Use of Telemetry to Record Body Temperature and Activity in Mice

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A complete, commercially available, integrated telemetry and data aquisition system is described, which is used to record core temperature and activity in mice. The system is comprised of a telemetry transmitter (implanted in the peritoneal cavity), a receiver (placed underneath the cage) connected to a computer with software (Dataquest), which converts the transmitter signals directly into core temperature and activity. The information is stored on either a floppy diskette or a hard disk in the computer.

The effects of anesthesia (sodium pentobarbital, halothane), handling, aggregation, restraint, a cholinergic agonist (oxotremorine), and an anticholinesterase agent, soman (pinacolyl methylphosphonofluoridate), on core temperature and activity were examined.

The telemetry system for the recording of core temperature and activity provides a more accurate assessment of the temporal effects of various drugs and is more efficient and less labor intensive than the use of a rectal temperature probe.

Key Words: Soman (pinacolyl methylphosphonofluoridate); Oxotremorine; Hypothermia; Core temperature; Telemetry.

INTRODUCTION

In a study examining the effects of poisoning by an anticholinesterase such as soman (pinacolyl methylphosphonofluoridate) on oxotremorine hypothermia, it was found that there was an experimentally induced mortality (Clement, 1988). The mice were dying, not from the drug treatment, but from a bacterial infection, the result of repeated insertions of the rectal temperature probe daily over a 4-day period. Thus, measurement of the temporal response to oxotremorine and the change in this temporal response, following soman poisoning, could not be determined when core temperature was measured while using a rectal temperature probe. Therefore, telemetry was used to measure the core temperature in mice. Measurement of body temperature by telemetry has been used in a number of laboratory situations and species (De Castro and Brower, 1977; Gallaher et al., 1985; Riley, 1970; Riley et al., 1978; Thorne et al., 1987). In the majority of cases, the components of the system have been made in the laboratory and interfaced with

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Received June 13, 1988; revised and accepted October 25, 1988.

Journal of Pharmacological Methods 21, 129–140 (1989)

various recording devices and, thus, are not generally available to the research community.

This report deals with the utility of a complete, commercially available, integrated telemetry system for the measurement of core temperature and activity in mice. The effects of various drugs and procedures on core temperature and activity were investigated.

METHODS AND MATERIALS

Description of the Telemetry System:

The telemetry system is comprised of Data Sciences (St. Paul, MN) implantable, wireless transmitters (TA11-TA-C20), telemetry receivers (RA1010), a consolidation matrix (BCM100), and a Dataquest III data acquisition system. The implantable transmitter is provided with a biocompatible silastic coating, occupying a volume of less than 1.4 cc and weighing approximately 2.5 g. The transmitter measures temperature with a resolution of 0.01°C and long-term stability of better than 0.05°C. The high level of accuracy and stability is achieved through the use of highly stable thermisters and by transmitter circuitry, which rejects artifacts caused by natural fluctuations in the battery voltage during discharge. This design offers a significant improvement in the drift due to battery voltage fluctuations, when compared to the simple blocking oscillator temperature measurement circuit, which is commonly used for temperature telemetry.

The transmitter passes the temperature measurement to a receiver located beneath the animal cage via a radio signal, and the receiver recreates a digital signal proportional to temperature. To avoid having to match individual transmitters and receivers, all transmitters operate on the same frequency, and the animal's therefore, must be singly housed. Interference and cross talk are eliminated by circuits in the receiver, which lock on to the strongest signal. Since the receiver will perceive the signal from the animal in the cage directly above it as being the strongest, signals from transmitters in adjacent cages are rejected.

In addition to temperature, the same transmitter also provides an estimate of the movement activity of the animal. As the animal moves about the cage, the strength of the received signal varies as a result of changes in distance and orientation relative to the receiving antennae. The receiver continually monitors the level of the received signal and generates one or more digital pulses each time the signal level changes by more than a predetermined amount. The number of pulses generated upon each movement is dependent on the distance the animal moves with a secondary, a minor dependence on position and orientation of the animal within the receiving field and the rate of movement. The data acquisition system contains one counter for each animal, with the appropriate counter being incremented once for each activity pulse generated by the telemetry system. Pulses are accumulated for the duration of the user-specified sampling interval prior to being stored on disk, and the counters are reset following storage.

Digital information from the telemetry receivers are relayed to the data acquisition system via a multiplexer (consolidation matrix). The consolidation matrix multi-

plexes the signals from several receivers together onto a pair of cables, which can be run several hundred feet to the data acquisition system. This allows the majority of the cabling to remain in the animal quarters and also allows the computer to be located in a convenient, remote location. The data acquisition system converts the raw telemetered data into common units (e.g., ° Celsius, activity counts) and stores the information on disk for later retrieval. The data acquisition system is controlled by a series of menus, which allow the user to control the sampling interval and the channels to be sampled. In addition, the system allows the user to view data in tabular or graphic form as they are being acquired.

Data Analysis

The data files created using Dataquest software can be converted into Lotus 123 (Lotus Development Corp.) compatible files using an enhanced sort/list program available as a software option. This allows one to transport the data files directly into a Lotus 123 spreadsheet and to perform the necessary calculations and collating of the data in preparation for printing or plotting. In the author's laboratory (J.G.C.), a number of Lotus 123 templates were constructed and stored, and these were then combined with the data worksheets prepared under the enhanced sort/list program. This combination provides the user with a very powerful data handling system and allows the user to customize the data handling to suit his or her own particular needs.

Animals

Male CD-1 mice (25–30 g) obtained from Charles River Canada Ltd., St. Constant, Quebec, were used in this study. The animals were acclimated in the vivarium at Defence Research Establishment Suffield for at least 1 wk, following their arrival, prior to experimentation. The animals were allowed access to food and water ad libitum. The room temperature was maintained at 21–22°C.

Implantation of the transmitters was performed by first anesthetizing the mice with an intraperitoneal (ip) injection of sodium pentobarbital (75 mg/kg). An abdominal incision was made and the telemetry transmitter, which was sterilized by immersion in 70% alcohol, was implanted in the peritoneal cavity. The abdominal incision was closed using sutures (000 plain gut), and the skin was closed using wound clips (9-mm Michel clips). The telemetry transmitter was then activated by bringing a magnet close to the abdomen, which activated a switch in the transmitter turning on the battery power. The proper functioning of the transmitter was checked by placing the mouse close to an AM radio. When the battery power to the transmitter was switched on, interference on the AM band was heard as high frequency pitch. The animal was then placed in an individual cage and placed on the receiver and allowed to recover. In our laboratory, we can easily implant 12 mice with telemetry transmitters in a 1-hr period.

Materials

The following materials were obtained from various commercial sources: oxotremorine (Aldrich Chemical Company); sodium pentobarbital (Somnotol, MTC

Pharmaceuticals); halothane (Ayerst laboratories). Soman (pinacolyl methylphosphonofluoridate) was prepared at Defence Research Establishment Suffield.

RESULTS AND DISCUSSION

Recovery Time

It was found that the mice had to recover for at least 4 days following sodium pentobarbital anesthesia and surgery for implantation of the telemetry transmitter before they started to demonstrate normal diurnal rhythm of body temperature. The appearance of diurnal rhythm was used as an indicator that the mice had recovered from the effects of the anesthetic and the surgery and were thus available for use in an experimental situation. Generally, the animals are allowed to recover for a period of 1 wk following implantation of the transmitter prior to use in an experimental situation.

The effects of various anesthetics on the core temperature and the diurnal rhythm of body temperature in mice are presented in Figure 1. Mice were implanted with telemetry transmitters 1 wk before being exposed to either an atmosphere of 3.5% halothane for 10 min or injected with sodium pentobarbital (75 mg/kg,ip) and then returned to their home cage. Following both anesthetics, there was a transient hypothermia. The anesthesia had a slight effect on the diurnal rhythm; however, normal diurnal rhythm reappeared within 2 days of exposure. It is also apparent that the increase in activity coincides with the increase in core temperature of the mice. The length of time it takes the mice to recover normal diurnal rhythm after implantation of the telemetry transmitter is probably the result of the stress induced by the surgery and, to a minor extent, due to the anesthetic.

It was suggested that the increased activity levels during the dark phase of the light/dark cycle may be responsible for the diurnal rhythm in temperature (Abrams and Hammel, 1965). However, De Castro (1978) concluded that "in the rat the diurnal variation in core temperature is produced by the diurnal cycle of activity *in combination* with a diurnal cycle of the thermoregulatory upper limit; the thermoregulatory lower limit remaining constant."

Effect of Handling

The results in Figure 2 show the effect of handling the mice on body temperature. Mice, which were implanted with telemetry transmitters, were removed from their cage and picked up and held (for 15 sec) as they would be if they were to be injected. The body temperature and the activity increased due to the handling. The effect of a sham ip injection of saline on the core temperature was also examined. Similar to the results for a single handling, the core temperature increased (Figure 2). Gallaher et al (1985) also reported that the handling of rats caused an increase in core temperature, which was evident for a number of hours.

Repeated handling (Figure 2) of the mice, at 5-min intervals over the first 30 min, also produced a marked but transient increase in the body temperature compared to the control. Again, this increase in core temperature coincided with an increase in the activity of the mice.

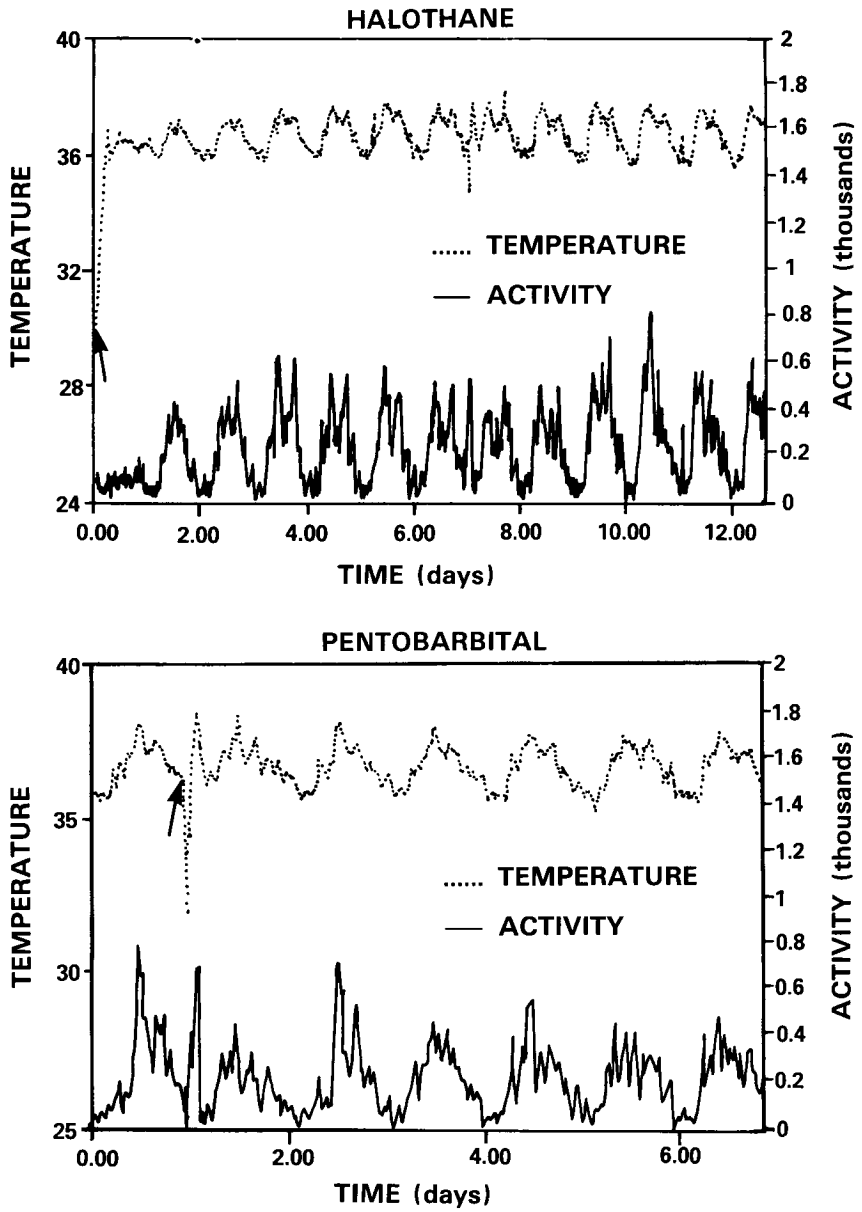


FIGURE 1. Effect of anesthesia by either sodium pentobarbital or halothane on the core temperature and activity and the diurnal rhythm of core temperature and activity in mice. The anesthetics were administered to the mice at the arrow. Time interval between measurements was 30 min. n = 12.

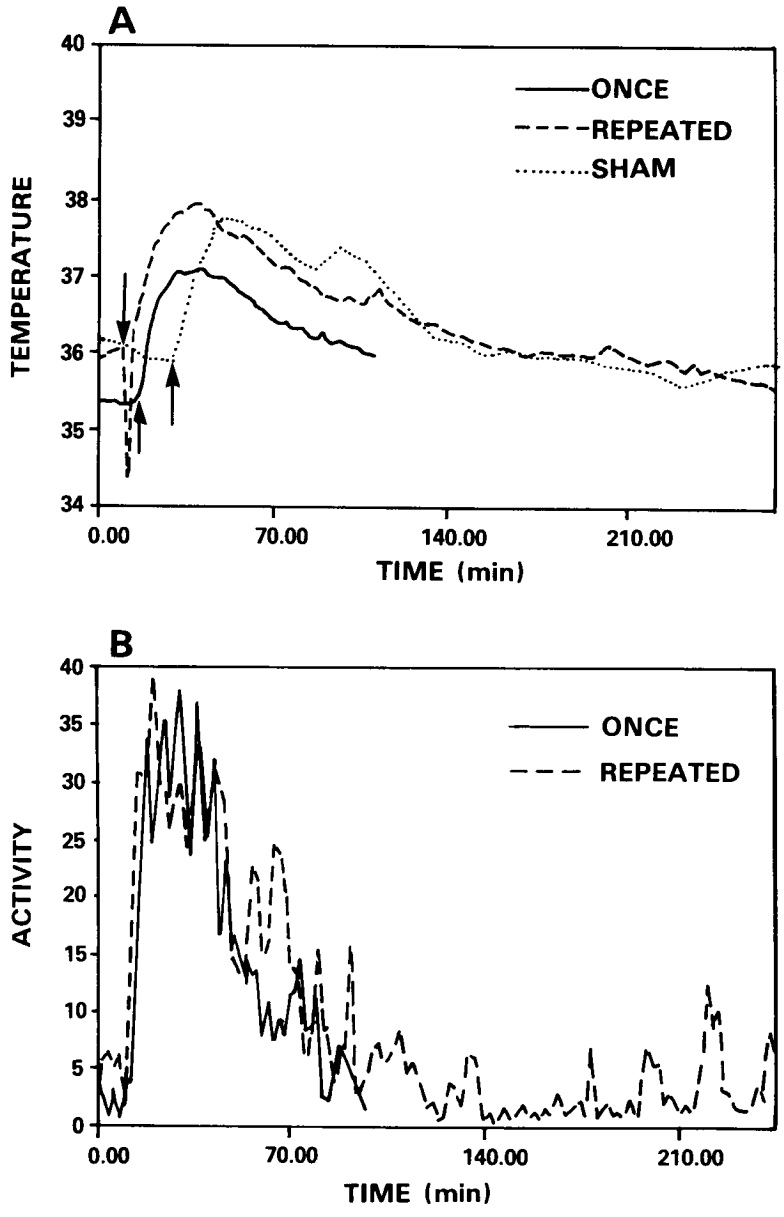


FIGURE 2. Effect of handling either once or repeatedly and sham injection on core temperature and activity in mice. Mice were picked up as they would be to give an ip injection either once (A) or at 5 min intervals over 30 min time period (n = 4). (B) Sham injected mice (n = 4) received an ip injection of saline. Time interval between measurements was 2.0 min. The arrow indicates the time at which either the handling began or the mice were injected.

Comparison of Core Temperature Recording Using Either Telemetry or the Rectal Probe

The core temperature of mice implanted with a telemetry transmitter was recorded using a rectal probe and compared to the core temperatures measured using telemetry transmitters. It was found that there was no significant difference between the core temperature values obtained using the two methods of measurement (Figure 3a). However, there was an experimental artifact induced by use of the rectal probe, i.e., an increase in the core temperature, probably the result of handling the mice.

Effect of Aggregation

Following implantation of the telemetry transmitter, the mice were housed in individual cages. The results in Figure 3b show the effect of aggregation on the core temperature. In this case, three nonimplanted mice were added to each cage, and the body temperature and activity of the implanted mouse was recorded. There was a significant and sustained increase in the body temperature and activity of the implanted mouse. This effect of aggregation was probably the result of the increased activity of the implanted mouse.

Effect of Restraint

Mice were placed in a restrainer[1] and then on the telemetry receiver. Initially, these mice showed a transient increase in body temperature, which was followed by a sustained decrease (Figure 3c), whereas the unrestrained mice (which were handled once) showed a slight, transient increase in body temperature, again most probably due to handling.

EFFECT OF VARIOUS DRUGS ON CORE TEMPERATURE

Oxotremorine

Induction of hypothermia by a centrally acting cholinergic agonist such as oxotremorine is the result of stimulation of muscarinic receptors in the hypothalamus (Lomax and Jenden, 1966). The results in Figure 4 show the time course of oxotremorine-induced hypothermia following ip administration of various doses. As the dose of oxotremorine was increased, the degree of hypothermia and the time course were increased. However, 250 min after administration of oxotremorine, the core temperature had returned to normal values. In addition, using a Lotus 123 template, the data can be analyzed to yield the mean minimum temperature and calculate the area under the curve (AUC), parameters that can be used in the estimation and analysis of the drug-induced effect. Presentation of the data in this form allows one to analyze the entire response to a particular drug rather than just at preselected

[1] The restraining device consisted of a 60-cc plastic syringe with the bottom cut off and the syringe plunger still in place. The plunger could be moved back and forth to accommodate animals of various sizes. Air holes were drilled along the barrel of the syringe, and the open end was plugged with a cork stopper with a "v" shape channel cut into it to allow the tail to protrude.

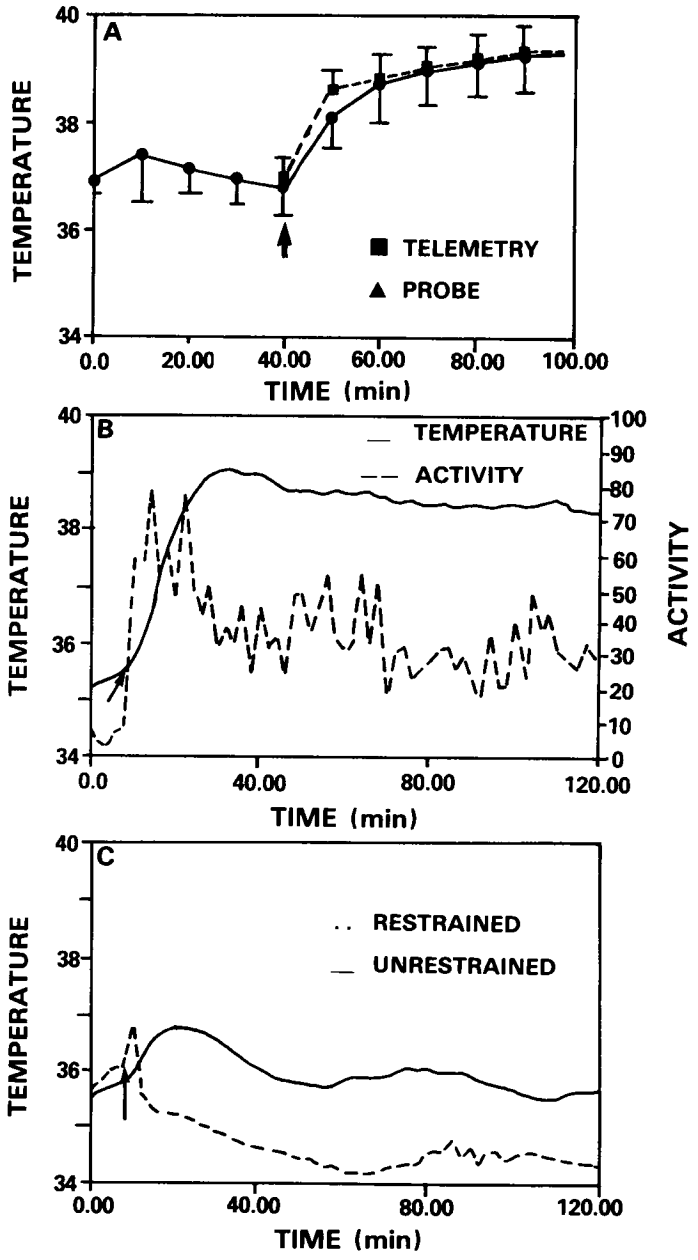
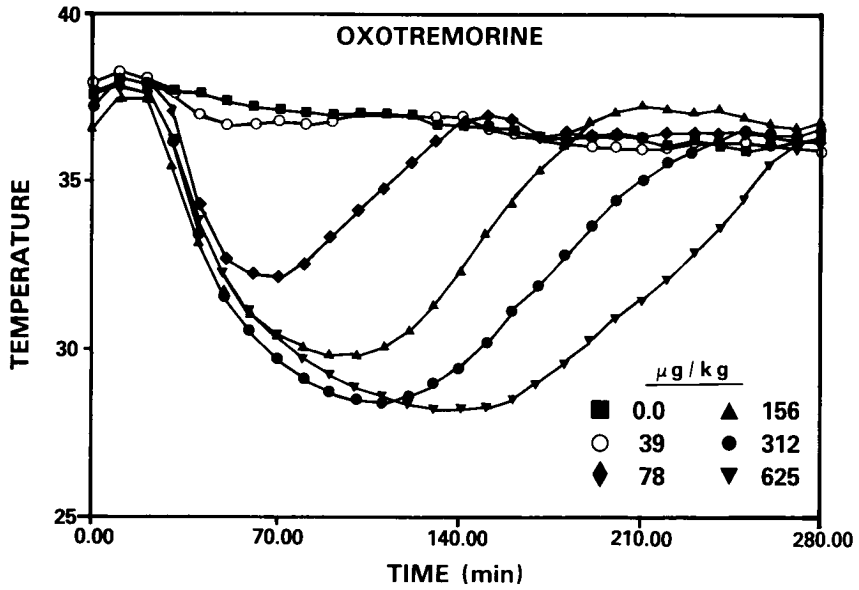


FIGURE 3. (A) Comparison of the core temperature in mice recorded by telemetry and the rectal probe. The core temperature of implanted mice was monitored by telemetry for 40 min, after which time the temperature of the mice was also recorded by insertion of a rectal temperature probe at the arrow. Time interval between measurements was 10.0 min. Each point is the mean ± sd. $n = 9$. (B) Effect of aggregation on the core temperature and activity in mice. Three nonimplanted mice were added to the cage (at the arrow) containing the mouse implanted with the telemetry transmitter. Time interval between measurements was 2.0 min. $n = 4$. (C) Effect of restraint on core temperature in mice. Mice were restrained at the arrow by placing the mouse in a 60-cc plastic syringe. Time interval between measurements was 2.0 min. $n = 4$.



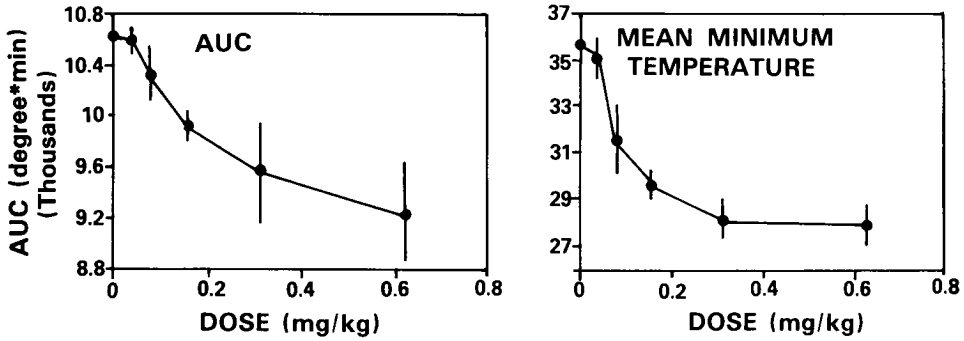


FIGURE 4. (A) Oxotremorine-induced hypothermia: Time course of various doses of oxotremorine injected ip at the arrow. (B) Area under the curve (AUC), expressed as degree X min, for the various doses of oxotremorine, determined by the trapezoidal method using a Lotus 123 template. Time interval between measurements was 10.0 min. Each point is the mean ± standard deviation of four observations for each dose of oxotremorine.

time intervals. The dose response relationship of oxotremorine on mean minimum temperature and AUC is presented in Figure 4.

Soman

Soman is a potent organophosphate anticholinesterase. The results in Figure 5 show the time course of the soman-induced hypothermia in mice. Twelve hours

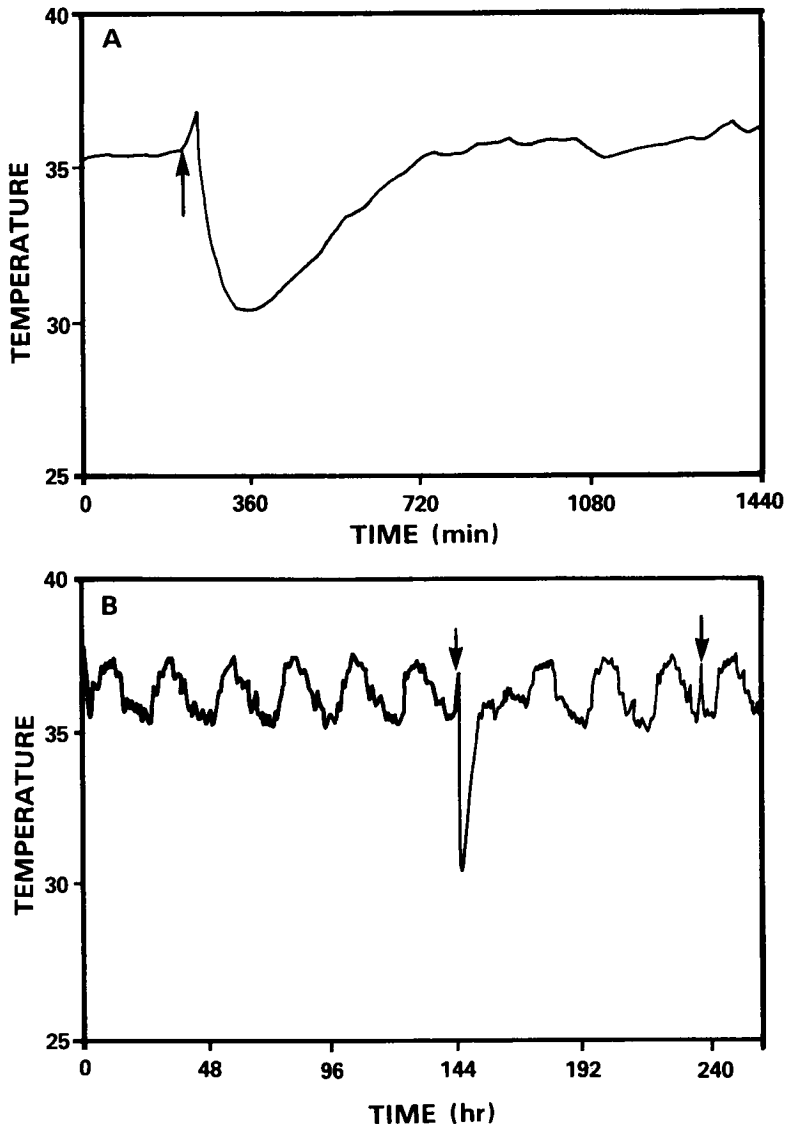


FIGURE 5. (A) Time course of soman-induced hypothermia in mice. Soman (100 μg/kg; sc) was injected at the arrow and the hypothermia was monitored. This dose of soman is equivalent to 0.75 LD_{50} dose. Time interval between measurements was 10.0 min. $n = 12$. (B) Effect of soman poisoning on the diurnal rhythm of core temperature. Soman (100 μg/kg; sc) was administered at the first arrow. The hyperthermia noted at the second arrow was in response to cleaning of the cages. Time interval between measurements was 30 min. $n = 12$.

after administration of soman, the core temperature returned to the control level. Due to the action of soman as a potent inhibitor of the enzyme acetylcholinesterase, it is tempting to speculate that the hypothermia following soman poisoning is caused by an increase in the concentration of acetylcholine in the brain. The effect of soman poisoning on the diurnal rhythm of core temperature was also investigated. Soman interfered with the normal rhythm for approximately 2 days after poisoning, at which point the mice appeared to reestablish their normal diurnal rhythm (Figure 5). The exact nature of the soman-induced hypothermia and its relationship to changes in neurotransmitter levels is under active investigation.

CONCLUSIONS

The results of this study demonstrate the applicability of the telemetry monitoring system for the recording of core temperature and activity in mice, as well as some of the variables that will affect the responses being monitored. It is apparent that the use of a telemetry system is a more cost effective procedure with respect to the technical time required to perform the experiment combined with the quality and quantity of data that can be acquired and analyzed. In addition, the telemetry system allows the experimenter to follow the time course of the drug rather than picking optimum points for measurement as determined from control experiments. It is possible that the time course of the drug effects are different under the experimental conditions and that an important effect of the drug might be missed and incorrect conclusions arrived at due to missing data points. This system of data collection gives the experimenter the entire view of the response without any additional effort.

In conclusion, the use of telemetry to monitor core temperature in laboratory animals has a number of advantages over use of the rectal temperature probe such as the following: more accurate representation of the effect of the drug on the body temperature without the added stress of repeated handling; less stressful to the animal with respect to repeated insertions of the rectal probe during a long term experiment; more efficient and less time-consuming in the collection and analysis of data; and more complete representation of the time course profile of the drug being investigated. The disadvantage of having to perform surgery on the animals for implantation of the transmitters and the length of the recovery period are minor compared to the advantages of the use of the telemetry system.

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