MEPERIDINE - HALOTHANE INTERACTION IN DOGS

E.P. STEFFEY, R. MARTUCCI, D. HOWLAND, J.H. ASLING, AND J.H. EISELE,
WITH THE TECHNICAL ASSISTANCE OF C. HIRSCH

INTRODUCTION

IT IS KNOWN that narcotics reduce the alveolar concentration of inhalation anaesthetics required for anaesthesia in man and in animals.¹⁻³ However, the magnitude and duration of the narcotic effect on inhalation anaesthesia is not known. Accordingly, we determined in dogs the temporal effect of various doses of meperidine, a commonly used anaesthetic adjuvant, on the minimum alveolar concentration (MAC) of halothane. In addition, because previous investigations have shown that halothane anaesthesia alters the plasma concentration time profiles of drugs administered concomitantly⁴⁻⁶ we compared plasma meperidine concentrations in dogs both awake and during halothane anaesthesia using an identical intramuscular dose of meperidine (2.75 mg/kg).

MATERIALS AND METHODS

Twenty-four healthy, unmedicated dogs of various ages, breeds, and weights ($17.0 \text{ kg} \pm \text{S.E. } 0.7$) and of either sex were divided into four equal groups. Group I received meperidine alone, while groups II, III, and IV received meperidine during anaesthesia with halothane in oxygen. To eliminate the possible effect of tolerance, each dog was used only once. In each group meperidine was injected on the basis of the dog's weight into the hind limb muscle (i.m.). Plasma samples for determination of meperidine content were obtained from catheters inserted percutaneously into a femoral artery. Lignocaine was injected for local analgesia prior to cannulation in the awake dogs (Group I).

Animal studies

Six dogs in Group I received meperidine 2.75 mg/kg. They were maintained with minimal manual restraint in lateral recumbency throughout the study period. Heparinized arterial plasma samples for measurement of meperidine content were obtained before meperidine injection (control), at 10-minute intervals during the first 60 minutes post-injection, and at 20-minute intervals during the second hour. Samples were not taken beyond 120 minutes in this group.

Dogs in Groups II, III, and IV were anaesthetized with halothane in oxygen using a face mask connected to a standard semiclosed anaesthetic circle system.

E.P. Steffey, V.M.D., Ph.D., D. Howland, B.S., Department of Veterinary Surgery; R. Martucci, B.S., M.S., J.H. Asling, M.D., J.H. Eisele, M.D., & C. Hirsch, B.A., Department of Medical Anesthesiology, University of California, Davis, CA 95616, U.S.A.

Address reprint requests to: E.P. Steffey, V.M.D., Ph.D., Department of Surgery, School of Veterinary Medicine, University of California, Davis, CA 95616, U.S.A.

A cuffed tracheal tube was introduced without the use of muscle relaxants. End-tidal gas samples were obtained from a nylon catheter positioned within 3 cm of the tip of the tracheal tube. Halothane was measured with a Beckman LB II infrared gas analyzer calibrated against a known halothane standard. For each animal, the minimal alveolar concentration (MAC) of halothane preventing purposeful movement in response to a large haemostat clamped across the tail was determined according to the method of Eger.⁷ Oesophageal temperatures were maintained normal by varying heating blanket temperatures. Following MAC determination, inspired concentration of halothane was reduced to an arbitrary level and meperidine was given as a single intramuscular injection according to the following schedule: Group II, 2.75 mg/kg; Group III, 5.5 mg/kg; Group IV, 11.0 mg/kg. MAC was then systematically redetermined. A constant alveolar halothane concentration was maintained and the response or lack of response to tail clamping was noted. Following a positive response the alveolar halothane concentration was raised by 15 to 30 per cent. At each level the average of the last minute for which a negative response was observed and the time of gross purposeful movement in response to the tail clamp was then plotted against alveolar halothane concentration. In this way MAC could be reasonably correlated with the rapidly declining meperidine concentrations at measured time intervals.

Sampling of arterial blood for determination of meperidine followed the Group I schedule. Beyond 120 minutes meperidine samples were collected at 30-minute intervals. Sampling was discontinued when halothane MAC returned to the pre-meperidine level.

During the halothane-meperidine studies, ventilation was spontaneous. Mean arterial P_{aCO_2} was 36.6 ± 0.9 (SE) mmHg and mean arterial pH was 7.37 ± 0.01 ($n = 91$).

Meperidine analysis

A gas chromatography method was used⁸ with a variation of the standard alkaline extraction into organic solvents.

Each plasma sample (1 ml) was placed in a round-bottom test tube and 0.5 ml of 1 μ g/ml phencyclidine HCl was added as an internal marker. The samples were alkalinized to pH 11 with Na_2HPO_4 - Na_3PO_4 buffer, and extracted twice with 4 ml of a mixture of 75 per cent pentane and 25 per cent diethyl ether (v/v). The two extracts were combined and evaporated to dryness at 37° C under nitrogen and the residues were redissolved in approximately 10 μ l of dioxane.

Aliquots of 3 μ l were analyzed on a Bendix 2600 gas-liquid chromatograph with flame ionization detectors. Columns were 3 per cent OV-25 on 80-100 mesh chromosorb W, with a temperature of 185° C at a flow rate of 30 cc/min N_2 . Meperidine concentrations were calculated by comparing the meperidine/phencyclidine peak height ratios to a standard curve.

RESULTS

The temporal effects of three intramuscular doses of meperidine on halothane MAC (Groups II, III, and IV) are shown in Figure 1. In every animal meperidine

FIGURE 1. The effect of an intramuscular meperidine injection (Groups II, III, and IV) on halothane MAC over four hours. Mean values $\pm$ 1 SE are represented, $n = 6$ dogs at each dose.

transiently reduced halothane MAC, and the magnitude and duration of MAC depression was dose related. When the dose of meperidine was increased from 2.75 mg/kg to 5.5 mg/kg, halothane anaesthetic requirement decreased and duration of MAC depression was prolonged. Although increasing the meperidine dose to 11 mg/kg did not markedly decrease the alveolar halothane concentration required for anaesthesia when compared to the 5.5 mg/kg group, a slight increase in duration of MAC depression was observed following injection of 11.0 mg/kg.

Plasma meperidine concentrations for dogs anaesthetized with halothane (Groups II, III, IV) are given in Table I and in Figure 2. Regression analysis of the average percentage change from control MAC compared to plasma meperidine concentrations suggests that $0.77 \mu\text{g}$ meperidine/ml of plasma is the equivalent of one-half MAC (Figure 4).

Plasma meperidine concentrations for awake (Group I) and anaesthetized (Group II) dogs given the same dose (2.75 mg/kg) are shown in Table I and in Figure 3. Meperidine levels were lower in Group I (half-life approximately 26.5 min*) than in Group II (half-life approximately 35 min*) (see Figure 3). These estimated half-lives of meperidine did not differ significantly, however ($P > 0.05$),

*Our data do not permit us to determine precise half-life for meperidine since additional samples at least 4-6 hours meperidine administration are necessary.

TABLE I
PLASMA MEPERIDINE CONCENTRATIONS ($\mu\text{g/ml}$) FOLLOWING INTRAMUSCULAR INJECTION

		Minutes											
		10	20	30	40	50	60	80	100	120	150	180	210
Awake													
2.75 mg/kg	0.75 ±0.05 (6)	0.57 ±0.07 (6)	0.41 ±0.05 (6)	0.33 ±0.07 (6)	0.26 ±0.08 (6)	0.18 ±0.04 (6)	0.12 ±0.03 (6)	0.12 ±0.04 (5)					
Halothane Anaesthesia													
2.75 mg/kg	1.10 ±0.17 (6)	0.88 ±0.18 (6)	0.73 ±0.18 (6)	0.57 ±0.14 (6)	0.56 ±0.20 (6)	0.41 ±0.13 (6)	0.28 ±0.06 (6)	0.21 ±0.02 (5)					
5.5 mg/kg	1.74 ±0.33 (6)	1.60 ±0.31 (6)	0.97 ±0.19 (6)	0.93 ±0.16 (6)	0.77 ±0.20 (6)	0.64 ±0.14 (6)	0.50 ±0.07 (6)	0.41 ±0.10 (6)	0.32 ±0.10 (6)	0.24 ±0.06 (6)	0.22 ±0.05 (6)		
11.0 mg/kg	3.17 ±0.49 (5)	2.39 ±0.42 (5)	1.94 ±0.39 (5)	1.51 ±0.30 (5)	1.18 ±0.23 (4)	0.77 ±0.08 (4)	0.89 ±0.24 (5)	0.61 ±0.13 (5)	0.54 ±0.11 (5)	0.48 ±0.11 (5)	0.47 ±0.07 (4)	0.41 ±0.07 (4)	

Data are presented as mean $\pm$ 1 S.E. Number of dogs is shown in parentheses.

FIGURE 2. Mean plasma concentrations of meperidine on a log scale following an intramuscular injection (Groups II, III, and IV) in halothane-anesthetized dogs over four hours.

between awake dogs and those anaesthetized with halothane as determined by student's *t*-test for unpaired data.

All unanaesthetized dogs became noticeably less responsive to environmental stimuli within ten minutes of meperidine injection. This persisted for only about 45 minutes, after which they showed progressively greater arousal in response to such things as noise and investigator movement.

DISCUSSION

Meperidine decreased the alveolar halothane MAC in all dogs (Figure 1). The magnitude of MAC depression was both dose and time dependent and supported

IM DOSE 2.75 mg/Kg

FIGURE 3. Mean plasma concentrations of meperidine on a log scale following an intramuscular injection of 2.75 mg/kg meperidine in awake dogs (Group I) and anaesthetized dogs (Group II).

a previous finding in rats.³ It is noteworthy that increasing the dose of meperidine from 5.5 mg/kg to 11 mg/kg almost doubled plasma levels (Figure 2), but resulted in a minimal reduction of halothane MAC and duration of MAC depression. The incidence of unwanted side effects (e.g., cardiovascular and respiratory depression) becomes greater with increasing dosage.^{9,10} Thus, if our data apply to man, they suggest that high doses of meperidine are unnecessary and, indeed, may be unwanted. While contributing little further depression of MAC (analgesia), the added meperidine may, in fact, produce more undesirable side effects.

The rapid decay of plasma meperidine observed in this study (about 70 per cent per hour) is in agreement with a previous investigation.¹¹ Man, on the other hand, is known to metabolize meperidine at the rate of only about 17 per cent per hour (biological half-life, 3–4 hours).^{11,12} Despite our knowledge of this species difference with regard to disappearance of plasma meperidine, we chose the dog as our experimental model for these studies because of the availability of pertinent comparative data in the dog. In addition, the animal's size allowed collection of adequate plasma samples for drug analysis. The amount of meperidine injected,

FIGURE 4. Regression analysis for the average change percentage from control MAC vs plasma meperidine concentration. The line of best fit is represented by percentage of control MAC = $40.9 - 34.5 \ln \mu\text{g meperidine/ml plasma}$, $r = 0.79$, $p < 0.05$.

although greater than commonly administered to a human, was based on clinical veterinary schedules.¹³

The influence of halothane anaesthesia on meperidine kinetics is of particular interest. Our data shows a greater mean plasma meperidine concentration in anaesthetized dogs than in awake unsedated controls. These findings, along with recent investigations of meperidine in man,¹² pentobarbitone in sheep⁴ and diazepam⁵ and ketamine⁶ in rats, strongly suggest that general anaesthesia prolongs the plasma half-life of concomitantly administered drugs. It has been proposed that the cause of these differences could be an impairment of hepatic circulation,^{5,14} a reduction in hepatic drug metabolism,^{15,16} and/or alterations in drug uptake and distribution⁶ associated with anaesthesia. Our study supports the proposal that halothane alters the action of concomitantly administered drugs at least in part by influencing their uptake and/or redistribution. Table I shows that meperidine levels in awake dogs are lower at 10 minutes than samples from anaesthetized dogs at the same time. This cannot be due to drug metabolism and is thus more likely a function of the uptake and/or distribution of meperidine. While further detailed examination of this interaction is necessary, available information suggests that prudence is indicated during concomitant administration of meperidine with potent general anaesthetics.

SUMMARY

We studied the interaction of meperidine and halothane in 24 unmedicated, spontaneously breathing dogs. Intramuscular (i.m.) injections of meperidine, 2.75 mg/kg, 5.5 mg/kg and 11.0 mg/kg reduced the minimal alveolar concentration (MAC) of halothane required for anaesthesia. The magnitude and duration of MAC depression were dose related. Plasma meperidine concentrations following an i.m. injection of 2.75 mg/kg were lower in the awake, unsedated dogs than in the dogs anaesthetized with halothane.

RÉSUMÉ

Nous avons étudié l'influence l'un sur l'autre de la Mépéridine et de l'Halothane chez 24 chiens non prémédiqués et respirant spontanément.

Des doses de Mépéridine de 2.75, de 5.5 et de 11 mg/kilo, abaissaient le MAC de l'Halothane, et ceci proportionnellement à la dose.

Les taux plasmatiques de Mépéridine, à la suite d'une injection de 2.75 mg/kilo, étaient plus bas chez le chien non prémédiqué et non anesthésié, que chez le chien anesthésié à l'Halothane.

ACKNOWLEDGMENTS

Supported by the Departments of Veterinary Surgery and Anesthesiology (School of Medicine) and the School of Veterinary Medicine's General Research Support, University of California, Davis, California. The authors gratefully acknowledge the assistance of Edmond I. Eger, II, in the preparation of this manuscript.

REFERENCES

1. SAIDMAN, L.J. & EGER, E.I., II. Effect of nitrous-oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *Anesthesiology* 25: 302 (1964).
2. MUNSON, E.S., SAIDMAN, L.J., & EGER, E.I., II. Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. *Anesthesiology* 26: 134 (1965).
3. HOFFMAN, J.C. & DIFAZIO, C.A. The anesthetic-sparing effect of pentazocine, meperidine and morphine. *Arch. Int. Pharmacodyn.* 186: 261 (1970).
4. PEARSON, G.R., BOGAN, J.A., & SANFORD, J. An increase in the half-life of pentobarbitone with the administration of halothane in sheep. *Brit. J. Anaesth.* 45: 586 (1973).
5. KANTO, J. & PIHLAJAMAKI, K. Interactions of diazepam and halothane in rats. *Ann Chir. Gynaecol. Fenn* 62: 247 (1973).
6. WHITE, P.F., JOHNSTON, R.R., & PUDWELL, C.R. Interaction of ketamine and halothane in rats. *Anesthesiology* 42: 179 (1975).
7. EGER, E.I., II, SAIDMAN, L.J., & BRANDSTATER, B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* 26: 756 (1965).
8. ASLING, J. H., SHNIDER, S.M., WILKINSON, G.R., & WAY, E.L. Gas chromatographic determination of mepivacaine in capillary blood. *Anesthesiology* 31: 458 (1969).
9. ECKENHOFF, J.E. & OECH, S.R. The effects of narcotics and antagonists upon respiration and circulation in man. A review. *Clin. Pharmacol. Ther.* 1: 483 (1960).
10. FREY, E. Cardiovascular effects of high dosages of fentanyl, meperidine and naloxone in dogs. *Anesth. and Analg.* 53: 40 (1974).
11. BURNS, J.J., BERGER, B.L., LIEF, P.A., WO-LACK, A., PAPPER, E.M., & BRODIE, B.B. The physiological deposition and fate of meperidine (Demerol) in man and a method for its estimation in plasma. *J. Pharmacol. Exp. Ther.* 114: 289 (1955).

12. MATHER, L.E., TUCKER, G.T., PFLUG, A.E., LINDOP, M.J., & WILKERSON, C. Meperidine kinetics in man. *Clin. Pharmacol. and Ther.* 17: 21 (1975).
13. SOMA, L.R. (ed.) Textbook of veterinary anesthesia. Baltimore: The Williams and Wilkins Co. (1971).
14. EPSTEIN, R.M., DEUTSCH, S., COOPERMAN, L.H., CLEMENT, A.J., & PRICE, H.L. Studies of the splanchnic circulation during halothane anesthesia in man. *Anesthesiology* 26: 246 (1965).
15. BROWN, B.R. The diphasic action of halothane on the exidative metabolism of drugs by the liver: an *in vitro* study in the rat. *Anesthesiology* 35: 241 (1971).
16. LO, J.N. & CUMMING, J.F. Interaction between sedative premedicants and ketamine in man and in isolate perfused rat livers. *Anesthesiology* 43: 307 (1975).