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

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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 miotic and subjective 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, 1969; 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 cyclazocine 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 and 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/70kg 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 naloxone 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 clearheaded 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.

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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 ($P > 0.1$).

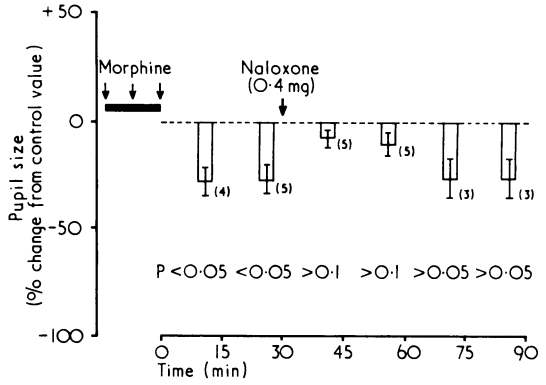

FIG. 1—Effect of intravenous naloxone 0·4 mg/70 kg on pupil size after intravenous morphine (mean dose 30 mg/70 kg) in five subjects. Effects are shown as the mean percentage change (± S.E.) from each subject's control value measured before drug administration. Changes are shown at 15-minute intervals before and after naloxone. Statistical significance of the changes is indicated by P values. Numbers of subjects are shown in parentheses.

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.

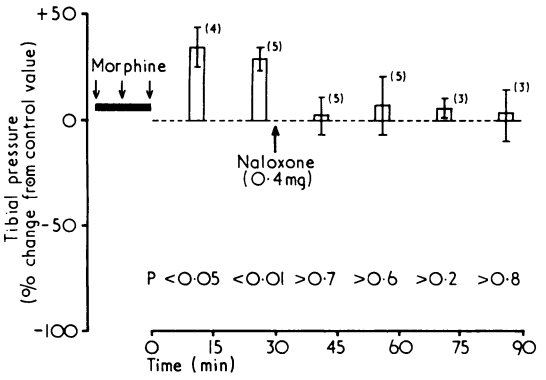

FIG. 2—Effect of intravenous naloxone 0·4 mg/70 kg on pain threshold after intravenous morphine (mean dose 30 mg/70 kg) in five subjects. Effects are shown as the mean percentage change (± S.E.) from each subject's control value measured before drug administration. Mean changes are shown at 15-minute intervals before and after naloxone. Statistical significance of the changes is indicated by P values. Numbers of subjects are shown in parentheses.

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.

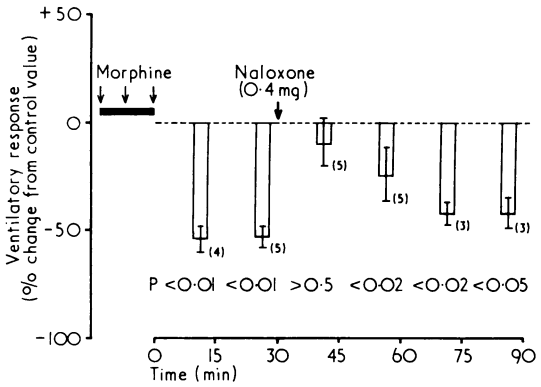

FIG. 3—Effect of intravenous naloxone 0·4 mg/70 kg on ventilatory response to 7% carbon dioxide after intravenous morphine (mean dose 30 mg/70 kg) in five subjects. Effects are shown as mean percentage change (± S.D.) from each subject's control value measured before drug administration. Mean changes are shown at 15-minute intervals before and after naloxone. Statistical significance of the changes is indicated by P values. Numbers of subjects are shown in parentheses.

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.

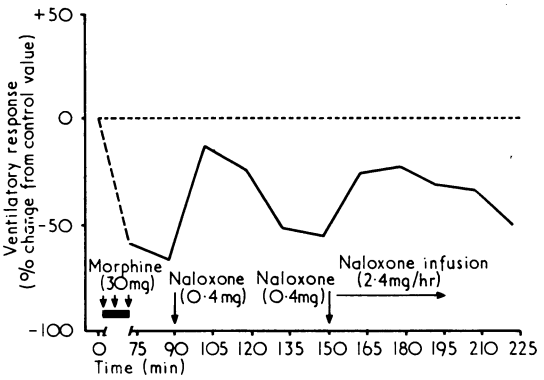

FIG. 4—The effect of intravenous naloxone on ventilatory response to 7% carbon dioxide of one subject after 30 mg of intravenous morphine. Naloxone was given as single dose of 0·4 mg/70 kg at 90 minutes and repeated at 150 minutes. Immediately after second dose an infusion of 2·4 mg/70 kg/hr of naloxone was begun and maintained for 45 minutes.

Discussion

The administration of morphine resulted in a significant change in pupil size, pain threshold, and ventilatory response to carbon

dioxide while psychomotor function and blood pressure were unchanged. Thus the antagonist effect of naloxone could be expected only in the former values. Naloxone was effective in producing a large degree of reversal of the miosis, analgesia, and respiratory depression produced by the morphine. It also consistently produced complete reversal of the subjective effects of morphine. Previously it has been suggested that naloxone may selectively antagonize the respiratory depressant effect of morphine but allow the other effects to persist (Hasbrouck, 1971; Heisterkamp, 1972). The measurements of pain threshold made in this study showed clearly that naloxone antagonizes both the analgesic and respiratory effects of morphine.

Immediately after the injection of naloxone the subjects were unaware of any residual effects of the morphine though in the first measurements made after the injection miosis and respiratory depression were still present. These measurements were made at about six and 12 minutes after naloxone had been given. It is possible, therefore, that complete reversal might have occurred shortly after the injection, and that by the time the particular measurements were made the antagonist action was already declining. Thus these measurements might have represented an underestimate of the degree of reversal produced by naloxone.

The return of respiratory depression after the administration of naloxone has been described in clinical practice (Hasbrouck, 1971; Kersh, 1973; Fink *et al.*, 1968). These reports suggested that the duration of action of naloxone may be relatively short, but they contrast with the findings of Jasinski *et al.* (1968), who found evidence of antagonist activity three to five hours later. The doses of naloxone used in these studies were variable and did not permit a direct comparison to be made. Our results indicated that the duration of action of an intravenous dose of 0·4 mg/70 kg was limited, and little if any effect persisted after 45 minutes. In vitro studies of receptor occupancy by Kosterlitz and Watt (1969) and Kosterlitz *et al.* (1972) have shown the half time of the action of naloxone to range from 12-20 minutes. The half time of recovery cannot be determined accurately from the results of the present study, but it can be roughly estimated in the case of ventilatory response to be between 15 and 20 minutes. In clinical practice the duration of action of naloxone will be influenced by many factors such as the type and amount of narcotic and non-narcotic drugs received by the patient and by the general condition of the patient.

The cause of the evanescent action is unexplained; metabolism or redistribution are both possible explanations. Fujimoto (1969) and Weinstein *et al.* (1971) have shown that naloxone can be metabolised and that after large doses metabolites appear in the urine of animals and man. The rate of metabolism is unknown, and its measurement awaits the development of a suitable method of assay.

Clearly naloxone is an effective morphine antagonist able to produce almost complete and simultaneous reversal of the principal effects of morphine. Other reports indicate that naloxone antagonizes the action of a wide range of narcotic drugs including pentazocine, for which there is no other effective antagonist (Evans *et al.*, 1973; Kallos and Smith, 1968). The absence of any demonstrable agonist side effects makes naloxone substantially superior to its predecessors, and it would seem to have considerable therapeutic potential (Evans *et al.*, 1974). The possibility that its antagonist action may wear off too soon is a hazard; agonist effects could then appear after a latent period. The action of naloxone could be prolonged by the administration of larger doses either intravenously or intramuscularly or by the use of an intravenous infusion. These problems, and the rate of metabolism, are currently under investigation.

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Cigarette Smoker's Bronchitis: The Effect of Relighting

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Summary

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

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-

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