NALOXONE: DOSE-DEPENDENT ANTAGONISM OF RESPIRATORY DEPRESSION BY FENTANYL IN ANAESTHETIZED PATIENTS

G. B. DRUMMOND, I. T. DAVIE AND D. B. SCOTT

Naloxone has been used to antagonize the respiratory depression caused by the administration of fentanyl 0.05 mg to patients anaesthetized with 0.5% halothane in 70% nitrous oxide in oxygen. Four groups of at least 10 patients each were studied. Doses of 0.1, 0.2 and 0.4 mg of naloxone were given, and an effect proportional to the logarithm of the dose was demonstrated.

Naloxone has been accepted as a clinically useful opiate antagonist with no intrinsic respiratory depressant, psychomimetic or analgesic activity (Keats and Telford, 1964; Jasinski, Martin and Haertzen, 1967; Foldes, Duncalf and Kuwabara, 1969; Evans et al., 1974). Therefore, in these respects it is superior to agents such as nalorphine which are known to have agonist activity (Weakley and Bergner, 1957). Hasbrouck (1971) suggested that naloxone could be used to antagonize respiratory depression caused by morphine in patients following operation, without antagonism of the analgesic effect of morphine. However, Heisterkamp and Cohen (1974), using incremental small doses of naloxone, showed that persistent analgesia could be achieved only if the narcotic antagonism was incomplete, although this was associated with an acceptable degree of respiratory depression.

If naloxone is to be used, during and after anaesthesia, for the antagonism of respiratory depression caused by narcotic analgesics, the dose–response relationship should be known. This study was designed to determine this relationship in anaesthetized patients who were in a steady state of nitrous oxide and halothane anaesthesia. A standard dose of a narcotic (fentanyl) and one of a series of graded doses of naloxone were given simultaneously. The resultant respiratory depression was analysed in relation to the dose of naloxone.

METHODOLOGY

Forty-four women, aged between 20 and 60 yr, weighing between 50 and 90 kg and free of any history or clinical signs of respiratory, cardiac, hepatic or renal disease, gave informed consent for the study. They were about to undergo laparoscopy, for gynaecological reasons, under general anaesthesia.

Atropine sulphate 0.6 mg was given i.m. for premedication, 1 h before anaesthesia. A cannula was placed in a vein on the dorsum of the hand, and all injections made through it. Anaesthesia was induced with sodium thiopentone 250 mg and maintained with a mixture of oxygen (3 litre/min), nitrous oxide (7 litre/min) and halothane 1%, using a non-rebreathing valve (Ambu Hesse) and a tightly fitting facemask. After 5 min, the halothane concentration was reduced to 0.5% for the duration of the measurements.

The anaesthetic circuit is shown in figure 1. Gases entered a reservoir bag and, during inspiration, passed through a previously calibrated dry gas meter (Parkinson Cowan) and a non-rebreathing valve. The meter dial had been modified to give a continuous electrical signal that was recorded using a hot pen recorder (Devices MX2). Excess gas escaped from a spill valve close to the reservoir bag. This valve was constructed to open at very low pressures so that gas only passed through the dry gas meter during the patient's inspiration.

Test solutions. Three test solutions were used, containing respectively 0.1, 0.2 and 0.4 mg of
naloxone, made up to a total volume of 5 ml with 0.9% saline. A fourth solution comprised saline only. Each solution was allocated randomly to one patient. The identity of the solutions remained unknown until after the study.

Ten minutes after the induction of anaesthesia, control measurements of respiratory frequency and minute volume were made for a further 10 min. Fentanyl citrate 0.05 mg, diluted to a total volume of 5 ml in 0.9% saline, was then given through the i.v. cannula, followed immediately by one of the four test solutions, and finally by 5 ml of 0.9% saline to flush the cannula.

Recordings of minute volume and respiratory frequency continued for a further 10 min, when the experiment finished and surgery started. If any patient became apnoeic after the injections, naloxone 0.4 mg was given i.v. and the study was terminated.

RESULTS

Details of the patients in each group are given in table I. There were no significant differences between the groups in respect of general characteristics. The expected weight for each patient was determined from the weight and age (Documenta Geigy), and the difference between actual and expected weight was calculated. Although there were more overweight (24) than underweight patients, there were no differences between the groups.

The mean minute volume and respiratory frequency over the whole control period showed no significant differences between the groups (table II).

The mean minute volume and respiratory frequency at each minute remained steady throughout the control period. Figure 2 shows the mean minute volume at each time interval for the group receiving naloxone 0.2 mg.

Absolute changes in minute volume and respiratory frequency relative to the control values were analysed in preference to proportions of the control value because the changes that occurred after the administration of fentanyl were not proportional to the magnitude of the preceding control value.

Five of the 10 patients in the group which received the saline-only solution became apnoeic after the administration of fentanyl. These patients were withdrawn from the study, and only data from the patients who continued to breathe have been used for subsequent comparison with other groups. Thus the effect of fentanyl in this group has been underestimated deliberately.

The patients who stopped breathing had a mean control minute volume (5.87 litre/min) less than the value for those who did not become apnoeic (6.62 litre/min). However, this difference was not statistically significant, nor were there significant differences in age, height or weight between these patients.

The mean changes in minute volume and respiratory frequency, relative to the control values, are shown in figures 3 and 4. The mean values of the maximum changes and the median time at which these changes occurred are given in table III.
ANTAGONISM OF FENTANYL BY NALOXONE

The group that did not receive naloxone differed markedly in response from the other groups. Analysis of variance for the overall results for the 10-min period after injection confirms this difference ($P<0.001$) for both minute volume and respiratory frequency. The overall differences between the groups that received naloxone were similar for both variables, with a significant logarithmic linear trend ($P<0.001$). The relationship between the maximum change in both minute volume and respiratory frequency and the dose of naloxone shows a similarly significant logarithmic linear trend.

The mean changes in minute volume 2 min after injection, in the three groups which received naloxone, were related also to the dose of naloxone (fig. 4). There was no significant correlation between the observed changes in any of the groups and the weight, predicted weight or calculated surface area of the patients.

DISCUSSION

Foldes, Duncalf and Kuwabara (1969) studied the effect of two dose regimes of naloxone (5 and 10 µg/kg) on the respiratory depression caused by oxymorphone. However, they used pentobarbitone for premedication, a variable dose of thiopentone for induction of anaesthesia, a varying concentration of nitrous oxide from a circle system, and assisted the respiration of some of the patients. Although an increase in effect was evident with the larger dose, they were unable to demonstrate a statistically significant difference between the effect of the two doses of naloxone.

The use of fixed doses of the agents in the present study, rather than doses related to body weight, appears to have been justified as the groups weights were comparable. Our doses of naloxone correspond to 1.7, 3.3 and 6.7 µg/kg. Because low doses were used, the residual respiratory depression was expected...
to be greater and it was hoped that this would highlight differences between the doses.

We used fentanyl to cause respiratory depression because its duration of action was unlikely to exceed that of naloxone. The dose was sufficient to cause apnoea in 50% of patients. This degree of respiratory depression is clearly greater than that produced by Foldes, Duncalf and Kuwabara (1969) and may be a further reason for the response to the doses of naloxone used in the present study as compared with their results.

The method of study allows the measurement of the immediate effects of the narcotic and the antagonist while the patient is in a steady state of anaesthesia. The factors causing the return of ventilation towards the control parameters are a reduction in depth of anaesthesia and retention of carbon dioxide. These influences will have different time courses and, therefore, after depression of respiration has been present for more than a few minutes, the groups of patients may not be comparable. The method used in this study seems to be a simple, sensitive and reliable method for the assessment of narcotic antagonist agents.

The results show that naloxone can be given in small doses to cause partial antagonism of the respiratory depression caused by a narcotic analgesic. In this way, an inadvertent overdose of a narcotic during anaesthesia may be ameliorated without the complete loss of the clinical advantages.

ACKNOWLEDGEMENTS
We should like to thank Mr J. G. Cleaver of the Department of Statistics, Sterling Winthrop Group Limited, for statistical analysis of the data, and Winthrop Laboratories for a generous supply of naloxone. We are grateful for the cooperation of the gynaecological consultants who allowed us to study patients under their care.

REFERENCES

LE NALOXONE: ANTAGONISTE, EN FONCTION DE LA DOSE, DE LA DEPRESSION RESPIRATOIRE CAUSEE PAR LE FENTANYL SUR DES PATIENTS ANESTHESIES

RESUME
On a utilisé du naloxone pour s’opposer à la dépression respiratoire causée par l’administration de fentanyl, à raison de 0,05 mg, à des patients anesthésiés à l’halothane 0,5% dans 70% de protoxyde d’azote et dans l’oxygène. Ces études ont porté sur quatre groupes comprenant chacun au moins 10 malades. On leur a administré des doses de 0,1, 0,2 et 0,4 mg de naloxone et on a ainsi démontré l’effet proportionnel au logarithme de la dose.

NALAXON: DOSISSAHANGIGES ANTAGONISTIKUM GEGEN ATMUNGSSCHWACHUNG DURCH FENTANYL IN ANÄSTHESIERTEN PATIENTEN

ZUSAMMENFASSUNG
Naloxon wurde als Mittel gegen die respiratorische Dämpfung verwendet, die sich aufgrund der Verabreichung von 0,05 mg Fentanyl an Patienten ergab, die mit 0,5% Halothan in 70% Stickstoff und Sauerstoff narkotisiert worden waren. Vier Patientengruppe zu jeweils wenigstens 10 Patienten wurden studiert. Dosen von 0,1, 0,2 und 0,4 mg Naloxon wurden verabreicht, und Wirkungen proportional zum Logarithmus der Dosis wurden demonstriert.

NALOXONA: ANTAGONISTA DOSIS-DEPENDIENTE DE LA DEPRESION RESPIRATORIA CAUSADA POR FENTANYL EN EL PACIENTE ANESTESIADO

SUMARIO
Se utilizó naloxona para antagonizar la depresión respiratoria causada por la administración de fentanyl 0,05 mg a pacientes anestesiados con 0,5% halotano en 70% de monóxido de nitrógeno en oxígeno. Se estudiaron cuatro grupos de por lo menos 10 pacientes cada uno, administrándose dosis de 0,1, 0,2, y 0,4 mg de naloxona, y se demostró un efecto proporcional al logaritmo de la dosis.