LACK OF A CEILING EFFECT FOR INTRATHECAL BUPRENORPHINE ON C FIBRE MEDIATED SOMATOMYOSYMPATHETIC REFLEXES

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SUMMARY

We observed that buprenorphine 20 μg kg⁻¹ i.v. in dogs caused an initial significant reduction in both Aδ and C fibre mediated somatosympathetic reflexes evoked by tibial and radial nerve stimulation, to approximately 75% and 70% of control values. Larger doses (up to 100 μg kg⁻¹ i.v.) had progressively less effect and the mean responses were depressed to only approximately 65% and 55% of control, indicating a ceiling effect. Buprenorphine 450 μg intrathecally (i.t.) completely abolished tibial C fibre reflexes, but 20% of Aδ responses could not be eliminated with doses up to 1050 μg i.t. Fentanyl 100 μg kg⁻¹ i.v. or 150 μg i.t. after buprenorphine i.v. or i.t., respectively, had little additional effect. This study confirms the limited ceiling effect of buprenorphine on nociceptive reflexes when administered systemically, and provides evidence that when administered i.t. in sufficient doses it abolishes the C responses (lack of ceiling effect for C responses), but the Aδ responses show a plateau or ceiling effect. (Br. J. Anaesth. 1993; 71: 528-533)

KEY WORDS

Partial opioid agonist-antagonists, such as buprenorphine, are considered to have a bell-shaped dose-response curve in their actions,—that is, a ceiling effect [1], such that analgesia can be achieved without respiratory or cardiovascular depression. However, severe respiratory depression and apnoea have been reported after administration of buprenorphine extradurally [2], sublingually [3] and i.m. [4], unresponsive to naloxone in doses of 0.2–1 mg i.v. [2, 3]. Thus it appears that there is no ceiling effect on respiratory depression. This is in disagreement with the concept of a ceiling effect, for example, for analgesia as suggested previously [1], although buprenorphine administered spinaly has in general produced satisfactory analgesia, for example in postoperative patients [1]. Also, there was no sign of a ceiling effect during studies of analgesia using rat tail-flick and writhing tests [5]. However, such studies are often limited in the amount of pain which can be induced in a conscious animal while avoiding tissue damage. Thus it is uncertain if buprenorphine has a ceiling effect on nociception in the spinal cord and the effects of the drug may differ when it is administered via the intrathecal (i.t.) or i.v. routes.

This study was undertaken to provide more information on the potential selectivity or otherwise of the ceiling effect of buprenorphine, for example, on the somatosympathetic responses evoked by small myelinated group III (Aδ) and unmyelinated group IV (C) fibres in the somatic nerves. This would provide a possible explanation of unexpected clinical phenomena inappropriate for its putative pharmacological profile.

METHODS

Experiments were approved by the Home Office (Project Licence No. PPL 70/01654). Eight greyhound dogs (weight 25.2–29.7 kg) were anaesthetized with 1% methohexitone 15–20 mg kg⁻¹ i.v. followed by 1% α-chloralose 30 mg kg⁻¹ i.v. as a bolus and thereafter 17–20 mg kg⁻¹ h⁻¹ by infusion. The trachea was intubated and the dog paralysed with suxamethonium 10 mg kg⁻¹ i.v. every 30 min; the lungs were ventilated mechanically with oxygen-enriched air. The femoral artery and vein were cannulated. pH, Pao₂, Paco₂, Pao₂, and oesophageal temperature were maintained in the ranges 7.30–7.35, 4.5–5.5 kPa, 23–27 kPa, and 37–39 °C, respectively, throughout. Mean arterial pressure (MAP) measured using a strain gauge transducer, together with beat-by-beat heart rate (HR) obtained from ECG were recorded on a heated stylus system [Devices M19] throughout.

Surgical procedures

Intrathecal cannulae (22G Y-can, Wallace Ltd) were inserted through the dura which was exposed by lumbar laminectomy (L2–3). The renal sympathetic nerves were exposed retroperitoneally along

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the renal artery. A lateral superficial branch of the radial nerve in the left foreleg and a tibial nerve in the right hindleg were exposed. All nerves were dissected, cut distally and desheathed at the recording and stimulating sites.

Nerve stimulation and recording
All nerves were mounted on silver–silver chloride electrodes in a warm paraffin pool. Supramaximal electrical stimuli (0.33 Hz, 30 V and 0.5 ms) were applied to the radial and tibial nerves using a Grass S88 stimulator with matching direct-coupled isolation units (Grass 478A).

The evoked responses in renal sympathetic nerves have two components corresponding to activation of Aδ and C fibre pathways, respectively [6, 7]. The signals from the renal sympathetic nerves were processed through a preamplifier (Tektronix 122) and displayed on an oscilloscope (Tektronix 565). Groups of 16 evoked responses were averaged (Neurolog NL750), rectified and integrated (Neurolog NL703). Both rectified and integrated signals were recorded on a hot stylos recorder (Lectromed multi trace 2). The integrated signals were displayed also on a Gould 1602 system which also measured the total averaged electrical activity in arbitrary units. On each occasion, two recordings of the averaged evoked responses were measured.

Drug administration

I.v. buprenorphine. A total dose of 100 µg kg⁻¹ was administered by an infusion in four preparations. The initial rate of infusion was 2.5 µg kg⁻¹ min⁻¹ to a total dose of 30 µg kg⁻¹ and thereafter 5 µg kg⁻¹ min⁻¹. After total doses of 10 µg kg⁻¹, 20 µg kg⁻¹, 30 µg kg⁻¹ and 50 µg kg⁻¹, the infusion was stopped and two averaged somatosympathetic reflexes were recorded which required approximately 5.0 min, after which the infusion was restarted. Fentanyl 100 µg kg⁻¹ was injected i.v. as a bolus 15 min after total doses of buprenorphine of 100 µg kg⁻¹.

I.t. buprenorphine was also administered in another four preparations in incremental doses of 20 µg, 20 µg, 40 µg, 80 µg, 140 µg and 150 µg, each in 0.5 ml diluted when necessary with physiological saline solution (0.9 %), and finally 600 µg in 2 ml, at intervals of 10 min. Fifteen minutes after the last dose of buprenorphine, fentanyl 150 µg (3 ml) was administered i.t.

Fifteen minutes after the last dose of fentanyl, naloxone was administered i.v. in two doses each of 2 mg at 10 min intervals, in all preparations.

Analysis of variance and paired t tests, where appropriate, were used for statistical analysis.

RESULTS

I.v. buprenorphine

Tibial nerve stimulation. The Aδ and C fibre-mediated somatosympathetic responses were reduced significantly, to 75.4 % and 72.1 % of control values, respectively (P < 0.05), after buprenorphine 20 µg kg⁻¹. However, a much greater dose produced little additional effect and when the dose was increased to a total of 100 µg kg⁻¹ the Aδ and C reflexes were depressed to only 67.5 % and 57.4 %, respectively, of control. There were no statistically significant differences between the effects of buprenorphine on the Aδ and C reflexes.

After buprenorphine, fentanyl 100 µg kg⁻¹ i.v. produced only a small further depression of the Aδ reflexes, but had no effect on C reflexes (figs 1, 2), whereas in an opioid naive preparation this dose of fentanyl would be expected to abolish both Aδ and C fibre-mediated somatosympathetic reflexes in an identical animal model [8].

Radial nerve stimulation. The effects of buprenorphine i.v., followed by fentanyl i.v., on the Aδ and C fibre-mediated somatosympathetic responses evoked by stimulation of the radial nerve were similar to its effect on tibial nerve responses.

I.t. buprenorphine

Tibial nerve stimulation. Both Aδ and C fibre-mediated somatosympathetic responses evoked by stimulation of the tibial nerve were depressed significantly, to approximately 65 % of control values (P < 0.05) after buprenorphine 80 µg. The Aδ and C reflexes were inhibited to approximately 55 % and 30 % of control, respectively, (P < 0.05) after total doses of buprenorphine 160 µg. Whereas the C reflexes were abolished completely after total doses of 450 µg, the Aδ reflexes were reduced on average to only 22.8 % of control (P < 0.01) and larger doses, even up to 1050 µg, produced no further effect on the Aδ responses, indicating a ceiling or plateau effect for the Aδ but not the C responses.

After buprenorphine i.t., fentanyl 150 µg i.t. produced no additional effect on Aδ reflexes (figs 2, 3) and this dose of fentanyl in the absence of buprenorphine would be expected to abolish this reflex [9].

Radial nerve stimulation. There were no statistically significant changes in the Aδ and C reflexes evoked by radial nerve stimulation throughout in the preparations receiving i.t. buprenorphine and fentanyl. Although both responses were reduced slightly after a total dose of 1050 µg, as a result of either systemic absorption or supraspinal spread, the reduction did not reach statistical significance (figs 2, 3).

Cardiovascular changes

The averaged MAP was reduced significantly, to 155 mm Hg and 145 mm Hg from the control value of 170 mm Hg after buprenorphine 50 and 100 µg kg⁻¹ i.v., respectively. HR was also depressed significantly, to 125, 95, 85 and 80 beat min⁻¹ from 140 beat min⁻¹ after buprenorphine 20, 30, 50 and 100 µg kg⁻¹ i.v., respectively. After buprenorphine, fentanyl 100 µg kg⁻¹ i.v. reduced the mean MAP to
Fig. 1. Effects of i.v. buprenorphine followed by fentanyl and naloxone on Aδ (early response) and C (late response) fibre-mediated somatosympathetic reflexes, in a renal sympathetic nerve evoked by supramaximal electrical stimulation of the radial and tibial nerves (0.33 Hz, 30 V, 0.5 ms duration), in one representative preparation. Upper traces are the rectified integral of averaged signals and lower traces are averaged transients of 16 responses. Left to right: 1 = control; 2 = buprenorphine total doses of 20 μg kg⁻¹ i.v.; 3 = buprenorphine total doses of 100 μg kg⁻¹ i.v.; 4 = 5 min after fentanyl 100 μg kg⁻¹ i.v.; 5 = 5 min after naloxone total dose 4 mg i.v.

Fig. 2. Effects of buprenorphine (i.v. and i.t.) followed by fentanyl 150 μg i.t. (F150) or 100 μg kg⁻¹ i.v. (F100) on the mean processed data (mean, SD as % of control; n = 4) of somatosympathetic reflexes evoked by supramaximal electrical stimulation of radial and tibial nerves. The dose of buprenorphine is shown on the logarithmic scale as the cumulative dose. ● = Response to Aδ fibres; ○ = response to C fibres. Aδ and C fibre-mediated responses relative to control: *P < 0.05, **P < 0.01; C reflexes compared with Aδ: †P < 0.05.
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135 mm Hg from 145 mm Hg and HR to 75 beat min⁻¹ from 80 beat min⁻¹ (fig. 4).

Buprenorphine i.t. had only a small depressant effect on MAP and HR, and after the larger dose (1050 µg i.t.) mean MAP was depressed to only 150 mm Hg from the control value of 175 mm Hg, while HR decreased from 150 to 125 beat min⁻¹. After i.t. buprenorphine, fentanyl 150 µg i.t. caused no further significant depression of either MAP or HR.

Naloxone

After naloxone 2 mg i.v., in the preparations receiving buprenorphine i.v. and fentanyl i.v. tibial Aδ and C reflexes returned to 51.3% and 56.9% of control values and radial Aδ and C reflexes returned to 49.5% and 53.0% respectively; in the preparations receiving opioids i.t., tibial Aδ and C reflexes returned to 76.6% and 88.9% of control values, respectively. These reflexes all returned to control values after the second dose of naloxone (total dose 4 mg). Naloxone 4 mg i.v. was required also to reverse fully the depressant effects of buprenorphine on MAP and HR.

DISCUSSION

This study clearly shows that, in common with opioid μ agonists, buprenorphine administered i.t. abolished the C fibre-mediated somatosympathetic reflexes. Unlike the μ agonists, it does not completely eliminate the Aδ reflexes,—that is, there is a plateau or ceiling effect for small myelinated fibre-mediated responses. However, when administered i.v., buprenorphine shows a smaller selectivity in depressing C reflexes compared with the i.t. route, and it has a ceiling effect for both Aδ and C fibre-mediated responses. Hence both the selectively and total effects of buprenorphine are in marked contrast with the pure μ agonists, with which selectivity for C reflexes and abolition of both Aδ and C responses occur after administration by i.v. and i.t. routes [8, 9].

A further increase in the dose of buprenorphine i.v. may possibly produce more depression of the Aδ and C reflexes. However, the dose used in the present study was 100 µg kg⁻¹ i.v., which is a very large dose. Moreover, after a dose of 20 µg kg⁻¹ i.v. there was only a small further reduction in both Aδ and C reflexes with greater doses. Thus, in therapeutic terms, a ceiling effect probably exists, as the dose–response curves for i.v. buprenorphine suggest that a greater depression leading to abolition of the Aδ and C fibre-mediated somatosympathetic reflexes is unlikely to occur. Moreover, Kato, Saeki and Ogawa [10] reported that, while buprenorphine 6 µg kg⁻¹ i.v. had no effect on either A or C fibre-
mediated somatosympathetic responses in cats, the somewhat larger dose of 60 μg kg⁻¹ markedly depressed the C responses, and that this effect was antagonized by much greater doses up to 300 μg kg⁻¹. Dickenson, Sullivan and McQuay [11] also showed that, in rats, buprenorphine i.v. had no effect on the C fibre-mediated spinal reflexes, even at a dose of 4000 μg kg⁻¹ i.v., but for i.t. buprenorphine a dose of only 125 μg depressed the C responses to 46% of control. Previously, other studies also found in rats that systemic buprenorphine had a bell-shaped dose–response curve for tail-flick [12, 13] and hot-plate tests [14]. In contrast, i.t. buprenorphine was effective against tail-flick and there was no indication of a ceiling effect against the writhing test, but it showed only a weak effect against the hot-plate test [5]. These previously reported differences between the i.v. and i.t. routes are supported by the findings of the present study. The existence of a ceiling effect for the Aδ reflexes for both i.t. and i.v. routes of administration could explain the lower efficacy of this drug in severe pain.

The fact that a ceiling effect may not always be present for a particular action of buprenorphine, as demonstrated in the present study for C fibre-mediated reflexes after i.t. administration, would imply that the drug could have a different mechanism of action for different modalities of effect—for example, in relation to the severe respiratory depression or apnoea reported previously [2–4].

Consistent with previous reports that buprenorphine antagonizes the effect of opioid μ agonists [1], our results also demonstrated that fentanyl had almost no further antinociceptive effect when administered after buprenorphine, either i.t. or i.v. The doses of fentanyl used in this study when administered alone, either i.v. or i.t., have been shown to abolish completely both Aδ and C reflexes [8, 9]. All opioid μ agonists may cause bradycardia and hypotension [15]. Buprenorphine administered i.v. caused a significant depression of arterial pressure and heart rate, but the reduction in heart rate was greater than that in arterial pressure. Cardiovascular depression occurred also after larger doses of i.t. buprenorphine, probably as a result of systemic absorption.

The effects of buprenorphine have been shown to be resistant to naloxone [2, 3, 11, 12]. However, Schmauss and Yaksh [5] found that the effect of i.t. buprenorphine can be antagonized by naloxone. In this study, naloxone was found also to antagonize the effects of buprenorphine, when administered either i.v. or i.t., but a relatively larger dose (4 mg i.v.) was required than the dose of 2 mg i.v. which has been shown to reverse μ agonists in a dog model [8, 9]. This could be attributable to the μ agonist properties of buprenorphine, as has been suggested previously [16].

**REFERENCES**


