CSF and plasma pharmacokinetics of the NMDA receptor antagonist CPP after intrathecal, extradural and i.v. administration in anaesthetized pigs

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Summary

The N-methyl-D-aspartate (NMDA) receptor complex plays a central role in the modulation of neuronal information in the central nervous system. This study was designed to examine the pharmacokinetics of the NMDA antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) in plasma and cerebrospinal fluid (CSF) and rostral spread in the CSF after lumbar intrathecal, extradural and i.v. administration. Anaesthetized pigs were given a lumbar intrathecal, lumbar extradural or an i.v. injection of a mixture of [3H]-labelled and unlabelled CPP. CSF was sampled over 10 h through intrathecal catheters positioned at the L1, T5 and C1 vertebral levels. Blood samples were obtained over the same period. Haemodynamic and arterial blood-gas variables and acid-base balance were monitored during the study. The area under the radioactivity concentration-time curves showed a gradient between cervical and lumbar CSF radioactivity of about 1:2500 after intrathecal administration and about 1:140 after extradural administration, indicating that only small fractions of lumbar administered CPP spread rostrally. About 2% of an extradurally administered dose was found in the CSF. After i.v. administration of [3H]CPP, clearance was mean 122 (SEM 16) ml min⁻¹ and the CSF:serum radioactivity gradient was approximately 1:4. The half-life of [3H]CPP varied little (mean range 94–191 min) irrespective of the route of administration or the level of sampling. Cervical radioactivity after lumbar intrathecal administration probably resulted from rostral transport via CSF bulk flow, whereas after extradural administration, systemic absorption and redistribution via the blood–brain barrier probably contributed. Renal excretion was the main route of systemic elimination. No effects on haemodynamics, arterial blood-gas tensions or acid-base balance could be correlated with intrathecal or extradural administration of CPP. The steep gradient between cervical and lumbar concentrations of [3H]CPP suggests that it may be possible to administer CPP spinally at the lumbar level in pharmacologically active doses with little distribution to the supraspinal level. (Br. J. Anaesth. 1995; 74: 193–200)

Key words


The N-methyl-D-aspartate (NMDA) receptor is involved in central transmission and modulation of nociceptive information. Indeed the NMDA receptor plays a significant role in spinal neuronal plasticity, such as central sensitization, wind-up and hyperalgesia [1–11]. Hence, interference with spinal NMDA receptors may offer alternative treatment options in different pain states. The competitive NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) is both highly potent and receptor-specific, acting at the NMDA recognition site of the NMDA receptor complex [12, 13]. CPP exhibited antinociceptive effects in behavioural studies in rat [14] and abolished central sensitization in electrophysiological experiments [10]. Spinal cord blood flow (SCBF) remained unchanged after intrathecal (i.t.) administration of CPP in rats [15, 16], while chronic i.t. administration did not cause morphological changes in the spinal cord [17]. However, as NMDA receptors are both widely distributed in the central nervous system and involved in a large number of neuronal processes [18], it may be difficult to produce an effective drug concentration near the target site, that is, the spinal cord, without affecting other NMDA receptor-regulated neuronal processes in the brain. Although the drugs may be administered near the target organ by i.t. or extradural injection, rostral spread of the drug via the CSF may produce side effects by interference with supraspinal NMDA receptors [19].

The aim of this study was to examine rostral spread of CPP following i.t. and extradural administration at the lumbar level using an experimental model in pigs [20]. Passage over the blood–brain barrier after i.v. administration of CPP, plasma and CSF pharmacokinetics, haemodynamic changes and route of systemic elimination were also studied.
Materials and methods

Male pigs of the Swedish native breed, weighing 25–32 kg and 12–14 weeks old, were used. The investigation was approved by the Ethics Committee for animal studies of the University of Uppsala. After premedication with pentobarbitone 15 mg kg⁻¹ i.p. and atropine 0.5 mg i.p., anaesthesia was induced with pentobarbitone 10 mg kg⁻¹ i.v. and maintained with a continuous infusion of methomidate 7.5 mg kg⁻¹ h⁻¹ and pancuronium 0.2 mg kg⁻¹ h⁻¹ and inhalation of 70% nitrous oxide in oxygen. Before the surgical procedure the animals received fentanyl 10 μg kg⁻¹ and, preceding all surgical incisions, lignocaine 10 mg ml⁻¹ was injected locally into the skin and subcutaneous tissues. Tracheotomy was performed and the lungs were ventilated mechanically to normocapnia with a Servo ventilator 900 B (Siemens Elema, Solna, Sweden). Body temperature, measured in the pulmonary artery, was maintained at 38 ± 1 °C by means of a heating blanket and infrared light.

Arterial and double-lumen central venous catheters were inserted via the right common carotid artery and the right external jugular vein, respectively. A 7-French gauge pulmonary artery catheter equipped with a thermistor was introduced via the right external jugular vein into a main branch of the pulmonary artery. The urinary bladder was cannulated via a small suprapubic incision.

ARTERIAL BLOOD-GAS TENSIONS, ACID-BASE BALANCE AND HAEMODYNAMIC MONITORING

Haemodynamic variables, arterial blood-gas tensions and acid–base balance were measured in the two groups of pigs in which CPP was given either extradurally or i.t. Heart rate, systemic and pulmonary artery pressure (MAP and MPAP, respectively), central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) were measured and recorded continuously (Siemens Sirecust 1281 and Siredoc 220, Siemens Medical Electronics Inc., Danvers, MA, USA). Cardiac output (CO) was measured by thermodilution using the thermistor in the pulmonary artery, and 10 ml of iced 5% glucose solution was used as indicator. Arterial and venous blood samples were obtained every hour for measurement of arterial blood-gas tensions, mixed venous oxygen saturation (SvO₂) and arterial acid–base balance (ABL2 and OSM2, Radiometer, Copenhagen, Denmark).

SPINAL AND EXTRADURAL CATHETERS

In the animals given the test drug i.t., four i.t. catheters were inserted. Two catheters (one for injection and one for sampling) were placed with the tip at the L1 level, whereas the other two i.t. catheters, used for CSF sampling, were placed with the tip at the T5 and C1 levels, respectively. In the animals given drugs extradurally, three i.t. catheters used for CSF sampling were introduced with the tip at the L1, T5 and C1 levels, respectively. In addition, an extradural catheter, used for administration of CPP, was placed with the tip at the same level as the tip of the lumbar i.t. catheter. In the animals where the drug was given i.v., only one i.t. catheter, used for CSF sampling, was placed with the tip at the C1 level.

SURGICAL PROCEDURES FOR PLACEMENT OF INTRATHECAL AND EXTRADURAL CATHETERS

The animals were placed in the prone position. Catheters used for drug injection or sampling of CSF at the lumbar level were introduced via the L5–S1 interspace after surgical incision and removal of the ligamentum flavum. To place a lumbar i.t. catheter, a plastic guide wire (1.05 mm, Viggo-Spectramed, Swindon, Wilt., UK) was introduced into the i.t. space via a small hole made with a needle. A polyethylene catheter (1.25 mm od, Viggo-Spectramed) was then threaded over the guide wire and advanced 10 cm in a cranial direction, leaving the tip of the catheter at about the L1 level. Care was taken to avoid leakage of CSF around the catheter. In the animals given an extradural injection of CPP, a catheter was introduced into the extradural space and advanced cranially to the same level as the lumbar i.t. catheter.

Catheters used for CSF sampling at the mid-thoracic and cervical levels were introduced into the i.t. space via the atlanto–cervical membrane. A midline incision was made between the occipital protuberance and the first thoracic spine. The muscles were cleaved bluntly and the atlanto–occipital membrane was exposed. Two plastic guide wires were introduced via a needle into the i.t. space and threaded with polyethylene catheters, one of which was advanced 1 cm and the other 15 cm caudally, thus leaving the catheter tips at about the C1 and T5 levels, respectively.

DRUGS AND EXPERIMENTAL PROCEDURE

Radiolabelled [¹H]CPP with a specific radioactivity of approximately 20 Ci mmol⁻¹ was supplied in an aqueous solution at 1 mCi ml⁻¹. Each of five pigs was given a single lumbar i.t. injection of [¹H]CPP 8 μCi and unlabelled CPP 0.2 μmol, dissolved in 0.9% saline to a total volume of 0.5 ml. Another five pigs were given single lumbar extradural injections of [¹H]CPP 57 μCi and unlabelled CPP 20 μmol, dissolved in 0.9% saline to a total volume of 0.5 ml. The doses of unlabelled CPP were chosen to give pharmacological active concentrations of CPP, as estimated from previous animal studies [14]. A 10-h sampling period followed, during which the anaesthetized animals remained prone. At the end of this experiment, the five pigs given [¹H]CPP i.t. were used in a third experiment together with one former, untreated pig. These six pigs were given [¹H]CPP 50 μCi i.v., dissolved in 0.9% saline to a total volume of 5 ml, injected into the pulmonary artery. To flush the catheters, all i.t. and extradural injections were followed by injection of 0.9% saline 0.5 ml, and the i.v. injections were followed by 0.9% saline 5 ml. The total injection time was 45 s. At the end of the experiment the animals were killed with an i.v. injection of KCl 20 mmol.
SAMPLING AND ANALYSIS

In the two groups where CPP was given spinally, samples of CSF (0.2–0.4 ml) from the lumbar, thoracic and cervical levels, and blood samples (3 ml) were obtained at 0, 20, 40, 60, 120, 180, 240, 300, 360, 420, 480, 540 and 600 min, respectively, and in the pigs injected i.t., a lumbar CSF sample was also obtained 10 min after administration. After i.v. administration of CPP, blood and CSF samples were obtained at 0, 20, 30, 40, 50, 60, 90, 120, 180 and 240 min and in addition blood samples were obtained at 1, 2, 3, 5 and 10 min. All blood samples were of arterial blood. Urine was sampled every hour from two pigs in the extradural and four pigs in the i.t. groups.

To the CSF, urine (1 ml) and separated serum (1 ml) samples was added 10 ml of scintillation cocktail (OptiPhase II, Fission, Wallac, Turku, Finland) and the radioactivity of the samples determined by liquid scintillation spectrometry (LKB Wallac 1215 Rackbeta II Liquid Scintillation Counter, Turku, Finland).

STABILITY OF $^{[3]H}$CPP

To demonstrate that radioactivity was non-volatile, samples of serum, CSF and urine were divided into two aliquots. One of the samples was dried in an oven at 40 °C for 24 h, before adding scintillation cocktail. The radioactivities of the dried and non-dried samples were compared to ascertain if degradation of $^{[3]H}$CPP to $^{3}$H$_2$O had occurred.

TISSUE RADIOACTIVITY

Tissue samples from two pigs given extradural $^{[3]H}$CPP were collected for analysis of tissue radioactivity. The tissue samples were rinsed with water and homogenized in ice-cold distilled water. Aliquots (0.1–0.2 g) of the tissue homogenates were mixed with cellulose powder, combusted in a sample oxidizer (Packard Oxidizer 306, Packard Instruments Co., Downers Grove, IL, USA) and the trapped $^{3}$H$_2$O was mixed with 10 ml of scintillation fluid (Monophase: Permafluor, 15:2, Packard) before analysis. The radioactivity in the sample was assayed in a Tri-Carb 460C spectrometer (Packard) with internal standardization. The results are presented as the mean of two samples from each tissue.

CALCULATIONS

The serum radioactivity concentration–time curve after i.v. drug administration was analysed using a biexponential equation to determine the rate constants of the initial distribution phase (0–5 min) and the elimination phase (60–240 min) [21]:

$$C(t) = C_1(0)e^{-\alpha t} + C_2(0)e^{-\beta t}$$

Otherwise, a monoexponential equation was fitted to the radioactivity concentration–time curves, using samples from 180 to 600 min in the spinal and 60–240 min in the i.v. groups:

$$C(t) = C(0)e^{-\beta t}$$

where $\alpha$ and $\beta$ are the respective rate constants, calculated by the least-squares method. The associated early ($T_1$) and late ($T_2$) half-lives were given as 0.693/$\alpha$ and 0.693/$\beta$, respectively.

The area under the radioactivity concentration–time curve obtained from CSF samples from 180 to 600 min at the lumbar level showed a monoequational pattern. The late half-life ($T_2$) was 109 (20) min. Rostral spread of radioactivity was evident from the CSF samples at the thoracic and cervical levels. The $t_{max}$ at the cervical level was 132 (12) min, at which time the cervical:lumbar CSF radioactivity ratio was 0.0005 (0.0002).

RESULTS

The surgical preparation and insertion of spinal catheters caused i.t. bleeding in two animals, which were subsequently excluded. In one animal it was not possible to obtain samples from the lumbar i.t. catheter. However, the animal was used for i.v. injection of $^{[3]H}$CPP as the i.t. catheter at the cervical level functioned satisfactorily.

STABILITY OF $^{[3]H}$CPP

Drying of the samples did not change the level of radioactivity in the CSF, serum or urine samples compared with identical non-dried samples, indicating that the $^{3}$H-labelled position was stable.

INTRATHECAL INJECTION (fig. 1, table 1)

Based on i.t. administration of $^{[3]H}$CPP in five pigs, the segment of the radioactivity concentration–time curve obtained from CSF samples from 180 to 600 min at the lumbar level showed a monoequational pattern. The late half-life ($T_2$) was 109 (20) min. Rostral spread of radioactivity was evident from the CSF samples at the thoracic and cervical levels. The $t_{max}$ at the cervical level was 132 (12) min, at which time the cervical:lumbar CSF radioactivity ratio was 0.0005 (0.0002).
AUC was 0.00042 (0.00016). The rmax at the thoracic level the lumbar (○), thoracic (●) and cervical (○) levels and in serum (▲). All values are mean, SEM from five pigs.

The plasma radioactivity concentration–time curve after i.v. administration of [3H]CPP appeared in the lumbar CSF samples with a rmax of 20 min, that is in the first sample after injection. A monoexponential equation applied to the samples obtained from 180 to 600 min revealed a $T_{1/2}$ of 133 (23) min. The $T_{1/2}$ of [3H]CPP in six pigs after i.v. administration of [3H]CPP was calculated as about 2%, whereas systemic availability was 92%.

EXTRADURAL INJECTION (fig. 2, table 1)

After extradural administration in five pigs, [3H]CPP appeared in the lumbar CSF samples with a rmax of 20 min, that is in the first sample after injection. A monoexponential equation applied to the samples obtained from 180 to 600 min revealed a $T_{1/2}$ of 133 (23) min. The $T_{1/2}$ of [3H]CPP in six pigs after i.v. administration of [3H]CPP was calculated as about 2%, whereas systemic availability was 92%.

I.V. INJECTION (fig. 3, table 2)

The plasma radioactivity concentration–time curve after i.v. administration of [3H]CPP in six pigs showed a biphasic pattern. The initial $T_{1/2}$ was 5.1 (1.1) min, and the initial volume of distribution ($V_d$) was 3.7 (0.2) litre. The plasma elimination half-life was 81 (10) min and the late apparent volume of distribution ($V_d$) was 13.8 (2.2) litre, that is about the size of the extracellular volume. As five of these pigs had been used previously for i.t.
AUC was 0.26 (0.04). Clearance of [3H]CPP was at that time the CSF:serum radioactivity concentration ratio was 0.28 (0.03), whereas the AUC was compensated. These values were 22, 16, 21, 23 dpm. In the CSF, rmax was 50 (10) min, and at that time the CSF:serum radioactivity concentration ratio was 0.28 (0.03), whereas the AUC/ AUCu was 0.26 (0.04). Clearance of [3H]CPP was 122 (16) ml min⁻¹.

**Table 2** Pharmacokinetic variables after i.v. injection of [3H]CPP (mean (SEM)). se = Serum, T½f = early and late half-lives, respectively, rmax = time of maximum radioactivity, Vd₁ = initial volume of distribution, Vd₂ = apparent volume of distribution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum, early phase (1-5 min)</th>
<th>Serum, late phase (60-240 min)</th>
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<tbody>
<tr>
<td>T½f (min)</td>
<td>5.09 (1.06)</td>
<td>3.65 (0.21)</td>
</tr>
<tr>
<td>Vd₁ (litre)</td>
<td></td>
<td></td>
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<tr>
<td>AUCₘ₁ (10⁻³ dpm x min x ml⁻¹)</td>
<td>987 (27)</td>
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</tr>
<tr>
<td>Vd₂ (litre)</td>
<td>13.8 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Clearance (ml min⁻¹)</td>
<td>122 (16)</td>
<td></td>
</tr>
<tr>
<td>CSF (60-240 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T½f (min)</td>
<td>139 (22)</td>
<td></td>
</tr>
<tr>
<td>AUCₘₛₖ (10⁻³ dpm x min x ml⁻¹)</td>
<td>276 (17)</td>
<td></td>
</tr>
<tr>
<td>AUCₘₛₖ/AUCu</td>
<td>0.26 (0.04)</td>
<td></td>
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<tr>
<td>rmax(CSF) (min)</td>
<td>50 (10)</td>
<td></td>
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<tr>
<td>CSF:serum radioactivity at rmax(CSF)</td>
<td>0.28 (0.03)</td>
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**Discussion**

We have found that only small fractions of [3H]CPP, administered i.t. or extradurally at the lumbar level, spread supraspinally. Rostral transport was time-dependent and the concentration of radioactivity decreased with the distance from the site of injection. After lumbar intrathecal administration of [3H]CPP, AUC₁/AUCu and the gradient between cervical and lumbar CSF radioactivity was 1:2500 at the time.
when the cervical CSF radioactivity was highest. AUC_CSF/AUC_serum was 1:140 and the cervical: lumber radioactivity gradient at rmax at the cervical level was about 1:60 after lumbar extradural injection. These large gradients suggest that it may be possible to obtain high concentrations in the spinal cord dorsal horn with only a small degree of rostral spread to supraspinal sites. Furthermore, i.t. administration may be safer than the extradural route in respect of supraspinal side effects.

We also found that [3H]CPP readily penetrated the blood–brain barrier after i.v. administration of [3H]CPP, as the CSF:serum radioactivity and AUC_CSF/AUC_serum were both about 1:4.

The cervical presence of CPP after lumbar i.t. administration was probably a result of rostral transport via CSF bulk flow [22], as the plasma radioactivity after i.t. [3H]CPP was too low to contribute to systemic reabsorption and redistribution over the blood–brain barrier. However, after extradural [3H]CPP, AUC_CSF/AUC_serum was about the same as that after i.v. administration of [3H]CPP. Hence, systemic reabsorption of extradurally administered [3H]CPP and redistribution to the CSF probably contributed to the presence of [3H]CPP at the cervical and supraspinal levels. This may explain why the cervical: lumber radioactivity gradient was larger after i.t. than extradural administration.

Peak concentrations at C1 occurred at 2–3 h after i.t. injection and about 1–2 h after extradural administration. This is consistent with a study in mice where the concentration of another hydrophilic NMDA antagonist, cis-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755), peaked in the frontal cortex about 4 h after lumbar i.t. administration [23]. In humans, peak concentrations of morphine in CSF, sampled at the C7–T1 level after lumbar extradural administration, occurred about 3 h after extradural injection [24]. Morphine concentrations in cisterna magna after lumbar i.t. injection in sheep also peaked at 90–190 min [25].

After i.v. administration of [3H]CPP, the CSF: serum radioactivity gradient was 28% (range 18–35%). This is somewhat surprising in view of the pronounced hydrophilic properties of CPP [26], as hydrophilic substances penetrate the blood–brain barrier poorly [27]. This suggests that, CPP may be effective when given systemically, although the supraspinal side effects would probably make this mode of administration difficult in clinical practice. Orally administered CPP was effective against experimental seizures in baboons [28].

The distribution of drugs from the intrathecal space depends on the physiochemical properties of the drug. Lipophilic drugs readily enter the spinal cord where they are absorbed systemically, whereas hydrophilic drugs tend to remain in the CSF [23,26,29]. Many other factors influence the distribution of i.t. administered drugs [30]. However, the risk of rostral spread is greater with hydrophilic drugs, but such drugs may be useful in that their duration of action may be longer and they may be less prone to produce systemic side effects.

In the tissue samples obtained about 10–11 h after administration of [3H]CPP, high levels of radioactivity were found in the kidneys, while liver tissue showed little radioactivity and none was found in the bile (table 3). About 50–65% of the administered [3H]CPP was recovered in urine 10 h after drug administration, suggesting that renal excretion was the main route of systemic elimination. This is in agreement with results obtained in mice after i.t. injection of [3H]CGS 19755 [23].

Haemodynamic variables decreased gradually. Reduced metabolic demands produced by prolonged anaesthesia may have been responsible for this decrease. CPP itself may also have been responsible, as it was shown that spinal NMDA receptors are involved in the regulation of cardiovascular sympathetic tone [31].

The calculated CSF availability of an extradural dose was about 2%. This is about the same as that found after extradural morphine and pethidine in humans, where values of 2–4% have been calculated [32,33].

Systemic availability after extradural [3H]CPP was about 92%, whereas after i.t. administration it was only about 60%. This low value may be acceptable when taking into account the inaccuracy associated with calculations based on low levels of radioactivity, as in the serum samples after i.t. administration. However, tissue radioactivity at the supraspinal level 10 h after extradural administration of [3H]CPP was not detected. Thus accumulation of [3H]CPP in the brain is unlikely to occur.

From a pharmacokinetic point of view, the CSF cannot be regarded as a single compartment, as it is not well stirred, hence the calculated pharmacokinetic variables are true only for an arbitrary volume at the sampling site. Despite these reservations there was a striking homogeneity in the late half-lives within the CSF, irrespective of the route of administration or the level of sampling. This suggests that the major route of elimination from the CSF was penetration into and systemic absorption from the spinal cord, in addition to systemic absorption from the surrounding pia, arachnoid and dural microcirculation.

In this model, frequent sampling was performed, which may have interfered with the results obtained after both i.t. and extradural administration. The fraction of the injected drug sampled could be calculated in the pigs given i.t. [3H]CPP. Less than 2% of the drug was sampled after 60 min, and the pharmacokinetic variables calculated from CSF samples from 3 to 10 h were probably unaffected by this sampling. However, a total of 33% of the i.t. administered [3H]CPP was sampled during the first hour of the study, of which 12% and 10% was sampled at 10 and 20 min, respectively. The CSF curves obtained from all three spinal levels and their AUC values were probably reduced, although the relation between the AUC of the curves was probably not affected. The sampled fraction of the radioactivity available for the CSF in the extradural group was less than 35%, as no lumbar sample was taken at 10 min.

The total amount of CSF in a 25-kg pig is about 50 ml, with 10 ml in the spinal canal, as extrapolated from humans [34]. Although the total volume of
CSF varies little because of the low compliance of the central nervous system, the production of CSF from the choroid arterial plexuses and reabsorption from the arachnoid villi may vary considerably depending on the osmotic and hydrostatic pressures in the CSF and blood, or on drug-induced effects [35]. The normal rate of CSF production may be about 0.13 ml min⁻¹, that is about 80 ml of CSF may be produced during the study, when estimated from humans [35] on the basis of body weight. Thus CSF turnover during the 10-h study may be estimated to be about 80 ml, of which 10–15 ml was sampled for analysis.

With the method used it was possible to monitor [³H]CPP in CSF at the lumbar, thoracic and cervical levels and in serum for 10 h after either i.t., extradural or i.v. administration. However, the insertion of 3–4 i.t. catheters may have disturbed CSF bulk-flow. The prone position, immobilization, anaesthesia and mechanical ventilation throughout the study should also be taken into consideration when extrapolating the results to humans.

These results suggest that it may be possible to administer CPP spinally at the lumbar level in pharmacologically active doses without the risk of distribution of clinically significant amounts to the supraspinal level, and that the i.t. route of administration may be safer than extradural administration when considering the risk of supraspinal side effects.

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