RESPIRATORY EFFECTS AND AMNESIA AFTER PREMEDICATION WITH MORPHINE OR LORAZEPAM

R. S. CORMACK, J. S. MILLEDGE AND C. D. HANNING

SUMMARY

Lorazepam, a new benzodiazepine, was compared with morphine for premedication. Ten patients received morphine 10 mg/70 kg i.m. and 10 received lorazepam 4 mg/70 kg i.m. Respiratory effects were assessed from the change in slope (S) and intercept (B) of the carbon dioxide response line, using a development of Read's rebreathing method. Morphine depressed S by 47% (P < 0.01), but after lorazepam S increased by 27% (P < 0.05), neither drug altering B significantly. In two volunteers lorazepam was assessed by both the rebreathing and the steady-state methods; after lorazepam S was smaller by the steady-state than by the rebreathing technique. The findings for lorazepam are consistent with the known effects of sleep on carbon dioxide sensitivity. Amnesia lasting 4-8 h occurred in all patients who received lorazepam so that pain and nausea during this period were not recalled, but no patient who received morphine experienced amnesia. We conclude that lorazepam merits further study, particularly where sedation without respiratory depression is needed, as in obstetrics, and where amnesia for uncomfortable procedures is required.

In the search for a sedative that does not depress respiration, lorazepam is promising because of its excellent therapeutic index. The LD_{50} in mice is 7000 times the ED_{50}, whereas for morphine the same study in the same species gave a ratio of only 40 (Alps, Harry and Southgate, 1973). Since morphine kills the animal by stopping breathing, we concluded that lorazepam cannot cause much respiratory depression in mice. Early reports in man suggested that lorazepam had no major respiratory effects (Elliott et al., 1971; Knapp and Fierro, 1974), therefore the main aim of this study was to evaluate lorazepam with the best technique currently available. The results were presented for discussion to the Anaesthetic Research Society (Cormack, Milledge and Hanning, 1976).

METHODS

Ventilatory response to carbon dioxide

Rebreathing method. In Read's (1967) method the subject rebreathes from a bag so that P_{CO_2} increases, causing ventilation to increase; plotting ventilation against P_{CO_2} produces a line with the same slope as the classical carbon dioxide response line. Our technique follows Read's in principle, but the procedure has been developed to trace out the carbon dioxide response line automatically. Electrical signals proportional to P_{CO_2} (X) and ventilation (Y) are fed into an X-Y recorder, which displays the response on-line (fig. 1.)

The apparatus was as described previously (Milledge, Minty and Duncalf, 1974), except that ventilation was measured with a Monaghan 403 electronic spirometer in place of the dry gas meter. The linearity of the flow signal was confirmed by calibration with a Harvard pump respirator at various tidal volumes and frequency, and the Harvard pump was checked against a Tissot spirometer. The linearity of the carbon dioxide analyser was checked using methods described previously (Cormack and Powell, 1972; Cormack and Heath, 1974) except that in this case the extra accuracy of a digital voltmeter was not needed. Both flow and carbon dioxide signals were calibrated before and after each pair of rebreathing tests, flow against one setting of the Harvard pump, and carbon dioxide against two mixtures from analysed cylinders.

The procedure described by Read (1967) was followed with the patient sitting up in his bed at an angle of 45°. The slope of the line was corrected for calibration drift, temperature change and the effect of oxygen change on carbon dioxide measurement (collision broadening), the calculation being facilitated by a short computer program.

Steady-state method. Two points on the carbon dioxide response line were obtained, the lower point while breathing 2 or 3% carbon dioxide, the upper point on 5 or 5.5% carbon dioxide, all mixtures containing 50% oxygen and the balance nitrogen. Seven minutes were allowed for equilibration after
which readings were taken over 3-min periods. Ventilation was measured with a dry gas meter (Parkinson–Cowan) modified to give an electrical output (Milledge, Minty and Duncalf, 1974). End-tidal carbon dioxide was obtained from the carbon dioxide analyser tracing while sampling continuously from between the ports of a Lloyd valve (Cunningham, Johnson and Lloyd, 1956).

Amnesia

Memory card. The patient was shown a card on which were six words (six farm animals) and was asked to read it aloud twice. Next day he was asked which of the words he could remember.

Pain and nausea. The incidence of postoperative pain, nausea and vomiting was noted by the nursing staff and the requirement for analgesics and antiemetics was recorded. The memory for this was assessed from a questionnaire the next day.

Design of patient study

Twenty fit adults undergoing routine surgery, having given their informed consent, were allocated randomly to two groups for premedication. One group received morphine sulphate 0.14 mg/kg i.m., the other received lorazepam 0.057 mg/kg i.m., both groups also having atropine 0.6 mg i.m. The procedure was double-blind. The nurses were taught to give the premedication by deep i.m. injection, not into fat because absorption of some benzodiazepines from fat is unreliable (Gamble, Dundee and Assaf, 1975).

About 2 h before operation control carbon dioxide response lines were obtained in duplicate (rebreathing method). Then the premedication was given and 90 min later the rebreathing measurements were repeated to give a pair of test lines. After this the patient was shown the “memory card”. The interval of 90 min was chosen because both drugs exert their maximum effect near this time; the concentration of morphine in blood peaks at about 1 h, lorazepam at 2 h. When the patient arrived in the anaesthetic room his level of sedation was assessed roughly by the anesthetist as “acceptable” or “unacceptable”. Next day a questionnaire relating to amnesia was completed.

The difference between the patients in the two groups was usually clear after the respiratory measurements; thus the questionnaire presented after operation was completed by someone who had not seen the rebreathing results.

Design of volunteer study

Measurements were made on two fit volunteers before and after lorazepam. The dose given and the timing of control and test periods were as in the study of patients. However, the procedure was not blind, the steady-state method was used, as was the rebreathing technique, and plasma bicarbonate was measured also.

RESULTS

Respiratory measurements

Study on patients. Figure 1 shows typical X–Y recordings after the two drugs and the data from all patients are summarized in tables I and II. Paired t tests were applied to the S values after logarithmic transformation, since this gives a slightly more discriminating index of significance when the change in the variable measured is proportional to its initial value (Snedecor and Cochrane, 1969a).

Figure 2 displays the main conclusions together with a visual presentation of the statistics. Bar lines commonly used to show standard errors are useful, but fail to show the point of main interest, namely how significant is the difference between control and test groups. To reveal this the 95% confidence limits of the difference in question were computed, using the logic of the t test (fig. 2).

The mean calibration drift in Pco2 and VE signals was 0.8% and 1.2% of the initial readings. The maximum variance of S that could have arisen from each of these two sources was computed and from this the combined SD of S attributable to electronic drift was found to be not more than 0.16 litre.min⁻¹. kPa⁻¹. The repeatability of S measurements in individual patients was estimated from the difference between duplicates. This gave the “within-patient”
Comparison of Morphine with Lorazepam

Table I. Effect of morphine on carbon dioxide sensitivity

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<th>Ht (cm)</th>
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<th>Test</th>
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Mean change = -47%  
*P* < 0.01

Table II. Effect of lorazepam on carbon dioxide sensitivity

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Mean change = +27%  
*P* < 0.01

Respiratory studies on 10 patients who received morphine (table I) and 10 who received lorazepam (table II) are summarized, together with details of sex, weight and height. The ventilatory response to carbon dioxide is described by the equation \( V = S(P_{CO_2} - B) \) and the values found for \( S \) (slope) and \( B \) (intercepts), before and after premedication are shown. \( B \) was not estimated in the first half of the trial.

The correlation between \( S \) and body weight (fig. 3) was analysed by the method of least squares:

\[
S \text{ against weight: } r = 0.73, P < 0.05 \quad \text{Females (9)} \\
S \text{ against weight: } r = 0.55, P = 0.08 \quad \text{Males (11)} \\
S \text{ against weight: } r = 0.61, P = 0.01 \quad \text{Both (20)}
\]

Volunteer study (table III). By the rebreathing method lorazepam caused a mean change in \( S \) in the two subjects of +10% and −10% respectively, which is less than the mean value for the patients, but not significantly so.
FIG. 2. The mean carbon dioxide response lines before and after premedication of all the patients: C—mean control value for both groups; L—mean test value after lorazepam; M—mean test value after morphine. The upper stippled area shows the 95% confidence limits of the difference between control S and test S in the lorazepam group; it includes the variance from both sources and does not imply that the control S has zero variance. The control S lies outside the stippled area, therefore the difference is only just significant. The lower stippled area shows the same analysis applied to the morphine data, where the change is more significant.

Comparing the rebreathing with the steady-state methods gave the following results. The rebreathing S and the steady-state S were not significantly different during the control period, in either subject. But after lorazepam both subjects had a lower S by the

steady-state method. In R. S. C. the difference was 34% and was virtually significant (P = 0.06 by unpaired t test). In J. S. M. the difference was 20% and, with only five estimates, was not statistically significant.

Amnesia

Memory card. All patients who received morphine recalled the memory card and from two to six of the
words (average, three). None of the lorazepam patients recalled any of the words, and only one had a recollection of the card.

**Incidence of pain and nausea.** This was similar in both groups. Eight in each group needed analgesics after operation. Three patients who received lorazepam required anti-emetics compared with five of those who received morphine.

**Recall of pain and nausea.** Seven patients who received morphine recalled pain and two remembered nausea. No patient who received lorazepam remembered pain or nausea after operation. The patients did not find the amnesia disturbing and the lack of unpleasant recall was welcomed.

One patient who received lorazepam, who did not remember the card or the pain after operation, did vaguely remember going to the operating suite. An unforeseen delay of 5 h had occurred between premedication and going to theatre.

**DISCUSSION**

**Respiratory effects.**

**Choice of method.** Respiratory depression has often been assessed from the change in resting $P_{\text{a}}CO_2$ or $\dot{V}$. However, this method is insensitive, mainly because depression of ventilation increases $PCO_2$; this stimulates breathing so that the depression is masked. A more discriminating index is obtained from carbon dioxide sensitivity—the increase in $\dot{V}$ per unit increase in $PCO_2$. Thus morphine 10 mg reduced carbon dioxide sensitivity by 47% in our study; the same dose increased $P_{\text{a}}CO_2$ by only 0.35 kPa (2.6 mm Hg), a 7% change (Loeschke et al., 1953). Because the relative inaccuracy of blood-gas analysis may obscure a change of only 0.35 kPa, a method which uses the superior accuracy of carbon dioxide analysis in gas is preferable.

In the past, measuring carbon dioxide sensitivity was troublesome because the classical steady-state method is tedious. Therefore the development of a rapid rebreathing method (Read, 1967), giving a complete carbon dioxide response curve in 4 min, roused much interest. Read's method is easy if automated, as described above.

**Accuracy.** The high accuracy of the basic techniques is well established, but there remain errors from electronic drifts. These were assessed by calibrating before and after each experiment. The mean change in deflection was about 1% of the initial reading, for both $PCO_2$ and $\dot{V}$ signals, but the scatter in the estimates of carbon dioxide sensitivity, $S$, from this source was not more than 0.16—less than one-tenth of the total SD for $S$. Thus measurement error caused little of the overall scatter, which must have been attributable mainly to factors within the patient.

The lability of carbon dioxide sensitivity is notorious. Carbon dioxide is a potent stimulus but it may not act alone; anxiety, pain and discomfort are strong stimuli also and may cause false high values for $S$. Thus care was taken to calm the patients and to ensure comfort. The success of this can be gauged partly from the scatter of the $S$ values and partly from the correlation between $S$ and body weight. The mean "within-patient" SD of control $S$ values was 1.8, giving a coefficient of variation of 14%. This compares favourably with other work using the rebreathing method in which coefficients of 16% (Read, 1967—three subjects) and 17% (Lyall, Bourne and Cameron, 1975—11 subjects) were obtained. The steady-state method gave a coefficient of 24% (Anderton, Harris and Slawson, 1964—six subjects).

The control $S$ values were plotted against body weight (fig. 3). Clearly $S$ must have some correlation with body size if extreme ranges of weight are considered. Studies confined to man have usually failed to show this, presumably because the scatter of the $S$ values obscures the correlation when the weight range is narrow (Schaefer, 1958—45 subjects; Hey et al., 1966—26 subjects; Read, 1967—27 subjects; Patrick and Howard, 1972—54 subjects). In contrast our results in 20 patients show a strong correlation between $S$ and body weight ($P<0.01$). Even if the analysis is confined to the nine females, the result reaches the conventional significance level ($P<0.05$). Thus a factor in scatter, which has occurred in other work, has been reduced. Trained subjects are not essential for good results, since this was a study on patients.

**Results with morphine and lorazepam.** Two factors have caused confusion in describing the effects of morphine and sleep on the carbon dioxide response. The term "shift to the right" is ambiguous, since it could mean a change in slope, or intercept. To avoid this the response can be defined by the equation $\dot{V} = S(PCO_2 - B)$, originated by Lloyd, Jukes and Cunningham (1958), in which $S$ is the slope and $B$ the intercept. These two parameters then define the whole of the linear part of the response, concisely and without ambiguity.

The second source of confusion is the non-linearity of the lower end of the carbon dioxide response, which has a "dog-leg" (Nielsen and Smith, 1952). The
slope is therefore best measured after ignoring points at or near the resting Pco₂; including them makes S too small. Examining the literature on morphine in this light shows the effect to be predominantly depression of S without much change in B. Loeschke and others (1953) measured the effect of morphine 10 mg with the classical steady-state method. In their figure 1A the line of best fit suggests 30% depression of S, with 5% increase in B. However, their data are consistent also with a larger change in S and do not differ significantly from the 47% depression we obtained with the rebreathing method. Similarly, morphine 7.5 mg s.c. caused 42% depression of S by the rebreathing method (Weil et al., 1975).

The lorazepam results present a more complex picture. The unexpected feature of our patient data was the increased S, suggesting that lorazepam is a respiratory stimulant. Most sedatives depress respiration markedly. Others cause less depression, which was not detectable in many studies because of the scatter of the measurements. However, stimulation is very rare and has been demonstrated for only one other sedative, benzoctamine, which increased S by about 25% (Geisler and Rost, 1970).

Therefore a follow-up study was performed in volunteers, measuring the effect of lorazepam by both the steady-state and the rebreathing method. This raised a second problem. The steady-state S agreed well with the rebreathing S during the control period, which confirms Read's (1967) finding. However, after lorazepam the results by the two methods differed, S being on average 27% less by the steady-state method.

Having considered many possibilities, the likeliest explanation seems to be varying levels of consciousness. After lorazepam the subject is drowsy but rousable. He can be wakened easily and made to read, but dozes off if left alone. Sleep is known to depress the carbon dioxide response, the largest study being that of Bülow (1963) in 50 normal subjects. Figure 21 of his paper shows S to be depressed by about 34% in light sleep, about 12% in drowsiness, and in neither case does B alter much. This resembles our steady-state data with lorazepam, a lengthy procedure in which the subject tends to sleep. The rebreathing method is much quicker and if the subject stays awake for 4 min, the higher S obtained is understandable.

Bülow (1963) stresses also the irregularity of breathing at the onset of sleep and his figure 21 also shows ventilation to be increased more, for short periods, at this stage than during wakefulness. This might explain the increased S found in our lorazepam patients. The greater scatter of the lorazepam results compared with those for morphine (figure 2) accords with this view.

Thirdly, Bülow (1963) states: "in more than two-thirds of subjects there was during the onset of sleep periodic breathing of more or less pronounced degree". One of our two volunteers had periodic breathing after lorazepam (fig. 4). In both cases periodicity is about 1 min.

Bülow's work may thus provide a simple explanation for the apparent anomalies in our results with lorazepam. Further study is required, but it seems reasonable to suggest that lorazepam has little, if any,
resistance. However, atropine does not alter carbon dioxide response (Loewy, 1891; Steinberg, Bellville and Seed, 1957).

Similarly, metabolic acidosis increases $S$ as measured by the rebreathing method (Linton et al., 1973). Therefore the plasma bicarbonate concentration was measured in all the volunteer experiments, but no consistent change was found after lorazepam. Catecholamines increase $S$ by about 30% without altering $B$ (Cunningham, Hey and Lloyd, 1958); this is a carotid body effect and a high $P_{O_2}$ abolishes it (Cunningham, Patrick and Lloyd, 1964; Cunningham, 1974). In the rebreathing method also the carotid body is silent since 50% oxygen is used, therefore the increase in $S$ after lorazepam is not a result of catecholamines.

**Amnesia**

The superiority of lorazepam over morphine for producing amnesia was overwhelming. Two patients who received lorazepam had incomplete amnesia, recalling the period before operation vaguely, but not pain after operation; the additional slight amnesia caused by the anaesthetic may account for this. A much larger series would be needed to determine the exact failure rate of lorazepam in this respect. This confirms other work: Knapp and Fierro (1974) obtained amnesia in 49 out of 50 patients after lorazepam 4 mg i.m.

The fact that lorazepam prevents recall of pain and nausea does not, of course, absolve the clinician from reducing these factors as far as possible. Perfect anaesthesia will abolish all unpleasant sensations before, during and after surgery, but while this ideal is not yet achieved it is an advance that the patient forgets the discomfort and leaves hospital unscarred by his experiences. This was certainly the view of some of our patients who received lorazepam, having received opiate premedications previously.

Sedation was not studied in depth, but requires brief discussion since this is the primary role of premedication. Major operations may be performed without premedication and the need for it has been questioned. Much effort has gone into recherché methods of quantifying anxiety objectively, but with only partial success. Even if exact measurement were possible it is doubtful whether this would answer the main question. The chief variable is individual susceptibility to fear. Some are made anxious by trifling stresses of everyday life, and if such a patient is anxious before operation this may be no worse than his daily experience. Since morphine would not be prescribed for daily use it is perhaps illogical in premedication. This dilemma is resolved by questioning after operation, which also has the merit of simplicity. If the patient remembers the period before operation and considers that his disquiet at that time was not excessive, then sedation was adequate. Brice, Hetherington and Utting (1970) questioned 56 patients after routine surgery with no premedication; 46% complained that anxiety before was worse than the pain after operation and only 21% said that pain was the most disagreeable aspect. Therefore premedication maybe useful.

In our study, questioning after operation revealed only one patient in the group who received morphine and who had severe anxiety before operation. The patients who received lorazepam did not remember this period, but some information was provided by the anaesthetist's ratings. One patient in each group was rated as having an unacceptable level of anxiety. The patient in the morphine group was referred to above, but the patient in the lorazepam group did not recall this period.

Thus good sedation was provided by both drugs, neither being always successful. Lorazepam has the advantage that if sedation is inadequate this is not remembered and also delay is tolerated better because of its longer action. This agrees with the studies of Norris (1969) and Norris and Wallace (1971), who measured sedation after morphine and lorazepam, given in the same doses as the present study. Their method, currently popular, is a scoring system in which five subjective and objective criteria are recorded. As the authors point out, the list of items in any scoring system is in some degree arbitrary. Thus if drowsiness is included lorazepam scores slightly better than morphine, but excluding this item reverses the position.

**Protective reflexes**

Some anaesthetists have reservations about drugs which cause drowsiness, since this may be associated with reduced protective reflexes. But the value of this sign is limited in this context. During natural sleep and drowsiness protective reflexes are not reduced dangerously; conversely, opiates may abolish protective reflexes while the patient remains awake.

We did not study reflexes after lorazepam and this should be done. A possible hazard could result from over-estimating the dose of lorazepam, for example in the ill or elderly patient, so that he is not merely asleep, but unrousable. The unrousable patient does not safeguard his airway adequately, even if protective
reflexes are intact, so that routine care of the unconscious would be needed.

**Diazepam**

Some authorities (Herxheimer, 1973) consider that the available benzodiazepines do not differ from each other significantly in their pharmacological actions. Several reports have claimed that lorazepam is more effective in causing amnesia than is diazepam, but the doses compared may not have been equipotent for sedation and the difficulty of measuring sedation makes some uncertainty inevitable.

However, if the two factors measured are amnesia and carbon dioxide sensitivity, the position is more hopeful. Thus Catchlove and Kafer (1971) found that diazepam 10 mg caused 29% depression of $S$ using Read's method (the method that gave 27% increase in $S$ after lorazepam 4 mg in our study). On the other hand, diazepam 10 mg produces less amnesia than lorazepam 3 mg (Wilson and Ellis, 1973; Heisterkamp and Cohen, 1975). This suggests that in doses equipotent for amnesia diazepam would be more depressant.

Dodson and others (1976) obtained respiratory stimulation after oral lorazepam 2.5 mg, and the same team, using the same method, had shown previously that oral diazepam 5 mg caused depression of respiration. This supports the view that the latter drug is more depressant. Comparison with other work is difficult, because the method used gave a mean control $S$ of 5.2 litre.min$^{-1}$.kPa$^{-1}$, well below the accepted value. Moreover the dose of lorazepam studied would cause amnesia in only about 50% of patients (Turner, 1973; Wilson, 1973; Heisterkamp and Cohen, 1975).

As noted earlier, the only other sedative to rival the respiratory effect of lorazepam is benzoctamine, a drug which, however, has no amnesic effect (Agostinis et al., 1975).

**CONCLUSIONS**

**Bronchitis**

Our study suggests that lorazepam may be of value where there is a special need for sedation without respiratory depression. Sedatives are a well-recognized hazard in respiratory cripples, but Denault, Yernault and de Coster (1975) found no untoward effects after giving lorazepam 2.5 mg i.v. to 20 patients with chronic bronchitis. Marked somnolence occurred, associated with a high blood concentration, and the increase in $P_{a\text{CO}_2}$ was similar to that in normal sleep.

**Obstetrics**

Unsupplemented nitrous oxide in oxygen anaesthesia in patients who have received a neuromuscular blocking drug is excellent for avoiding depression of the neonate and is satisfactory in about 83% of cases, but in the remaining 17% the mother has unpleasant recall (Wilson and Turner, 1969). Because of this, supplements of trichoroethylene or opiates may be given, but these are known depressants and may account for the 28% incidence of depressed babies reported in the Birmingham survey of 1707 Caesarean sections (Crawford and Opit, 1975). Lorazepam may be valuable in this type of anaesthesia.

Diazepam has been used in obstetrics with varying reports, some of which are unfavourable (Flowers, Rudolph and Desmond, 1969; Turner and Wilson, 1969). Neonatal flaccidity may occur after giving diazepam to the mother, possibly because of selective uptake of this drug by plasma proteins in the foetus (Iðanpiaán-Heikkilá et al., 1971). Lorazepam may not have the same disadvantages, since its fat-solubility is different.

Lorazepam 2.5–5 mg was given to 342 normal patients in labour with no obvious neonatal depression (Mertens, 1974). Contrary findings of neonatal hypotonia were obtained in a preliminary trial of lorazepam for Caesarean sections (J. Wilson, personal communication). Neither study included respiratory measurements, or comparisons with a rival regime, so the question remains open.

Respiratory depression is particularly undesirable in the new-born because, although its cardiovascular system is robust compared with an adult, its respiratory system is feeble. The high urinary $P_{N\text{H}_2}$ shows air and blood to be very unevenly distributed throughout the lung (Ledbetter, Homma and Fahri, 1967). Moreover, hypoxia does not stimulate breathing, but diminishes it (Cross, Hooper and Lord, 1954; Rigatto, Verduzzo and Cates, 1975).

**Routine anaesthesia**

Some of the virtues of lorazepam in routine premedication have been discussed earlier. In addition, lorazepam may help to prevent unpleasant recall of awareness during anaesthesia which, although it occurs in obstetric anaesthesia most commonly, is not confined to this sphere. Even when nitrous oxide is supplemented with other agents a small percentage of patients have unpleasant memory of the operation itself, even accurate factual recall in some cases.

In the largest survey (Hutchinson, 1961), of 656 patients, eight reported awareness during surgery,
which was unpleasant in six either because of pain or anxiety, about 1%. A second large study, of 490 patients, recently showed similar results with 1% of patients having factual recall of the operation (Wilson, Vaughan and Stephen, 1975). Some patients, without accurate recall, experienced bad dreams or hallucinations, sometimes with feelings of pain, the total incidence of unpleasant recall in Wilson’s survey being 3%. In both surveys unpleasant recall was not related to the agent used to supplement nitrous oxide, the incidence being similar with inhalation agents such as halothane, and with i.v. agents such as opiates or neuroleptanalgesics.

Other surveys have reported an absence of awareness, but these are inconclusive because the samples were too small. A routine statistical calculation (Snedecor and Cochrane, 1969b) shows that even with zero incidence the results would not differ significantly from Hutchinson’s (at the 5% level) unless the sample contained at least 460 patients.

From the two large surveys quoted the true incidence of unpleasant recall probably lies between 1 and 3%, so that a busy anaesthetist can expect one such occurrence every few months. The apparent incidence is much less, because the patient usually fails to complain. Technical errors may explain some cases, but in others this can be excluded. Standard anaesthetics, satisfactory for the vast majority, appear to be inadequate for about 1% of patients. Resistant patients form the tail-end of a Gaussian distribution. Since they cannot be identified in advance no satisfactory solution exists at present. Producing deep anaesthesia in all cases would jettison the major advance of modern technique, jeopardizing 99 patients to prevent discomfort in one. Nor would this necessarily solve the problem, since accurate recall has been obtained even after very deep ether anaesthesia (Levinson, 1965). Hyperventilation can, by itself, render the patient unconscious, but has gone out of favour for a number of reasons.

In this predicament lorazepam seems worth testing. The patient who is resistant to nitrous oxide may be resistant to lorazepam also, but a reduction in the incidence of unpleasant recall is likely. The number of cases needed to make this statistically significant is, however, daunting.

It remains to be seen whether lorazepam solves the problem of the resistant patient, but in other fields its value is already clear. About half the patients undergoing routine surgery have unpleasant recall of the period following operation and lorazepam abolishes this in nearly all cases. Apart from surgery, many other procedures in the intensive therapy unit and endoscopy cause a measure of discomfort for which a safe amnesic drug would be valuable.

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REFERENCES


EFFETS RESPIRATOIRES ET AMNESIE APRES PREMEDICATION A L'AIDE DE MORPHINE OU DE LORAZEPAM

RESUME

On a comparé le lorazepam, qui est un nouveau benzodiazépine, à la morphine en tant qu'agent de prémédication. Dix malades ont reçu par voie intramusculaire de la morphine à raison de 10 mg/70 kg et 10 autres ont reçu par voie intramusculaire du lorazepam à raison de 4 mg/70 kg. On a évalué les effets respiratoires à partir du changement de pente (S) et de la ligne entre deux points (B) de la ligne de réaction à l'acide carbonique, en se servant d'une amélioration de la méthode de re-respiration de Read. La morphine a modéré S de 47% (P<0.01) mais après le...
lorazepam $S$ has increased by 27% ($P < 0.05$), none of these two medicaments are modifying $B$ in a manner significant. On two volunteers, lorazepam has been evaluated also well by the method of re-respiration because by the method of equilibrium, $S$ has been more significant than by the technique of re-respiration. This is because one has discovered in this context that the lorazepam is in accordance with the effects known of the somnolence on the sensitivity to carbon dioxide. It produces an amnesia from 4 to 8 hours in all patients treated with lorazepam in a manner that they do not remember neither the pain nor the nausea during this period, but no patient treated with morphine suffered from amnesia. We conclude from this that the study of lorazepam is worth being deepened, especially for the cases where one needs sedation without respiratory depression, for example in obstetrics, and where one needs amnesia for disturbing procedures.

**ZUSAMMENFASSUNG**

Es wurde das neue Benzodiazepin Lorazepam als Vorbehandlungsmittel mit Morphin verglichen. Zehn Patienten erhielten intramuskulär 10 mg/70 kg Morphin und zehn erhielten intramuskulär 4 mg/70 kg Lorazepam. Die Atmeeinwirkung wurde von der Veränderung in der Steigung ($S$) und dem Auffangen ($B$) der Kohlensäurereaktionskurve unter Anwendung des Readschen Rückatmungsverfahrens eingeschätzt. Morphin setzte $S$ um 47% herab (Druck $P < 0.01$), nach Lorazepam jedoch erhöhte sich $S$ um 27% (Druck $P < 0.05$), wobei keine der beiden Drogen $B$ bedeutsam veränderte. In zwei freiwilligen Versuchspersonen wurde das Lorazepam sowohl mit dem Rückatmungsverfahren als auch mit der konstanten Methode bewertet; nach Lorazepam war $S$ mit der konstanten Methode niedriger, als mit dem Rückatmungsverfahren. Der Lorazepam-Befund entspricht der bekannten Wirkung, die der Schlaf auf Kohlensäureempfindlichkeit hat. In allen Patienten, die Lorazepam erhielten, trat eine 4–8 Stunden dauernde Amnesie ein, so dass der Schmerz oder die Übelkeit während dieser Zeitspanne später nicht wieder wachgerufen wurden, die Patienten aber, die Morphin erhielten, erlitten keine Amnesie. Wir schliessen daraus, dass das Lorazepam es verdient, weiter studiert zu werden, besonders in solchen Fällen, wo Beruhigungsmassnahmen ohne Atemherabsetzung benötigt werden, wie z.B. in der Geburtshilfe, und wo für unbehandelte Verfahren Amnesie erforderlich ist.

**SUMARIO**

Lorazepam, una nueva benzodiacepina, fue comparada con morfina para la premedicación. Diez pacientes recibieron morfina 10 mg/70 kg i.m. y 10 recibieron lorazepam 4 mg/70 kg i.m. Se evaluaron los efectos respiratorios partiendo del cambio en la vertiente ($S$) e interceptación (ordenada en origen) ($B$) de la línea de respuesta del dióxido de carbono, empleando un desarrollo del método de Read de reinalación. La morfina deprimió $S$ en un 47% ($P < 0.01$), pero tras lorazepam $S$ aumentó en un 27% ($P < 0.05$), y ninguno de los fármacos alteró $B$ significativamente. En dos voluntarios se evaluó lorazepam con ambos métodos, de reinhalación y de régimen permanente; tras lorazepam $S$ fue más pequeña por el método de régimen permanente que por la técnica de reinhalación. Los hallazgos para lorazepam son consistentes con los efectos conocidos de sueño sobre sensibilidad al dióxido de carbono. La amnesia duró 4–8 horas en todos los pacientes que recibieron lorazepam, de modo que no se recordaron el dolor ni náuseas durante este periodo, pero ningún paciente que recibió morfina padeció de amnesia. Concluimos que lorazepam merece mayor estudio, particularmente para los casos en que se precisa sedación sin depresión respiratoria, como en obstetricia, y donde se requiere amnesia de procedimientos molestos.