LABORATORY AND CLINICAL EXPERIENCE WITH PHENAZOCINE DURING ANAESTHESIA*

C. R. STEPHEN, M.D., AND ROBERT W. MACMILLAN, M.D.

THE IDEAL ANALGESIC DRUG would be one which produced relief of pain consistently without such deleterious side-effects as respiratory depression, cardiovascular depression, addiction liability, and nausea and vomiting. In spite of the fact that meperidine is capable of exerting these several side-effects, it has, since the Second World War, become firmly established as a synthetic narcotic useful for pre-anaesthetic medication, to reinforce analgesia during anaesthesia,^{1,2,3} and in providing pain relief postoperatively. None of the numerous synthetic narcotic drugs introduced during the interim has proved more advantageous than meperidine. Phenazocine (Prinadol®), a benzomorphan derivative recently made available, has been recommended as a postoperative analgesic^{4,5} because it provides consistent relief of pain without a high incidence of side-effects. There is some doubt regarding the dosage of phenazocine which is equianalgesic with morphine 10 mg., but it is believed that a dosage of 1.5 to 3.0 mg. is approximately equivalent.

These studies are concerned with the effects of different dosages of phenazocine on the cardiovascular and respiratory systems compared with meperidine, and with the effects of ultra-short-acting barbiturates and phenazocine as they might be employed together in clinical anaesthesia.

LABORATORY STUDIES

Method

Mongrel dogs weighing from 6.0 to 13.0 kg. were prepared for continuous recording of the electroencephalogram, electrocardiogram, respiration, and arterial blood pressure on a modified Grass electroencephalograph. To record the electroencephalogram, frontoparietal electrodes were embedded directly into the bones of the skull. The electrocardiogram, usually Lead II, was recorded by limb needle electrodes. Respiratory activity was recorded by means of a pneumotachygraph included in the inhalation circuit. Arterial blood pressure was measured from a polyethylene catheter in the femoral artery, utilizing a Statham transducer. Drugs were administered through a polyethylene catheter, which was threaded into the inferior vena cava through the femoral vein. Tidal volumes were measured with a Monaghan ventilation meter. Arterial blood pH estimations were made with a Beckman pH meter and arterial oxygen saturations were made with a Cuvette oximeter. During the experiments 100 per cent oxygen was administered to the animals through a cuffed endotracheal tube utilizing a non-rebreathing system: respirations were assisted or controlled only when adequate oxygenation of the arterial blood was believed to be in jeopardy. When apnoea

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occurred, inflation of the lungs was performed only at 30-second intervals to avoid the decreased respiratory centre response associated with hyperventilation.

In the first group of four dogs, the acute reactions to the intravenous administration of meperidine and phenazocine were observed. An experiment with one of the drugs was followed several days later by a similar experiment with the other drug. The ultra-short-acting barbiturate, thiamylal sodium 20 to 30 mg./kg. intravenously, provided anaesthesia for preparation of the animals. The test drugs were administered at 10 to 15 minute intervals, but injections were not begun until the animals showed by reflex indication that they were in a light plane of anaesthesia (bucking on endotracheal tube, responding to painful stimulation). Each dose of meperidine was 5.0 mg./kg., and the dosages of phenazocine ranged between 0.1 and 1.0 mg./kg.

In a second group of five dogs, one experiment consisted of the intravenous injection of phenazocine 0.25 mg./kg. at 10 to 15 minute intervals: anaesthesia for preparation consisted of nitrous oxide-oxygen in a 75:25 ratio and succinylcholine 0.5 mg./kg. intravenously. In the same animals on another occasion phenazocine 0.25 mg./kg. intravenously was alternated with thiamylal sodium

FIGURE 1. Repeated injections of meperidine 5.0 mg. per kg. intravenously to a dog. Note marked reductions in blood pressure with simultaneous depression of electroencephalogram.

DOG 8

PHENOZACINE
(THIAMYLAL INDUCTION)

120 K G

FIGURE 2. Repeated injections of phenazocine 0.1 mg. per kg. intravenously to same dog as in Figure 1. The cardiovascular dynamics remain relatively stable.

1.0 mg./kg. intravenously at the same time intervals: in these experiments preliminary anaesthesia was with thiamylal sodium as noted above. The test drugs were not administered until the animals were breathing adequately and showed evidence of being in light planes of anaesthesia.

Results

In the first group of experiments, the changes in respiratory dynamics were similar for meperidine and phenazocine. Figure 1 shows excerpts from recordings of an animal which received repeated injections of meperidine 5 mg./kg. The rate of respiration slowed markedly, but no significant change occurred in tidal volume. A similar reduction in the respiratory rate without significant change in tidal volume occurred when phenazocine was administered in what are considered to be equianalgesic doses to the same animal (Fig. 2). Tables I and II show the mean reductions in respiratory rate which occurred following several injections of the drugs. Higher dosages of phenazocine produced significant periods of apnoea. Higher doses of meperidine were not utilized because of the marked change in cardiovascular dynamics. The reduction in the minute volume of respiration following the narcotic administrations, due to reductions in

TABLE I
MEAN CHANGES IN VITAL SIGNS BEFORE AND AFTER REPEATED ADMINISTRATION
OF MEPERIDINE AT 10 TO 15 MINUTES INTERVALS

	Respiration rate and tidal volume		Pulse rate		Blood pressure	
	Before	After	Before	After	Before	After
Dog A (5 mg./kg.)	12(100)	12(100)	168	175	210/150	75/50
Dog B (5 mg./kg.)	57(125)	23(175)	168	188	190/125	80/50
Dog C (5 mg./kg.)	54(125)	12(130)	234	164	250/150	125/80
Dog D (5 mg./kg.)	18(75)	Apnoea to 25(60)	156	152	175/130	45/30

TABLE II
MEAN CHANGES IN VITAL SIGNS BEFORE AND AFTER ADMINISTRATION OF PHENAZOCINE

	Respiration rate and tidal volume		Pulse rate		Blood pressure	
	Before	After	Before	After	Before	After
Dog A (1.0 mg./kg.)	12(60)	Apnoea 41 min. to 15(125)	168	60	180/120	145/55
Dog B (0.1 mg./kg.)	27(150)	12(140)	216	135	250/120	170/85
Dog C (1.0 mg./kg.)	30	Apnoea 59 min.	210	55	225/150	170/70
Dog D (0.5 mg./kg.)	24	Apnoea 34 min	204	56	225/150	165/90

respiratory rate, resulted in an arterial blood pH of between 6.90 and 7.25. However, ventilation with 100 per cent oxygen prevented the arterial oxygen saturation falling below normal.

The significant findings in this group of experiments related to the changes in cardiovascular dynamics. When the dogs were given meperidine, the pulse rate altered little, whereas after phenazocine a significant bradycardia occurred. Meperidine injections also produced a marked reduction in blood pressure, sufficient to produce obvious depression of the electroencephalographic activity (Fig. 1), whereas injections of phenazocine, even in relatively higher dosages, resulted in only moderate reductions in blood pressure.

In the second group of experiments, when phenazocine alone was administered in doses of 0.25 mg./kg., the following changes occurred:

1. Phenazocine quietened the animals and appeared to provide a fair degree of sedation. There were no spontaneous movements, respirations were regular, and the endotracheal tube could be moved within the trachea without the production of bucking or breath-holding. Some high-voltage waves appeared in

FIGURE 3. Repeated injections of phenazocine 0.25 mg. per kg. intravenously to a dog. Note reactions to painful stimuli, stability of blood pressure, and reversal of bradycardia by atropine 0.09 mg. per kg.

the electroencephalogram (Fig. 3). However, painful stimulation (at 3.37 and 4.09, Fig. 3), initiated by squeezing the hind paws with a Halsted clamp, was associated with the disappearance of the high-voltage waves and a marked temporary stimulation of respiration and an increase in pulse rate. At this dosage in the dog, phenazocine produced sedation, but not marked analgesia.

2. After the first doses of phenazocine, a reduction in pulse rate of more than 50 per cent occurred. This bradycardia persisted, but could be reversed by intravenous administration of atropine (Fig. 3).

3. Repeated injections of phenazocine did not produce apnoea, but the rate of respiration was slowed significantly. Respirations were regular except when painful stimulation was applied.

4. During these experiments the blood pressure did not change significantly.

In the same animals, when thiamylal sodium was administered in association with phenazocine, the cardiovascular dynamics showed little change from the previous experiments, but in other respects differences were observed:

1. The animals were more sedated. There were no responses to painful stimulation at different time intervals throughout the experiments (Fig. 4)

FIGURE 4. Repeated injections of phenazocine 0.25 mg. per kg. and thiamylal sodium 1.0 mg. per kg. intravenously to same dog as in Figure 3. Note periods of apnoea following administration of both drugs, stability of blood pressure, and reversal of bradycardia by atropine 0.09 mg. per kg.

2. Each injection of phenazocine 0.25 mg./kg. produced periods of apnoea which varied from 30 seconds to 11 minutes. In addition, the alternating injections of thiamylal sodium 1.0 mg./kg. resulted in periods of respiratory arrest varying from 30 seconds to 6 minutes. The duration of the apnoeic periods was not more prolonged with repeated doses, thus indicating the absence of a cumulative effect. It was interesting to note that, when artificial respiration was being administered during apnoea, slight manual pressure on the reservoir bag often initiated a single spontaneous respiration. When spontaneous respiration was present, the rate was consistently slower than the control.

CLINICAL OBSERVATIONS

A total of 125 patients received phenazocine intravenously in the operating room. The drug was administered prior to induction of anaesthesia, to reinforce sedation and analgesia during regional and spinal analgesia, as an adjunct during

the course of general anaesthesia, and in two patients as the sole agent to reinforce the action of nitrous oxide. For the most part, it was injected intermittently in doses varying between 0.25 and 1.0 mg., but in 20 patients it was administered as a continuous drip in a concentration of 1.0 mg./100 ml. of 5.0 per cent dextrose in water. Existing data indicated that this dilution was comparable to a dilution of 50 mg. of meperidine in 100 ml. of solution, a mixture we have used for several years.

In the majority of patients, phenazocine was used as an adjunct to general anaesthesia. In none was there any alteration in cardiovascular dynamics which could be attributed to the narcotic. The pulse rates remained stable and within normal limits, and bradycardia was rarely below 60 per minute; however, all patients received an anticholinergic drug preoperatively. The analgesia conferred by phenazocine appeared to be significant and clinically satisfactory.

In a number of patients manual control of the respiration was instituted shortly after induction of anaesthesia: the prior administration of phenazocine appeared to facilitate this manoeuvre.

In 33 patients under general anaesthesia with thiamylal sodium and nitrous oxide with oxygen, the spontaneous respiratory changes associated with phena-

FIGURE 5. Effect of phenazocine, 1 mg. given three times, on vital functions in 26-year-old patient anaesthetized with thiamylal sodium and nitrous oxide-oxygen. Note reduction in rate of respiration and stability of cardiovascular system.

zocine administration were followed. The rate of respiration invariably slowed with intravenous phenazocine, although the measured tidal volume did not change significantly. Anaesthesia time varied between 45 minutes and three and three-quarters hours, with the average period of narcosis being two hours. The amount of thiamylal sodium administered ranged between 100 mg. and 1700 mg., with the average dose being 617 mg. The total amount of phenazocine injected varied between 0.5 and 6.5 mg., with an average of 1.8 mg. The maximum reduction in rate of respiration from the pre-anaesthetic control varied from 11 per cent to 100 per cent (in one patient), and averaged 52 per cent.

Figure 5 is the anaesthetic record of a 26-year-old patient who received phenazocine 3.0 mg. over a period of 15 minutes at the beginning of an anaesthetic in which thiamylal sodium 360 mg. and nitrous oxide-oxygen were also administered. Following the third dose of phenazocine, the respiratory rate fell to three per minute and did not increase beyond six per minute for almost two hours. Blood pressure and pulse rate remained stable during this period.

Figure 6 is the anaesthetic record of a 27-year-old patient in whom the rate of

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FIGURE 6. Anaesthetic record of 27-year-old patient who received phenazocine 1 mg. intravenously on two occasions while anaesthetized with thiamylal sodium and nitrous oxide-oxygen. Note stability of cardiovascular signs, and reduction of respiratory rate to 8 per minute following second injection.

respiration fell from 20 to 16 per minute following phenazocine 1.0 mg. intravenously prior to induction of anaesthesia. After anaesthesia was established with thiamylal sodium and nitrous oxide, a second injection of phenazocine 1 mg. intravenously was followed by a slowing of the respiratory rate from 16 to 8 per minute.

DISCUSSION

In the experiments with dogs, the respiratory depression produced by phenazocine was qualitatively similar to that seen with meperidine, and the slowing of the rate without marked alteration in tidal volume was that to be expected of a narcotic compound. There seems little doubt that phenazocine is capable of producing marked respiratory depression, although the ratio of analgesic action to respiratory depression remains undecided.⁶

The marked difference in cardiovascular dynamics between dogs receiving phenazocine and those receiving meperidine was of interest. It seems probable that the profound reduction in blood pressure following intravenous meperidine was due to a histamine release phenomenon. Similar reductions in blood pressure were noted in dogs by Zeppa *et al.*⁷ when either meperidine 5 mg. per kg. or histamine 0.03 mg./kg. was given intravenously. Moreover, significant increases in histamine were found in the blood after administration of meperidine. Although histamine release is more likely to occur in the dog than in man, red-streaking along the vein used for injection is seen in about three per cent of human subjects receiving meperidine,² and occasionally cardiovascular collapse follows the injection of meperidine. In the numerous dogs to which phenazocine was administered, no evidence of this histamine release phenomenon was noted, nor was any evidence of histamine release seen in the human patients to whom phenazocine was administered. Following premedication with meperidine 50 mg., secobarbital 50 mg., and atropine 0.6 mg., intramuscularly, an 18-year-old male arrived in the operating room in the clinical syndrome of shock. He was restless, nauseated, with cold clammy extremities and an arterial blood pressure of 80/60. The respiratory rate was 10 per minute. After 60 minutes, when his clinical condition had improved, he was anaesthetized with thiamylal sodium and nitrous oxide-oxygen, and phenazocine 0.5 mg. was administered intravenously. Although the respiratory rate fell from 18 to 10 per minute, the cardiovascular system remained normal.

The reason for the bradycardia following phenazocine administration is unknown. The fact that it was reversed with atropine, and occurred only rarely in human patients who had received anticholinergic drugs preoperatively, would be presumptive evidence that the drug produces an increase in vagal tone.

The apparent greater depression which phenazocine produced on the respiratory rate when it was combined with thiamylal sodium in dogs is of importance. The combination of the ultra-short-acting barbiturate and phenazocine also produced significant reductions in respiratory rate in man. Similar marked depression of the respiratory rate has been noted by other observers in anaesthetized patients.^{8,9} The explanation of this finding is obscure. It may be that the patient, when awake, is able to initiate reflex compensation for the depressant

effects of phenazocine more readily than when anaesthetized, so that the depressing effects of the drug are not evident by clinical observation. The carefully controlled studies of Berkowitz and his co-workers¹⁰ tend to substantiate this possibility. On the other hand, it is conceivable that certain anaesthetic drugs, such as thiamylal sodium, react in a synergistic manner with phenazocine to produce significant respiratory depression.

SUMMARY

Similar to other narcotic compounds, phenazocine is capable of inducing a reduction of the respiratory rate in animals and in man. This depression of respiration becomes more marked during a state of anaesthesia induced with thiamylal sodium.

The cardiovascular dynamics remain stable during phenazocine administration, although bradycardia develops, which is reversible by anticholinergic drugs. Phenazocine does not possess the histamine-releasing properties associated with meperidine.

RÉSUMÉ

Les auteurs ont étudié les effets de la phénazocine et de la mépéridine sur les systèmes respiratoire et cardiovasculaire de chiens dans le laboratoire et sur une série de malades. Ils ont également étudié les effets d'un mélange d'un barbiturique à action très courte et de phénazocine, car ces deux médicaments peuvent être employés ensemble en anesthésie clinique.

Chez les chiens, la dépression respiratoire produite par la phénazocine était qualitativement semblable à celle produite par la mépéridine. Comme on pouvait s'attendre de ce narcotique, il a produit un ralentissement du rythme respiratoire sans modifications importantes de l'air courant. Il semble douteux que la phénazocine soit capable de produire une dépression respiratoire, bien que le rapport de l'action analgésique sur la dépression respiratoire demeure indéterminé.

Les auteurs ont observé une grande différence dans la dynamique cardiovasculaire entre les chiens qui avaient reçu de la phénazocine et ceux qui avaient reçu de la mépéridine. La chute marquée de la pression artérielle qui s'observait à la suite de l'administration endoveineuse de mépéridine était attribuable, selon toute probabilité, à la libération d'histamine. Des chutes semblables de la pression artérielle ont été observées chez des chiens par Zeppa et ses associés⁷ après injection endoveineuse soit de mépéridine à 5 mg. par kilo, soit d'histamine à 0.03 mg. Bien plus, on a même trouvé des augmentations importantes d'histamine dans le sang à la suite de l'administration de mépéridine. Bien que la libération d'histamine soit susceptible de survenir plus souvent chez le chien que chez l'homme, on peut observer à l'occasion un collapse cardiovasculaire à la suite de l'injection de mépéridine. Chez les nombreux chiens à qui nous avons injecté de la phénazocine, nous n'avons observé aucun signe de ce phénomène de libération d'histamine pas plus que chez les malades à qui nous l'avons injectée.

À la suite de l'administration de la phénazocine, il est apparu de la bradycardie. On n'a pas pu expliquer ce fait. On a corrigé cette bradycardie par de

l'atropine; chez l'humain prémédiqué avec des médicaments anticholinergiques, il est rare que cette bradycardie soit apparue. On peut présumer que ce médicament produit une prédominance vagale.

Il est important de signaler que, associée au thiamylal sodium, la phénazocine produit, selon toute apparence, une dépression plus marquée du système respiratoire. Le mélange d'un barbiturique à action très courte et de phénazocine produit également chez l'homme une diminution importante du rythme respiratoire. D'autres chercheurs^{8, 9} ont également observé cette dépression marquée du rythme respiratoire chez le malade anesthésié. On s'explique mal ce phénomène. Il se peut que le malade éveillé soit capable de déclencher un réflexe de compensation aux effets dépresseurs de la phénazocine plus facilement que s'il est anesthésié, de sorte que les effets dépresseurs du médicament échappent à l'observation clinique. D'autre part, il est possible que certains agents anesthésiques produisent un effet synergique à la phénazocine et entraînent une dépression respiratoire marquée.

REFERENCES

1. RANDALL, H. S.; BELTON, M. K.; & LEIGH, M. D. Continuous Infusion of Demerol during Anesthesia. *Canad. M.A.J.* 67: 311 (1952).
2. AUSERMAN, H. A.; NOWILL, W. K.; & STEPHEN, C. R. Controlled Analgesia with Continuous Drip Meperidine. *J.A.M.A.* 160: 175 (1956).
3. RATELLE, A. E. & KIM, M. K. Demerol as an Anesthetic Agent Used in 9,000 Surgical Cases. *Minnesota Med.* 43: 22 (1960).
4. ECKENHOFF, J. E. Phenazocine, A New Benzomorphan Narcotic Analgesic. *Anesthesiology* 20: 355 (1959).
5. DE KOMFELD, T. J. & LASAGNA, L. A Controlled Clinical Evaluation of Two New Analgesics, Phenazocine and Phenampromid. *Anesthesiology* 21: 159 (1960).
6. SHEMANO, I.; WENDEL, H.; & ROSS, S. D. A Pharmacological Comparison of Phenazocine Hydrobromide and Morphine Sulfate as Narcotic Analgesics. *J. Pharmacol. & Exper. Therap.* 132: 258 (1961).
7. ZEPPA, R.; GROSSKREUTZ, D. C.; & SUGIOKA, K. Histamine Release into the Circulation by Meperidine (Demerol). *Proc. Soc. Exptl. Biol. & Med.* 106: 794 (1961).
8. SHAW, R. Correspondence. *Brit. Med. J.* 1: 825 (1961).
9. McEWAN, I. P. Correspondence. *Brit. Med. J.* 1: 1763 (1961).
10. BERKOWITZ, R.; RODMAN, T.; & CLOSE, H. P. Effect of Phenazocine on Respiration. *J.A.M.A.* 176: 1092 (1961).