COMPARISON OF THE CALMING AND SEDATIVE EFFECTS OF NALBUPHINE AND PENTAZOCINE FOR PAEDIATRIC PREMEDICATION

LUCIDA RITA, FRANK SELENY AND MASHALLAH GOODARZI

ABSTRACT

Nalbuphine (EN2234A) is an agonist-antagonist analgesic. It is structurally related to the narcotic analgesic oxymorphone and to the narcotic antagonist naloxone. A double blind study was carried out in 400 children in ASA classification I, ranging from 10 months to 14 years of age, to compare nalbuphine, pentazocine and placebo for paediatric premedication. Our results showed that nalbuphine is comparable to pentazocine as a premedicating agent and superior to placebo, in the doses used, and that premedication is an important adjunct to anaesthesia in children. Following premedication with nalbuphine or pentazocine, there were fewer apprehensive children at the time of induction of anaesthesia and in the recovery room when compared to those receiving placebo injections.

NALBUPHINE (EN2234A), N-cyclobutyl-methyl-7,8-dihydro-14,hydroxynormorphine hydrochloride is an agonist-antagonist analgesic. Structurally, it is related to the narcotic analgesic oxymorphone and to the narcotic antagonist naloxone. In nalbuphine the methyl group on the nitrogen is replaced by a cyclobutyl methyl group and the carbonyl group in the six position is in the reduced hydroxyl form rather than in the keto form as in oxymorphone (Figure 1).[1,2]

The ratio of analgesic potency of morphine compared to pentazocine is 1:4, morphine 10 mg – pentazocine 40 mg.[3] The analgesic potency of morphine is equal to that of nalbuphine on a milligram basis.[4] Therefore, we used the 1:4 dose ratio of nalbuphine to pentazocine for premedication.

We evaluated nalbuphine as a premedicant in children and compared its effectiveness to pentazocine, which we have used in our practice of anaesthesia for many years,[5] to determine if nalbuphine might be better than pentazocine.

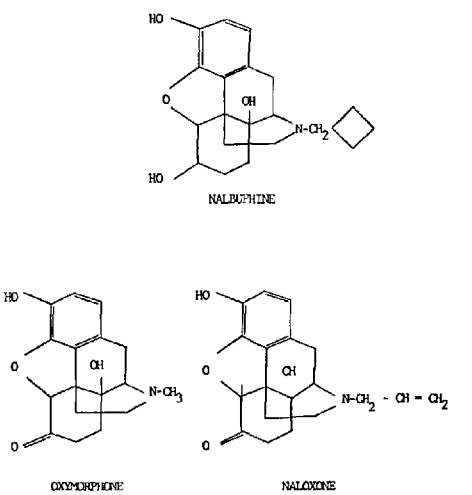

FIGURE 1 Chemical formulae of nalbuphine, oxymorphone and naloxone.

METHODS

The study was approvied by our Research Committee and the Human Ethics Committee and written parental consent was obtained before each administration of the drug.

Lucida Rita, M.D., Attending Anesthesiologist; Frank Seleny, M.D., F.R.C.P. (C), Head Department of Anesthesia; Mashallah Goodarzi, M.D., Attending Anesthesiologist, Children's Memorial Hospital, Northwestern University Medical School, Chicago, Illinois.

Request reprints to: Dr. Lucida Rita, Children's Memorial Hospital, Department of Anesthesia, 2300 Children's Plaza, Chicago, Illinois 60611.

Before undertaking the investigation, a preliminary study of 20 children of varying ages was conducted to determine the appropriate dose of nalbuphine. The nalbuphine was given intramuscularly and blood pressure and pulse and respiratory rates along with each patient's emotional state were recorded at five-minute intervals. The patients were also observed in the operating room during induction of anaesthesia and later in the recovery room during emergence. Having obtained better sedation with a dose of 0.2 $mg \cdot kg^{-1}$ of nalbuphine, we arranged to have coded ampules filled by the manufacturer with equipotent doses/ml of either nalbuphine or pentazocine or with a placebo. The placebo con-

sisted of the base used with nalbuphine hydrochloride (citric acid 12.62 mg, sodium citrate 9.41 mg, sodium metabisulfite 1.0 mg, sodium chloride 2.7 mg, methylparaben 1.8 mg, propylparaben 0.2 mg and water for injection to 1 ml).

The double blind study was carried out in 400 ASA classification I patients weighing 10 kg or more; 152 were in-patients and 248 were out-patients. The youngest child was ten months old, the oldest 14 years. Patients undergoing neurosurgical and cardiovascular surgery were excluded from the study. The children were assigned randomly to one of three treatment groups: nalbuphine, 0.2 $mg \cdot kg^{-1}$ and atropine 0.03 $mg \cdot kg^{-1}$, pentazocine 0.8 $mg \cdot kg^{-1}$ and atropine 0.03 $mg \cdot kg^{-1}$ or placebo and atropine 0.03 $mg \cdot kg^{-1}$.

Preoperative visits were made on all children by one of the anaesthetists participating in the study.

Preoperatively, in the holding area, the emotional state of each child was observed by the anaesthetist. The scoring classification for emotional state was *apprehensive* (crying, agitated or tense) or *calm* (quiet, sedated or sleepy). Premedication was then given intramuscularly.

The anaesthetist made similar observations in the operating room immediately before induction of anaesthesia. In no case was induction less than 25 minutes or more than 55 minutes after premedication. All patients had a mask induction with halothane and nitrous oxide in oxygen. Induction of anaesthesia was considered smooth when the child accepted the mask and went to sleep quietly. Maintenance of anaesthesia was with halothane and 50:50 nitrous oxide and oxygen in all patients.

In the recovery room the child was again evaluated by one of the investigators, making the same observations as before.

The code was broken at the end of the study.

Data were analyzed using chi-square analysis. $P < 0.05$ was considered significant.*

Results

The number of patients of the different age groups for each type of premedication are given in Table I. The mean time interval (±SE) between the premedication and the induction of anaesthesia in the different age groups for each type of premedication is given in Table II.

*Analysis using 2 × 2 contingency tables was considered to be more relevant to the clinican than 2 × 3 analysis.

TABLE I

DISTRIBUTION OF PATIENTS BY AGE AND TYPE OF PREMEDICATION

	Nalbuphine	Pentazocine	Placebo
Total no. patients	125	133	132
Age:			
10 mos.–4 yrs.	47	78	76
5–9 yrs.	57	44	46
10–14 yrs.	21	11	10

The effects of active drug or placebo treatment on the emotional state and smoothness of induction of anaesthesia in children of different age groups are given in Table III. There was no difference between nalbuphine and pentazocine in any age group with respect to emotional state before premedication, at the time of induction of anaesthesia or in the recovery room. Neither was there a difference in the smoothness of induction of anaesthesia (Table IV).

When compared to placebo in the different age groups, nalbuphine had a sedative effect in children ten months to nine years only in the recovery room. When patients of all ages were considered together, the sedative effect of nalbuphine was significant at induction and in the recovery room, as was its effect on the smoothness of induction.

Pentazocine, compared to placebo, was more effective in sedating patients ten months to nine years at the induction of anaesthesia and in the recovery room and in smoothing the induction of children ten months to four years. Considering patients of all ages together, pentazocine provided significantly more sedation at induction and in the recovery room and a smoother induction.

Older children (5 to 14 years) were significantly calmer before premedication with active drug or placebo than were younger children (ten months to four years) (Table V). The older children were also more calm in the recovery room and had smoother induction of anaesthesia. There was no difference in calmness between the two age groups before induction of anaesthesia.

Discussion

Emotional trauma often accompanies anaesthesia and surgery in children, especially in the younger age groups. They do not comprehend the events that are occurring – the physical separation from parents, strange environment, and unfamiliar faces. A preanaesthetic visit by an anaesthetist helps by establishing rapport with the child, but does not allay all of his fears. We

TABLE II

MEAN TIME IN MINUTES (± SE) BETWEEN PREMEDICATION AND INDUCTION OF ANAESTHESIA* IN DIFFERENT AGE GROUPS AND TYPE OF PREMEDICATION

Age	Nalbuphine	Pentazocine	Placebo
10 mos.–4 yrs.	30.0 ± 1.61	30.8 ± 1.63	30.1 ± 1.90
5–9 yrs.	32.3 ± 2.63	31.2 ± 2.79	30.3 ± 2.33
10–14 yrs.	30.0 ± 2.44	32.3 ± 3.46	29.5 ± 2.83

*In no instance was anaesthesia induced less than 25 minutes or more than 55 minutes after premedication.

TABLE III

DISTRIBUTION OF PATIENTS IN DIFFERENT AGE GROUPS ACCORDING TO EMOTIONAL STATE BEFORE PREMEDICATION, AT TIME OF INDUCTION AND IN RECOVERY ROOM AND SMOOTHNESS OF INDUCTION

	Emotional state (% calm)			
	Before premedication	Induction	Recovery room	Smooth induction (%)
Nalbuphine				
10 mos.–4 yrs.	47.4	61.4	68.4	49.1
5–9 yrs.	40.4	71.9	86.0	73.7
10–14 yrs.	38.1	81.0	81.0	81.0
Pentazocine				
10 mos.–4 yrs.	47.5	74.5	66.7	50.0
5–9 yrs.	47.7	81.9	88.7	79.6
10–14 yrs.	36.4	81.9	90.9	72.8
Placebo				
10 mos.–4 yrs.	50.0	46.9	46.1	34.2
5–9 yrs.	43.5	56.6	65.2	60.9
10–14 yrs.	20.0	50.0	70.0	67.0

TABLE IV

P-VALUES* FROM CHI-SQUARE ANALYSIS COMPARING NALBUPHINE AND PENTAZOCINE, NALBUPHINE AND PLACEBO, AND PENTAZOCINE AND PLACEBO

	Emotional state			
	Before premedication	Induction	Recovery room	Smooth induction
Nalbuphine–pentazocine				
10 mos.–4 yrs.	NS†	NS	NS	NS
5–9 yrs.	NS	NS	NS	NS
10–14 yrs.	NS	NS	NS	NS
All ages	NS	NS	NS	NS
Nalbuphine–placebo				
10 mos.–4 yrs.	NS	NS	0.05	NS
5–9 yrs.	NS	NS	0.05	NS
10–14 yrs.	NS	NS	NS	NS
All ages	NS	0.01	0.001	0.01
Pentazocine–placebo				
10 mos.–4 yrs.	NS	0.01	0.05	0.05
5–9 yrs.	NS	0.05	0.05	NS
10–14 yrs.	NS	NS	NS	NS
All ages	NS	0.001	0.001	0.05

*P-Values less than 0.05 indicate that a greater proportion of patients experience effects from the first-named drug.

†NS = Not statistically significant at $p > 0.05$.

TABLE V

P-VALUES* FROM CHI-SQUARE ANALYSIS COMPARING YOUNGER TO OLDER CHILDREN WITH DIFFERENT TYPES OF PREMEDICATION ACCORDING TO EMOTIONAL STATE PRIOR TO PREMEDICATION, AT TIME OF INDUCTION, AND IN RECOVERY ROOM AND SMOOTHNESS OF INDUCTION

	Emotional state			
Age group comparison	Before premedication	Induction	Recovery room	Smooth induction
Nalbuphine Younger–Older†	0.01	NS‡	0.05	0.01
Pentazocine Younger–Older†	0.001	NS	0.01	0.01
Placebo Younger–Older†	0.01	NS	0.05	0.01

*P-values less than 0.05 indicate more calm patients, more smooth inductions in the older group as compared to the younger.

†Younger = 10 months to 4 years; older = 5 to 14 years.

‡Not statistically significant at $p > 0.05$.

believe that good pharmacological preparation is also necessary. Adequate doses of a narcotic or narcotic antagonist and an anticholinergic agent provide this preparation. Vagal reflexes are readily elicited in children, indicating a need for large doses of atropine (0.03 $mg \cdot kg^{-1}$ to a maximum dose of 0.6 mg).[6]

For this study, we chose nalbuphine 0.2 $mg \cdot kg^{-1}$ for premedication instead of the 0.1 $mg \cdot kg^{-1}$ recommended by others,[4-7] since we had found in a preliminary study that 0.1 $mg \cdot kg^{-1}$ provided inadequate sedation.

We believe that the greater incidence of smooth induction in most older children 5 to 14 years than those ten months to four years was because we could establish better rapport with them. They listened when we talked to them and followed instructions, which the younger age group did not do.

Nalbuphine and pentazocine were probably more effective than placebo in calming patients in the recovery room because of their analgesic effect.

Our impression was that, during induction, pentazocine had a greater calming effect than nalbuphine in patients aged ten months to nine years, although this was not supported by the statistical analysis as shown in Table IV. Our data support the conclusion that nalbuphine is an adequate substitute for pentazocine in premedication for children.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Harry Linde for his assistance in preparing this manuscript.

REFERENCES

1. ELLIOT, H.W., NAVARRO, G. & NOMOF, N. A double blind controlled study of the pharmacological effects of nalbuphine (EN2234). J. Med. *1*: 74 (1970).
2. BLUMBERG, H., DAYTON, H.B. & WOLF, P.S. Analgesic properties of the narcotic antagonist EN-2234-A. The Pharmacologist *10*: 198 (1968).
3. LASAGNA, L. Drug interaction in the field of analgesic drugs. Lancet *1*: 906 (1965).
4. FRAGEN, R.J. & CALDWELL, N. Acute intravenous premedication with nalbuphine. Anesth. Analg. *56*: 808 (1977).
5. RITA, L., SELENY, F.L. & LEVIN, R.M. A comparison of pentazocine and morphine for pediatric premedication. Anesth. Analg. *49*: 377 (1970).
6. LEVIN, R.M. Pediatric Anesthesia Handbook, 1st edition, Flushing, N.Y., Medical Examination Publishing Co. (1973).
7. BIKHAZI, G.B. Comparison of morphine and nalbuphine in postoperative pediatric patients. Anesthesiology Review *5*: 34 (1978).

RÉSUMÉ

La nalbuphine (EN2234A) est un analgésique du type agoniste-antagoniste. Sa structure s'apparente à celle du narcotique analgésique oxymorphone et à celle du narcotique antagoniste naloxone. Elle a été comparée à la pentazocine et à un placebo comme agent de prémédication dans le cadre d'une étude à double insu conduite chez 400 enfants en bon état général (classe I de l'ASA) et âgés de 10 mois à 14 ans. Nos résultats ont montré qu'elle est comparable à la pentazocine et supérieure au placebo comme agent de prémédication. Ils ont également fait ressortir l'importance de la prémédication en anesthésie pédiatrique, le nombre d'enfants anxieux au moment de l'induction de l'anesthésie et dans la salle de réveil, étant inférieur à celui trouvé chez ceux ayant reçu le placebo.