Differential Effects of Alfentanil, Fentanyl, Pethidine and Lignocaine Administered Intrathecally on Nociceptive Responses Evoked by Low and High Frequency Stimulation of Somatic Nerves


Summary

We have studied in anaesthetized dogs the effects of alfentanil, fentanyl, pethidine and lignocaine administered intrathecally on nociceptive responses evoked by low and high frequency supramaximal electrical stimulation of the tibial and radial nerves. Doses were selected to abolish both Aδ and C fibre somatosympathetic reflexes to single stimuli. Pethidine and lignocaine eliminated reflex pressor and heart rate responses to repeated single stimuli and almost completely abolished responses to train stimulation. The pressor response to single stimuli was abolished by fentanyl and reduced by alfentanil, but these drugs did not reduce significantly this response to train stimulation, suggesting a stimulation rate-dependent effect. Of the opioids, only pethidine had an effect comparable to that of lignocaine. The absence of sympathetic block and antagonism by naloxone imply a lack of significant local anaesthetic effect. We suggest that the greater analgesic efficacy of pethidine is a result of endogenous synergism between a minor local anaesthetic and a major opioid effect.

Key Words


Opioids and local anaesthetic drugs cause analgesia when applied to the spinal cord; however, the efficacy of opioids for the relief of acute pain in some circumstance (for example during surgical or obstetric procedures) is often inadequate compared with local anaesthetics [1, 2]. The addition of small concentrations of local anaesthetics to opioids may be used to improve the quality of pain relief [2, 3]. Differences in the efficacy of the analgesic response to opioids may relate to the type of stimulation which presents to the dorsal horn cells. It is known that acute pain is accompanied usually by sympathetic responses which have been used to measure pain by recording either sympathetic nerve activity or, for example, changes in arterial pressure. In contrast, pain without acute episodes may not be accompanied by overt sympathetic responses. The differences in the type of stimulation are either its origins or its severity, which would include intensity and the numbers and firing frequency of afferent fibres.

This study was undertaken to test if the frequency of stimulation can modulate the antinociceptive effects of alfentanil, fentanyl, pethidine and lignocaine. We chose two different types of afferent somatic stimuli. The first was a series of single electrical stimuli supramaximal for activation of both Aδ and C fibre-mediated responses at 0.33 Hz, and the second comprised stimuli of the same intensity applied as 10-s trains at 30 Hz.

Materials and Methods

Investigations were carried out in 15 greyhound dogs weighing between 27.6 and 32.6 kg (approved under Home Office Licence No PPL 70/01654). Anaesthesia was induced with methohexitone 15 mg kg⁻¹ i.v., the trachea was intubated and the lungs ventilated with oxygen enriched air. Anaesthesia was maintained using 1% α-chloralose in an initial bolus dose of 30 mg kg⁻¹ i.v. followed by a continuous infusion of 17.5 mg kg⁻¹ h⁻¹ i.v. and muscle paralysis was maintained using suxamethonium 10 mg i.v. every 30 min. The left femoral artery and vein were cannulated for arterial pressure recording, blood sampling, drug administration and fluid infusion. Arterial pH was maintained in the range 7.30–7.35, \( P_{\text{a}O_2} \) 20–27 kPa, \( P_{\text{a}CO_2} \) 4.5–5.5 kPa and oesophageal temperature 37–39 °C.

A site for intrathecal (i.t.) drug injection was prepared by removal of the lamina of the 2nd and 3rd lumbar vertebrae, exposure of the dura mater and intradural cannulation with a 22-gauge Y-can. Lateral superficial branches of the radial and tibial
nerves were exposed in the left foreleg and right hind leg, respectively. Both nerves were desheathed, cut distally, immersed in mineral oil and mounted on silver electrodes. The renal sympathetic nerves were exposed retroperitoneally along the right renal artery. Single fascicles of nerve were desheathed, cut distally near the kidney, immersed in a mineral oil pool and mounted on silver–silver chloride electrodes. The preparation was maintained throughout in a lateral position with head up tilt of 15° to prevent ascending spread of intrathecal drugs.

The mean arterial pressure (MAP) was measured with a calibrated strain gauge and displayed together with the beat-by-beat heart rate (HR) using a heated stylus recording system (Devices M19).

Repeated single supramaximal electrical stimuli (frequency 0.33 Hz, intensity 30 V and duration 0.5 ms) and 10-s trains of high frequency stimuli (30 Hz, intensity 30 V and duration 0.5 ms) were applied to both the tibial and radial nerves using a Grass S88 stimulator with matched directly coupled isolation unit (Grass 478A). Efferent activity in renal sympathetic nerves was processed through a preamplifier (Tektronix type 122) and displayed on a dual-beam oscilloscope (Tektronix type 565). Average transients of the evoked sympathetic responses were obtained using a Neurolog system (NL750 Digitimer) and 16 responses were averaged on each occasion. The averaged responses were rectified and integrated (Neurolog NL90) and both signals were displayed on a pen recorder (Devices MX2).

After being set up, the preparation was allowed to stabilize for 30 min, when control data were obtained. To record the evoked responses in MAP and HR caused by repeated single stimuli, the stimulation was sustained for up to 1 min to allow development and stabilization of the maximal response in MAP and HR. The changes in MAP and HR evoked by repeated single and train stimuli were measured as the peak responses (fig. 1). The MAP and HR were then allowed to return to prestimulus control values. The evoked response in renal sympathetic nerves could not be recorded during train stimulation, as the repeated stimulus artefact interferes with and distorts the sympathetic signal.

The doses of alfentanil, fentanyl, pethidine and lignocaine were chosen to just abolish the evoked reflexes in renal sympathetic nerves to repeated single stimuli applied to the tibial nerve in a series of preparations. The doses for alfentanil 7.5 mg (5 mg ml\(^{-1}\)) and fentanyl 0.15 mg (0.05 mg ml\(^{-1}\)) had been determined in previous studies [4, 5]. In the
INTRATHecal OPIOIDS AND SYMPATHETIC REFLEXES

Figure 2. Typical recording of the effects of pethidine administered i.t. followed by naloxone i.v. on the responses in a renal sympathetic nerve evoked by a single electrical stimulus (30 V, 0.5 ms duration, 0.33 Hz) applied to the tibial (T) and radial (R) nerves. Lower trace: average transient of 16 responses. Upper trace: rectified integral of averaged signal. 1 = Control; 2 = 5 min after pethidine 30 mg i.t.; 3 = 5 min after naloxone 2 mg i.v. It can be seen that pethidine did not affect the radial somatosympathetic reflexes (upper traces) to any significant degree and that its effect on tibial nerve stimulation was antagonized completely by naloxone. This indicates that the action of pethidine is not primarily a local anaesthetic effect.

Figure 3. Effects of alfentanil administered i.t. followed by naloxone i.v. on the responses in a renal sympathetic nerve evoked by a single electrical stimulus (30 V, 0.5 ms duration, 0.33 Hz) applied to the tibial (T) and radial (R) nerves. Lower trace: average transient of 16 responses. Upper trace: rectified integral of averaged signal. 1 = Control; 2 = 5 min after alfentanil 7.5 mg i.t.; 3 = 5 min after naloxone 2 mg i.v.

above was repeated to confirm that the preparation had returned to its control state. Lignocaine 10 mg (10 mg ml⁻¹) was then injected i.t. in all preparations and a similar random series of stimulations and measurements was repeated. The duration of these experiments varied between 7 and 9 h.

Statistical analysis was performed with analysis of variance, where appropriate, followed by paired Student's t tests.

Results

Somatosympathetic reflexes

Tibial nerve stimulation. Alfentanil 7.5 mg, fentanyl 0.15 mg, pethidine 30 mg and lignocaine 10 mg administered i.t. abolished both the Aδ and C-reflexes in the renal sympathetic nerves evoked by single stimuli applied to the tibial nerves of all the dogs (figs 2-4).

Radial nerve stimulation. The somatosympathetic reflexes evoked by radial nerve stimulation were unaffected by fentanyl and pethidine (fig. 2). In contrast, in preparations receiving alfentanil, whereas the Aδ fibre-mediated reflexes in renal sympathetic nerves did not change significantly, the C fibre-mediated longer latency reflex was abolished, suggesting either systemic absorption or supraspinal spread (fig. 3) [4]. Lignocaine i.t. completely abolished the reflexes in renal sympathetic nerves to both tibial and radial nerve stimulation (fig. 4), because it blocks the efferent sympathetic nerves.
control values after alfentanil and fentanyl. While this was also true for MAP with pethidine (table I), the response in HR to low frequency stimulation was reduced. However, in the group receiving pethidine there was an increase in resting mean heart rate of 9 beat min⁻¹ after i.t. administration (table I) (ns). This could explain this phenomenon, as, during train stimulation, a larger sympathetic response occurred which increased the HR to a mean value of 201 beat min⁻¹—a mean increase of 39 beat min⁻¹ in the pethidine group compared with an increase in HR in the fentanyl group of 34 beat min⁻¹ (table I). Lignocaine i.t. caused a small but statistically nonsignificant reduction in the reflex increases in MAP and HR in response to both low and high frequency stimulation (table I).

**DISCUSSION**

High strength electrical stimulation of somatic nerves causes reflex responses in the autonomic nervous system which are manifest, for example, by changes in arterial pressure [6, 7]. Directly recorded sympathetic nerve responses to single electrical stimuli applied to a somatic nerve show two bursts of activity mediated by afferent Aδ and C fibres [8, 9]. In this study the doses of alfentanil, fentanyl, pethidine and lignocaine used were the minimal required to just eliminate both the Aδ and C fibre-mediated responses evoked in renal sympathetic nerves to repeated single supramaximal electrical stimuli applied to the tibial nerve. The increase in MAP in response to repeated single stimulation was also abolished completely by fentanyl, pethidine and lignocaine. A large dose of alfentanil was required to abolish the Aδ reflex, with evidence of baroreflex sensitization causing a significant reduction in both MAP and HR (P < 0.05) (table I, fig. 3) and a small arterial pressure response persisted (fig. 5). This confirms previous observations which also indicated that the elimination of the tibial Aδ fibre-mediated reflex after alfentanil required a dose which had more general central effects, resulting either from systemic absorption or from supraspinal spread [4].

During high frequency train stimulation with the same stimulus intensity, the reflex increase in MAP was abolished almost completely by pethidine and abolished completely by lignocaine. In contrast, the evoked increases in MAP did not change significantly from control values after both alfentanil and fentanyl; this suggests that the antinociceptive effect of these opioids is dependent on the frequency of stimulation. Thus a dose which abolishes the effect of low frequency afferent stimulation does not necessarily provide adequate “analgesia” at higher frequencies of stimulation even when its duration is relatively short—10 s in the present study. This phenomenon could be one factor explaining the relative ineffectiveness of the opioids, compared with local anaesthetic drugs, in relieving severe intraoperative pain.

A further increase in the intrathecal dose of fentanyl could possibly cause depression of the nociceptive response in arterial pressure evoked by high frequency stimulation. However, this may not
### Table I

Mean (SD) mean arterial pressure (MAP) and heart rate (HR) from non-stimulation control values (resting), repeated single stimulation (0.33 Hz, 30 V, duration 0.5 ms) and 10-s train of stimulation (30 Hz, 30 V, duration 0.5 ms) applied to the tibial and radial nerves before and after drug treatment. *P < 0.05: * compared with non-stimulation either during control or after drug administration; † compared with non-stimulated control values before and after drug administration, indicating a degree of baroreceptor sensitization in the alfentanil group.

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<th>Tibial nerve</th>
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<td><strong>Control</strong></td>
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<td>Alfentanil 7.5 mg i.t. (n = 5)</td>
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<td>MAP (mm Hg)</td>
<td>154 (7)</td>
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<td>HR (beat min⁻¹)</td>
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<td>Fentanyl 0.15 mg i.t. (n = 5)</td>
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<td>MAP (mm Hg)</td>
<td>154 (7)</td>
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<td>HR (beat min⁻¹)</td>
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<td>Pethidine 30 mg i.t. (n = 5)</td>
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<td>MAP (mm Hg)</td>
<td>165 (13)</td>
<td>179 (14)*</td>
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<td>HR (beat min⁻¹)</td>
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<td>170 (9)*</td>
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<td>MAP (mm Hg)</td>
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<td>HR (beat min⁻¹)</td>
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<td>MAP (mm Hg)</td>
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<td>HR (beat min⁻¹)</td>
<td>80 (13)†</td>
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<td>HR (beat min⁻¹)</td>
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<td>MAP (mm Hg)</td>
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<td>HR (beat min⁻¹)</td>
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**Fig. 5.** Percentage increase (mean, SD) in mean arterial pressure (MAP) from non-stimulation control evoked by repeated single stimulation (S) and 10-s train tetanic stimulation (T) applied to the tibial nerve before and after alfentanil 7.5 mg (n = 5), fentanyl 0.15 mg (n = 5), pethidine 30 mg (n = 5) and lignocaine 10 mg (n = 15), administered i.t. *P < 0.05 compared with control.

**Fig. 6.** Percentage increase (mean, SD) in heart rate (HR) from non-stimulation control evoked by a repeated single stimulation (S) and 10-s train tetanic stimulation (T) applied to the tibial nerve before and after alfentanil 7.5 mg (n = 5), fentanyl 0.15 mg (n = 5), pethidine 30 mg (n = 5) and lignocaine 10 mg (n = 15), administered i.t. *P < 0.05 compared with control.
occur with alfentanil, because the dose used in these experiments was very large—7.5 mg i.t., with evidence of cardiovascular effects related to either systemic absorption or supraspinal diffusion. In addition, the depression and abolition of the reflex nociceptive cardiovascular response to train stimuli may not be achieved even when the dose of fentanyl is increased to a very high concentration. It is reported that the effectiveness of spinal opioids in providing further analgesia in man does not always occur with an increase in dose beyond an adequate level of analgesia [2]. The dose of fentanyl administered in this study was greater than that used usually in clinical practice [2]. Moreover, the potential risk of respiratory depression is also increased when larger doses of opioids are used.

The site of action of spinally applied opioids is in the dorsal horn [10, 11] and fentanyl, alfentanil and pethidine act via mu opioid receptors which involve potassium channels [12], whereas local anaesthetic drugs act predominantly on the sodium channels in axonal membranes [13]. There is evidence that the effect of local anaesthetics may differ on sympathetic, sensory and motor fibres [14]. Cousins [13] suggested that block of primary afferent transmission is a more potent method of producing pain relief than local inhibition in the spinal cord—a view based on evidence from clinical pain studies with spinally applied opioids and local anaesthetics.

Pethidine was introduced in 1939 [15]. In 1946, Way [16] showed that it could produce corneal analgesia, sciotic nerve block and intradermal analgesia, suggesting that it was a local anaesthetic. Until the present study, this was the basis of the explanation for its superiority over other opioids as an analgesic drug when applied topically [2, 17]. However, in this study pethidine had an effect similar to that of lignocaine on the reflex increase in MAP in response to both repeated single and train stimulation applied to the tibial nerve. This could be interpreted as a local anaesthetic effect but there was no evidence for this, as its effects were antagonized completely by naloxone (fig. 2). Also, comparison of the effects of pethidine and lignocaine on the somatosympathetic responses evoked by radial nerve stimulation showed that, while pethidine (fig. 2) blocked the afferent pathway, there was no evidence of efferent sympathetic block. This contrasts with lignocaine, which blocked both the efferent sympathetic and afferent nociceptive pathways (fig. 4). The increase in MAP evoked by both single and train stimulation of the radial nerve was reduced slightly after lignocaine, compared with pethidine, which would be compatible with limited local block of the efferent sympathetic system.

Pain relief in labour following extradural opioids has been disappointing and the addition of bupivacaine is recommended [18-20]. However, i.t. pethidine has been used successfully in labour [21] and for Caesarean section [22, 23]. It has provided satisfactory saddle block for perineal surgery [24], and it has been used for prostatic surgery [25]. It has also been reported that, after major abdominal surgery, a combination of extradural morphine and local anaesthetic provided better analgesia than morphine alone [3] and there is synergism between morphine and lignocaine [26]. Synergism between this putative local anaesthetic property and the major opioid action, observed in the present study, could explain its greater effectiveness compared with fentanyl and alfentanil. For example, a combination of 0.0625 % bupivacaine and 0.0002 % fentanyl has been shown to produce analgesia in labour [27].

Another possible explanation for the effectiveness of pethidine is that it could, conceivably, act at kappa receptors, in addition to mu receptors, in the spinal cord. Kappa receptors account for more than 50 % of opioid receptors in the human spinal cord [28]. The kappa receptor may also predominate in some other higher mammalian species [29].

In conclusion, this study shows that an intrathecal dose of opioids which causes a reduction in the reflex sympathetic and cardiovascular responses to repeated single nociceptive stimuli may not depress such reflexes to stimulation of the same intensity but at a greater frequency. It provides a hypothesis for one contributory factor to the observation of the relative ineffectiveness of opioid analgesia in many clinical situations. It also shows that pethidine is a more effective "analgesic" drug than either fentanyl or alfentanil. It does not cause measurable block of efferent sympathetic activity, which could be an advantage compared with lignocaine. The fact that its effects are antagonized by naloxone allow a further intriguing hypothesis that a single drug, pethidine, may provide endogenous synergism between a small local anaesthetic effect and a major opioid action, which would explain or reconcile many previous experimental and clinical observations.

REFERENCES
10. Hammond DL. Intrathecal administration: methodological


