Nalbuphine is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the agonist analgesic oxymorphone and the antagonist naloxone.

It has been recommended for the relief of moderate to severe pain, and can be administered by the subcutaneous (Stambaugh, 1982), i.m. (Beaver and Feise, 1978), and i.v. routes (Tammisto and Tigerstedt, 1977). It has been used both as a preoperative premedicant (Fahmy, 1977) and as a component of “balanced” surgical anaesthesia (Fahmy, 1980).

In the conventional dose range, nalbuphine produces a similar degree of respiratory depression to morphine (Fragen and Caldwell, 1977; Gal, DiFazio and Moscicki, 1982). However, it has been reported that in conscious subjects a "ceiling" was reached and, with higher doses, further depression of respiration did not occur (Romagnoli and Keats, 1980).

Since such a limit to the degree of respiratory depression would be a valuable safeguard for any narcotic drug, this study was designed to assess the effects of equianalgesic doses of nalbuphine and morphine, on respiration in spontaneously breathing, anaesthetized patients.

PATIENTS AND METHODS

Patients admitted for elective surgery were invited to participate in an open randomized study approved by the hospital ethics committee. The patients were aged 18–60 yr, between 50 and 80 kg body weight and in good general health. The nature of the study was explained to all patients and written consent obtained.
and steady end-tidal carbon dioxide for 5 min) had
been achieved, a single dose of nalbuphine 4.5, 8, 15 or 25 mg/70 kg or morphine 3, 5, 10 or 17.5 mg/70 kg was administered i.v. over 10 s and the cannula flushed. These were the equianalgesic doses found in a study with self-administered analgesia (Bahar, Rosen and Vickers, 1985). A further group who received nalbuphine 50 mg in the same manner was added to clarify the effects of nalbuphine. Artificial ventilation was commenced if apnoea of more than 30 s duration occurred.

Following the administration of the test drug, carbon dioxide concentrations and tidal volumes were recorded for 10 min before the commencement of surgery. Total ventilation was calculated from the recording of the tidal volume and verified with a dry gas meter. During the study the electrocardiogram (ECG) was monitored continuously, and arterial pressure measured at regular intervals.

RESULTS

Details of the nine groups are shown in table I. In all groups depression of ventilation was observed. Plots of total ventilation against time (not reproduced here) showed that maximum depression occurred 1–2 min after the administration of nalbuphine and 2–3 min after the administration of morphine. This was followed by recovery to a “steady” level of depression of ventilation after 5 min with nalbuphine, and after 4 min with the lower doses and after up to 10 min with the higher doses of morphine.

The minimum ventilation, averaged over any 1-min period within the 10-min observation period, was expressed as a percentage change from the steady-state value and plotted against dose (fig. 1).

The percentage decrease in ventilation from the steady-state value was accumulated over the 10-min period and divided by 10 to give a mean percentage decrease (fig. 2).

The end-tidal carbon dioxide tension at the end of the 10-min period was expressed as a percentage change from the steady-state control value (fig. 3).

In the group receiving the largest dose of morphine (17.5 mg/70 kg), prolonged apnoea (> 60 s) occurred in two patients, necessitating their elimination from and substitution in the study. This group is thus “censored”, but it is apparent that the dose of maximum effect was being reached for morphine. In contrast, apnoea did not occur in any of the subjects receiving nalbuphine.

In all three graphs (figs 1–3) the effect of the smallest dose of nalbuphine is about twice that of the smallest dose of morphine. The effects of the middle doses are similar for the two drugs. The depressant effects of morphine increase systematically with dose, approaching (and in some patients reaching) apnoea with the highest dose, whereas the depressant effect of nalbuphine appears to reach a limit and there is even an indication of reversal at the highest dose.

Statistical evaluation

To test the apparent ceiling and reversal effects of nalbuphine, linear and quadratic equations were fitted to the results using the least-squares technique. For all three morphine response curves, only the linear coefficients were statistically significant ($P < 0.001$). In contrast, for all the nalbuphine response curves, the quadratic equation gave a better fit than the linear. Testing the coefficient of the squared term in the equation (on the basis that the alternative to the null hypothesis is that there is curvature in the direction consistent with reversal of effect at high doses) showed it to be significant for all three measures of depression: $P = 0.027$, 0.006 and 0.048 for figures 1, 2 and 3, respectively.

DISCUSSION

There are several advantages of using anaesthetized patients for the study of respiratory depression associated with drug administration. These include
Fig. 1. Minimum ventilation, averaged over any 1-min period, within 10 min of i.v. morphine and nalbuphine as a percentage difference from the control steady state (+2SEM).

Fig. 2. The mean depression of ventilation over 10 min following i.v. morphine and nalbuphine as a percentage difference from the control steady state (+2SEM).

Fig. 3. End-tidal carbon dioxide concentration, 10 min after i.v. morphine and nalbuphine, as a percentage difference from the control steady state (+2SEM).
the absence of involuntary alterations in respiration such as occur in conscious subjects and the production of reproducible conditions for study, permitting accurate, continuous assessment of respiratory performance. In addition, the increased sensitivity to respiratory depression in anaesthetized subjects permits the safe administration of drugs to apnoeic levels since smaller doses will produce apnoea, and positive pressure ventilation can be instituted immediately.

It is recognized that direct comparison with the depressant effects of these drugs in conscious subjects is not wholly justifiable, since both premedication (Gasser and Belville, 1976) and anaesthesia (Knill and Gelb, 1978) produce additive depressant factors. However, during a "steady-state" of anaesthesia and respiratory function, the effects of i.v. boluses of narcotic drugs are easily distinguished and comparative studies are readily achieved.

A further problem associated with the use of anaesthetized patients arises from the more rapid onset of action of nalbuphine. This is revealed by the peak depression occurring 1 min earlier than with morphine, and suggested a risk that the consequent effects upon the continuing uptake of the inhaled anaesthetics will lead to different "steady-states" for the two drugs at the end of the 10-min observation period. However, the three indices of depression reveal three aspects of the actions of the drugs: peak effect (minimum total ventilation); mean effect over 10 min (mean depression of total ventilation), and cumulative effect over 10 min (increase in end-tidal carbon dioxide concentration). Yet the three nalbuphine: morphine ratios of depression (peak, mean and cumulative) are very similar: 2.2, 2.0, 2.0 for the lowest pair of doses; 0.74, 0.63, 0.65 for the 25.0/17.5-mg pair of doses.

The analgesic potency ratio of nalbuphine to morphine is variously reported between 0.7 times and equipotency according to mode of administration and method of assessment (Forrest, 1971; Bikhazi, 1978). Our own observations have suggested a potency ratio approximating to the former value and, accordingly, this was used here. In the study of the respiratory effects it could be argued that this ratio weighs unfavourably against nalbuphine. However, in clinical practice it will be the analgesic efficiency which is the prime determinant of dose and an assessment using this equipotent ratio is therefore justified.

Our results are in agreement with observations made in conscious subjects (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982). Over the conventional dose range there is virtually no difference in the respiratory depressant effects of nalbuphine and morphine. At the higher dose, however, morphine produced apnoea in approximately 30% of subjects representing a maximal depressant effect on respiration. Apnoea did not occur with any of the patients receiving nalbuphine. A limit to the extent of respiratory depression was demonstrated and the quadratic regressions showed that the maximum effect occurred at a dose of 15–16 mg.

The attraction of analgesic agents with partial antagonist activity lies in the possibility of a decrease in abuse potential and a limitation to the extent of side effects, particularly respiratory depression. This latter feature might be expected in all agents with partial antagonist properties but, currently, has been demonstrated in man only with nalorphine, butorphanol and nalbuphine (Keats and Telford, 1965; Kallos and Caruso, 1979; Bahar, Rosen and Vickers, 1985).

Limitation to respiratory depression with increasing dosage would be very useful if high dosage were required were it not for the suggestion that the analgesic efficacy also reaches a limit with increasing dosage (Gal, DiFazio and Moscicki, 1982; Murphy and Hug, 1982). However, it remains a useful safeguard in the event of inadvertent overdosage.

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REFERENCES


NALBUPHINE AND MORPHINE: RESPIRATORY FUNCTION


