Degree and Duration of Reversal by Naloxone of Effects of Morphine in Conscious Subjects

J. M. EVANS, M. I. J. HOGG, J. N. LUNN, M. ROSEN

British Medical Journal, 1974, 2, 589-591

Summary
The effects of intravenous naloxone on several of the actions of intravenous morphine (mean dose 30 mg/70 kg) were studied in six volunteer subjects. Naloxone produced a well defined reversal of the respiratory depression, analgesia, and micturition effects of the morphine. The agonist action of morphine outlasted the antagonist action of a single dose of naloxone. The effect of repeated doses of naloxone was also short-lived, but continuous infusions were effective in maintaining reversal.

Introduction
In conscious and anaesthetized subjects naloxone reverses the depressant effects of narcotics (Foldes et al., 1963; Sadove et al., 1963). Hasbrouck (1971) showed the reversal of morphine-induced respiratory depression and electroencephalographical changes in the postoperative period. It has been suggested that naloxone may preserve the analgesic action of morphine while effectively reversing respiratory depression (Hasbrouck, 1971; Heisterkamp, 1972). Jasinski et al. (1968) showed that naloxone could antagonise the behavioural and pupillary effects of cyclohexizine in addition to its respiratory depressant effect. The duration of action of naloxone has been claimed to be several hours (Jasinski et al., 1968), but other investigators have suggested that it is very much shorter (Hasbrouck, 1971; Fink et al., 1968; Evans et al., 1973).

Naloxone is evidently an effective narcotic antagonist; its duration of action, however, and relative effect on analgesia and respiratory depression on the subjective effects produced by narcotics are not yet clear. The antagonist properties of naloxone were therefore studied to elucidate these points.

Method
Six informed volunteer male medical practitioners were studied. An experimental protocol similar to that previously described in a study of naloxone and levallorphan was used (Evans et al., 1974). The subjects were starved for four hours beforehand and lay semi-recumbent on a bed during the study. A cannula was inserted into a vein on the dorsum of the non-dominant hand. Each study was made up of consecutive 15-minute periods of measurement. The 15-minute period began with an injection of drug or placebo into the cannula. The subject then rested for five minutes during which time he was asked to report any subjective changes. Measurement of systolic blood pressure, pupil size, psychomotor function, and pain threshold were made in the next five minutes. The ventilatory response to a standardized carbon dioxide challenge was measured in the final five minutes (Lambertsen and Wendel, 1960).

The first period of each study began with an injection of saline. The subsequent two injections were given double-blind, one consisting of saline and the other of morphine 10 mg/70 kg in saline. Morphine was chosen as the agonist drug as it is a commonly used and representative narcotic. Additional doses of morphine (10 mg/70 kg) were given at 15-minute intervals at the discretion of the investigators until a depression of ventilatory response of about 50% had developed. To ensure that the depressant effects of the morphine persisted without change the measurements were repeated in the next period after an injection of saline. Naloxone was then given, unknown to the subject; five subjects received 0-4 mg/70 kg and one subject received 1-6 mg/70 kg. Thereafter injections of saline were given at 15-minute intervals. Additional naloxone was given as necessary.

All observations and measurements were performed by the same investigators.

Results
The mean dose of morphine needed to produce 50% depression of ventilatory response was 30 mg/70 kg; one subject received 20 mg/70 kg, another 40 mg/70 kg, and the remaining four subjects 30 mg/70 kg.

Subjective and Behavioural Responses
Morphine caused the subjects to be moderately sedated and they usually lay resting with their eyes closed. One subject felt nauseated after receiving the morphine but did not vomit. Within two minutes of being given saline there was a prompt and obvious arousal of the subjects from their sedated state. The arousal was often described dramatically by the subjects, a common description being, “it was as if a curtain or blind had been lifted suddenly.” The subjects invariably felt clear headed immediately after the naloxone and were unaware of any residual effects of the morphine. Within 15 to 30 minutes, however, the subjects reported that they were feeling less alert, and objectively, they became more drowsy. Within 45 minutes of receiving naloxone all the subjects again became sedated as after the initial dose of morphine. One subject was given 1-6 mg/70 kg of naloxone as a first dose; a rapid arousal occurred, within 30 seconds, but otherwise the effects were indistinguishable from those of the smaller dose.

Subsequent doses of naloxone again produced arousal of a similar duration, but the effects became less easy to define as the investigation progressed. A dose of 1-6 mg/70 kg was given as a second dose of naloxone to another subject. This produced a rapid arousal but further sedation occurred again within 45 minutes. This subject experienced a transient feeling of anxiety followed by sweating, palpitation, and hypertension (blood pressure 160/110) during the reversal. In two subjects an intravenous infusion of naloxone of 1-2 mg/hr in one and of 2-4 mg/hr in the other was begun immediately after the second dose of 0-4 mg of naloxone had been given. The infusion was maintained for 45 minutes. The arousal produced by the second dose of naloxone was maintained during the infusion, but on stopping the infusion the subjects again noticed a return of the effects of morphine.

Department of Anaesthetics, Welsh National School of Medicine, Heath Park, Cardiff CF4 1XN

J. M. EVANS, M.B., F.F.A. R.C.S., Research Fellow
M. I. J. HOGG, B.SC., Research Assistant
J. N. LUNN, M.D., F.F.A. R.C.S., Senior Lecturer
M. ROSEN, M.B., F.F.A. R.C.S., Consultant Anaesthetist
OBJECTIVE RESULTS

Changes in the recorded values were expressed as a percentage change from the subjects' own control measurements made after the first injection of saline. The percentage changes for each value were then calculated and plotted against time. The period of time over which the morphine was given varied between subjects, and for this reason the moment at which the first injection of naloxone was given was taken as the common reference time.

Blood pressure did not change after morphine or naloxone.

Pupil size (see fig. 1) decreased by 30% after morphine (P<0.05). Naloxone produced a partial reversal of this miosis, but pupil size remained 10% less than the control level. In the subsequent 45 minutes pupil size decreased to 28% below the control value but the change was not statistically significant (P>0.1).

There were no statistically significant changes in reaction time, digit span score, or arithmetic ability after the morphine or naloxone. The results of the arithmetic tests in one subject were excluded because he was unable to focus on the written tests after receiving the morphine; the administration of naloxone resulted in an immediate return of normal vision.

Pain threshold rose after morphine (P<0.05) and returned to normal after the first dose of naloxone (fig. 2). There was a slight but statistically non-significant rise in pain threshold over the next 45 minutes.

The ventilatory response to carbon dioxide was reduced (P<0.01) to almost 50% below the control value when measured in the two 15-minute periods after the final dose of morphine (fig. 3). This depression was reversed by naloxone to a mean ventilation 9%, below the control value. Within 15 minutes of receiving naloxone ventilation had fallen to 28% below the control value, and 45 minutes later it had fallen to 43% below the control value. The return of the ventilatory depression was always associated with the return of the subjective effects of morphine.

The changes in ventilatory response in one subject are shown in fig. 4. A total dose of 30 mg/70 kg of morphine was given during the first 45 minutes of the study and produced the intended degree of respiratory depression. Naloxone 0.4 mg/70 kg reduced the depression to 13% below the control value. Forty-five minutes later ventilation had fallen back to 56% below control value and a further dose of naloxone 0.4 mg/70 kg was followed by an infusion at the rate of 2.4 mg/kg/hr for 45 minutes. The second dose and infusion of naloxone resulted in a limited improvement in the ventilatory response, which was sustained only during the infusion. The other subject who was given an infusion of naloxone responded in a similar manner.

Discussion

The administration of morphine resulted in a significant change in pupil size, pain threshold, and ventilatory response to carbon
Cigarette Smoker’s Bronchitis: The Effect of Relighting

J. RIMINGTON

British Medical Journal, 1974, 2, 591-593

Summary

Male volunteers for mass radiography examination aged 40 or more were questioned about their sputm production, smoking habits, and, when applicable, their method of smoking cigarettes.

St.Thomas's Hospital, Stockport SK3 8BL

J. RIMINGTON, M.D., Medical Director and Consultant Chest Physician, Regional Mobile X-Ray Service, Southern Division, North Western Regional Health Authority

Of 5,438 cigarette smokers 1,051 (19%) claimed that when smoking a cigarette they usually extinguished it at some stage and later relit it to smoke again. Anyone who admitted to producing sputum from his chest on most days of the year or on most days for a minimum of three months of the year for at least the last two years was classed, in the absence of other causative disease, as a chronic bronchitic. Such chronic bronchitics totalled 1,864 (34%).

The rate of chronic bronchitis among relighters (39.7%) was higher than the rate (32.9%) among the remaining cigarette smokers. The difference was of high statistical significance (P < 0.001), and the same pattern was maintained when age and consumption were standar-