnastic athletes	Faster disappearance rate	Gikalov and Bircher 1977
			Long-distance runners	No effects on aminopyrine metabolism	Ducry, Howald et al. 1979
	Antipyrine (phenazone)	Intravenous injection of 10 mg/kg during exercise	Treadmill walking at 3 mph for 20 each half hour for 3 hours	Initial decrease in plasma concentration, but no change in hepatic CL	Swartz, Sidell et al. 1974
		Oral ingestion	Chronic exercise (running >80 km/week)	Reduced $t_{1/2}$ by 31% and increased CL by 26%	Villa, Bayon et al. 1999
Non-steroidal anti-inflammatory drugs	Indomethacin	Oral ingestion of 50 mg at 3, 2, 1 h, respectively before exercise	Ergometeric cycling at a heart rate of 160-180 beats/min for 5 min with 30 min resting, 3 times	No effects	Henry, Iliopoulou et al. 1981
	Lidocaine: a high CL drug with a small V_d	Intravenous bolus and constant infusion at 2.16 mg/min for 4 h during exercise	Ergometeric cycling at 60% $Vo_{2\ max}$ for 60 min commenced at 3 h after initial drug infusion	Increased plasma drug concentration	Sweeney 1981

Category	Drugs	Routes of administration	Exercise intensity	Effects	Author(s) & Year
Non-steroidal anti-inflammatory drugs (continued)	Sodium salicylate	Oral ingestion of 10 mg/kg	Ergometeric cycling at 600 and 450 kpm/min respectively for males and females with alternating 5-min periods of work and rest for 3 h	No effects on plasma concentration	Aslaksen and Aanderud 1980
Antibiotics	Doxycycline	Oral ingestion of 100 mg at 15 min after exercise	A basketball match for 50 min every hour for 4 consecutive hours	Increased AUC and C_{max}	Ylitalo, Hinkka et al. 1977
	Tetracycline	Oral ingestion of 500 mg at 15 min after exercise			
Anti-hypertensives	Acebutolol: a cardioselective β blocker	Oral ingestion of 200 mg at 3, 2, 1 h, respectively before exercise	Ergometeric cycling at a heat rate of 160-180 beats/min for 5 min with 30 min resting, 3 times	Increased mean plasma concentration by 9.8%	Henry, Iliopoulou et al. 1981
	Atenolol: a β1 receptor specific antagonist	Oral ingestion of 100 mg at about 1.5 h before exercise	70% maximal aerobic power for 25 min	No changes in plasma drug concentration	van Baak, Mooij et al. 1992
		Intravenous bolus of 35 µg/kg and constant infusion at 5 µg/min during exercise	Exercise at 50% maximal aerobic power on a cycle ergometer for 10 min		
	Bispoprolol: a β1-selective β-blockers	Oral ingestion of 20 mg before exercise	Ergometeric bicycling at 75% maximum workload	7.5% decrease in AUC	Coz, Sauleman et al. 1991

Category	Drugs	Routes of administration	Exercise intensity	Effects	Author(s) & Year
Anti-hypertensives (continued)	Carvediolol: a β-blocker	Oral ingestion of 40 mg before exercise	Ergometeric cycling until exhaustion	No effects	Stoschitzky, Zweiker et al. 2002
	Propranolol: a non-selective β-blocker	Oral ingestion of 80 mg at 30 min before exercise	Ergometeric cycling at 50% maximal work capacity for 20min, 35 min of outdoor walking	Reduced AUC	Arends, Bohm et al. 1986
		Intravenous injection of 0.2 mg/kg at 30 min before exercise		Reduced terminal half-life	
		Oral ingestion of 80 mg at about 1.5 h before exercise	Exercise at 70% maximal aerobic power on a cycle ergometer for 25 min	Increased plasma drug concentration	van Baak, Mooij et al. 1992
		Intravenous bolus of 195 µg/kg and constant infusion at 42 µg/min during exercise	Exercise at 50% maximal aerobic power on a cycle ergometer for 10 min	No change in plasma drug concentration	
		Oral ingestion of 200 mg at 3, 2, 1 h, respectively before exercise	Ergometeric cycling at a heat rate of 160-180 beats/min for 5 min with 30 min resting, 3 times	Increased mean plasma concentration by 16.4%	Henry, Iliopoulou et al. 1981
		Oral ingestion of 80 mg	Training for 16 weeks consisted of treadmill walking, stair climbing 3 times per week for 40 min at 70-85% of maximal heart rate	No effects	Panton, Guillen et al. 1995

Category	Drugs	Routes of administration	Exercise intensity	Effects	Author(s) & Year
Anti-hypertensives (continued)	Propranolol: a non-selective β-blocker (continued)	Intravenous injection of 1 mg	Exercise for 20 min every hour for 8 h to a level which was 60% of $Vo_{2\ max}$	No effects likely due to a wide individual variation in the results for each healthy subject	Frank, Somani et al. 1990
		Oral ingestion of 67 mg before exercise	Ergometeric cycling with increasing workload by steps of 25 W every 2 min up to a maximum workload of 144 W	Increased plasma drug concentration	Stoschitzky, Schumacher et al. 1996
	Verapamil: a calcium antagonist	Intravenous bolus of 225 µg/kg and constant infusion at 60 µg/min during exercise	Ergometeric cycling at 50% maximum workload for 10 min	Increased plasma concentration and decreased V_d	van Baak, Mooij et al. 1992
		Oral injection of 80 mg at 30 min prior to exercise	Ergometeric bicycling at 50% maximum workload for 20 min and 30 min of walking around	No effects	Mooy, Arends et al. 1986
		Intravenous injection of 0.13 mg/kg at 30 min prior to exercise			
Asthma medications	Atropine: an anticholinergic	Intramuscular injection of 2 mg at 25 min after exercise	Stationary cycling at 40% $Vo_{2\ max}$ for 25 min	Decreased V_d	Kamimori, Smallridge et al. 1990
		Intramuscular injection of 2 mg prior to exercise	Stationary cycling at 40% $Vo_{2\ max}$ for 25 min 3 times with 5 min of seated rest	Decreased $t_{1/2}$, CL and increased $C_{max,}$ AUC	

Category	Drugs	Routes of administration	Exercise intensity	Effects	Author(s) & Year
Asthma medications (continued)	Atropine: an anticholinergic (continued)	Intramuscular injection of 2 mg after first bout of exercise	Stationary cycling at 40% $Vo_{2\ max}$ for 25 min 4 times with 5 min of seated rest	Decreased $t_{1/2}$, CL and increased $C_{max,}$ AUC	Kamimori, Smallridge et al. 1990
	Terbutaline: a β_2-adrenergic receptor agonist	Inhalation of 0.5 mg before exercise	Ergometeric cycling at 50% maximal work capacity for 30min	Increased C_{max} due to increased absorption	Schmekel, Borgstrom et al. 1992
Antidepressants	Amitriptyline/ nortriptyline	Oral ingestion of 150 mg	Running 2-5 miles on treadmill	Serum concentration increased by 14.9%	de Zwaan 1992
	Desipramine	Oral ingestion of 150 mg		Serum concentration increased by 10%	
Sedatives	Diazepam	Intravenous injection of 0.1 mg/kg at 10 min before exercise	5-min maximum ergometeric cycling	No effects on hepatic metabolism	Klotz and Lucke 1978
	Midazolam	Oral ingestion of 15 mg at 20 min before exercise	3 sessions of 10-min treadmill-running with 10-min break	Reduced absorption rate and C_{max}	Stromberg, Vanakoski et al. 1992
Alertness management medications	Caffeine	Oral ingestion of 250 mg right before exercise	Ergometeric cycling at 30% of $Vo_{2\ max}$ for 1 h	Increased $C_{max,}$ reduced $t_{1/2}$ and V_d	Collomp, Anselme et al. 1991
		Oral ingestion of 6 mg/kg at 1 h before exercise	Ergometeric cycling at 65% of $Vo_{2\ max}$ for 1.5 h	No effects on AUC, C_{max} , $t_{1/2}$, V_d , and CL	Graham 2001
		Oral ingestion of 304 mg at 1 h before exercise	Ergometeric cycling at 75-80% of maximum heart rate for 30 min	No differences in AUC, C_{max} , $t_{1/2}$ and CL	Haller, Duan et al. 2008

Category	Drugs	Routes of administration	Exercise intensity	Effects	Author(s) & Year
Nicotine replacement therapy	Nicotine patch	Trandermal delivery of 14 mg/24h with daily replacement of a new patch for 2 days prior to exercise	Ergometeric cycling at 80% of maximum heart rate for 20 min	Up to 30% increase in nicotine plasma concentration	Homsy, Yan et al. 1997
		Trandermal delivery of 14 mg/24h for 11 h before exercise	Bicycling at a heart rate of 130 min^{-1} for 20 min	An averaged increase from 9.8 to 11.0 ng/mL in nicotine plasma concentration	Klemsdal, Gjesdal et al. 1995

AUC = Total area under the plasma concentration-time curve, C_{max} = maximum plasma concentration, $t_{1/2}$ = distribution half-time and V_d = volume of distribution =dose/plasma concentration, CL=clearance; $Vo_{2\,max}$ = maximum O_2 uptake

The proposed mechanism has not been fully supported by the experimental results. Furthermore, it is noteworthy that little information is available for the effects of exercise on drug absorption through the lung. The mechanism is potentially more complex and depends on the rate and depth of respiration. Therefore, the exercise intensity and the particle size of aerosols are important parameters to be considered. It is difficult to provide a general statement on the effects of exercises on pharmacokinetics. Future studies may require standardization of experimental procedures and conditions and in the selection of drugs.

Although less well documented, chronic exercise or exercise training has also been shown to alter pharmacokinetics, likely in a different manner from acute exercise due to different underlying mechanisms, such as increased drug oxidative metabolism (Mauriz, Tabernero et al. 2000) (Dossing 1985; Villa, Cuadrado et al. 1998; Persky, Eddington et al. 2003). For example, the difference in the effects on aminopyrine was ascribed to dietary content (Vesell 1984), but it could also result from different types of training (gymnastic vs. running) which may induce biological changes, in particular hepatic functions, to various extents. Further research in this field will prove whether or not this is a confounding factor contributing to some of the conflicting results in this field.

Table 6: Summary of the effects of exercise on pharmacokinetics (Somani, Gupta et al. 1990).

<table>
<tr><td rowspan="3">Absorption</td><td colspan="3">Route of administration</td></tr>
<tr><td colspan="2">Intramuscular or Subcutaneous</td><td>Oral or Rectal</td></tr>
<tr><td colspan="2">⇑</td><td>⇓</td></tr>
<tr><td rowspan="2">Pharmacokinetic processes</td><td colspan="3">Type of drugs</td></tr>
<tr><td colspan="2">Flow-limited</td><td>Capacity-limited</td></tr>
<tr><td>Distribution</td><td colspan="2">⇓</td><td>⇑</td></tr>
<tr><td>Metabolism</td><td colspan="2">⇓</td><td>↓↑</td></tr>
<tr><td rowspan="3">Elimination</td><td colspan="2">Eliminating organ</td><td rowspan="3">⇑</td></tr>
<tr><td>Hepatic/renal</td><td>Lung/skin</td></tr>
<tr><td>⇓</td><td>⇑</td></tr>
</table>

⇓ Decrease, ⇑ Increase, ↓↑ Either decrease or increase. Flow-limited is defined as drugs bound less than 90% to plasma proteins and having an extraction ratio larger than 0.5; while capacity-limited is defined as drugs strongly bound and poorly extracted.

5.3 Other physiological stressors

Another common stressor shown to affect a drug's pharmacokinetics is environmental temperature; either extreme heat (hyperthermia) (Vanakoski and Seppala 1998) or extreme cold (hypothermia) (Tortorici, Kochanek et al. 2007). The former is encountered in tropical/desert regions, chemotherapy and during exercise and recreational activities (e.g., sauna). Cold exposure occurs during medical treatment, e.g., cardiopulmonary bypass and cerebral aneurysm clipping, and in cold weather regions, such as the Arctic. The studies on the effects of extreme temperatures are summarized in Table 7. These thermal conditions lasted from hours to a few days. It is noteworthy that long-term impacts of climatic extremes on human health and medications have been reviewed (Beggs 2000). Furthermore, tropical climatic conditions have been reported to change pharmacokinetics due to reduced formulation stability (Risha, Vervaet et al. 2003)

In addition to the physiological effects of environmental and body temperatures on drug pharmacokinetics, possible changes in the physiochemical properties of drugs with temperature may be also important in the pharmacokinetic process (Ballard 1974). For example, the aqueous solubility of a drug usually increases with increasing temperature, which can in turn augment drug absorption through the gastrointestinal epithelium if the dissolution or disintegration step is the rate-limiting factor. There are also possible effects of temperature on other intrinsic properties of a drug including acid dissociation constant (pK_a), partition and diffusion coefficients and protein binding constant (Ballard 1974).

Table 7: Effects of various physiological stressors on the pharmacokinetics of commonly prescribed drugs in the military.

Categories	**Drugs**	**Routes of administration**	**Stresses**	**Effects**	**References**
Analgesics	Fentanyl	Intravenous bolus of 50 or 30 µg/kg followed by constant infusion of 0.15 or 0.3 µg/kg min before hypothermia	Hypothermia 18-25°C for 100-140 min during cardiopulmonary bypass	No significant effects on plasma drug concentration	Koren, Barker et al. 1987
		Intravenous bolus of 1.5-2.5 µg/kg followed by infusion at 150 µg/h before, during and after hyperthermia	Hyperthermia 38-39.5ºC during isolated lung perfusion	No differences in plasma drug concentration	Williams, Susla et al. 1998
		Transdermal delivery of 25 µg/h	Local heat on transdermal patch at 42 ºC for 1-4 h initially and for 15 min at 12- and 16-h time points	Increased AUC, and C_{max} during heat application	Ashburn, Ogden et al. 2003
	Lidocaine	Intravenous bolus of 0.69 or 0.75 mg/kg immediately at hyperbaric condition	Hyperbaric hyperoxia for 75 min at 0.25 MPa, alternating 100% O_2 for 20 min and air breathing for 5 min	No change in drug disposition	Rump, Siekmann et al. 1999
	Meperidine	Intramuscular injection of 0.75 mg/kg	Altitude at 4360 m for 24 h and 10 months	Reduced drug elimination	Ritschel, Paulos et al. 1996a, b
	Remifentanil	Intravenous infusion of 1, 2 or 3 µg/kg min before, during and after hypothermia	Hypothermia down to 29.6°C for up to 57 min during cardiopulmonary bypass	Decreased systemic clearance by 6.37% per degree Celsius	Michelsen, Holford et al. 2001
Non-steroidal muscle relaxants	Atracurium	Intravenous bolus of 0.5 mg/kg during hypothermia	Hypothermia down to 34°C for ~200 min in healthy volunteers	Increased duration of drug action	Leslie, Sessler et al. 1995

Categories	Drugs	Routes of administration	Stresses	Effects	References
Anaesthetics	Propofol	Intravenous bolus of 1 mg/kg followed by 4-h infusion at 5 mg/kg h during hypothermia	Hypothermia down to 34°C for ~200 min in healthy volunteers	Increased plasma drug concentration by 28%	Leslie, Sessler et al. 1995
		Titrated infusion to maintain a bispectral index of 40-60	Hypothermia at 34°C for ~3 h during craniotomy	Increased plasma drug concentration	Leslie, Bjorksten et al. 2002
Antibiotics	Amoxycillin	Oral ingestion of 250 mg	Walking	Increased plasma concentration compared to bed rest and sleep	Roberts and Denton 1980
	Gentamicin	Intravenous infusion at 1.5 mg/kg over 30 min under normal or hyperbaric conditions	Exposure to 100% oxygen at 2.4 atmospheres absolute for 90 min	No differences in C_{max} , $t_{1/2}$, V_d and CL	Merritt and Slade 1993
	Tetracycline	Oral ingestion of 400 mg	76-87°C for 3 min with 5-min cooling, 3 times	Reduced excretion	Vanakoski and Seppälä 1997
Anti-hypertensives	Clonidine	Transdermal delivery of 6 mg over 96 h	Hot bath at 40°C for 5 min	No effects	Fujimura, Sasaki et al. 1996
	Furosemide	Oral ingestion of 40 mg	Altitude at 3600 m for 15 h and 6 months	Increased plasma drug concentration	Arancibia, Nella Gai et al. 2004
		Oral ingestion 40 mg or intravenous injection of 20 mg combined with 500 mg oral paracetamol	Hypoxemia for 72 h	No effects	Rowett, Latimer et al. 1996
	Propranolol	Oral ingestion of 40 mg at 35 min prior to hyperthermia	85-100°C for 10 min separated by 5-min cooling, 3 times	Increased plasma concentration and C_{max}	Vanakoski and Seppälä 1995
		Oral ingestion of 80-200 mg night before hypothermia	Hypothermia at 32~34°C during cardiopulmonary bypass	Increased distribution $t_{1/2}$, V_d	Carmona, Malbouisson et al. 2005

Categories	Drugs	Routes of administration	Stresses	Effects	References
Anti-hypertensives (continued)	Verapamil	Intravenous infusion of 5 mg over 10 min	Hypoxia for 14 h during which the oxygen level in the chamber was reduced to 12%, equivalent to an altitude of 4,500 m	No effects on C_{max}, $t_{1/2}$, V_d and CL	Streit, Göggelmann et al. 2005
Asthma medications	Prednisolone	Oral ingestion of 80 mg	Altitude at 3600 m for 15 h and 6 months	No effects	Arancibia, Gai et al. 2005
	Theophylline	Intravenous infusion of 6 mg/kg over 20 min	Hypoxia for 14 h during which the oxygen level in the chamber was reduced to 12%, equivalent to an altitude of 4,500 m above sea level	No effects on C_{max}, t_{max}, $t_{1/2}$, V_d and CL	Streit, Göggelmann et al. 2005
Mountain sickness medications	Acetazolamide	Oral ingestion of 250 mg on the day after arrival at altitude	Altitude 4360 m for 24 h and 10 months	Increased elimination	Ritschel, Paulos et al. 1998a, b
Sedatives	Midazolam	Oral ingestion of 15 mg at 20 min prior to hyperthermia	80-100°C for 10 min separated by 10-min cooling, 3 times	Reduced absorption and mean plasma concentration	Vanakoski, Stromberg et al. 1993
		Oral ingestion of 15 mg immediately after first sauna	85-100°C for 10 min separated by 5-15-min cooling, 4 times	Increased C_{max}, elimination $t_{1/2}$	Vanakoski, Idänpään-Heikkilä et al. 1996
		Intravenous bolus of 0.05 mg/kg		No differences in plasma drug concentration, CL, and elimination $t_{1/2}$	
		Intravenous bolus of 10 mg before and 5 µg/kg min during hypothermia	Hypothermia 32-34°C for 3-4 days in brain-injured patients	Increased V_d and decreased elimination	Fukuoka, Aibiki et al. 2004

Categories	Drugs	Routes of administration	Stresses	Effects	References
Alertness management medications	Caffeine	Oral ingestion of 4 mg/kg	Altitude 4300 m for 16 days	Reduced plasma concentration, $t_{1/2}$ and increased CL	Kamimori, Eddington et al. 1995
		Oral ingestion of 600 ml coffee before hyperbaric conditions	Hyperbaric and hyperoxia for 110 min at 0.25 MPa, alternating O_2 and air breathing every 20 and 5 min	No effects on C_{max} t_{max}, $t_{1/2}$, V_d and CL	Rump, Siekmann et al. 1997
Nicotine replacement therapy	Nicotine patch	Transdermal delivery of 25 mg/16 h at 5 h before sauna	77-84°C for 10 min separated by 5-min cooling, 3 times	Increased C_{max} and plasma concentration	Vanakoski, Seppala et al. 1996

AUC = Area under the plasma concentration-time curve from the time of dosing to the end of the observation period, C_{max} = maximum plasma concentration, t_{max} = time to reach C_{max} , $t_{1/2}$ = half-time and V_d = volume of distribution =dose/plasma concentration, CL=clearance.

As shown in Fig 7, as a result of entering a hypoxic environment at high altitudes, major physiologic changes occur which include; an increase in hematocrit, erythrocytes, blood flow to the brain and cardiac output., and a decrease in oxygen and vasoconstrictor response (Heistad, Wheeler et al. 1971; Ritschel, Paulos et al. 1998a) and (Doyle, Wilson et al. 1952). Therefore, a number of mechanisms could be involved in the pharmacokinetic changes at high altitude. For example, drug metabolism may be affected under hypoxia due to a change in the activity and expression cytochrome P450 enzymes (Fradette and Du Souich 2004).

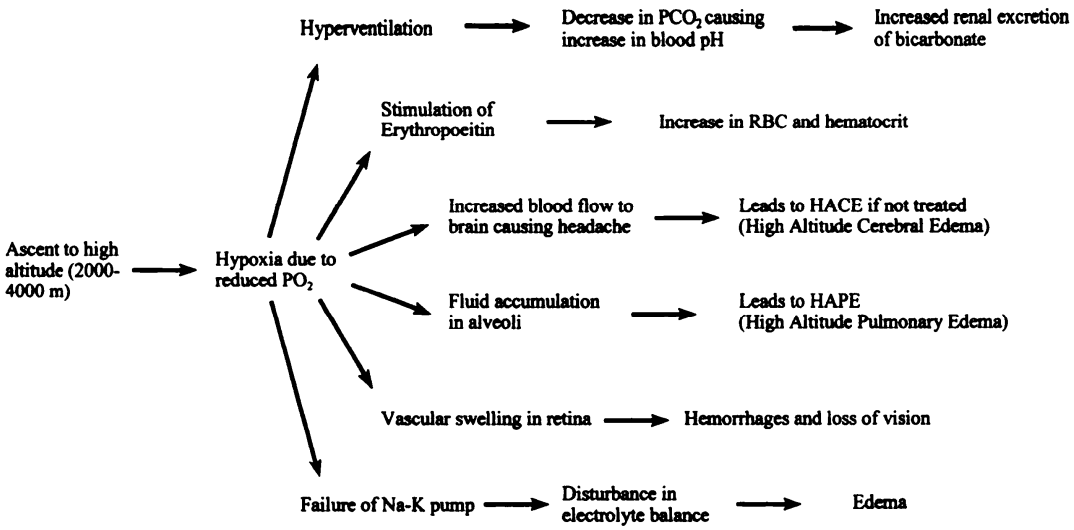


Figure 7:Physiological changes at high altitude (Ritschel, Paulos et al. 1998a).

In contrast to hypobaric conditions, hyperbaric and hyperoxic stressors could trigger different physiological changes in the hemodynamics properties (blood volume and flow rate), respiration, homeostasis and central nervous system. From a theoretical point of view, under hyperbaric conditions, drug pharmacokinetics may be modified as a result of (1) changes in the activity of metabolism enzymes by oxygen free radicals; (2) alterations of blood flow through tissues; (3) changes in tissue membrane permeability. However, the pharmacokinetic effects have not been observed in humans for a single dose of drugs eliminated by the kidney (gentamycin) or by the liver with a capacity-limited clearance (pertobarbital, theophylline, caffeine) or with a flow-limited clearance (pethidine, lidocaine) (Rump, Siekmann et al. 1999) under hyperbaric and hyperoxic conditions (2.4 – 2.5 bar, 100% O_2). Nonetheless, these studies were performed with healthy volunteers and may not be applicable to patients. Ultimately, clinical trials in patients need to be conducted.

Furthermore, physical trauma and injuries, such as thermal/burn injuries (Martyn 1986; Shikuma, Ackerman et al. 1990; Conil, Georges et al. 2007; Han, Harmatz et al. 2007), head injuries (Boucher and Hanes 1998), organ transplantation (Crone and Gabriel 2004), sepsis and septic shock (De Paepe, Belpaire et al. 2002) and surgery (Kennedy and Riji 1998) all affect pharmacokinetics to various extents. These effects have been ascribed to pathophysiological changes including organ dysfunction, blood loss (Lagneau, Marty et al. 2005), changes in blood flow and protein binding (Kotsiou, Anagnostou et al. 2006). The same theories remain for pharmacokinetic alternations under stress conditions. For example, regardless of cause, decreased perfusion of muscles, skin and splanchnic organs would reduce drug absorption through intramuscular, subcutaneous, transdermal and oral administration in burn patients (Martyn 1986) and hypothermic cardiopulmonary bypass (Hall 2002).

In conclusion, the observed pharmacokinetic effects described above could be ascribed to environmental and pathological modification of drug absorption (Martinez and Amidon 2002), disposition, metabolism and excretion (Sanvordeker and Lambert 1975) depending on the route of administration, physicochemical properties of the drug and elimination pathways. For example, environmental heat may influence transdermal or subcutaneous drug absorption due to its induced local vasodilatation and acceleration of cutaneous blood flow, but have less effect on gastrointestinal absorption. Compared to the extensive studies on the effects of physical exertion and temperature extremes on drug pharmacokinetics, human studies on pharmacokinetic changes in response to hypobaric and hyperbaric stresses, especially for the latter, are still sparse although some basic concepts underlying the changes have been reviewed (Rump, Siekmann et al. 1999).

5.4 Psychological stressors

In addition to physiological stresses, psychological stressors may also affect pharmacokinetics (Flaten, Simonsen et al. 1999; Martens-Lobenhoffer, Eisenhardt et al. 2001; Flaten, Asli et al. 2006), but there is limited information about the effects and its underlying mechanisms. For example, both exercise and heat resulted in pharmacokinetic changes with midazolam (Stromberg, Vanakoski et al. 1992; Vanakoski, Stromberg et al. 1993), a sedative drug. In contrast, personality traits and anxiety appear to have no effects on the pharmacokinetics with midazolam as can be seen in Table 8 (Martens-Lobenhoffer, Eisenhardt et al. 2001). Drug-related information, also known as placebo effects, might affect pharmacokinetics in a very different manner (Benedetti 2008). Sympathetic activation was speculated to result in the reduced secretion of hydrochloric acid and motility in the gastrointestinal tract, with the consequence of slower absorption of carisoprodol (Flaten, Simonsen et al. 1999). Interestingly, a study showed that crying significantly reduces absorption of an aerosolised drug, sodium cromoglicate, in infants, but the underlying mechanisms is unknown (Iles, Lister et al. 1999). Sleep deprivation and mental challenge could induce the effects of hemodynamics, in particular cardiac output (Goldstein, Eisenhofer et al. 1987; James and Gregg 2004), which can alter drug absorption. In addition, psychological stress-related changes in renal functions were reported during a Stroop word color conflict test (Fauvel, Hadj-Aissa et al. 1991). Emotional stressors could increase plasma concentration of low density lipoproteins and free fatty acids (Buckley 1972). Further studies are required to confirm the influence of the psychological effects on pharmacokinetics.

Table 8: Effects of psychological stressors on pharmacokinetics.

Category	**Drugs**	**Route of administration**	**Stresses**	**Number of subjects**	**Pharmacokinetic effects**	**Author(s) & Year**
Analgesics	Acetaminophen	Oral ingestion of 500 mg at 20 min after movie started	Movie-induced and music-reduced stresses	24 males 19-39 years old	No effects	Flaten, Asli et al. 2006
Sedatives	Carisoprodol	Oral ingestion of 525 mg	Relaxant information	66 subjects 18-38 years old (36 men, 30 women)	Increased serum concentration	Flaten, Simonsen et al. 1999
	Midazolam	Oral ingestion of 15 mg	Anxiety & personality	26 patients 22-49 years old (23 men and 3 women)	No effects	Martens-Lobenhoffer, Eisenhardt et al. 2001

5.5 Endogenous and exogenous compounds

As mentioned briefly in the above, various stressors could activate the sympathetic nervous system which regulates hormones, neurotransmitters and cytokines (McEwen 2004) and influences physiological changes (Frecska, Lukacs et al. 1988; Gomez-Merino, Chennaoui et al. 2002; Falaschi, Proietti et al. 2003; Gomez-Merino, Drogou et al. 2005). However, studies need to be performed for the baseline values of endogenous substances and their possible variations associated with daily rhythm, age and sex in order to confirm any pharmacokinetic effects of stressors for exogenous compounds, especially for the hormone-therapeutic drugs, such as corticosteroids and melatonin. Any exogenous compounds may, in turn, alter the metabolic and hormonal responses to stress (Cheatham, Caine-Bish et al. 2006) and may also suppress endogenous release (for example, the release of melatonin in the pineal gland by exogenous melatonin). On the other hand, the pharmacodynamic effects could likely occur due to the changes in receptor binding under stress (Liberzon, Taylor et al. 2007). Such complex interactions make the study of pharmacokinetic and pharmacodynamic changes of exogenous substances a great challenge. Table 9 summarizes a number of stress hormones and their biological functions. Readers can refer to a number of special reports for further information about hormone responses to military stressors (Krahenbuhl and Harris 1984; Leino 1999; O'Donnell, Morgan et al. 2003).

Among the listed hormones, cortisol is a well known stress hormone which belongs to corticosterioids, a class of steroid hormones that are naturally produced in the adrenal cortex and can also be man-made for medication ranging from brain tumours to skin diseases. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response, and the regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behaviour (Gomez-Merino, Drogou et al. 2005). Although referring to both glucocorticoids and mineralcorticoids, the corticosterioids' term is often used as a synonym for glucocorticoids. The circadian rhythm of corticosteroids secretion has been established (Seckl and Meaney 2004). Recently, Semmar and Simon reviewed pharmacokinetic models on endogenous and exogenous corticosteroids (Semmar and Simon 2006). Contribution of endogenous corticosteroids at a constant or varied secretion rate was reflected in pharmacokinetic modeling of exogenous corticosteroids.

Table 9: Hormones involved in the stress response.

Stressors	Hormones altered	Sources	Functions	References
Exercise, heat, noise, G-forces, mental, sleep deprivation	Cortisol	Corticosteroid hormone produced by the adrenal gland	Increases blood glucose level; gluconeogenesis and deamination of proteins; suppresses inflammation	Kukkonen-Harjula, Oja et al. 1989; Vgontzas, Tsigos et al. 1998; Morgan, Wang et al. 2000; Veltman 2002; Mujika, Padilla et al. 2004; Spreng 2004
Exercise, heat	Aldosterone	A steroid hormone produced by the outer-section of the adrenal cortex in the adrenal gland	Increases sodium absorption, which increases water retention	Montain, Laird et al. 1997
	Vasopressin	Synthesized in the hypothalamus and stored in vesicles at the posterior pituitary	Increases water retention; vasoconstrictor	
Physical exertion plus sleep restriction, heat	Growth hormone	Produced primarily by the anterior pituitary gland	Associated with postnatal longitudinal growth in targeted tissues, e.g., liver, muscle	Kukkonen-Harjula, Oja et al. 1989; Nindl, Rarick et al. 2006
Military survival training	Thyroid hormones	Produced by the thyroid gland	Elevate metabolism, respiration, temperature, oxygen consumption, gastrointestinal motility; affect protein synthesis; increases the sensitivity to catecholamines	Morgan, Wang et al. 2000

Stressors	Hormones altered	Sources	Functions	References
Heat	Prolactin	Secreted by lactotrope cells in the anterior pituitary gland	Peptide hormone primarily associated with lactation	Kukkonen-Harjula, Oja et al. 1989
Sports tapering and training, heat, noise, sleep deprivation, mental	Catecho-lamines	Released by the adrenal glands	Increase blood pressure, heart rate and contractility, respiration, and perspiration; Liberates nutrient stores for fuel	Baron, Petschnig et al. 1992; McMurray, Kocher et al. 1994; Vgontzas, Tsigos et al. 1998; Babisch, Fromme et al. 2001; Gold, Zakowski et al. 2004; Mujika, Padilla et al. 2004
Sleep deprivation	Melatonin	Produced by pinealocytes in the pineal gland (located in the brain) and also by the retina, lens and GI tract	Activation of melatonin receptors, inhibition of tumour growth, blood pressure regulation, retinal physiology and control of circadian rhythms	Sekula, Lucke et al. 1997; Srinivasan, Smits et al. 2006

GI = gastrointestine

In theory, it is possible to model normal pharmacokinetics and extrapolate the model to include impacts attributable to a particular endogenous agent. This may be achieved by dividing the spectrum of biochemical and biological events into modular components, e.g., pharmacokinetics, biochemical/molecular (including cellular signalling), and cellular response/dynamics. A flexible mathematical procedure that is capable of modeling and integrating each of these components would be desirable. However, a real biologically-based model is not yet feasible because of a lack of necessary biological information. Alternatively, Bright and colleagues developed a new pharmacokinetic model comprised of a compartment model for exogenous administration of growth hormone, and a cosine function for endogenous secretion (Bright, Veldhuis et al. 1999).

5.6 Summary

In conclusion, it is noted that exercise has an impact on a broad range of drugs (from analgesics to alertness medications) representing most categories, compared to the other stressors which may only affect certain types of drugs. Although each stressor may modify physiological conditions through a common pathway (e.g., activation of the sympathetic nervous system), other mechanisms such as temperature effects on drug properties may exist that are ascribing to different effects and need to be considered when investigating the pharmacokinetic changes under stress conditions.

In addition, intrinsic factors such as inter-individual differences in age, gender, race, body weight etc., daily variations in the body functions (i.e., chronobiology and pharmacology) (Lemmer 2000), posture (Hallworth, Fernando et al. 2005), and extrinsic factors such as drug formulations (instant vs. controlled release), administration routes (oral vs. intravenous) and food (fasted vs. fed) (Singh 1999) may also contribute to the pharmacokinetic effects of the stressors.

The clinical significance for the drugs that exhibit different pharmacokinetics under stresses has not been well addressed. In theory, the changes in drug concentrations at an action site can be related to drug responses, and stressors may alter the sensitivity of drug receptors leading to deviation from normal dose-response relationship (van Praag 1979).

It should be noted that most studies were focused on the effects of a single stressor. It would be important to investigate the effects of multiple stressors, similar to what the CF experience during military operations, from both a physiological and psychological perspective.

Lastly, it should be noted that stressors could play a positive (adaptive) effect on human well-being (McEwen 2007) and the benefits of stressors for pharmacokinetics and pharmacodynamics deserve more attention. The stress-induced psychophysiological changes may be combined with pharmacotherapy to achieve better drug delivery and more effective treatment. For example, heat may be used to channel drug disposition to the brain when needed by taking advantage of its increased blood-brain-barrier permeability. Moderate exercise can improve physical and mental health and may be used concurrently with pharmacotherapy for superior therapeutic responses (Myslobodsky and Weiner 1988). Apparently, implementation of the concept relies on an understanding of the stress responses and their time related changes. In addition, studies have

been conducted to understand the effects of drugs on the responses to physiological and psychological stresses (Eliasson, Kahan et al. 1987).

6 Pharmacokinetic modeling of drugs in response to operational stressors

Mathematical modelling is a cost effective, safe and powerful alternative to human trials for investigating a drug's pharmacokinetics under various stressors. Mathematical modeling provides an opportunity to study a drug under the conditions where significant risk(s) would prevent experimental measurements in humans. Furthermore the model may help design human studies by defining the conditions where marked changes in pharmacokinetics would occur.

Although mathematical models have been extensively used to study pharmacokinetics as discussed in Section 4, their use for predicting the effects of stressors on drug pharmacokinetics has been limited. Instead, the studies were mainly conducted experimentally as reviewed in Section 5. On the other hand, as indicated in Table 10, the modeling approach has been taken to simulate the pharmacokinetic effects of certain factors including mechanistic predictions in pathological patients and children. In general, the model predictions were consistent with literature data and reports. For example, a three-compartment model was reported to predict the effects of cardiopulmonary bypass on the pharmacokinetics of fentanyl in patients (Hudson, Thomson et al. 2003) in agreement with a review of the pharmacokinetic changes associated with the use of the surgical procedure (Hall 2002). In theory, the same principle can be employed to understand pharmacokinetics under operational stressors by altering model input variables (e.g., cardiac output and tissue blood flow rates) in accordance with physiological changes. However, the approach has not been well used and is limited to experimental fitting of pharmacokinetic data (Stromberg, Vanakoski et al. 1992; Beovic, Mrhar et al. 1999). Alternatively, pharmacokinetic studies of the effects of exercise and other stressors on chemical exposure were conducted where a physiologically-based model was used to understand the fate and transport of a chemical on an individual (Watson 2001; Reddy, Andersen et al. 2003).

To our knowledge, no significant efforts have been reported to model pharmacokinetics under the stressors of our interests. Given the current CF operation in Afghanistan, environmental stressors (e.g., physical exertion, altitude, heat, humidity) should be considered in addition to common combat stressors such as thermal strain, hypoxia, inadequate rest, high levels of physical work, traumatic exposure, and isolation. As illustrated in Figure 8, building on our current knowledge of pharmacokinetic modeling and effects of stressors on physiology and pharmacokinetics, we will develop and validate pharmacokinetic models with the ultimate goal of obtaining appropriate drug inventories and dosages unique to military operations.

Table 10: Applications of pharmacokinetic models to predict the influence of changes in physiological conditions.

Drugs	Models	Impact factors	Predictions	References
Amoxicillin-clavulanate	PBPK model	Hemorrhagic shock followed by fluid resuscitation	Consistent with the knowledge in the field and useful to optimize drug dosing regimens	Tod, Lagneau et al. 2008
Cefazolin	PBPK model	Blood flow, blood loss, plasma protein concentration, GFR (liver surgery)	Minimum inhibitory concentration agaist bacteria likely encountered during the surgery	Lagneau, Marty et al. 2005
Ceftazidime	Two-compartment model with first order elimination	Mechanical ventilation (burn patients)	Consistent with other reports and significant individual variability emphasized	Conil, Georges et al. 2007
Fentanyl, Alfentanil, Thiopental	PBPK model	Cardiac output and regional blood blow (anesthesia and surgery)	Pharmacokinetics modestly influenced by the physiological changes	Wada, Bjorkman et al. 1997; Wada and Stanski 1998
Drug candidates from F. Hoffmann-La Roche Ltd	ACAT model	Stomach emptying time, hepatic blood flow (fasted vs. fed)	The magnitude of the food effects well captured by the model	Jones, Parrott et al. 2006a
Digoxin	PBPK model	Increases in regional blood flow to GI tract, liver and kidneys	Able to show the dependence of digoxin absorption on gastrointestinal blood flow	Carlton, Pollack et al. 1996
Lidocaine	PBPK model	Cardiac arrest	Optimal dose regime suggested	Grillo, Venitz et al. 2001

PBPK = Physiologically-Based Pharmacokinetic; GFR = Glomerular Filtration Rate; ACAT = Advanced Compartmental Absorption and Transit; GI = gastrointestinal

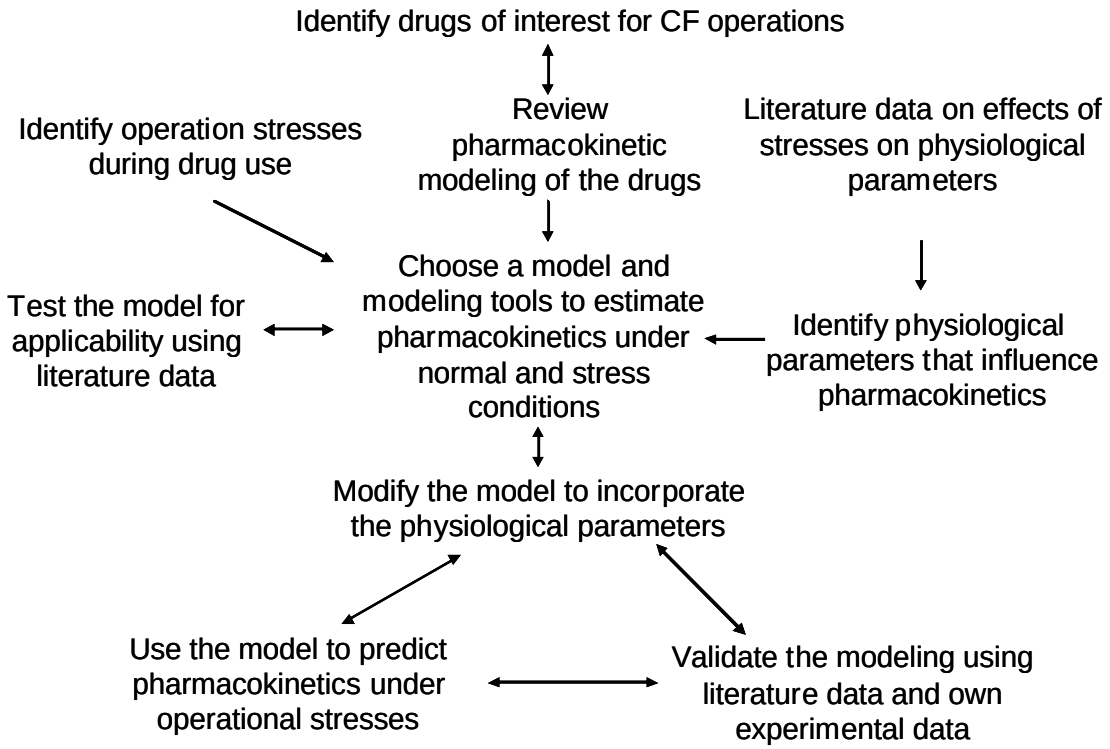


Figure 8: A flowchart demonstrating the development toward a physiological-based pharmacokinetic model unique to military operational pharmacokinetics.

6.1 Selection criteria for drugs

6.1.1 Considerations

We may wish to select the drugs with pharmacokinetics that are well understood and most likely affected by the military environmental stressors while least likely affected by inter- and intra-subject variability. Orally administered drugs are good candidates due to patient compliance and wide prescription. On the other hand, the routes of administration should be considered as they could influence the extent of the effects of stressors on drug absorption. For example, transdermal drug absorption may be more affected by heat and exercise compared to other absorption routes (Abrams, Skee et al. 2001). Furthermore, therapeutic range may play a role, such that drugs with a narrow therapeutic range may need to be considered due to the greater implications of any pharmacokinetic changes that they might have. In addition, considering the narrow therapeutic range of fentanyl between 1 to 3 ng/ml (Lee, Kern et al. 2003; Mystakidou, Katsouda et al. 2006), the pharmacological effects of the drug is also likely changed under the stressor.

A change in cardiac output would have a significant impact on the behaviour of the fast-acting drugs with flow-limited (plasma protein binding < 90% and systemic extraction ratio ≥ 0.5) absorption, distribution, or clearance such as may be the case with thiopental, lidocaine, alfentanil

and propofol (Reekers, Boer et al. 2003). Table 11 summarizes the two parameters for the drugs potentially to be investigated. Based on their protein binding and extraction ratio, the pharmacokinetics of the following drugs may be affected by physical exertion and heat due to changes in blood flow rates: fentanyl, venlafaxine, pyridostigmine.

Table 11: Plasma protein binding and extraction ratio of short-listed drugs.

Drug categories	Drugs	Plasma protein binding	Extraction ratios	References
Antimalarials	Mefloquine	98%	<0.3	Simpson, Watkins et al. 2000; Brocks and Mehvar 2003
	Malarone: combination of atovaquone and proguanil	>99% and 75%		Na-Bangchang, Manyando et al. 2005
Non-steroidal anti-inflammatory drugs	Ibuprofen	99%	0.36	Whitlam, Crooks et al. 1979; Shah and Jung 1987
Analgesics	Fentanyl	80%	0.53	Björkman, Wada et al. 1994; Mystakidou, Katsouda et al. 2006
Antidepressants	Venlafaxine	27%	0.7	Morton, Sonne et al. 1995; Troy, Parker et al. 1997; Charlier, Pinto et al. 2000
	Citalopram	80%	0.2	Friberg, Isbister et al. 2005
	Bupropion	82-88%		Jefferson, Pradko et al. 2005
Nicotine replacement therapy	Nicotine	5%	0.1	Benowitz, Jacob III et al. 1982; Foth, Walther et al. 1990
Sedatives	Diazepam	97%	0.03	Klotz, Antonin et al. 1976; Rump,

				Siekmann et al. 1999
Drug categories	**Drugs**	**Plasma protein binding**	**Extraction ratios**	**References**
Other medications	Pyridostigmine	81%	>0.5	Abu-Qare and Abou-Donia 2002; Zhao, Moochhala et al. 2006

Extraction ratio was defined as the fraction of drug removed by the organ from the blood and calculated as $CL_{12}/(CL_{12}+Q_T)$, where CL_{12}, Q_T are intrinsic distribution clearance from the vascular to a parenchymal organ and tissue blood flow.

6.1.2 Exogenous hormones

As discussed in Section 5, kinetic behaviour of endogenous and exogenous substances may be profoundly affected by physiological conditions. Stress hormones and neurochemicals are good candidates because their natural production is likely changed during military training and operation (Morgan, Wang et al. 2000) which may subsequently affect the pharmacology of their exogenous counterparts. For example, cortical levels are altered in response to various stressors such as G forces (Veltman 2002), sleep disorders (Vgontzas, Tsigos et al. 1998), mental stress (Ng, Koh et al. 2003), depression (Taylor, Conrad et al. 2006) and post-traumatic stress disorder (de Kloet, Vermetten et al. 2007). Therefore, their potential interactions with exogenous cortisol-like drugs need to be investigated. Melatonin is another hormone whose secretion is disturbed in patients with mood disorders (Srinivasan, Smits et al. 2006). Therefore, the pharmacokinetics of exogenous melatonin in such populations may be different. Given their homeostatic roles and large kinetic variations associated with daily rhythm and individuals, it is very challenging to investigate the pharmacokinetics of exogenous substances under stress.

6.2 Selection of stressors

Military personnel encounter multiple stressors during military missions (McNulty 2005). These stressors can be physiological and/or psychological, and vary in their types and severities during pre-deployment, deployment, and post-deployment phases. Typical stressors include physical exertion, dehydration, sleep deprivation and disruptions to circadian rhythms during night and extended operations, hypoxia at high altitude, hyperbaria during diving, temperature extremes in cold or hot environments, motion disturbance as well as a variety of psychological factors such as traumatic exposure, anxiety, isolation and difficulties with family. These stressors may result in different physiological alterations, such as changes in hormone levels that may have both positive (adaptive) and negative (damaging) effects on human well-being and performance (McEwen 2007).

We need to define the stressors encountered during a specific military operation and investigate their effects on pharmacokinetics. Given the complexity of the issue, a simple scenario will be

selected to study the pharmacokinetics of short-listed drugs only through modeling and experiments. For example, the daily marching regime of a Canadian soldier in Afghanistan can be simulated by walking on a treadmill in a climatic chamber.

6.3 Development of a model

The type of model needed depends on the questions to be answered. For any pharmacokinetic changes as a result of physiological alternations under stressors, rational predictive models can be developed that incorporate basic physiochemical input data and mechanistic descriptions of the underlying biophysical and biochemical processes. PBPK modeling that describes the system in physiological terms and considers the route of drug administration, drug formulation and physicochemical properties of the drug is a promising tool. It has been demonstrated that PBPK gave better predictions of pharmacokinetic parameters and plasma concentration-time profiles than other approaches (Jones, Parrott et al. 2006b). With the drugs and stressors in mind, we can select the type of models suitable for predicting the effects of the stressors on the pharmacokinetics of the drugs.

Having selected the PBPK model, we need to identify the parameters which are required to develop it (see Table 12). This would depend on the software packages. For example, only drug-specific data, such as lipophilicity, protein binding, solubility, pK, hepatic and renal clearance are required when using PK-Sim to predict pharmacokinetic parameters and plasma concentration of a drug. Anatomical and physiological data (e.g., body weight, blood flows, etc.) have been derived from population databases, but can be user-defined as well (Willmann, Höhn et al. 2007). It should be noted that any model-derived quantities rely on the accuracy and certainty of model parameter estimation.

There are several commercial software tools, with pros and cons, for PBPK modeling. For comparisons, refer to Table 13 (Schmitt and Willmann 2005). An appropriately designed dataset is required to develop predictive models to simulate *in vivo* responses from *in vitro* inputs (Grass and Sinko 2001).

Table 12: Basic input data for PBPK models and possible changes in their values to simulate pharmacokinetics under different stressors (Wosilait and Luecke 1988; Boobis, Gundert-Remy et al. 2002).

	Parameters	Model representations[+]	Stressors
Drug-specific data	Tissue to plasma partition coefficients P_t = f(drug M_w, solubility, vapour pressure	$V_t \frac{dC_t}{dt} = Q_t (C_p - \frac{C_t}{P_t})$	Temperature extremes, physical trauma
	Metabolic and elimination rate constants K_m and K, respectively.	$V_{li} \frac{dC_{li}}{dt} = Q_{li} (C_p - \frac{C_{li}}{P_k}) - \frac{V_{\max} C_{li}}{K_m + C_{li}} - KC_{li} V_{li}$	Exercise, heat/cold, altitude, liver dysfunction
	Renal excretion rate constant ($K_{k)}$	$V_k \frac{dC_k}{dt} = Q_k (C_p - \frac{C_k}{P_k}) - K_k \frac{C_k}{P_k} V_k$	Exercise, renal dysfunction
	Drug to plasma protein or tissue binding constants ($K_{b)}$ and maximum capacity (B)	$C_b = \frac{BK_b C_f}{1 + K_b C_f}$	Physical trauma
Physiological data	Cardiac output and organ blood flows (Q) = f(age, gender, body mass)	$V_p \frac{dC_p}{dt} = \sum Q_i \frac{C_i}{R_i} - QC_p$	Exercise, heat, injuries
	Blood and organ volumes (V)	$V_p \frac{dC_p}{dt} = \sum Q_i \frac{C_i}{R_i} - QC_p$	Exercise,
	Alveolar ventilation rate (S)	$C_a = \frac{SC_{in} + QCv}{Q + S / Pai}$	Exercise

[+] Perfusion-limited drug distribution is assumed. R_m = maximum metabolism rate, C_p = plasma drug concentration, C_f C_b are free and bound drug concentration, Q_i blood flow rate through each organ, R_i = tissue to plasma partition coefficient, V_{max} =maximum metabolism rate, Subscripts li, ai represent liver, lung air

Table 13: Comparison of software for PBPK modeling.

Software	Venders	Pros	Cons	References
AcslExtreme™	Aegis Technologies	Flexible for varied model structures	Simulation expertise needed; no model parameterization.	Dong 1994; Thomas, Yang et al. 1996
GastroPlus™	Simulations Plus	No simulation expertise needed; easily obtained input data	Single process simulation for absorption	Wei and Lobenberg 2006
IDEA™	Lion Bioscience			Parrott and Lavé 2002; Stoner, Cleton et al. 2004
SimCyp®	SimCyp	No modeling expertise needed; extensive database with physiological information	Physiologically modeling only for metabolism; fixed model structure	Johnson, Tucker et al. 2003
CloePK™	Cyprotex	No modeling expertise needed; whole pharmacokinetic processes; easily determined input data	Strong simplifications in distribution modeling	http://www.cyprotex.com/products/cloe_pk.htm
pkEXPRESS™	Lion Bioscience			http://www.lionbioscience.com
PK-Sim®	Bay Technology Services	No modeling expertise needed; whole body PBPK; easily determined input parameters	Fixed model structure	Willmann, Lippert et al. 2003

PBPK = Physiologically-Based Pharmacokinetic

Our strategy is to solve appropriate PBPK models identified in the literature using normal values of physiologic parameters and then validate the models using reported pharmacokinetic data. The selected models can be applied to predict pharmacokinetic profiles under stressful conditions by adjusting only those parameters changed with the stress followed by comparison between the

predicted and experimental data and reiterated model modification. The model parameters can be systematically varied to elucidate the magnitude of the effect of such variations on the pharmacokinetics of the drug and to determine optimum timing and frequency of data acquisition in animal or human study design. Although preliminary, the approach proves to be capable of simulating the effects of exercise on plasma concentration of caffeine, ibuprofen and venlafaxine (Tuladhar 2008).

It is noteworthy that in addition to the systematic approach using the PBPK models, considerable progress has been made in the past decade in the development of computational approaches for the prediction of absorption, distribution and metabolism based on molecular structure-property relationship and biochemical processes (Boobis, Gundert-Remy et al. 2002; Mager 2006). Their potential for our applications should not be underestimated.

6.4 Validation of the model

Similar to other types of modeling effort, pharmacokinetic modeling is also subjected to appropriate validation. However, model validation could be contentious. As a model can never be proven, only disproved, using the term 'validation' would technically be incorrect. However, we adopted the term in this report following the Food and Drug Administration guidance on population pharmacokinetic analysis (United States Department of Health and Human Services 1999) and exposure-response analysis (United States Department of Health and Human Services 2003).

Model validation may be broadly defined as the assessment and extent to which a model is founded and fulfilled the purpose for which it was developed (Cobelli, Carson et al. 1984). The variability and uncertainty in the PBPK model arises from the following reasons (Jang, Droz et al. 1999; Nestorov 2003):

1. Variability and uncertainty in the model parameters, such as physiological values, metabolic constants and partition coefficients,

2. Complexity and unknown nature of the phenomena involved, such as conversion between enantiomers,

3. Lack of perfect instrumentation and methods of information processing, such as artificial neural networks.

Various methods have been used to conduct sensitivity and uncertainty analysis, such as Monte Carlo simulation, population pharmacokinetic approaches, Bayesian method and Fuzzy Set Theory (Seng, Nestorov et al. 2008). Many different tests and statistical analyses exist to compare predicted and observed data. Goodness-of-fit tests have been widely used based on a calculation of some metrics like the coefficient of determination, the correlation coefficient, and the concordance coefficient (Bonate 2006). Optimal experimental design for pharmacokinetic models is important and may be achieved using a computer program (Gueorguieva, Ogungbenro et al. 2007).

In addition to visual inspection via plotting predicted and experimental data (Figure 9), different parameters can be calculated and statistical analysis performed. Percent performance error as per

the equation below, examines the accuracy of pharmacokinetic models for predictingcase plasma fentanyl concentrations:

$$(C_{pm} - C_p)/C_p \times 100, \quad (4)$$

where C_{pm} and C_p represent measured and model-predicted plasma drug concentration, respectively (Shibutani, Inchiosa et al. 2004).

Fold error was simply calculated as the ratio between predicted and observed values where the larger value (numerator) was divided by the smaller one (denominator). A 2-fold error or less was classified as an accurate prediction of pharmacokinetic food effects using biorelevant solubility media and physiologically-based modeling (Jones, Parrott et al. 2006).

Edginton et al. (2006) used a mean relative deviation (MRD) calculation defined by the following equation to assess appropriateness of a physiologically-based pharmacokinetic model in a study involving children (Edginton, Schmitt et al. 2006a). For example, an MRD value of ≤ 2 meant that the average of the predicted values was equal to or less than a factor of 2 from the observed values and was considered a reasonable prediction by the model:

$$MRD = 10^x, \quad (5)$$

where $x = \sqrt{\frac{\sum_{i=1}^{n} (\log y_i - \log \hat{y}_i)^2}{n}}$, and $\log y_i, \log \hat{y}_i, n$ are the logarithms of observed and predicted plasma concentration and the number of observed values, respectively.

Others use Bias and Precision as defined according to equations 6 and 7 below to evaluate their model (Conil, Georges et al. 2007):

$$Bias = \frac{1}{N} \sum_{i=1}^{N} C_{pred} - C_{obs} \text{ , and} \quad (6)$$

$$\Pr ecision = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (C_{pred} - C_{obs})^2} \text{ .} \quad (7)$$

where C_{pred}, C_{obs} and N are the predicted and observed drug concentrations and the number of observed values, respectively.

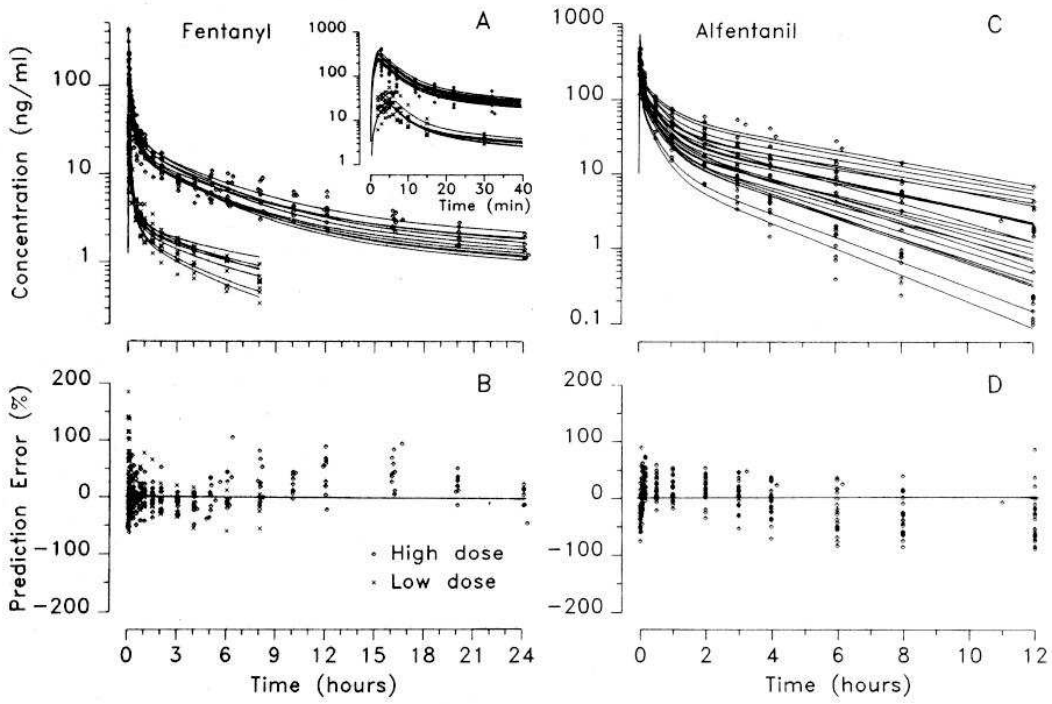


Figure 9: (A) Model-predicted arterial plasma concentration curves and measured concentrations of fentanyl in study I (high dose) and in study II (low dose). (B) Prediction error versus time for the two studies. Early prediction errors tended to be negative in study I but positive in study II. (C) Model-predicted central venous plasma concentration curves and measured concentrations of alfentanil in study I. (D) Alfentanil prediction error versus time (Bjorkman, Wada et al. 1998).

The results calculated from the equations can be presented as graphs. Good graphs should be simple in design and complex in data (Bonate 2006).

Another issue on model validation is the accuracy of model predictions in the absence of experimental data. Although there is a lack of a definitive answer, examination of the model assumptions and parameter identifiability could provide partial support. For example, the model should differentiate between linear and nonlinear kinetic processes, and represent a flow-limited or membrane-limited organ structure in agreement with established mechanisms for drug distribution. Nevertheless, the model should be validated by enough animal data to allow allometric predictions of human plasma drug concentrations.

7 Conclusions

Our literature review provides sufficient evidence to suggest that stressors such as extreme physical exertion and extreme environmental temperature conditions may significantly change a drug's pharmacokinetics. The pharmacokinetic changes under the stressors depend on a number of factors such as the route and timing of drug administration, duration and intensity of the stress, and physiochemical properties of the drug. Multiple mechanisms have been proposed, with the changes in cardiac output and regional blood flow being the most prominent. Some inconsistencies in the literature exist which need further investigations. Physiological-based pharmacokinetic models are valuable tools for predicting the pharmacokinetic effects of the stressors based on stress-induced physiological changes, especially when blood flow rates are altered. Our ultimate goal is to improve medication for CF. Our research approach will be the development of a physiological-based pharmacokinetic model combined with data derived from human trials.

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Annex A Literature search

A.1 Search keywords and hits

The systematic search was conducted using the following terms on PubMed without date limitations. Medline and Scopus were searched for those with limited findings on PubMed. Additional publications were selected from the references found from the original search. The search normally started board and narrowed if there were too many hits or vice versa.

The review focuses on human studies of extrinsic variables affecting the pharmacokinetics of drugs. The abstracts were reviewed to determine the relevance of each document and inquiry of whole article.

Table A-1: Summary of keywords and hits in the literature search.

Keywords/phrases*	**Database**	**Hits**	**Relevant Hits**	**Notes**
Pharmacokinetic* model* & review	PubMed	1807		
Pharmacokinetic model* & review		271		
Physiological* and pharmacokinetics and model*		0		
Physiological* & pharmacokinetics & model*		2299		
Physiological* & pharmacokinetics & model* & review		283		
Pharmacokinetic model* & anti-inflammatories & review		7	2	
pharmacokinetic model* & antihypertensive* & review		0		
pharmacokinetic model* & asthma* & review		1	1	
pharmacokinetic model* & anticholinergic* & review		1	1	
pharmacokinetic model* & antidepressant* & review		15	4	
Pharmacokinetic model* & anti-motion & review		0		
Physiological model* & review		116	21	
Pharmacokinetic model* & sympathomimetics		17	6	
Pharmacokinetic model* & analgesics & review		12	6	
pharmacokinetic model* & analgesics		306		
Pharmacokinetic model* & antilipemics & review		6	3	

Keywords/phrases*	Database	Hits	Relevant Hits	Notes
Pharmacokinetic model* & military	PubMed	18	4	
Pharmacokinetic model* & environment* & stress*		27	4	
Pharmacokinetic model* & physiologically based* & analgesic* (T,T, AF)				
Pharmacokinetic* & military & review		41		
pharmacokinetic* & analgesic*		108		
Military* and Analgesic*		3	1	
Pharmacokinetic model* & Analgesic*		43	3	
stress* & analgesic*		161	11	
Pharmacokinetic model* & analgesic* & Review*		5	2	
Pharmacokinetic model* & physiologically based* & analgesic*		11	5	
pharmacokinetic model* & malaria*		74	5	
military* & antimalarial*		36	4	
military* & antihistamine*		15	4	
pharmacokinetic model* & antihistamine*		22	3	
stress* & antihistamine*		8	3	
military* & antihypertensive*		6	2	
Model* & Antihypertensive* & pharmacokinetic*		4	4	
stress* & Antihypertensive*		31	8	
military* & asthma* & medicine*		51		
pharmacokinetic model* & asthma*		103	9	
Effect of stress* & asthma*		10		
Military* & antidepressant*		15	2	
Pharmacokinetic model* & antidepressant*		71	5	
Stress* & pharmacokinetic* antidepressant*		54	3	Most related to treatment of stress
Exercise* & pharmacokinetic* antidepressant*		11	2	
Stress* & buproprion & pharmacokinetic*		0		
Stress* & citalopram & pharmacokinetic*		10	2	
Stress* & venlfaxine & pharmacokinetic*		5	1	
motion sickness* & military*		78	8	
drug* & motion sickness* & pharmacokinetic model*		3	0	

Keywords/phrases*	Database	Hits	Relevant Hits	Notes
stress* & medicine* & motion sickness*	PubMed	37	2	
military* & statin*		17	3	
military* & scopolamine*		17	1	
military* & Dimenhydrinate*		4	1	
pharmacokinetic model* & statins*		9	2	
pharmacokinetic model* antilipemic*		27	2	
Stress* & antilipemics*		185	7	
military* & stress* & sedative*		3	2	
Military* & stress* & sedative		35	3	
pharmacokinetic model* & stress & hypnotics*		1	1	
physiological* & pharmacokinetic model* & hypnotics*/Sedative* (duplicates removed)		5	2	
Pharmacokinetic model* & compartment* & hypnotics*/Sedative* (duplicates removed)		60	4	
Physical Stress* & hypnotics*		46	4	
Pharmacokinetic model* & mefloquine	PubMed	17	9	
	Scopus	46	13	
	ISI	7	5	No additional hits
	Medline	3	3	
Pharmacokinetic model* & malarone	PubMed	1	1	
	Scopus	4	1	
	ISI	0		
	Medline	0		
Pharmacokinetic model* & atovaquone	PubMed	7	2	
Pharmacokinetic model* & proguanil	PubMed	9	4	
Pharmacokinetic model* & pyridostigmine	PubMed	11	2	
	Scopus	26	5	
	ISI	3	2	
	Medline	2	1	
Pharmacokinetic model* & venlafaxine	PubMed	9	5	
	Scopus	39	7	
	ISI	15	5	
Pharmacokinetic model* citalopram	Scopus	84		
Pharmacokinetic model* & buproprion	Scopus	17	10	
Pharmacokinetic model* & imipramine	PubMed	31	5	
Pharmacokinetic model* & promethazine		6	1	
Pharmacokinetic model* & dextroamphetamine		5	0	

Keywords/phrases*	Database	Hits	Relevant Hits	Notes
Pharmacokinetic model* & scopolamine	PubMed	19	8	
Pharmacokinetic model* & dimenhydrinate		0		
Model* & dimenhydrinate		5	1	
Pharmacokinetic model* & meclizine		0		
Pharmacokinetic model* & meclizine		15	0	
Model* & fenofibrates		0		
Pharmacokinetic model* & niacin		6	0	
Pharmacokinetic model* & simvastatin	PubMed	21	5	
	Scopus	55		
Pharmacokinetic model* & rosuvastatin	PubMed	2	2	
	Scopus	14	3	
Pharmacokinetic model* & atorvastatin	PubMed	9	3	
	Scopus	49	4	
Pharmacokinetic model* & zaleplon	PubMed	3	0	
Pharmacokinetic model* & melatonin		17	3	
Pharmacokinetic model* & lorazepam		29	11	
Pharmacokinetic model* & zopiclone		5	3	
Pharmacokinetic model* & temazepam		12	1	Pharmacodynamic modeling
Pharmacokinetic model* & zolpidem		10	2	
Pharmacokinetic model* & diazepam		98	15	
Pharmacokinetic model* &				
Pharmacokinetic model* & bupropion		7	2	
Pharmacokinetic model* & sertraline		12	3	
Pharmacokinetic model* & citalopram		27	6	
Pharmacokinetic model* & escitalopram		21	5	
Pharmacokinetic model* & modafinil		2	0	
Physiologically based* & pharmacokinetic model* & caffeine*/modafinil*/amphetamine* (duplicates removed)		9	6	
military* & caffeine*/modafinil*/amphetamine* (duplicates removed)		107	5	(lots are related, only picked 5 examples)
stress* & military* & caffeine*/modafinil*/amphetamine* (duplicates removed)		17	1	
stress* & caffeine*/modafinil*/amphetamine* (duplicates removed)		26	2	

Keywords/phrases*	Database	Hits	Relevant Hits	Notes
pharmacokinetic model* & alertness managment medicine*	PubMed	0	0	
Pharmacokinetic model* & MatLab		13	8	
Hypothermia & pharmacokinetics & review		35	10	
Hypobaric* & pharmacokinetic*		27	5	
Hyperbaric* & pharmacokinetic*		105	15	
Mefloquine & pharmacokinetic & exercise or heat or cold or altitude		0		
Malarone pharmacokinetic & exercise or heat or cold or altitude		0		
Fentanyl & pharmacokinetic & exercise		0		
Fentanyl & pharmacokinetic & temperature				
Fentanyl & pharmacokinetic & heat		9	2	
Fentanyl & pharmacokinetic & cold		4	0	
Fentanyl & pharmacokinetic & blood loss		19	5	
Atorvastatin & pharmacokinetic* & exercise		4	0	
simvastatin & pharmacokinetic* & exercise		4	0	
rosuvastatin & pharmacokinetic* & exercise		1	0	
Mefloquine & exercise*		3	3	
Malarone & exercise*		0		
Pyridostigmine & exercise*		55		
Buproprion & exercise*		2	0	
Venlafaxine & exercise*		17	0	
Citalopram & exercise*		7	0	
Diazepam & exercise*		66	3	
Pharmacokinetic* & psychological stress*		153	10	Lots of studies on animals
Pharmacokinetic* & stress* & fear*		15	5	
Fentanyl & lozenge		16	14	

ISI = Institute of Scientific Information

A.2 Examples of relevant literature with abstracts

A.2.1 Pharmacokinetic model* & review

Biopharm Drug Dispos. 2007 Apr;28(3):135-43. Links

Recent advances in pharmacokinetic modeling.Ahmad AM.

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A major part of the science of pharmacokinetics is the modeling of the underlying processes that contribute to drug disposition. The purpose of pharmacokinetic models is to summarize the knowledge gained in preclinical and clinical studies at various stages in drug development and to rationally guide future studies with the use of adequately predictive models. This review highlights a variety of recent advances in mechanistic pharmacokinetic modeling. It is aimed at a broad audience, and hence, an attempt was made to maintain a balance between technical information and practical applications of pharmacokinetic modeling. It is hoped that drug researchers from all disciplines would be able to get a flavor of the function and capacity of pharmacokinetic modelers and their contribution to drug development. While this review is not intended to be a technical reference on modeling approaches, the roles of statistical applications and population methodologies are discussed where appropriate.

Expert Opin Drug Metab Toxicol. 2005 Oct;1(3):555-64. Links

truPK -- human pharmacokinetic models for quantitative ADME prediction.Subramanian K.

Strand Genomics, 237 C. V. Raman Avenue, Sadashivanagar, Bangalore-560080, India. kas@strandgenomics.com

The use of in silico prediction of absorption, distribution, metabolism and excretion (ADME) properties is gaining acceptance as a useful assessment tool for early identification of likely drug candidate failures. However, it has been difficult to locate reliable models for the prediction of human pharmacokinetics (PK) in silico Currently available methods for estimating ADME and toxicity properties, such as in vitro and animal models, are not very predictive of what is observed in the clinic. Existing in silico ADME prediction tools concentrate on physicochemical properties, such as solubility, log P, rule-of-five compliance, Caco-2 permeability, blood-brain barrier and so on, or only classify drug-like candidates as 'poor', 'medium' or 'good' for a PK parameter, without ascribing values. Although physiology-based pharmacokinetic -models can predict ADME properties, they rely on using various measured properties as input for better accuracy. Strand Genomics has developed a tool, truPK, that predicts the properties of a molecule (bioavailability, protein binding, volume of distribution, elimination half-life and absorption rate) that affect its dose and dose frequency in humans. truPK's five models built using sophisticated machine methods have predicted with > 75% accuracies in external validation sets.

Mini Rev Med Chem. 2006 Apr;6(4):417-28. Links

Review in pharmacokinetic models on corticosteroids.Semmar N, Simon N.

Laboratory of Medical Pharmacology, Medical School of Marseilles, UPRES EA 3784, 27 bd Jean Moulin, 13385 Marseilles Cedex 5, France. nabilsemmar@yahoo.fr

The pharmacokinetics of corticosteroids provides a large set of mathematical models which led to analyse many kinetic profiles corresponding to many clinical and/or physiological situations. In this paper, we present a review on the usefulness, advantages and limits of such models which could find a large application in medicinal chemistry.

Basic Clin Pharmacol Toxicol. 2005 May;96(5):335-42. Links

New mathematical methods in pharmacokinetic modeling.Durisová M, Dedík L.

Institute of Experimental Pharmacology, Slovak Academy of Sciences, 841 04 Bratislava 4, Slovak Republic. maria.durisova@savba.sk

In recent years, several new methods for the mathematical modeling have gradually emerged in pharmacokinetics, and the development of pharmacokinetic models based on these methods has become one of the most rapidly growing and exciting application-oriented sub-disciplines of the mathematical modeling. The goals of our MiniReview are twofold: i) to briefly outline fundamental ideas of some new modeling methods that have not been widely utilized in pharmacokinetics as yet, i.e. the methods based on the following concepts: linear time-invariant dynamic system, artificial-neural-network, fuzzy-logic, and fractal; ii) to arouse the interest of pharmacological, toxicological, and pharmaceutical scientists in the given methods, by sketching some application examples which indicate the good performance and perspective of these methods in solving pharmacokinetic problems.

Risk Anal. 2004 Dec;24(6):1697-717. Links

Framework for evaluation of physiologically-based pharmacokinetic models for use in safety or risk assessment.Clark LH, Setzer RW, Barton HA.

U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Experimental Toxicology Division, Research Triangle Park, NC 27711, USA.

Proposed applications of increasingly sophisticated biologically-based computational models, such as physiologically-based pharmacokinetic models, raise the issue of how to evaluate whether the models are adequate for proposed uses, including safety or risk assessment. A six-step process for model evaluation is described. It relies on multidisciplinary expertise to address the biological, toxicological, mathematical, statistical, and risk assessment aspects of the modeling and its application. The first step is to have a clear definition of the purpose(s) of the model in the particular assessment; this provides critical perspectives on all subsequent steps. The second step is to evaluate the biological characterization described by the model structure based on the intended uses of the model and available information on the compound being modeled or related

compounds. The next two steps review the mathematical equations used to describe the biology and their implementation in an appropriate computer program. At this point, the values selected for the model parameters (i.e., model calibration) must be evaluated. Thus, the fifth step is a combination of evaluating the model parameterization and calibration against data and evaluating the uncertainty in the model outputs. The final step is to evaluate specialized analyses that were done using the model, such as modeling of population distributions of parameters leading to population estimates for model outcomes or inclusion of early pharmacodynamic events. The process also helps to define the kinds of documentation that would be needed for a model to facilitate its evaluation and implementation.

Adv Exp Med Biol. 2003;523:19-26.Links

Basic concepts of recirculatory pharmacokinetic modeling.Reekers M, Boer F, Vuyk J.

Best Pract Res Clin Anaesthesiol. 2003 Jun;17(2):191-205.Links

Pharmacokinetics in the elderly. Sadean MR, Glass PS.

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The elderly are an expanding population of patients presenting for anaesthesia. The pharmacokinetics of anaesthetic agents in the elderly deserves special attention because the normal ageing process and the effect of age-related diseases affect organ systems in a heterogeneous way with unpredictable consequences. The pharmacokinetics of each drug is also affected by these changes in a specific way and, together with the pharmacodynamic consequences, makes drug use and drug dosing challenging in this population. Although a decrease in bolus and infusion rates is a common theme, only pharmacokinetic modeling of drug disposition in the elderly will provide accurate dosing guidelines and increase the margin of safety.

Clin Pharmacokinet. 2001;40(6):395-403.Links

Pharmacokinetic software for the health sciences: choosing the right package for teaching purposes.Charles BG, Duffull SB.

The Australian Centre for Paediatric Pharmacokinetics, School of Pharmacy, The University of Queensland, Brisbane. B.Charles@pharmacy.uq.edu.au

Computer assisted learning has an important role in the teaching of pharmacokinetics to health sciences students because it transfers the emphasis from the purely mathematical domain to an 'experiential' domain in which graphical and symbolic representations of actions and their consequences form the major focus for learning. Basic pharmacokinetic concepts can be taught by experimenting with the interplay between dose and dosage interval with drug absorption (e.g.

absorption rate, bioavailability), drug distribution (e.g. volume of distribution, protein binding) and drug elimination (e.g. clearance) on drug concentrations using library ('canned') pharmacokinetic models. Such 'what if' approaches are found in calculator-simulators such as PharmaCalc, Practical Pharmacokinetics and PK Solutions. Others such as SAAM II, ModelMaker, and Stella represent the 'systems dynamics' genre, which requires the user to conceptualise a problem and formulate the model on-screen using symbols, icons, and directional arrows. The choice of software should be determined by the aims of the subject/course, the experience and background of the students in pharmacokinetics, and institutional factors including price and networking capabilities of the package(s). Enhanced learning may result if the computer teaching of pharmacokinetics is supported by tutorials, especially where the techniques are applied to solving problems in which the link with healthcare practices is clearly established.

Adv Drug Deliv Rev. 2001 Jun 11;48(2-3):265-300. Links

Noncompartmentally-based pharmacokinetic modeling. Veng-Pedersen P.

University of Iowa, College of Pharmacy, S227, Iowa City, IA 52242, USA. veng@uiowa.edu

OBJECTIVE: To present an overview of noncompartmentally-based modeling which is a modeling that makes use of systems analysis, predominantly linear systems analysis (LSA). FINDINGS: Fundamental elements of LSA presented from a linear operational viewpoint have a sound foundation in molecular stochastic independence (MSI). Powerful LSA procedures based on MSI presented such as convolution, deconvolution and disposition decomposition analysis (DDA) enable PK predictions and evaluations of drug input and delivery using models with simple general structures and few verifiable assumptions. DDA nonparametrically differentiates the unit impulse response (UIR) into generalized elimination and distribution functions. DDA applied in a linear and nonlinear context is central to many LSA procedures such as analytically exact direct deconvolution, nonparametric evaluation of drug elimination and distribution, steady state predictions, evaluation of mean time parameters for drug delivery and disposition (mean residence time, mean transit time, mean arrival time), relative tissue affinity (residence time coefficients), nonparametric exact clearance correction of UIR, and time variant convolution and deconvolution. The general response mapping operation procedure of LSA presented provides a powerful rational alternative to problematic structured modeling of multivariate PK systems. CONCLUSION: The wide arsenal of underutilized LSA-based kinetic analysis tools provide a rational, powerful alternative to traditional kinetic modeling.

BMJ. 1999 Apr 10;318(7189):984-90. Links

Computer support for determining drug dose: systematic review and meta-analysis.Walton R, Dovey S, Harvey E, Freemantle N.

ICRF General Practice Research Group, University of Oxford, Department of Public Health and Primary Care, Institute of Health Sciences, Oxford OX3 7LF. robert.walton@public-health.oxford.ac.uk

OBJECTIVE: To review the effectiveness of computer support for determining optimum drug dose. DESIGN: Systematic review of comparative studies where computers gave advice to clinicians on the most appropriate drug dose. Search methods used were standard for the Cochrane Collaboration on Effective Professional Practice. SUBJECTS: Comparative studies conducted worldwide and published between 1966 and 1996. MAIN OUTCOME MEASURES: For qualitative review, relative percentage differences were calculated to compare effects of computer support in different settings. For quantitative data, effect sizes were calculated and combined in meta-analyses. RESULTS: Eighteen studies met the inclusion criteria. The drugs studied were theophylline, warfarin, heparin, aminoglycosides, nitroprusside, lignocaine, oxytocin, fentanyl, and midazolam. The computer programs used individualised pharmacokinetic models to calculate the most appropriate dose. Meta-analysis of data from 671 patients showed higher blood concentrations of drug with computer support (effect size 0.69, 95% confidence interval 0.36 to 1.02) and reduced time to achieve therapeutic control (0.44, 0.17 to 0.71). The total dose of drug used was unchanged, and there were fewer unwanted effects of treatment. Five of six studies measuring outcomes of care showed benefit from computer assistance. CONCLUSIONS: This review suggests that using computers to determine the correct dose of certain drugs in acute hospital settings is beneficial. Computers may give doctors the confidence to use higher doses when necessary, adjusting the drug dose more accurately to individual patients. Further research is necessary to evaluate the benefits in general use.

A.2.2 Physiological* & pharmacokinetics & model* & review

Expert Opin Drug Metab Toxicol. 2007 Apr;3(2):235-49. Links

Whole-body physiologically based pharmacokinetic models.Nestorov I.

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This review summarizes the most recent developments in and applications of physiologically based pharmacokinetic (PBPK) modeling methodology originating from both the pharmaceutical and environmental toxicology areas. It focuses on works published in the last 5 years, although older seminal papers have also been referenced. After a brief introduction to the field and several essential definitions, the main body of the text is structured to follow the major steps of a typical PBPK modeling exercise. Various applications of the methodology are briefly described. The major future trends and perspectives are outlined. The main conclusion from the review of the available literature is that PBPK modeling, despite its obvious potential and recent incremental developments, has not taken the place it deserves, especially in pharmaceutical and drug development sciences.

Curr Opin Drug Discov Devel. 2007 Jan;10(1):84-96.Links

The pharmacokinetics and pharmacodynamics of monoclonal antibodies--mechanistic modeling applied to drug development.Mould DR, Sweeney KR.

Projections Research Inc, 535 Springview Lane, Phoenixville, PA 19460, USA. drmould@attglobal.net

The pharmacology of therapeutic monoclonal antibodies (mAbs) is complex and dependant on both the structure of the antibody and the physiological system that it targets. Patient exposure and responses to mAbs are also related to the structure and activity of mAbs. Furthermore, the pharmacokinetics and pharmacodynamics of mAbs are often inter-related. Pharmacokinetic and pharmacodynamic modeling have been used to elucidate or support the mechanisms of antibodies in development and can be used to identify appropriate dose regimens. Consequently, pharmacokinetic and pharmacodynamic modeling often plays a larger role during the development of therapeutic mAbs than for small molecules.

J Toxicol Environ Health B Crit Rev. 2006 Nov-Dec;9(6):457-83. Links

From a theoretical framework of human exposure and dose assessment to computational system implementation: the Modeling ENvironment for TOtal Risk Studies (MENTOR).Georgopoulos PG, Lioy PJ.

Exposure Measurement and Assessment Science Division, Environmental and Occupational Health Sciences Institute, UMDNJ- Robert Wood Johnson Medical School and Rutgers University, Piscataway, New Jersey 08854, USA. panosg@ccl.rutgers.edu

Georgopoulos and Lioy (1994) presented a theoretical framework for exposure analysis, incorporating multiple levels of empirical and mechanistic information while characterizing/reducing uncertainties. The present review summarizes efforts towards implementing that framework, through the development of a mechanistic source-to-dose Modeling ENvironment for TOtal Risks studies (MENTOR), a computational toolbox that provides various modeling and data analysis tools to facilitate assessment of cumulative and aggregate (multipathway) exposures to contaminant mixtures.MENTOR adopts a "Person Oriented Modeling" (POM) approach that can be applied to either specific individuals or to populations/subpopulations of interest; the latter is accomplished by defining samples of "virtual" individuals that statistically reproduce the physiological, demographic, etc., attributes of the populations studied. MENTOR implementations currently incorporate and expand USEPA's SHEDS (Stochastic Human Exposure and Dose Simulation) approach and consider multiple exposure routes (inhalation, food, drinking water intake; non-dietary ingestion; dermal absorption). Typically, simulations involve: (1) characterizing background levels of contaminants by combining model predictions and measurement studies; (2) characterizing multimedia levels and temporal profiles of contaminants in various residential and occupational microenvironments; (3) selecting sample populations that statistically reproduce essential demographics (age, gender, race, occupation, education) of relevant population units (e.g., census tracts); (4) developing activity event sequences for each member of the sample by matching attributes to entries of USEPA's Consolidated Human Activity Database (CHAD); (5) calculating intake rates for the sample population members, reflecting physiological attributes and activities pursued; (6) combining intake rates from multiple routes to assess exposures; (7) estimating target tissue doses with physiologically based dosimetry/toxicokinetic modeling.

Expert Opin Drug Metab Toxicol. 2006 Aug;2(4):619-28. Links

Integrating in vitro ADMET data through generic physiologically based pharmacokinetic models.Leahy DE.

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Early estimation of kinetics in man currently relies on extrapolation from experimental data generated in animals. Recent results from the application of a generic physiologically based model, Cloe PK) (Cyprotex), which is parameterised for human and rat physiology, to the estimation of plasma pharmacokinetics, are summarised in this paper. A comparison with predictive methods that involve scaling from in vivo animal data can also be made from recently published data. On average, the divergence of the predicted plasma concentrations from the observed data was 0.47 log units. For the external test set, > 70% of the predicted values of the AUC were within threefold of the observed values. Furthermore, the model was found to match or exceed the performance of three published interspecies scaling methods for estimating clearance, all of which showed a distinct bias towards overprediction. It is concluded that Cloe PK, as a means of integrating readily determined in vitro and/or in silico data, is a powerful, cost-effective tool for estimating exposure and kinetics in drug discovery and risk assessment that should, if widely adopted, lead to major reductions in the need for animal experimentation.

Eur J Pharm Sci. 2006 Nov;29(3-4):215-30. Epub 2006 May 22. Links

An integrated approach to model hepatic drug clearance.Liu L, Pang KS.

Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ontario, Canada M5S 2S2.

It has been well accepted that hepatic drug extraction depends on the blood flow, vascular binding, transmembrane barriers, transporters, enzymes and cosubstrate and their zonal heterogeneity. Models of hepatic drug clearances have been appraised with respect to their utility in predicting drug removal by the liver. Among these models, the "well-stirred" model is the simplest since it assumes venous equilibration, with drug emerging from the outflow being in equilibrium with drug within the liver, and the concentration is the same throughout. The "parallel tube" and dispersion models, and distributed model of Goresky and co-workers have been used to account for the observed sinusoidal concentration gradient from the inlet and outlet. Departure from these models exists to include heterogeneity in flow, enzymes, and transporters. This article utilized the physiologically based pharmacokinetic (PBPK) liver model and its extension that include heterogeneity in enzymes and transporters to illustrate how in vitro uptake and metabolic data from zonal hepatocytes on transport and enzymes may be used to predict the kinetics of removal in the intact liver; binding data were also necessary. In doing so, an integrative platform was provided to examine determinants of hepatic drug clearance. We used enalapril and digoxin as examples, and described a simple liver PBPK model that included transmembrane transport and metabolism occurring behind the membrane, and a zonal model in which the PBPK model

was expanded three sets of sub-compartments that are arranged sequentially to represent zones 1, 2, and 3 along the flow path. The latter model readily accommodated the heterogeneous distribution of hepatic enzymes and transporters. Transport and metabolic data, piecewise information that served as initial estimates, allowed for the unknown efflux and other intrinsic clearances to be estimated. The simple or zonal PBPK model provides predictive views on the hepatic removal of drugs and metabolites.

J Toxicol Environ Health A. 2005 Jun 11-25;68(11-12):889-900. Links

Computational pharmacokinetics during developmental windows of susceptibility.Barton HA.

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Computational modeling has an increasing role in analyses of biological effects, including how the body handles chemicals (i.e., pharmacokinetics or toxicokinetics) and how the body responds to chemicals (i.e., pharmacodynamics or toxicodynamics). Pharmacokinetic models increasingly describe not just adult humans and animals, but also changes with age and life stage (e.g., pregnancy and fetal exposures, lactational exposures, and childhood growth). Physiologically based pharmacokinetic models provide an important route to estimate the potential changes in internal dose that may occur throughout the life cycle. These models require inputs describing changes in physiology, metabolism, and exposure with age and life stage. A particular challenge exists when the "equivalent" developmental period in the rodents and humans differs (e.g., early postnatal in rats and in utero in humans) such that the "equivalent" window of susceptibility to toxic effects of the chemical may involve substantially different exposures (e.g., lactational versus placental transfer). Pharmacodynamic modeling could similarly address changes with age, but few such models currently exist. The growth of systems biology is anticipated to change this over the coming decade.

Basic Clin Pharmacol Toxicol. 2005 Mar;96(3):212-24. Links

Mechanism-based modeling of complex biomedical systems.Mosekilde E, Sosnovtseva OV, Holstein-Rathlou NH.

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Mechanism-based modeling is an approach in which the physiological, pathological and pharmacological processes of relevance to a given problem are represented as directly as possible. This approach allows us (i) to test whether assumed hypotheses are consistent with observed behaviour, (ii) to examine the sensitivity of a system to parameter variation, (iii) to learn about processes not directly amenable to experimentation, and (iv) to predict system behavior under conditions not previously experienced. The paper illustrates different aspects of the application of mechanism-based modeling through three different examples of relevance to the treatment of

diabetes and hypertension: subcutaneous absorption of insulin, pulsatile insulin secretion in normal young persons, and synchronization of the pressure and flow regulation in neighbouring nephrons. The underlying ideas are that each regulatory mechanism represents the target for intervention and that the development of new and more effective drugs must be based on a deeper understanding of the biological processes.

J Toxicol Environ Health A. 2004 Feb 27;67(4):297-329.Links

Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: implications for assessing children's risks from environmental agents.Ginsberg G, Hattis D, Russ A, Sonawane B.

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Children's risks can differ from those in adults for numerous reasons, one being differences in the pharmacokinetic handling of chemicals. Immature metabolism and a variety of other factors in neonates can affect chemical disposition and clearance. These factors can be incorporated into physiologically based pharmacokinetic (PBPK) models that simulate the fate of environmental toxicants in both children and adults. PBPK models are most informative when supported by empirical data, but typically pediatric pharmacokinetic data for toxicants are not available. In contrast, pharmacokinetic data in children are readily available for therapeutic drugs. The current analysis utilizes data for caffeine and theophylline, closely related xanthines that are both cytochrome P-450 (CYP) 1A2 substrates, in developing PBPK models for neonates and adults. Model development involved scale-up of in vitro metabolic parameters to whole liver and adjusting metabolic function for the ontological pattern of CYP1A2 and other CYPs. Model runs were able to simulate the large differences in half-life and clearance between neonates and adults. Further, the models were able to reproduce the faster metabolic clearance of theophylline relative to caffeine in neonates. This differential between xanthines was found to be due primarily to an extra metabolic pathway available to theophylline, back-methylation to caffeine, that is not available to caffeine itself. This pathway is not observed in adults exemplifying the importance of secondary or novel routes of metabolism in the immature liver. Greater CYP2E1 metabolism of theophylline relative to caffeine in neonates also occurs. Neonatal PBPK models developed for these drugs may be adapted to other CYP1A2 substrates (e.g., arylamine toxicants). A stepwise approach for modeling environmental toxicants in children is proposed.

Crit Rev Toxicol. 2003;33(5):469-503.Links

Modeling interindividual variation in physiological factors used in PBPK models of humans.Price PS, Conolly RB, Chaisson CF, Gross EA, Young JS, Mathis ET, Tedder DR.

LINEA, Inc., 129 Oakhurst Road, Cape Elizabeth, ME 04107, USA.

Modeling interindividual variation in internal doses in humans using PBPK models requires data on the variation in physiological parameters across the population of interest. These data should also reflect the correlations between the values of the various parameters in a person. In this project, we develop a source of data for human physiological parameters where (1) the parameter values for an individual are correlated with one another, and (2) values of parameters capture interindividual variation in populations of a specific gender, race, and age range. The parameters investigated in this project include: (1) volumes of selected organs and tissues; (2) blood flows for the organs and tissues; and (3) the total cardiac output under resting conditions and average daily inhalation rate. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. A computer program, Physiological Parameters for PBPK Modeling (P3M), is developed that allows records to be retrieved randomly from the database with specification of constraints on age, sex, and ethnicity. P3M is publicly available. The database and accompanying software provide a convenient tool for parameterizating models of interindividual variation in human pharmacokinetics.

Curr Opin Drug Discov Devel. 2003 Jul;6(4):470-80.Links

Predicting ADME properties and side effects: the BioPrint approach.Krejsa CM, Horvath D, Rogalski SL, Penzotti JE, Mao B, Barbosa F, Migeon JC.

Cerep, 15318 NE 95th Street, Redmon, WA 98052, USA. ckrejsa@cerep.com

Computational methods are increasingly used to streamline and enhance the lead discovery and optimization process. However, accurate prediction of absorption, distribution, metabolism and excretion (ADME) and adverse drug reactions (ADR) is often difficult, due to the complexity of underlying physiological mechanisms. Modeling approaches have been hampered by the lack of large, robust and standardized training datasets. In an extensive effort to build such a dataset, the BioPrint database was constructed by systematic profiling of nearly all drugs available on the market, as well as numerous reference compounds. The database is composed of several large datasets: compound structures and molecular descriptors, in vitro ADME and pharmacology profiles, and complementary clinical data including therapeutic use information, pharmacokinetics profiles and ADR profiles. These data have allowed the development of computational tools designed to integrate a program of computational chemistry into library design and lead development. Models based on chemical structure are strengthened by in vitro results that can be used as additional compound descriptors to predict complex in vivo endpoints. The BioPrint pharmacoinformatics platform represents a systematic effort to accelerate the process of drug discovery, improve quantitative structure-activity relationships and develop in vitro/in vivo associations. In this review, we will discuss the importance of training set size and diversity in model development, the implementation of linear and neighborhood modeling approaches, and the use of in silico methods to predict potential clinical liabilities.

Clin Pharmacokinet. 2003;42(10):883-908.Links

Whole body pharmacokinetic models.Nestorov I.

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The aim of the current review is to summarise the present status of physiologically based pharmacokinetic (PBPK) modelling and its applications in drug research, and thus serve as a reference point to people interested in the methodology. The review is structured into three major sections. The first discusses the existing methodologies and techniques of PBPK model development. The second describes some of the most interesting PBPK model implementations published. The final section is devoted to a discussion of the current limitations and the possible future developments of the PBPK modelling approach. The current review is focused on papers dealing with the pharmacokinetics and/or toxicokinetics of medicinal compounds; references discussing PBPK models of environmental compounds are mentioned only if they represent considerable methodological developments or reveal interesting interpretations and/or applications.The major conclusion of the review is that, despite its significant potential, PBPK modelling has not seen the development and implementation it deserves, especially in the drug discovery, research and development processes. The main reason for this is that the successful development and implementation of a PBPK model is seen to require the investment of significant experience, effort, time and resources. Yet, a substantial body of PBPK-related research has been accumulated that can facilitate the PBPK modelling and implementation process. What is probably lagging behind is the expertise component, where the demand for appropriately qualified staff far outreaches availability.

J Toxicol Environ Health A. 2003 Mar 14;66(5):417-33.Links

Physiological modeling of age-specific changes in the pharmacokinetics of organic chemicals in children.Price K, Haddad S, Krishnan K.

Groupe de recherche en toxicologie humaine (TOXHUM) Faculté de médecine, Université de Montréal, Montreal, Quebec, Canada.

Age-specific changes in the pharmacokinetics of chemicals are primarily due to differences in physiological and biochemical factors. For integrating the available information on the age-dependent changes in the physiological and biochemical factors, and for evaluating their combined influence on the pharmacokinetics of chemicals, physiologically based pharmacokinetic (PBPK) models are potentially useful. The objectives of this study were, therefore, (1) to assemble information on age-specific differences in physiological parameters such as alveolar ventilation rate, cardiac output, tissue volumes, tissue blood flow rates, and tissue composition for children of various age groups, and (2) to incorporate these data within a PBPK model for simulating the inhalation pharmacokinetics of a highly metabolized, volatile organic chemical (furan) in children of specific age groups (6, 10, and 14 yr old). The age-specific data on various physiological parameters were assembled following a review of the relevant literature and the hepatic metabolism rate of furan was set equal to the liver blood flow rate in adults and children. The blood:air and tissue:blood partition coefficients were calculated using molecular structure information along with the data on the blood and tissue composition (lipid and water contents) in children and adults. The PBPK model was used to simulate the pharmacokinetics of furan in adults and children (6, 10, and 14 yr old) exposed continuously for 30 h to 1

microgram/L of this chemical in inhaled air. The model simulations suggest that, for the same exposure conditions, the blood concentration of furan is likely to be greater in children by a factor of 1.5 (at steady state) than in adults, and the maximal factor of adult-children differences in liver concentration of furan metabolite is about 1.25. The PBPK model framework developed in this study should be useful for predicting the adult-children differences in internal dose of chemicals for risk assessment applications.

Eur Rev Med Pharmacol Sci. 2002 Mar-Jun;6(2-3):33-44.A short introduction to pharmacokinetics.Urso R, Blardi P, Giorgi G.

Dipartimento di Farmacologia "Giorgio Segre", Universita di Siena (Italy).

Phamacokinetics is proposed to study the absorption, the distribution, the biotransformations and the elimination of drugs in man and animals. A single kinetic profile may be well summarized by Cmax, Tmax, t 1/2 and AUC and, having more than one profile, 8 parameters at least, the mean and standard deviation of these parameters, may well summarize the drug kinetics in the whole population. A more carefull description of the data can be obtained interpolating and extrapolating the drug concentrations with some mathematical functions. These functions may be used to reduce all the data in a small set of parameters, or to verify if the hypotheses incorporated in the functions are confirmed by the observations. In the first case, we can say that the task is to get a simulation of the data, in the second to get a model. The functions used to interpolate and reduce the pharmacokinetic data are the multiexponential functions and the reference models are the compartmental models whose solutions are just the multiexponential functions. Using models, new meaningfull pharmacokinetic parameters may be defined which can be used to find relationships between the drug kinetic profile and the physiological process which drive the drug absorption, distribution and elimination. For example, compartmental models allow to define easily the clearance which is dependent on the drug elimination process, or the volume of distribution which depends on the drug distribution in the tissues. Models provide also an easy way to get an estimate of drug absorption after extravasculare drug administration (bioavailability). Model building is a complex multistep process where, experiment by experiment and simulation by simulation, new hypothesis are proven and disproven through a continuous interaction between the experimenter and the computer.

Environ Health Perspect. 2002 Dec;110 Suppl 6:1025-9. Links

BioMOL: a computer-assisted biological modeling tool for complex chemical mixtures and biological processes at the molecular level.Klein MT, Hou G, Quann RJ, Wei W, Liao KH, Yang RS, Campain JA, Mazurek MA, Broadbelt LJ.

Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, New Jersey, USA.

A chemical engineering approach for the rigorous construction, solution, and optimization of detailed kinetic models for biological processes is described. This modeling capability addresses

the required technical components of detailed kinetic modeling, namely, the modeling of reactant structure and composition, the building of the reaction network, the organization of model parameters, the solution of the kinetic model, and the optimization of the model. Even though this modeling approach has enjoyed successful application in the petroleum industry, its application to biomedical research has just begun. We propose to expand the horizons on classic pharmacokinetics and physiologically based pharmacokinetics (PBPK), where human or animal bodies were often described by a few compartments, by integrating PBPK with reaction network modeling described in this article. If one draws a parallel between an oil refinery, where the application of this modeling approach has been very successful, and a human body, the individual processing units in the oil refinery may be considered equivalent to the vital organs of the human body. Even though the cell or organ may be much more complicated, the complex biochemical reaction networks in each organ may be similarly modeled and linked in much the same way as the modeling of the entire oil refinery through linkage of the individual processing units. The integrated chemical engineering software package described in this article, BioMOL, denotes the biological application of molecular-oriented lumping. BioMOL can build a detailed model in 1-1,000 CPU sec using standard desktop hardware. The models solve and optimize using standard and widely available hardware and software and can be presented in the context of a user-friendly interface. We believe this is an engineering tool with great promise in its application to complex biological reaction networks.

Toxicol Lett. 2003 Feb 18;138(1-2):143-50. Links

The Bayesian population approach to physiological toxicokinetic-toxicodynamic models--an example using the MCSim software.Jonsson F, Johanson G.

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The calibration of physiologically based toxicokinetic models against experimental data encompasses the merging of prior knowledge with information present in the data. This prior knowledge is manifested in the scientific literature and associated with various degrees of uncertainty. The most convenient way to combine these sources of information is via the use of Bayesian statistical methods. Furthermore, toxicokinetic models are subject to both inter- and intra-individual variability. This variability may be handled statistically by the use of a population model. The MCSim software, which is available for free download on the Internet, permits the use of a population model in combination with a Bayesian statistical approach. An example of the use of MCSim in a recent model-based risk assessment of dichloromethane (DCM) is given and discussed.

A.2.3 Pharmacokinetic model* & anti-inflammatories & review

J Pharmacol Exp Ther. 2004 Nov;311(2):617-24. Epub 2004 Jun 14. Links

Beta-adrenergic blockade affects initial drug distribution due to decreased cardiac output and altered blood flow distribution.Avram MJ, Krejcie TC, Henthorn TK, Niemann CU.

Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, 303 E. Chicago Avenue, Ward Bldg. 13-199, Chicago, IL 60611-3008, USA. mja190@northwestern.edu

Beta-adrenergic receptor blockers decrease intravenous anesthetic dose requirements. The present study determined the effect of propranolol on indocyanine green and antipyrine disposition from the moment of rapid intravenous injection. Anti-pyrine is a physiological marker that distributes to a volume as large as total body water in a blood flow-dependent manner and is a pharmacokinetic surrogate for many lipophilic drugs, including intravenous anesthetics. Antipyrine and indocyanine green disposition were determined twice in five healthy adult males in this Institutional Review Board-approved study, once during propranolol infusion. After rapid indocyanine green and antipyrine injection, arterial blood samples were collected frequently for 2 min and less frequently thereafter. Plasma indocyanine green and antipyrine concentrations were measured by high-performance liquid chromatography. Indocyanine green and antipyrine disposition were characterized, using SAAM II, by a recirculatory pharmacokinetic model that describes drug disposition from the moment of injection. Parameters were compared using the paired t test. The disposition of indocyanine green demonstrated that propranolol decreased cardiac output at the expense of the fast peripheral (nonsplanchnic) intravascular circuit. The area under the antipyrine concentration versus time relationship was doubled for at least the first 3 min after injection due to both decreased cardiac output and maintenance of nondistributive blood flow at the expense of a two-thirds reduction of blood flow (intercompartmental clearance) to the rapidly equilibrating (fast, splanchnic) tissue volume. The increase in antipyrine area under the curve due to propranolol-induced alteration of initial antipyrine disposition could explain decreased intravenous anesthetic dose requirements in the presence of beta-adrenergic receptor blockade.

J Allergy Clin Immunol. 1998 Apr;101(4 Pt 2):S440-6. Links

Pharmacokinetics and pharmacodynamics of inhaled corticosteroids.Derendorf H, Hochhaus G, Meibohm B, Möllmann H, Barth J.

University of Florida, Gainesville 32610, USA.

There are significant differences in the pharmacokinetic properties of inhaled corticosteroids currently used in medical practice. All are rapidly cleared from the body but they show varying levels of oral bioavailability and more importantly variation in the rate of absorption after inhalation. Oral bioavailability is lowest for fluticasone propionate, indicating a low potential for unwanted systemic corticosteroid effects. Mathematical modeling has shown pulmonary residence times to be longest for fluticasone propionate and triamcinolone acetonide but shortest for budesonide and flunisolide. These properties appear to relate to pulmonary solubility, which appears to be the rate-limiting step in the absorption process.

A.2.4 Pharmacokinetic model* & asthma* & review

Acta Physiol Hung. 1994;82(4):327-30.Links
Adaptive control in drug therapy.Deutsch T.
Computer Centre, Semmelweis University of Medicine, Budapest, Hungary.

In medical practice, drugs are administered with the goal of attaining a therapeutic effect without exceeding predetermined safety limits on any adverse action. This paper is intended to provide an introduction to pharmacokinetic-model based adaptive control of drug levels that can be of use in achieving such therapeutic objectives. The principles are illustrated by the problem of providing rapid relief of acute asthmatic symptoms by infusing theophylline.

A.2.5 Pharmacokinetic model* & corticosteroids & review

J Pharm Sci. 2002 Nov;91(11):2441-51. Links

Quantitative structure-pharmacokinetic/pharmacodynamic relationships of corticosteroids in man.Mager DE, Jusko WJ.

Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Buffalo, New York 14260, USA.

The purpose of this study was to develop quantitative structure-activity/pharmacokinetic relationships (QSAR/QSPKR) for 11 selected corticosteroids in man. Multiple linear regression analysis with an automatic forward step-wise inclusion algorithm was used to construct QSAR/QSPKR models from molecular and submolecular descriptors that were generated using the SYBYL and KowWin computer programs. The final equations describing steroid relative receptor affinity, systemic clearance, volume of distribution, fraction unbound in plasma, and percent of oral absorption, all showed significant correlations (R(2) range 0.841 to 0.977). These relationships were crossvalidated using the leave-one-out method, and appeared to have good predictive performance (Q(2) range 0.715 to 0.912). In addition, a general method for integrating QSAR/QSPKR data to predict the time course of pharmacologic effects is presented. This approach, termed quantitative structure-pharmacodynamic relationships modeling, was successfully applied to predict the rapid cortisol suppressive effects of triamcinolone acetonide after a 2-mg intravenous bolus dose in healthy volunteers. Copyright 2002 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 91:2441-2451, 2002

List of symbols/abbreviations/acronyms/initialisms

ACE	Angiotensin-Converting Enzyme
ADME	Absorption, Distribution, Metabolism, Excretion
ARP	Applied Research Project
AUC	Area Under the Curve
CF	Canadian Forces
D Med Pol / Pharm Pol & Stds	Director of Medical Policy/Pharmacy Policy & Standards
DGHS	Direct General of Health Services
DND	Department of National Defence
DRDC	Defence Research & Development Canada
DRDKIM	Director Research and Development Knowledge and Information Management
PBPK	Physiologically-Based Pharmacokinetic
R&D	Research & Development

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A review on pharmacokinetic modeling and the effects of environmental stressors on pharmacokinetics for operational medicine: Operational pharmacokinetics

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In this report, we conducted a comprehensive literature review on the effects of a range of physiological and psychological stressors on drug absorption, distribution and elimination (pharmacokinetics), and current pharmacokinetic models (including computerized modeling tools and algorithms) used to predict pharmacokinetic changes. Although sophisticated computerized mathematical models have been widely used to quantitatively describe the pharmacokinetics of drugs in the human body, limited experimental data for both descriptive and predictive purposes were available. The effects of isolated physical activities on pharmacokinetics have been documented. However, some inconsistencies need to be addressed, such as the intensity and duration of each physical activity, and timing of drug administration. Other physiological stressors, such as temperature, hypoxic, hyperbaric and hyperoxic conditions have been studied to a lesser extent. There are only a few reports describing the psychological effects on drug pharmacokinetics. After carefully reviewing the literature, our goal is to develop a physiologically-based pharmacokinetic model to predict the absorption, distribution and elimination of drugs employed under various military physiological and psychological stressors.

Dans le cadre de ce compte rendu, nous avons procédé à un vaste examen de la documentation portant sur les effets d'un ensemble d'agents stressants physiologiques et psychologiques, sur l'absorption des médicaments, la distribution et l'élimination (pharmacocinétique), ainsi que sur les modèles pharmacocinétiques actuels (notamment les outils de modélisation et les algorithmes informatisés), servant à prédire les changements pharmacocinétiques. Bien que des modèles mathématiques complexes aient été largement utilisées afin de décrire quantitativement la pharmacocinétique de divers médicaments dans l'organisme humain, les données expérimentales descriptives et prédictives étaient rares. Les effets de diverses activités physiques sur les paramètres pharmacocinétiques ont été étudiés. Cependant, certaines contradictions demeurent inexpliquées, notamment en ce qui a trait à l'intensité et à la durée de chaque activité physique ainsi qu'au moment de l'administration du médicament. Les effets d'autres agents stressants physiologiques tels que la température et les états hypoxique, hyperbare et hyperoxique, ont été étudiés mais, dans une moindre mesure. Peu de comptes rendus décrivent les effets des facteurs psychologiques sur la pharmacocinétique des médicaments. Après avoir révisé attentivement la documentation déjà disponible, nous nous sommes fixé comme objectif de développer un modèle de pharmacocinétique basé sur les paramètres physiologiques qui permettrait de prédire l'absorption, la distribution et l'élimination des médicaments consommés par les militaires alors qu'ils subissent l'influence d'agents stressants physiologiques et psychologiques.

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Pharmacokinetic modeling; Operational stress; Physiologically based pharmacokinetic models

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