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Respiratory Depression Produced by Diazepam in Cats: Effect of Anaesthesia (1)

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Abstract—Diazepam (Valium®, Roche; 0.37 mg/kg) was given by slow injection into the left femoral vein and flushed in with 0.9 % saline. Within 3 min following the i.v. injection of diazepam spontaneous respiration ceased in cats anaesthetized with chloralose; mean arterial pressure fell from a control level of 99.4 (±28.03) mmHg to 32.5 (±13.44) mmHg. If artificial ventilation was initiated immediately upon cessation of respiration, the animal recovered. Cats anaesthetized with ketamine (Ketaset®, Rogar; 44 mg/kg i.m.) showed no respiratory depression following i.v. diazepam injection.

Introduction

Diazepam (Valium®) marketed by Hoffmann-La Roche in 1963 is one of the most widely prescribed drugs in the world. Clinically diazepam is administered intravenously as an induction agent before general anaesthesia, as a psychosedative premedication for cardioversion, endoscopic and bronchoscopic procedures, as an anticonvulsant to control intractable seizure activity and as an anxiolytic to moderate anxiety and agitation (Sellers, 1978).

Various clinical reports (Buskop *et al.*, 1967; Greenblatt and Koch-Weser, 1973; Brauninger and Ravin, 1974) have indicated that diazepam causes respiratory depression upon intravenous (i.v.) administration. In experimental animals, e.g. cats, diazepam has also been reported to cause respiratory depression (Catchlove and Kafer, 1971; Flörez, 1971; Chai and Wong, 1966; Sharer and Kutt, 1971). The purpose of this study was to investigate the effect of anaesthesia on the respiratory depressive action of diazepam in cats.

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Methods

Adult cats of either sex, mean weight 2.73 kg, were anaesthetized with either chloralose alone (1 % solution, 50 mg/kg i.p.), xylazine (2.2 mg/kg s.c.; Rompun, Bayvet Co.) followed by chloralose (1 % solution, 50 mg/kg i.p.), or ketamine (44 mg/kg i.m.; Ketaset®, Rogar). When a suitable level of anaesthesia was reached, the animal was placed on a warm operating table (McKay and Clement, 1977). A tracheostomy was performed and a polyethylene cannula inserted. Both vagi were isolated; P.E. catheters were placed in the left carotid artery for recording arterial blood pressure, left femoral artery for the collection of arterial blood samples and in the left femoral vein for the injection of diazepam. A ligature was sutured through the skin at the xiphoid process and connected to a Harvard 386 Heart/Smooth Muscle Transducer to record the chest movements. Arterial blood pressure was measured using a Bell and Howell Physiological Transducer and all recordings made on a Beckman R611 Dynagraph.

Blood was taken from the femoral artery in heparinized plastic syringes and analysed immediately for pH, pCO_2 and pO_2 using an International Laboratories Model 713 blood gas analyser. Hemoglobin was measured by the cyanmethemoglobin method; hematocrit was measured by the microtube method (CRC Manual of Clinical Laboratory Procedures, 2nd Ed., Faulkner, W. R. and J. W. King (eds), 1970). The total amount of blood taken at one time was 0.8 ml which was replaced by an equal volume of 0.9 % saline.

The animals were allowed to stabilize for one-half hour following surgery, at which time a control blood sample was taken. Fifteen minutes later both vagi were cut and another control sample was taken. Blood samples were taken 5 min before and 2, 5, 10, 20 and 30 min following the administration of diazepam (0.37 mg/kg). As recommended by the manufacturer, the diazepam was injected slowly over 1 min and flushed in with 0.9 % saline.

Animals were divided into three groups: Group 1 was anaesthetized with chloralose alone (1 % solution 50 mg/kg, i.p.); Group 2 was anaesthetized with xylazine (2.2 mg/kg, s.c.) and chloralose (1 % solution 50 mg/kg, i.p.); and Group 3 was anaesthetized with ketamine (44 mg/kg, i.m.). Results are expressed as the per cent change from control.

Results

Group 1, Chloralose alone. All cats anaesthetized with chloralose alone died within 5–10 min after receiving i.v. diazepam (0.37 mg/kg). Results from Fig. 1 demonstrate that diazepam caused a very rapid and precipitous decrease in respiratory rate, heart rate and mean arterial pressure. The blood pH and pO_2 levels also decreased with a concomitant rise in pCO_2 levels. In

other cats tested, if artificial ventilation was initiated at the time respiration ceased, the animal recovered and subsequent injections had little effect. Also, animals that were administered diazepam i.v. while being ventilated artificially showed only a transient fall in arterial blood pressure and pO_2.

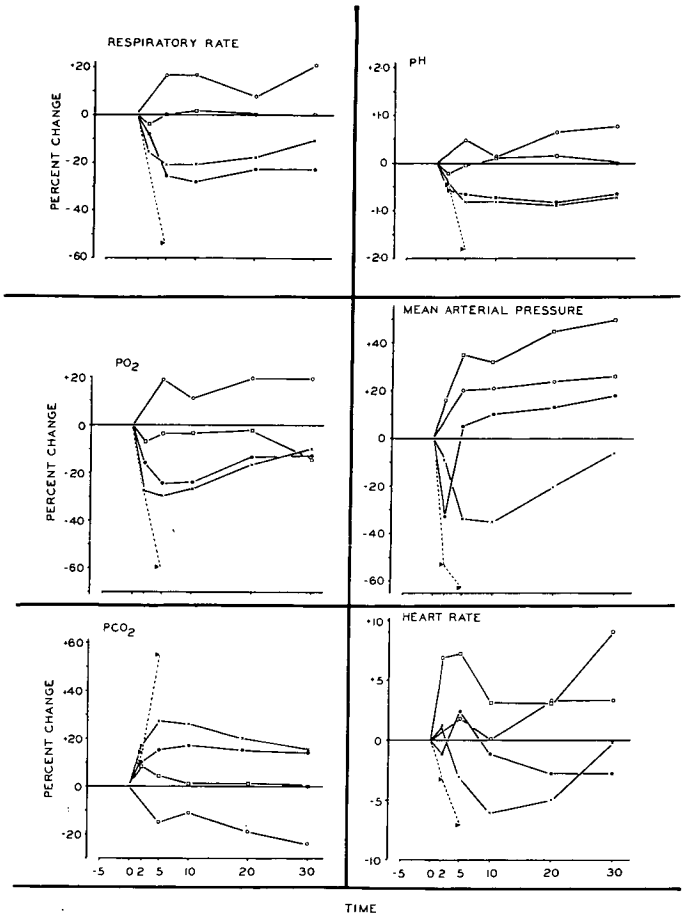

FIG. 1

Effect of method of induction of anaesthetia on diazepam-induced respiratory depression in cats.

Group 1 ▲ chloralose, diazepam, N = 3– 5

Group 2 □ xylazine + chloralose, diazepam solvent, N = 3
● xylazine + chloralose, diazepam, N = 3
× xylazine + chloralose, RO 21-3981, N = 3

Group 3 ○ ketamine, diazepam, N = 3

The abscissa is time in minutes following the i.v. administration of diazepam (0.37 mg/kg) at O time. The ordinate is the per cent change from the control values immediately prior to i.v. administration of diazepam.

Group 2, Xylazine premedication + chloralose. Animals in this group showed a sudden drop on arterial pO_2 and pH accompanied by a rise in pCO_2 within 2 min following an i.v. injection of diazepam (Fig. 1). The mean arterial blood pressure fell dramatically in the first 2 min but rapidly rose to a higher than control level and remained elevated throughout the observation period. There was a marked slowing (26 %) of the respiratory rate following injection of diazepam which remained depressed over the 30 min observation period.

RO 21-3981 (Medazolam®) is a water-soluble benzodiazepine derivative. Following an i.v. injection of RO 21-3981 (0.37 mg/kg) in 0.9 % saline in cats anaesthetized with xylazine + chloralose, there was a decrease in the respiratory rate, heart rate, mean arterial pressure, pH and pO_2 which tended to return to control levels by 30 min post-injection. Coincident with the above decreases, the pCO_2 increased.

Some cats received an i.v. injection of the diazepam solvent (Korttila *et al.*, 1976) only. The results in Fig. 1 demonstrate that the solvent had no significant effect on the respiratory parameters; however, it did produce a significant increase in the heart rate and mean arterial pressure.

Group 3, Ketamine. In contrast to the previous results, animals anaesthetized with ketamine showed no respiratory depression following i.v. administration of diazepam (0.37 mg/kg). An increase in respiratory rate was accompanied by increases in pO_2 and pH with a decrease in pCO_2. The mean arterial blood pressure was also elevated over the 30 min observation period (Fig. 1).

Discussion

As reported by various investigators (see Introduction), diazepam administered i.v. produced a profound and sustained respiratory depression in cats. This was evidenced by a decrease in the pH, pO_2 and respiratory rate and an increase in the pCO_2 levels in chloralose anaesthetized cats. Diazepam also produced respiratory depression in decerebrate cats (Flörez, 1971) and in cats anaesthetized with sodium pentobarbital (Sharer and Kutt, 1971). The results in this study demonstrate that the toxicity and degree of respiratory depression of i.v. administration of diazepam can be prevented by pretreatment with xylazine in cats anaesthetized with chloralose. However, the respiratory depression can be prevented completely if the anaesthetic ketamine is used. RO 21-3981 (Medazolam®), a water-soluble benzodiazepine derivative, produced slightly greater respiratory depression than the equivalent dose of diazepam as evidenced by the changes in pO_2 and pCO_2. Forster *et al.* (1979) reported that RO 21-3981 depressed respiration in man by a direct action on the respiratory centre in the central nervous system.

The apparent protective action of ketamine anaesthesia against diazepam-induced respiratory depression could be accounted for by the fact that ketamine does not depress respiration whereas chloralose has a significant respiratory depressant action (Borison, 1978). Thus it appears that the respiratory depressant actions of diazepam are manifested in a system where the respiratory system is already in a depressed state.

In summary, when diazepam is to be used in *in vivo* experiments in cats, particular attention should be paid to the choice of anaesthetic.

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