THE USE OF PHENAZOCINE (PRINADOL®) AS AN ADJUNCT IN PAEDIATRIC ANAESTHESIA*

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IN THE SEARCH for a potent, non-addicting analgesic, phenazocine (Prinadol®) was synthesized by Eddy, Murphy and May in 1957.¹ This drug is a benzomorphan compound, somewhat similar in structure and general characteristics to morphine.

Clinical trials with phenazocine were undertaken in adults by Eckenhoff,² Krumpferman,³ and others whose findings were sufficiently favourable to suggest the use of the agent in children. Consequently, we have made a study to evaluate the effectiveness of phenazocine when used in children, (1) for preoperative sedation, (2) as a supplement to nitrous oxide-oxygen anaesthesia, and (3) for relief of restlessness and pain following operation.

Before comparing phenazocine to other sedative or analgesic agents, an attempt was made to find the most effective dose of phenazocine on a body-weight basis. Twenty children between the ages of 3 and 12 years were chosen, and using only atropine as a supplement, phenazocine was administered in doses varying from 0.005 to 0.02 mg. per kg. On the bases of finding maximum sedation without cardiorespiratory depression,⁴ it was decided that a dosage of 0.02 mg. per kg. in children of 25 kg. or less, and that of 0.015 mg. per kg. in children of more than 25 kg. body weight was most effective. Small children, as noted by Walton,⁵ require relatively greater amounts of narcotic agents than older children and adults.

1. *Use in Preoperative Sedation*

In order to evaluate the effectiveness of phenazocine for preoperative sedation, a group of 224 children was studied. Five subgroups were used employing atropine alone as a control in the first, and atropine plus phenazocine, morphine, meperidine, or pentobarbital in the remaining subgroups. One of the major difficulties in such a study is to choose comparable doses of the different drugs employed. This report is open to criticism on this account, since definitive dosage-response curves were not calculated on all drugs used. Table I shows that phenazocine was used in dosage of 0.02 mg./kg. in children of 25 kg. or less and 0.015 mg./kg. in larger children.

Medications were administered by double-blind technique, neither the observer nor the patient being aware of the agents used. All children received the medication by intramuscular injection one hour prior to induction of anaesthesia.

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TABLE I
DOSAGES OF DRUGS USED FOR PREOPERATIVE SEDATION

Kg body weight	Atropine	Phenazocine	Morphine	Meperidine	Pentobarbital
10	0.2	0.2	2.0	20	40
15	0.3	0.3	3.0	30	60
20	0.4	0.4	4.0	40	80
25	0.5	0.5	5.0	50	100
30	0.5	0.5	5.0	50	100
40	0.6	0.6	6.0	60	120
60	0.6	0.8	8.0	80	150

All were normal children, most of them being prepared for tonsillectomy. Induction of anaesthesia was accomplished by blowing nitrous oxide and oxygen over the child's face, and subsequently adding di-vinyl and di-ethyl ether by open drop technique. The effect of the sedative agents was evaluated by observing the child's attitude prior to administration of the drug for control, then one hour after medication, as well as his reaction during induction, maintenance, and recovery from anaesthesia.

Results showed the sedative effect of phenazocine to be comparable to that of meperidine. (Tables II-IV.) All three narcotics tested showed a tendency to increase calmness, but did not make the children sleepy before operation. Pentobarbital, however, did induce drowsiness in 55 per cent of that group.

None of the children showed respiratory or cardiovascular depression prior

TABLE II
CONDITION PRIOR TO MEDICATION

Subgroup Number of cases	Control 35	Phenazocine 57	Morphine 40	Meperidine 46	Pentobarbital 46
Percentage excited or crying	6	5	2	6	4
Percentage apprehensive	30	42	21	25	46
Percentage calm	64	53	75	69	50
Percentage drowsy or asleep	0	0	2	0	0

TABLE III
CONDITION ONE HOUR AFTER MEDICATION

Subgroup	Control	Phenazocine	Morphine	Meperidine	Pentobarbital
Percentage excited or crying	6	11	2	17	0
Percentage apprehensive	28	15	18	17	13
Percentage calm	63	65	78	66	33
Percentage drowsy or asleep	3	9	2	0	55

TABLE IV
REACTION TO INDUCTION OF ANAESTHESIA

Subgroup	Control	Phenazocine	Morphine	Meperidine	Pentobarbital†
Percentage who struggled or cried	14	18	8	11	17
Percentage giving verbal complaint	14	0	6	6	4
Percentage awake, calm	70	74	72	67	50
Percentage drowsy, giving wordless resistance	0	8	7	6	3
Percentage who slept through induction	0	0	0	0	26

to induction, nor were there any other distressing side effects. During ether anaesthesia for tonsillectomy, several children showed definite respiratory depression.

In the children's reaction to induction, those who had received one of the three narcotics behaved much like one another. In each group, approximately 70 per cent remained calm. Although children who had received pentobarbital showed greater tendency to become sleepy, this group included more excited and resistant children than the groups that received narcotics. In brief, our figures demonstrated effectiveness of all four agents, but failed to show evidence of superiority of any single sedative or narcotic.

2. *Phenazocine as Supplement to General Anaesthesia*

Since morphine and meperidine have been widely used to supplement nitrous oxide anaesthesia, an attempt was made to employ phenazocine in a similar manner in children. A series of 50 normal children of 5 or 6 years or more was undertaken, these being patients about to have operations that would allow them to be supine, and would not require relaxation. In these children anaesthesia was induced with nitrous oxide and oxygen, an intravenous infusion was started, and phenazocine was administered, the initial doses approximating those shown in Table I, and subsequent doses being about half the initial amount. It was found that the patient's respiratory drive was markedly reduced almost immediately after administration of the initial dose of phenazocine. Upon gently assisting the patient's respiration by manual bag pressure, control of respiration could be taken over rapidly. During this period of respiratory depression, the patient could easily be induced to tolerate operation if he were given nitrous oxide in 66 to 75 per cent concentration.

As the effect of the narcotic decreased, the patients usually did not show reflex gagging or coughing, but would appear to wake up abruptly, turn their heads, and move their limbs as if annoyed at the nuisance. Addition of more phenazocine would be followed by rapid return of respiratory depression and the desired absence of movement.

No fall in blood pressure was associated with the use of phenazocine during anaesthesia. The intravenous administration of phenazocine was frequently followed, however, by a mild to moderate decrease in pulse rate. This was in distinct contrast to the intravenous administration of meperidine, which was often associated with a moderate tachycardia.

Owing to the evident respiratory depression noted when phenazocine was used with thiopental, it seems possible that there might be a synergistic action of these two agents.

During the use of any of the narcotics for general anaesthesia, there was a general tendency for patients not intubated to show moderate resistance to ventilation. On two occasions on which cyclopropane had been used as supplement to phenazocine for induction or for intubation, severe laryngeal constriction occurred. Since that time, cyclopropane has been avoided in conjunction with phenazocine.

Although the respiratory resistance just described could be overcome by endotracheal techniques, it has been observed that administration of relaxants is followed by complete correction of the airway obstruction. Ventilation then can be performed without intubation, and also without inflation of the stomach. This technique has proved very popular in patients who are supine, undergoing orthopaedic operations.

At the end of the operation, children usually resumed respiratory exchange and awakened on elimination of the nitrous oxide. In two cases in which there was persistence of respiratory depression patients also showed delay in awakening. The use of nalorphine (Nalline®) or levallorphan (Lorfan®) was followed by immediate and striking return of consciousness and respiratory drive. The post-operative course following phenazocine-nitrous oxide was remarkable in the early return of mental clarity and resumption of oral feeding and normal ward activities. This factor was the outstanding feature of the narcotic-nitrous oxide technique. It should be noted that there are a number of other advantages in this form of anaesthesia. These include complete elimination of explosive hazard, freedom from toxicity to liver and kidneys, and from depression of metabolic activity, and absence of myocardial irritability. Finally, it is a very inexpensive method.

3. Phenazocine for Relief of Postoperative Pain and Restlessness

One hundred children between the ages of 2 and 12 were treated for post-operative pain or restlessness with phenazocine, morphine or meperidine. After major operative procedures, children were taken to the recovery room. Those who showed marked restlessness or complained of pain were observed closely for ten minutes during which time efforts were made to reassure them, and rule out simulated pain or excitement that did not require medicinal therapy. If this proved unsuccessful, an analgesic agent was given, the type and amount of which was unknown to recipient and observer. Phenazocine was given in dosages of 0.01 mg. and 0.02 mg./kg., morphine in dosages of 0.1 and 0.2 mg./kg. and meperidine in dosages of 1.0 and 2.0 mg./kg. These narcotics were administered either by slow intravenous infusion (two-minute interval) or by intramuscular

injection. The results showed that the two methods had almost identical effects.

Record was made of the indication for the narcotic, the patient's pulse, blood pressure, respiratory rate, and the time and route of medication. Results were listed as partial or complete relief, and an attempt made to estimate duration of effect. Since the full effect of the narcotic came on rapidly, this was easier to evaluate than the duration. All three drugs tested proved effective. (See Table V.) In higher doses almost perfect results could be expected. Frequently, however, postoperative relief could be obtained using the reduced dosages shown. Consequently, it is felt that reduced dosage should be used whenever possible, and full dosage only when smaller amounts prove inadequate.

TABLE V
EFFECT OF NARCOTICS IN RELIEF OF POSTOPERATIVE PAIN AND
RESTLESSNESS IN CHILDREN

	Dose (mg./kg.)	Number of patients	Percentage with relief
Phenazocine	0.01	11	54
	0.02	16	91
Morphine	0.10	17	82
	0.20	14	92
Meperidine	1.0	15	75
	2.0	17	88

It was remarkable, in most cases, how quickly children who had been crying and uncontrollable would fall back into a quiet sleep. This usually occurred in 3 to 5 minutes after medication either by the intravenous or intramuscular route. Since preoperative use of narcotics was rarely, if ever, associated with drowsiness, it was surprising to see how commonly sleep occurred following postoperative medication.

Depression of respiration was noted in occasional cases and was manifested by reduction in rate rather than amplitude of respiration. Under the dosages used, this depression was related to all agents in approximately the same degree. No depression of blood pressure was observed, but mild bradycardia was noted following use of phenazocine. Generalized itching was seen in two children who had received phenazocine, but other side effects were not remarkable.

In the role of postoperative sedative and analgesic, phenazocine appeared to play its best part. It compared favourably with morphine and meperidine, and showed no serious side reactions. The dosage range of 0.01 to 0.02 mg. per kg. appeared to be effective and safe. As with other narcotics, over-dosage is evident primarily in respiratory depression, and suitable precautions should always be taken to recognize and treat this complication. Danger of respiratory depression due to narcotics probably is greater in children than in adults; consequently narcotic agents should rarely be employed with infants under one year of age.

SUMMARY

Phenazocine is an effective agent for use in children. The dosage range varies between 0.01 and 0.02 mg./kg. A reasonable dosage of phenazocine may be

calculated as being approximately 1/10 that of morphine and 1/100 that of meperidine. Phenazocine is an effective adjunct for use with nitrous oxide-oxygen anaesthesia, especially if the anaesthesiologist is skilled in assisted or controlled respiration techniques.

RÉSUMÉ

Nous avons entrepris cette étude dans le but de déterminer la valeur analgésique du benzomorphan phénazocine (Prinadol) songeant à l'employer chez les enfants, (1) soit comme sédation pré-opératoire, (2) soit au cours de l'anesthésie générale en complément du protoxide d'azote, (3) soit au cours des suites opératoires pour calmer l'agitation et la douleur.

(1) Après avoir déterminé au préalable la courbe dose-réponse de la phénazocine chez les enfants, nous avons cherché la valeur de cette substance comme sédatif préopératoire, en employant la technique du double inconnu avec le pentobarbital, la morphine et le mépéridine. 224 enfants, dont l'âge variait de 1 an à 12 ans, ont été observés et les résultats ont été compilés en comparant le degré de sédation et de dépression cardio-respiratoire et les autres effets secondaires.

(2) Chez 50 enfants qui devaient subir une opération majeure, nous avons employé la phénazocine comme complément de l'anesthésie générale au protoxide d'azote. Une fois l'induction au protoxide d'azote terminée, nous avons injecté la phénazocine par voie endoveineuse à des doses calculées à 0.02 mgm par kilo. Nous avons vérifié si l'analgésie était adéquate et nous avons tenu compte de la fréquence des spasmes des cordes vocales et des dépressions respiratoires et cardio-vasculaires. Ce produit s'est avéré utile et efficace.

(3) Nous avons employé la phénazocine chez 100 enfants pour calmer l'agitation et la douleur post-opératoires. Toujours en utilisant la technique du double inconnu, nous avons fait une étude comparée en employant les doses suivantes: 0.02 mgm par kilo de phénazocine, 0.2 mgm par kilo de morphine et 2.0 mgm par kilo de mépéridine. Nous avons étudié l'intensité et la durée d'action et la fréquence d'effets secondaires. De façon générale, cet agent se compare favorablement aux autres narcotiques.

REFERENCES

1. EDDY, N. B., MURPHY, J. G., & MAY, E. L. Structures Related to Morphine, Extension of Grewe Morphenan Synthesis in Benzomorphan Series and Pharmacology of Some Benzomorphans. *J. Org. Chem.* 22: 1370 (1957).
2. ECKENHOFF, J. E. Phenazocine, a new Benzomorphan Narcotic Analgesic. *Anesthesiology* 20: 355 (1959).
3. KRUMPERMAN, L. W.; GREISHEIMER, E. M., RUSY, B. F., & ELLIS, D. W. Comparison of Effects of Phenazocine and Meperidine on Respiration. *Anesthesiology* 21: 370 (1960).
4. SMITH, R. M., & JEFFRIES, M. The Evaluation of Sedative Agents for Preoperative Use. in Children. *Anesth. & Analg.* 38: 166 (1959).