Laboratory Investigation

Antinociceptive effects of epidural and intravenous ketamine to somatic and visceral stimuli in rats

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Purpose: To evaluate the antinociceptive effect of epidural and intravenous ketamine on somatic and visceral stimuli and to address the emergency reaction.

Methods: Rats were randomly allocated into nine groups ($n = 6$); five groups with chronically implanted epidural catheters received saline or 0.5, 1, 2 and 4 $\text{mg} \cdot \text{kg}^{-1}$ ketamine epidurally, four groups received saline, or 1, 5 and 10 $\text{mg} \cdot \text{kg}^{-1}$ ketamine iv. To assess somatic and visceral antinociceptive effects, tail flick (TF) test and colorectal distension (CD) test were carried out, respectively. Emergence reactions were graded. Maximal possible effects (% MPE) were calculated.

Results: Epidural ketamine increased % MPE in both tests in a dose-dependent fashion for 30 min (vs saline group, $P < 0.05$). Epidural ketamine 0.5 $\text{mg} \cdot \text{kg}^{-1}$ produced an increase in % MPE in the CD test ($P < 0.05$) but failed in the TF test. Intravenous ketamine, 10 $\text{mg} \cdot \text{kg}^{-1}$, produced 100 ± 0 (mean $\pm$ SE) % MPE in the CD test but 36 ± 15 % MPE in the TF test. Dose response curves indicated greater visceral antinociception than somatic. All rats showed emergence reactions following intravenous ketamine 10 and 5 $\text{mg} \cdot \text{kg}^{-1}$.

Key words

ANALGESICS: ketamine;
ANAESTHETIC TECHNIQUES: epidural, intravenous;
MEASUREMENT: somatic, visceral;
PAIN RECOVERY: emergence reactions.

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Conclusion: Both epidural and intravenous ketamine produce greater antinociceptive effects to visceral than to somatic stimulation, and that epidural ketamine has a low incidence of emergence reactions.

Objectif: Evaluer les effets antinociceptifs de la kétamine épidurale et intraveineuse sur les stimuli somatiques et viscéraux et étudier la réaction d'urgence.

Méthodes: Des rats ont été répartis de façon aléatoire en neuf groupes ($n = 6$); chez cinq de ceux-ci, un cathéter épidural a été implanté en permanence par lequel ils ont reçu soit du sol. physiologique, soit 0,5, 1,2 ou 4 $\text{mg} \cdot \text{kg}^{-1}$ de kétamine; quatre groupes ont reçu par la voie intraveineuse, soit du sol. physiologique, soit 1, 5 ou 10 $\text{mg} \cdot \text{kg}^{-1}$ de kétamine. Pour évaluer les effets antinociceptifs somatiques et viscéraux, les épreuves de latence de déviation de la queue (flicker test: FT) et de distension colorectale (DC) ont été réalisées. Les réactions d'émergence ont été divisées en degrés. L'effet maximal possible (% MPE) a été calculé.

Résultats: La kétamine épidurale a augmenté le MPE pour les deux épreuves de façon proportionnelle à la dose pendant 30 min (vs groupe sol. phys. $P < 0,05$). La kétamine épidurale 0,5 $\text{mg} \cdot \text{kg}^{-1}$ a produit une augmentation de MPE% pour l'épreuve de DC ($P < 0,05$) mais a échoué pour l'épreuve du FT. La kétamine intraveineuse 10 $\text{mg} \cdot \text{kg}^{-1}$ a produit 100 ± 0 (moyenne $\pm$ ET) de MPE pour l'épreuve de DC et 36 ± 15 pour l'épreuve du FT. Les courbes de relation dose-effet ont montré que l'antinociception viscérale était plus importante que la somatique.

Conclusion: Que ce soit par la voie épidurale ou par la voie intraveineuse, la kétamine produit des effets antinociceptifs plus importants sur la stimulation viscérale que la somatique, et la kétamine épidurale possède une faible incidence de réaction d'émergence.

It has been reported that epidurally administered ketamine provides postoperative analgesia without the associated ventilatory depression or cardiovascular stimulation.^{1,2} Recently, the caudal administration of ketamine in children produced satisfactory postoperative analgesia without side effects.³ It has been demonstrated that ketamine produced insufficient protection against visceral pain but was effective against somatic pain involving the extremities and skeleton.⁴ Another study has shown that the only advantage of epidural ketamine is in the relief of somatic pain.⁵ However, previous studies did not clearly compare somatic with visceral antinociception of ketamine, because it is difficult to separate and quantify the visceral antinociception from somatic antinociception in human studies. Animal models for assessing antinociceptive effects may answer whether ketamine possesses different antinociceptive effect to somatic and visceral stimuli. Apart from its antinociceptive effect ketamine possesses some disturbing adverse effects.⁶

The present study was designed to evaluate the antinociceptive effect of epidural and intravenous ketamine on somatic and visceral stimuli. The second purpose was to evaluate emergence reactions following epidural and intravenous ketamine.

Methods

After Institutional Animal Care approval, Sprague-Dawley rats weighing 300–400 g were used. They were randomly allocated to nine groups (six in each group); five groups with chronically implanted epidural catheters for epidural study and four groups for intravenous study. Animals were used only in a single experiment. To reduce the influence of handling on nociceptive responses, all animals were handled and trained in the test situation for at least four days before the experiment. All tests were performed during the day i.e., two to four hours after the onset of the light period.

Epidural study

Heat connected tubes of PE-10 (1.5 cm) and PE-20 (16 cm) were inserted caudally at the T₁₃–L₁ interspace using an aseptic technique in rats anaesthetized with 2.5% halothane in oxygen. The day before the experiment, the location of the catheter was verified by epidural injection of 40 µl of lidocaine 2%. If there was concern about the location of the catheter or about other health problems the rats were excluded. At the end of the experiment indigocarmine dye 0.1 ml was injected through the catheter to confirm that the PE-10 tip was in the epidural space. Ketamine (SIGMA CHEMICAL Co., U.S.A.), 0.5, 1, 2 and 4 mg · kg⁻¹ dissolved in sterile saline to a volume of 40 µl was administered through

the epidural catheter followed by 12 µl normal saline to flush the dead space. Animals in the control group received a similar volume of saline.

Intravenous study

Rats received injections into the lateral tail vein. Animals were excluded if more than two vein pricks were necessary. Ketamine, 1, 5 and 10 mg · kg⁻¹, dissolved in normal saline solution in a volume of 0.5 ml, was administered through the tail vein. The same volume of saline was administered to the control group.

Nociceptive tests

Tail flick (TF) test: To assess somatic antinociceptive effects, the TF test was carried out using the Analgesia Meter (Ugo Basile, Model-DS20, Socrel-Italy). A beam of light (100 Watts) was focused on the dorsal surface of the tail about 5 cm from the tip. A cut-off time of 10 sec was used to avoid tissue damage.

Colorectal distension (CD) test: The visceral antinociceptive effect was assessed using the CD test. A 7–8 cm long, flexible latex balloon was inserted *pr* during halothane anaesthesia and consisted of a proximal large stimulating balloon, and a distal small sensing balloon. Pressures within the balloons were monitored continuously by an on-line pressure transducer (SAN-EI Instrument Co. Ltd., Japan) and recorded during measurement. The pressure in the stimulating balloon was increased steadily at a rate of 2.5 mmHg · sec⁻¹ beginning at 0 mmHg. The minimal distending pressure necessary to evoke a rapid increase of the pressure in the sensing balloon was assessed as threshold pressure. A cut-off distension pressure of 60 mmHg was employed to avoid tissue damage.

Emergence reactions

Emergence reactions were graded as follows: 0 = calm and quiet, 1 = restless but not violent, 2 = restless and violent movement with or without tail stiffness. The criteria for recovery from emergence reactions were disappearance of involuntary movement, head movement and of tail rigidity. Animals were excluded if emergence scores exceeded 1.

Measurements

To establish baseline values, in each test, the mean of three measurements at intervals of two minutes were obtained. Then, measurements were repeated at 5, 10, 15, 20, 30, 45 and 60 min after either drug or normal saline administered manually over a period of 20–30 sec. Following measurement of TF latency, CD threshold was measured.

FIGURE 1 Time course of % MPE effects in the tail flick (TF) and colorectal distension (CD) tests after epidural administration of saline ($\square$) or ketamine $0.5 \text{ mg} \cdot \text{kg}^{-1}$ ($\blacktriangle$), $1 \text{ mg} \cdot \text{kg}^{-1}$ ($\triangle$), $2 \text{ mg} \cdot \text{kg}^{-1}$ ($\bullet$), $4 \text{ mg} \cdot \text{kg}^{-1}$ ($\circ$) [$n = 6$]. Each point represents the mean $\pm$ SEM. * ($P < 0.05$) vs saline group.

FIGURE 2 Dose-response curve for epidural ketamine in the tail flick ($\bullet$) [$r = 0.98$] and colorectal distension ($\circ$) [$r = 0.98$] tests reported as percent maximal possible effects (% MPE) vs doses $\text{mg} \cdot \text{kg}^{-1}$.

Data analysis and statistics

To assess the antinociceptive effects, percent maximal possible effect (%MPE) were calculated as follows:

$$\% \text{ MPE} = \frac{\text{post-drug value} - \text{baseline value}}{\text{cut-off value} - \text{baseline value}} \times 100$$

TABLE Incidence of emergence reactions induced by epidural and intravenous ketamine in rats

Time (min)	5	10	15	20	30	45	60
<i>Epidural study (n = 6)</i>							
4 mg Ket	0	3	3	3	3	0	0
2 mg Ket	0	2	2	2	0	0	0
1 mg Ket	0	2	0	0	0	0	0
0.5 mg Ket	0	0	0	0	0	0	0
Saline	0	0	0	0	0	0	0
<i>Intravenous study (n = 6)</i>							
10 mg Ket	6*	6*	6*	6*	6*	0	0
5 mg Ket	6*	6*	6*	6*	6*	0	0
1 mg Ket	4	4	0	0	0	0	0
Saline	0	0	0	0	0	0	0

The number indicates the number of animals showing emergence reactions score = 1.

* $P < 0.05$ vs saline.

Changes in % MPE after epidural and intravenous administration were analyzed using repeated measure ANOVA followed by Fisher's PLSD test. Data for emergence reactions were analyzed by Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

A total of 72 rats were used. Epidural data were analyzed from 30 rats and intravenous data from 24 rats. Twelve rats were excluded from the epidural study due to unilateral hindlimb block or catheter blockade. In the

FIGURE 3 Time course of % MPE effects in the tail flick (TF) and colorectal distension (CD) tests after intravenous saline ($\square$) or ketamine $1 \text{ mg} \cdot \text{kg}^{-1}$ ($\triangle$), $5 \text{ mg} \cdot \text{kg}^{-1}$ ($\bullet$), $10 \text{ mg} \cdot \text{kg}^{-1}$ ($\circ$) [$n = 6$]. Each point represents the mean $\pm$ SEM. * $P < 0.05$ vs saline group.

FIGURE 4 Dose-response curve for intravenous ketamine in the tail flick ($\bullet$) [$r = 0.96$] and colorectal distension ($\circ$) [$r = 0.98$] tests reported as percent maximal possible effects (% MPE) vs dose $\text{mg} \cdot \text{kg}^{-1}$.

intravenous study six rats who showed emergence reactions >1 after ketamine were also excluded.

The baseline values in TF and CD tests were not different among the nine groups.

Epidural study

Epidural administration of ketamine increased % MPEs in both tests in a dose-dependent fashion while saline

produced no change. Epidural ketamine, $4 \text{ mg} \cdot \text{kg}^{-1}$, showed a maximum increase of %MPE in TF test at 10 min and the increase of % MPE persisted from 5 to 30 min compared with the saline group ($P < 0.05$). Epidural ketamine, $0.5 \text{ mg} \cdot \text{kg}^{-1}$, increased the % MPE in CD test ($P < 0.05$) but not in the TF test (Figure 1).

Dose-response curves in the CD test were located to the left of those in the TF test, indicating greater antinociceptive effects of epidural ketamine to visceral stimulation than somatic (Figure 2).

The incidence of emergence reactions after epidural ketamine was not different from that in the saline group (Table). None of the rats showed any motor block or respiratory depression or cyanosis during the study.

Intravenous study

Intravenous saline produced no effects on any measurement. Intravenous ketamine, at the highest dose ($10 \text{ mg} \cdot \text{kg}^{-1}$), produced increases of % MPE in the TF test for only 20 min compared with the saline group ($P < 0.05$) and the maximum increase of % MPE was $36 \pm 15\%$ (mean $\pm$ SEM) at five minutes. In contrast, intravenous ketamine of $10 \text{ mg} \cdot \text{kg}^{-1}$ produced the maximum effects of $100 \pm 0\%$ MPE in the CD test at five minutes and increases of % MPE were also shown after the administration of $5 \text{ mg} \cdot \text{kg}^{-1}$ and $1 \text{ mg} \cdot \text{kg}^{-1}$ ($P < 0.05$) (Figure 3).

Dose-response curves in the CD test were located to the left of those in the TF test, indicating greater antinociceptive effects of intravenous ketamine to visceral than to somatic stimulation (Figure 4).

At five minutes after intravenous ketamine, 10 and 5 mg · kg⁻¹, all rats showed emergence reactions for 30 min ($P < 0.05$ vs saline group) (Table). Intravenous ketamine was associated with profuse salivation and truncal rigidity. Ataxia of the extremities appeared progressively with the higher doses of ketamine but the animals continued to move in an uncoordinated manner. None of the rats showed motor block or respiratory depression or cyanosis during the study.

Discussion

The present study showed that epidural ketamine produced dose and time dependent somatic and visceral antinociceptive effects and few emergence reactions. Regardless of the route of administration, greater antinociception to visceral than to somatic stimulation was shown. The study cannot explain the different antinociceptive effects. However, anatomical features of visceral sensory processing in the spinal cord, such as the small number of nociceptive afferent fibres and the extensive divergence involving supraspinal loops,⁷ may contribute to the greater antinociception.

Previous reports demonstrated that epidural ketamine caused effective analgesia when the source of the pain was somatic rather than visceral.^{4,5} However, the data obtained after epidural administration in this study are not in agreement with these clinical reports. The differences may be attributed to the nociceptive tests used and to different assessments in different species. In addition, it is difficult to separate the visceral from somatic antinociception in human studies.

Intravenous ketamine, 10 mg · kg⁻¹, which produced similar antinociceptive effects to the CD test and less antinociceptive effect to the TF test compared with epidural ketamine of 4 mg · kg⁻¹, caused emergence reactions in all rats. In contrast, epidural ketamine caused only delayed emergence reactions in a few rats. The emergence reaction may be due to a supraspinal action of ketamine attributed to a slow vascular absorption, possibly through the sigma receptor.⁸ Epidural ketamine, at low doses, produced antinociceptive effects without any emergence reactions. The occurrence of emergence reactions was dose-dependent. The results suggest that epidural ketamine may offer some advantage over intravenous ketamine in clinical practice. However, we could not compare the antinociceptive effects between the two routes precisely since they were difficult to study the higher dose because of the severe emergence reactions.

The exact mechanisms and sites of action of ketamine remain unknown. Ketamine suppresses the dorsal horn neuronal activity evoked noxious stimulation in the spinal cord.^{9,10} Other reports suggest that ketamine pro-

duces analgesic effects by activating a descending inhibitory system.^{11,12} Epidurally administered ketamine may act on both the spinal and supraspinal sites and produce antinociceptive effects by, at least in part, acting as a non-competitive NMDA receptor antagonist.^{13,14}

The important finding, relevant to clinical practice from the present study, is that epidural ketamine has greater antinociception to visceral than somatic stimulation suggesting that epidural ketamine may be useful in controlling postoperative, obstetric and cancer-related pain because some components of the pain in these situations is of visceral origin.¹⁵ From its action as an NMDA antagonist, epidural ketamine has the possibility of providing analgesia in opioid-tolerant patients or in patients suffering from hyperalgesia¹⁶ because recent studies have demonstrated that activation of spinal cord NMDA receptors is involved in the development of tolerance to the antinociceptive effects of morphine^{17,18} and the development of hyperalgesia.^{19,20}

It is concluded that epidural and intravenous ketamine produce greater antinociceptive effects to visceral than to somatic stimulation, and that epidural ketamine produces a low incidence of emergence reactions.

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