THE ROLE OF NALOXONE INFUSIONS IN THE TREATMENT OF OVERDOSES OF LONG HALF-LIFE NARCOTIC AGONISTS: APPLICATION TO NOR-METHADONE

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This report describes the use of a naloxone infusion at a rate of 300 $\mu\text{g/h}$ to provide constant antagonism of the respiratory depressant effects of a near fatal nor-methadone dose in a 2 year old boy. The terminal half-life for nor-methadone was calculated to be 13.5 h. The results indicate that a single dose of a narcotic antagonist with a short half-life (e.g. naloxone) will probably be inadequate to provide long lasting reversal of the effects of overdoses of long half-life narcotic agonists, and that continuous infusion may be the preferable to repeated bolus doses.

Introduction

Nor-methadone (Ticarda®) is structurally similar to methadone and differs only in the absence of one methyl group attached to the α carbon. The analgesic activity of nor-methadone is similar to that of methadone in mice, as assessed by the time to peak analgesic activity and duration of analgesia following subcutaneous administration (Eddy *et al.*, 1950). However, Kirchhof (1948) found that an oral dose of 50 mg was required for analgesia in man, and this dose was associated with a significant incidence of side effects (unspecified) precluding the widespread clinical use of nor-methadone as an analgesic agent. The primary indication for nor-methadone is as a long acting cough suppressant at the recommended adult dose of 7.5–10 mg twice daily. This report describes the pharmacokinetic and pharmacodynamic data from a near fatal dose of nor-methadone administered to a two year old boy (weight 12.5 kg).

Methods

Nor-methadone solution (10 mg/ml of nor-methadone, 20 mg/ml of *p*-hydroxy-ephedrine, Ticarda®) was prescribed at a dose of 5 drops (approximately 2.5 mg) twice daily for the treatment of croup. A single dose of 5 ml (corresponding to a dose of 4 mg/kg body weight) was administered at 20.00 h due to an incorrectly labelled bottle dispensed by a community pharmacist. Seven hours later, the child was noted to be apnoeic, cyanosed and stiff. He was revived but continued to have shallow respiration and was un-

responsive to command. There was another period of apnoea some 30 min later which was similar in nature to the first episode.

The child was transferred to hospital with oxygen therapy and his respiratory rate was 12 breaths/min. At this time, he responded to command with pin point pupils which reacted to light. However, on admission, he was responsive only to painful stimulation with a respiratory rate of 16 breaths/min. During the next hour, the extent of CNS depression oscillated between the extremes described above. A provisional diagnosis of nor-methadone overdose was made and a blood sample for nor-methadone concentration collected. Additional blood samples were collected for estimation of nor-methadone concentration at the times indicated in Figure 1. The gas chromatographic technique used to measure the amount of nor-methadone in the blood samples was identical to that used for methadone as previously published (Gourlay *et al.*, 1983). The retention times for nor-methadone and bupivacaine (internal standard) were 1.9 and 3.4 min respectively. The standard curves were linear and passed through the origin.

Results

Naloxone (100 μg) was administered intravenously, and produced an immediate response consisting of dilated pupils, spontaneous movement, crying and a significant croup-like cough. Over the following 1–2

Figure 1 Naloxone dose, respiratory rate and blood nor-methadone concentration as a function of time (min) following a 50 mg dose administered to a 2 year old boy.

(a) Naloxone dose (μg). The tip of the arrows indicate the naloxone dose (either 100, 200, 300 or 400 μg) administered at the time indicated. Naloxone was administered as an intravenous infusion at a rate of 300 $\mu\text{g}/\text{h}$ from 1680 min to 2300 min with a continuous improvement in the child's condition. Total naloxone dose was 7000 μg .

(b) Changes in respiratory rate (breaths/min) resulting from naloxone administration. Pre-naloxone rates were generally between 12–16.

(c) Blood nor-methadone concentration (ng/ml) as a function of time. The initial blood nor-methadone concentration of 710 ng/ml was collected prior to any naloxone being administered.

h, the patient became progressively drowsy with pin point pupils and only responding to painful stimuli. Additional and increased naloxone doses were administered as indicated in Figure 1a which resulted in reversal of narcosis, for example, the respiratory rate increased from 12–16 breaths/min to 24–32 breaths/min (Figure 1b) and pupils dilated. However, a progressive deterioration in the child's condition always occurred 30–60 min following i.v. naloxone. Naloxone was administered by continuous i.v. infusion at a rate of 300 $\mu\text{g}/\text{h}$ commencing from 1680

min and terminating at 2300 min following nor-methadone ingestion (Figure 1) to constantly antagonise the narcotic effects of nor-methadone. The total naloxone dose was 7.0 mg administered over 28 h. The child recovered without any apparent sequelae and was discharged from hospital 3 days after admission.

The linear relationship shown on the log blood concentration–time curve (Figure 1c) suggests that all the blood samples were collected in the elimination phase, with the terminal half-life calculated to be 13.5 h. The first blood sample collected 13.8 h after nor-methadone ingestion and prior to any naloxone administration had a nor-methadone concentration of 710 ng/ml which was associated with shallow respiration at a rate of 16 breaths/min.

Discussion

At the present time, there are no blood concentration–response relationships available for nor-methadone. However, for comparison, the minimum effective analgesic blood concentration for methadone in adults with post-operative pain (following the i.v. administration of 20 mg methadone) ranges from 20–60 ng/ml (mean value of 30 ng/ml). The terminal half-life varies from 10–78 h in these post-operative patients (Gourlay *et al.*, 1983). Both nor-methadone and methadone are metabolised by similar routes in a range of animal species which involves *N*-demethylation followed by spontaneous rearrangement to produce pyrrolidine derivatives and *N*-oxide formation (Beckett *et al.*, 1971a). There were, however, quantitative differences with nor-methadone being metabolised by *N*-oxidation to a larger extent and *N*-demethylation by a lesser extent when compared to methadone in various animal species (Beckett *et al.*, 1971b). Similar metabolic pathways have been shown for the metabolism of methadone in man.

Although this report only considered data following a single dose in a young child, there are the expected similarities in pharmacokinetics between methadone in various animal species (Beckett *et al.*, supports the empirically obtained frequency of dosing of once or twice daily for nor-methadone. The calculated blood nor-methadone concentration at the initial apnoeic period (7 h from dosing) would be 1050 ng/ml assuming that drug absorption was complete at that time. Experimental evidence in support of this assumption obtained from methadone studies were the findings that: (1) peak methadone concentrations occurred between 2–3 h following oral doses in chronic pain patients referred to the pain management unit; and, (2) methadone has a rapid distribution phase with a mean value of 7 min (calculated from i.v. pharmacokinetic data).

Naloxone, which is almost devoid of agonist

effects, has become the agent of choice to antagonise the respiratory depressant effects of relative overdoses of narcotics. The extent of antagonism depends on the nature and dose of agonist and the naloxone dose. However, the recommended naloxone dose (5–10 $\mu\text{g/kg}$) frequently provides only a short duration of reversal as a result of the short naloxone elimination half-life, necessitating repeated intravenous bolus doses of naloxone. This treatment regimen is inconvenient, requires constant supervision and can allow the patient to frequently relapse into narcosis. Continuous i.v. infusion of naloxone would be an alternative method of administration which would overcome many of these disadvantages. Bradberry & Raebel (1981) have shown that a continuous i.v. naloxone infusion at a rate of $2.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ provided prolonged antagonism following overdose of either methadone or heroin in two adult patients. However, in the present study, a much greater rate (i.e. $24 \mu\text{g kg}^{-1} \text{h}^{-1}$) was required to

provide optimal and prolonged antagonism of the narcotic effects of nor-methadone overdose with no apparent adverse effects suggestive of naloxone toxicity.

This greater rate of naloxone infusion may possibly reflect the large relative overdose of nor-methadone (4 mg/kg) and indicates the necessity to titrate the naloxone dose to obtain optimal reversal of narcosis.

This report indicates that a single dose of a short half-life narcotic antagonist, naloxone, will probably be inadequate to provide continuous antagonism of the effects of overdoses of long half-life narcotic agonists e.g. methadone and nor-methadone.

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