Elliot T. Hudes MD FRCPC,
Howard J. Marans MD MSc FRCSC,
Kevin Shine BSc MD FRCPC,
Andrew C. Scott MB FFARCS,
Gail M. Hirano MD FRCPC

A comparison of morphine-perphenazine and midazolam on preoperative sedation and arterial oxygen saturation

The effectiveness of midazolam and a mixture of morphine-perphenazine premedication to produce sedation and their effects on preoperative oxygen saturation (SaO_2) were examined. Eighty-five patients whose SaO_2 measured with a pulse oximeter was $>90\%$ and who were not receiving narcotic sedatives or oxygen were randomized to three groups. Each patient had his SaO_2 recorded before premedication with placebo (saline), midazolam $0.08 \text{ mg} \cdot \text{kg}^{-1}$ or morphine $0.15 \text{ mg} \cdot \text{kg}^{-1}$ with perphenazine $2.5\text{--}5.0 \text{ mg im}$. From 30–90 min later, prior to anaesthesia SaO_2 was repeated, and a sedation score was obtained by a blinded observer using a seven point scale. Median sedation scores were greater for midazolam (4) than for morphine-perphenazine (2) and placebo (1) ($P < 0.0001$). As well, there was a decrease in the SaO_2 in the morphine-perphenazine group ($1.7 \pm 2.7\%$, $P < 0.001$) but not in the midazolam and placebo groups ($0.1 \pm 2.3\%$, $-0.8 \pm 2.1\%$). In conclusion midazolam produced greater sedation than morphine-perphenazine and placebo without effect on SaO_2 whereas morphine-perphenazine showed a decrease in SaO_2 preoperatively.

Nous avons évalué l'efficacité du midazolam et d'un mélange de morphine et de perphénazine en tant que sédatifs pré-opératoires et avons mesuré leurs effets sur la saturation en oxygène (SaO_2). Nous avons randomisé en trois groupes 85 patients qui ne prenaient pas de narcotiques et dont la saturation artérielle à l'oxymètre digital était $>90\%$ à l'air ambiant. Par

voie intramusculaire, on leur injectait soit un placebo (NaCl 0,9%), soit $0,08 \text{ mg} \cdot \text{kg}^{-1}$ de midazolam, soit $0,15 \text{ mg} \cdot \text{kg}^{-1}$ de morphine et 2,5 à 5 mg de perphénazine. On observateur neutre mesurait la SaO_2 et le degré de sédation avant et 30 à 90 minutes après l'injection. La valeur médiane de ce dernier était plus grande avec le midazolam qu'avec les deux autres régimes ($P < 0,0001$) toutefois, la SaO_2 diminuait avec la morphine-perphénazine ($1,7 \pm 2,7\%$, $P < 0,0001$) mais non avec le midazolam ($0,1 \pm 2,3\%$) ni le placebo ($-0,8 \pm 2,1\%$). Donc, le midazolam produit plus de sédation qu'un mélange de morphine et perphénazine, sans les inconvénients de ce dernier sur la SaO_2 .

One purpose of premedication is to produce a calm patient before surgery. The ideal drug would have good anxiolytic and sedating qualities but few or no harmful side-effects. Many drugs given before operation reduce arterial oxygenation.^{1–5}

Morphine has been found by some, but not all, authors to decrease oxygen tension and saturation.^{1,5–7} As well, atropine has been found to reduce oxygen tension or to have no effect on oxygenation.^{3,8} Further studies have implicated other narcotics and vagolytics in reducing arterial oxygenation.^{2,4,5} This study was designed to determine whether midazolam and morphine-perphenazine mixture had an effect on arterial oxygenation and whether the level of sedation was correlated with the degree of arterial desaturation.

Methods

This study was approved by our institution's medical care evaluation and pharmacy and therapeutics committees. Informed consent was obtained. Eighty-five ASA physical status I–III inpatients booked for elective surgery were studied. Patients who were >70 or <15 yr, were morbidly obese ($>200\%$ of ideal body weight), or receiving sedative, anxiolytic, narcotic drugs, or oxygen

Key words

COMPLICATIONS: hypoxaemia;
MONITORING: oxygen;
PREMEDICATION: morphine, midazolam.

From the Department of Anaesthesia, Peel Memorial Hospital, 20 Lynch Street, Brampton Ont., L6W 2Z8.

Address correspondence to: Dr. E. Hudes.

Accepted for publication 6th November, 1990.

TABLE I Sedation Scale

1	Awake, nervous; patient relates no effect of premedication.
2	Awake, not obviously drowsy but the patient claims to feel calmer/drowsy.
3	Awake, obviously drowsy to observer, e.g., slurred speech, eyes closing.
4	Asleep; rouses to verbal stimuli.
5	Asleep; rouses to tactile stimuli and is articulate and coherent.
6	Asleep; rouses to tactile stimuli; not able to speak clearly.
7	Asleep; not rousing to tactile stimuli (gently shaking shoulder).

therapy or had allergic reactions to the drugs involved were excluded.

The patients were randomized into three groups and the study was double-blinded. Group one received midazolam $0.08 \text{ mg} \cdot \text{kg}^{-1}$ im for preoperative premedication. Group two received morphine $0.15 \text{ mg} \cdot \text{kg}^{-1}$ with perphenazine $0.05 \text{ mg} \cdot \text{kg}^{-1}$ im and group three received saline im as a placebo. To achieve these doses and to allow the anaesthetist to order the drugs on an $\text{ml} \cdot \text{kg}^{-1}$ basis but remain blinded to the drug administered they were mixed as follows. Morphine $15 \text{ mg} \cdot \text{ml}^{-1}$, 1 ml, plus perphenazine $5 \text{ mg} \cdot \text{ml}^{-1}$, 1 ml, and 1 ml saline were mixed for a final concentration of morphine $5 \text{ mg} \cdot \text{ml}^{-1}$ and perphenazine $1.67 \text{ mg} \cdot \text{ml}^{-1}$. Midazolam $5 \text{ mg} \cdot \text{ml}^{-1}$, 2 ml, plus saline 1 ml were mixed for a final concentration of $3.33 \text{ mg} \cdot \text{ml}^{-1}$. The premedication was then ordered as $0.03 \text{ ml} \cdot \text{kg}^{-1}$ to achieve the desired doses. The premedication was mixed in our pharmacy and the syringe assigned a code number. Only the pharmacist was aware of the contents of the syringe.

Prior to the administration of the premedication arterial oxygen saturation (SaO_2) was determined with patients breathing room air using a pulse oximeter (Physiocontrol Lifestat 1600 oximeter and finger probe).

The patients were evaluated by the anaesthetist in the preoperative holding room between 30 and 90 min after receiving their premedication. Four anaesthetists took part in the study. The patients were left undisturbed while they were evaluated using a sedation scale (Table I). Oxygen saturation was repeated using the same pulse oximeter while breathing room air. The code for the premedication was not broken until all data had been

collected. The results are expressed as mean values $\pm$ SD except where stated otherwise.

Statistical analysis was performed using the Student-Neuman-Keuls test, chi-square, and analysis of variance (ANOVA). The patient characteristics were evaluated with ANOVA (age, initial SaO_2) and contingency tables based on the chi-square statistic (sex, ASA status). The experimental data were evaluated using ANOVA (change in SaO_2), Kruskal-Wallis non-parametric ANOVA (sedation scale) (see Table I), Student's *t* test (correlation between changes in SaO_2 and sedation scale), and the Student-Neuman-Keuls test to analyze further any differences found. An overall alpha level <0.05 was chosen for the study.

Results

Eighty-five patients met the inclusion criteria. We were unable to evaluate six patients due to incorrect premedication administration ($n = 5$) and failure to record the initial SaO_2 ($n = 1$). For the remaining 79 patients, 36 were male, 43 were female, and the mean age was 41.8 ± 14.5 yr (range 15 to 68). Median ASA physical status was 1. No significant differences were found among premedication groups for these patient characteristics (Table II). There was no difference in the incidence of patients who smoked, had asthma, COPD or obesity among the premedication groups. While SaO_2 prior to premedication is not an epidemiological variable, we felt it was important to assess any differences in this measurement between groups as an added measure of group similarity. Again, no statistically significant difference was found (Table III).

The 79 patients studied were nearly equally distributed among the three groups. The 26 placebo patients had a mean increase in SaO_2 of $0.7 \pm 2.1\%$ and a median sedation score of 1. The 25 patients who received midazolam premedication had a mean decrease in SaO_2 of $0.1 \pm 2.3\%$ with a median sedation score of 4, and the 28 patients who received morphine-perphenazine had a mean decrease in SaO_2 of $1.7 \pm 2.7\%$ with a median sedation score of 2. Statistically significant differences ($P < 0.0001$) were found among all groups for sedation score. Midazolam produced the greatest degree of sedation followed by morphine-perphenazine compared with pla-

TABLE II Patient characteristics

Group	(n) patients	Age (yr $\pm$ SD)	Sex M:F	ASA Status median/range
Placebo	26	40.0 ± 14.4	11:15	1/1-3
Midazolam	25	43.1 ± 13.7	12:13	1/1-2
Morphine-perphenazine	28	42.3 ± 9.0	13:15	1/1-2
Total	79	41.8 ± 14.4	36:43	1/1-3

TABLE III Experimental Data

Group	Placebo	Midazolam	Morphine-perphenazine
Patients (n)	26	25	28
Initial SaO ₂ %	97.0 ± 1.9	96.4 ± 1.2	97 ± 1.3
Range	91–99	94–99	95–100
Post-sedation SaO ₂ %	97.7 ± 1.6	96.3 ± 2.1	95.3 ± 2.7
Range	95–100	92–99	88–100
SaO ₂ difference% (median)	-0.7 ± 2.1	0.1 ± 2.3	1.7 ± 2.7†
Sedation scale (median)	1*	4*	2*
Range	1–3	1–5	1–4

* $P < 0.0001$. This indicates significant differences in sedation scale scores between all three groups.

† $P < 0.001$. This indicates a significant decrease in SaO₂.

cebo. The significant decreases in SaO₂ were seen only ($P < 0.001$) for morphine-perphenazine (Table III). Placebo and midazolam groups exhibited no differences in their initial and post-premedication saturations. No statistical correlation was found between the degree of sedation and the change in SaO₂ using the Student's *t* test.

Discussion

In this study we wished to examine whether the level of sedation was a factor in any change in SaO₂ after premedication. Many scoring systems for sedation have been formulated, but no universal scale is accepted. Separating sedation from anxiolysis, using self-assessment versus observer impression and the use of physiological variables and hormonal measurement can affect the assessment made.⁹ We chose to modify a previously used scale which assessed sedation primarily by observer impression using objective end-points.¹⁰ This gave us an easily reportable and quick measure of the patient's level of sedation.

The Physiocontrol Lifestat 1600 pulse oximeter was an appropriate monitor to observe the small changes in saturation seen in the morphine-perphenazine group as it is accurate even at low oxygen saturation.¹¹

Midazolam did not affect the patient's SaO₂ regardless of the level of sedation produced. The level of sedation was greater than with morphine-perphenazine which did cause a mean decrease in SaO₂ of 1.7%. Whether deeper levels of sedation with morphine-perphenazine would be associated with larger levels of desaturation could not be assessed due to the small number of patients who were at these deeper levels of sedation. The patients who smoked, had COPD, asthma or were obese were too few to assess whether they would desaturate to a greater degree with the premedications used.

Other studies have found unacceptable levels of arterial desaturation after premedication. Kopman *et al.* found

that morphine with scopolamine caused five patients' PaO₂ to decrease.¹ Overall, PaO₂ decreased from 72 ± 8 mmHg to 60 ± 6 mmHg! Hensley *et al.* found that in 20 cardiac patients premedicated with morphine 0.1 mg · kg⁻¹ and scopolamine 0.4 mg im and given up to 5 mg diazepam and/or 100 µg fentanyl, 12 desaturated to SaO₂ <90% during the insertion of invasive monitors.¹² These patients represented a different patient population from our elective surgery patients, and also received multiple premedication drugs. No effort was made to assess the degree of the sedation other than stating that they could be roused. Also, the Trendelenberg position was used in almost half the patients which may have contributed to their findings.

Other authors have found that the decrease in SaO₂ or PaO₂ is modest after narcotic premedication. In one study im meperidine, promethazine and pentobarbital decreased PaO₂ from 83 to 67 mmHg.⁵ Intravenous sufentanil decreased SaO₂ to 92.6 ± 1%¹³ and morphine with scopolamine decreased PaO₂ by 6.6 ± 2.1 mmHg.¹⁴ In our study the average decrease with morphine was 1.7% with a range of 0–8% and only one patient had an SaO₂ <90%. Although statistically significant, this did not have clinical importance except for those patients whose initial SaO₂ borders on hypoxaemia or for patients with ischaemic heart disease.

Midazolam given iv for sedation during dental surgery and titrated to a specific level of sedation has not affected patients' SaO₂.¹⁵ Although SaO₂ decreased to <90% there were no differences from the control group. The desaturation occurred during surgery and often with breath holding.

The decreased saturation with morphine-perphenazine is mild and no more severe than in normal patients during natural night-time sleep.¹⁶

One cannot assume that the change in the arterial saturation was due to the opioid alone. Consideration of the phenothiazine as a contributing factor perhaps by adding to the hypoventilation caused by narcotics should be examined.

We conclude that midazolam in the dose employed, as premedication, produced the most effective sedation but with no effect on SaO₂ whereas morphine-perphenazine mixture did not produce as good sedation but caused mild decreases in SaO₂. This decrease may be of clinical importance in patients at risk for hypoxaemia.

References

- 1 Kopman EA, Ramirez-Inawat RC. Arterial hypoxaemia following premedication in patients with coronary artery disease. *Can Anaesth Soc J* 1980; 27: 132–4.
- 2 Pierce JA, Garofalo ML. Preoperative medication and its effect on blood gases. *JAMA* 1965; 194: 487–90.

- 3 Tomlin PJ, Conway CM, Payne JP. Hypoxaemia due to atropine. *Lancet* 1964; 1: 14-6.
- 4 Hetreed MA. Hypoxaemia after premedication in cardiac patients. Glycopyronium compared with hyoscine. *Anaesthesia* 1988; 43: 52-3.
- 5 Mostert JW, Evers JL, Hobika GL *et al.* Cardiorespiratory effects of anaesthesia with morphine or fentanyl in chronic renal failure and cerebral toxicity after morphine. *Br J Anaesth* 1971; 43: 1053-9.
- 6 Fletcher G, Barber JL. Lung mechanics and physiologic shunt during spontaneous breathing in normal subjects. *Anesthesiology* 1966; 27: 638-47.
- 7 Swenson EW, Stallberg-Stenhagen S, Beck M. Arterial oxygen, carbon dioxide and pH levels in patients undergoing pulmonary resection. *J Thorac Cardiovasc Surg* 1961; 42: 170-92.
- 8 Medrado V, Stephen CR. Effect of premedication with atropine sulphate on arterial blood gases and pH. *Lancet* 1966; 1: 734-5.
- 9 Madej TH, Paasuke RT. Review article: anaesthetic premedication: aims, assessment and methods. *Can J Anaesth* 1987; 34: 259-73.
- 10 Ramsay MAL, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974; 2: 656-9.
- 11 Severinghaus JW, Naifeh KH. Accuracy of response of six pulse oximeters to profound hypoxia. *Anesthesiology* 1987; 67: 551-8.
- 12 Hensley Jr FA, Dodson DL, Martin DE, Stauffer RA, Larach DR. Oxygen saturation during placement of invasive monitoring in the premedicated, unanesthetized cardiac patient. *Anesthesiology* 1986; 65: A22.
- 13 Helmers JHJH, Noordvin H, Van Peer A, Van Leeuwen L, Zuurmond WWA. Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth* 1989; 36: 494-7.
- 14 Nadeau SG, Roblee JA. The effect of premedication on arterial blood gases in cardiac surgical patients. *Anesth Analg* 1986; 65: S110.
- 15 Rodrigo MRC, Rosenquist JB. Effect of conscious sedation with midazolam on oxygen saturation. *J Oral Maxillofac Surg* 1988; 46: 746-50.
- 16 Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. *Thorax* 1982; 37: 840-4.