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Cerebral physiological responses to bolus infusion of racemic, S(+)- or R(-)-ketamine in the pig

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Short title:

BRAIN EFFECTS OF KETAMINE ENANTIOMERS

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Background: Little is known about the influence of ketamine and its enantiomers on cerebral haemodynamics, and directly comparable reports are lacking. This study was designed to evaluate cerebrovascular responses to bolus infusions of racemic, S(+)- and R(-)-ketamine in an established experimental model.

Methods: Anaesthesia was induced with propofol in 14 pigs and maintained with fentanyl and vecuronium. The intra-arterial xenon clearance technique was used to calculate cerebral blood flow (CBF). Eight pigs (part I) were given three consecutive 60-second intravenous (iv) bolus infusions of $10 \text{ mg} \cdot \text{kg}^{-1}$ of racemic ketamine (Ketalar[®], Pfizer), and cerebral and systemic physiological responses were studied for 30 minutes after each infusion. Following determination of equipotent doses of the racemate and its enantiomers by recumbency tests, bolus infusions of racemic ketamine ($10 \text{ mg} \cdot \text{kg}^{-1}$), S-ketamine ($5 \text{ mg} \cdot \text{kg}^{-1}$) and R-ketamine ($20 \text{ mg} \cdot \text{kg}^{-1}$) were given in randomised sequence in another six pigs (part II) and evaluated at 1, 5, 10, 15, 25 and 40 minutes.

Results: No statistically significant acute-tolerance in CBF response to racemic ketamine was found in part I of the study. In part II, the reductions of mean arterial pressure (MAP) and CBF by S-ketamine were significantly smaller than those by racemic and R-ketamine (both $P < 0.001$). No study drug had any significant effect on the cerebral arteriovenous oxygen content difference (CavO_2) over time, but S-ketamine was associated with lower CavO_2 than racemic ($P = 0.008$) and R-ketamine ($P = 0.016$).

Conclusions: S(+)-ketamine was associated with less cerebral and systemic haemodynamic depression than racemic or R(-)-ketamine in equipotent doses in this experimental model. These findings indicate possible advantages of S-ketamine over racemic ketamine.

Key words: Anesthesia, intravenous; cerebral blood flow; enantiomers; fentanyl; ketamine, racemic; R-ketamine; S-ketamine; swine; vecuronium; xenon.

Racemic ketamine hydrochloride, a phencyclidine derivative with unique analgesic and hypnotic properties, is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist containing equal proportions of the S(+)- and R(-) enantiomers. Since clinical introduction 40 years ago its use has been addressed in numerous experimental and clinical studies and reviewed extensively. In contrast, little is known about the influence of the enantiomers, particularly S-ketamine, on cerebral haemodynamics.

To date no systematic study has been carried out regarding the cerebral haemodynamic effects of racemic ketamine and its enantiomers. The present study was designed to evaluate and compare, in the same animals, cerebral and systemic haemodynamic responses to sequential intravenous (iv) equipotent bolus infusions in random order of each of these three ketamine compounds.

Materials and methods

The experiments were carried out at the Department of Experimental Research, Malmö University Hospital, after approval of the study design by the Medical Ethics Committee on Animal Studies, Lund University, Malmö, Sweden.

Animals

Fourteen juvenile domestic pigs (Swedish landrace/Yorkshire/Hampshire) weighing (mean \pm SD) 23.6 ± 2.3 kg, were used in two series of eight (part I) and six (part II) animals. The animals were kept in laboratory stables and deprived of food overnight but had free access to water.

Anaesthesia

Anaesthesia was induced with intravenous (iv) propofol $4\text{--}6 \text{ mg} \cdot \text{kg}^{-1}$, and the animals were then endotracheally intubated in the prone position. The animals' eyes were closed and their ears plugged. Surgery was carried out in the supine position, and measurements made in the right lateral position.

General anaesthesia was maintained with 6.6% of desflurane in 40% of oxygen – corresponding to 0.5 minimal alveolar concentration (MAC) in the present experimental model (1) – together with continuous iv infusions of fentanyl $0.040 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and vecuronium $2.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ during surgical preparation, and with continuous infusions of fentanyl $0.040 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and vecuronium $2.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ during the experimental period (Fig. 1).

[FIGURE 1 NEAR HERE]

Ventilation

Ventilation was accomplished with a volume-controlled ventilator (Servo-Ventilator 900, Siemens-Elcoma, Solna, Sweden) delivering tidal volumes of 14-16 ml kg⁻¹ at a respiratory rate of 12-14 min⁻¹. Normoventilation was maintained (PaCO₂ 5.6 kPa). Inspired and expired concentrations of carbon dioxide, oxygen and desflurane were monitored with an Ohmeda 5250 RGM gas analyser (Ohmeda, Helsinki, Finland).

Miscellaneous

Intravascular catheters were inserted by surgical cutdown under clean though non-sterile conditions. Electrocautery was used to minimise blood loss.

Animals in part II were kept normothermic (38.0°C) by the use of an external heating blanket (Warm-touch™, Mallinckrodt, Northampton, UK) as required.

Anaesthetic drugs and a balanced 2.5% glucose solution (Rehydrex[®], Pharmacia, Sweden) was infused at a rate of 3-4 ml kg⁻¹ h⁻¹ in a hind leg, and urine output was measured via a suprapubic (cystostomy) catheter.

Cerebral haemodynamics and metabolism

Surgical preparation has been reported in detail elsewhere (2). The right common carotid artery was cannulated with a 45 mm 20 G catheter for infusion of the ¹³³Xe tracer substance (Mallinckrodt, Northampton, UK). The two main branches, the occipital and external carotid arteries, were both identified and ligated 5 mm distal to their bifurcations (3).

Cerebral blood flow (CBF) measurements based on a modification of the Kety-Schmidt method were carried out with ¹³³Xe as a tracer. The tracer substance was injected into the internal carotid artery, and the cerebral clearance curve was recorded with an extracranial sodium-iodide scintillation detector over the ipsilateral parietotemporal region. Between 0.5

and 1 MBq of isotope dissolved in saline was used for each measurement. A Novo Cerebrograph 10a CBF device (B Simonsen Medical AS, Randers, Denmark) was used to record the detector counts and calculate mean cortical hemispheric CBF by mono-exponential approximation of the initial segment of the clearance curve corrected for background activity. The estimated cerebral vascular resistance (CVRe; $\text{kPa} \cdot 100 \text{ g} \cdot \text{min} \cdot \text{ml}^{-1}$) was calculated from corresponding mean arterial pressure (MAP) and CBF values as $\text{CVRe} = \text{MAP} / \text{CBF}$, assuming intracranial pressure to be zero. Global cerebral arteriovenous oxygen content difference (CavO_2 ; $\text{ml STPD} \cdot 100 \text{ ml}^{-1}$), i.e. extraction of oxygen by the brain, was calculated between arterial and internal jugular venous blood as reported elsewhere (4).

Systemic and pulmonary haemodynamics

A 20 G 45 mm teflon catheter (Intraflow, Viggo AB, Helsingborg, Sweden) was inserted in the right femoral artery and used for invasive pressure measurements and blood sampling. Heparin $250 \text{ IU} \cdot \text{kg}^{-1}$ iv was given soon after all catheters had been inserted, and their correct positions were verified at autopsy.

Study drugs

The commercially available racemic ketamine (Ketalar[®], Pfizer, USA), $10 \text{ mg} \cdot \text{ml}^{-1}$, was used in parts I and II and S(+)- and R(-)-ketamine in part II. The S- and R-enantiomers, provided as salt bases (5), were soluted in sterile water to concentrations of 5 and $20 \text{ mg} \cdot \text{ml}^{-1}$, respectively.

Doses

Previously, the induction dose of racemic ketamine ($10 \text{ mg} \cdot \text{ml}^{-1}$) in juvenile domestic pigs has been found to be $10.0 \pm 2.6 \text{ mg} \cdot \text{kg}^{-1}$ using a lateral recumbency test (2). This test was

repeated with the two enantiomers S-ketamine ($15 \text{ mg} \cdot \text{ml}^{-1}$) and R-ketamine ($60 \text{ mg} \cdot \text{ml}^{-1}$) in six non-premedicated animals (weight $23 \pm 1.2 \text{ kg}$) by constant iv infusion of approximately 1 ml per 3 s until lateral recumbency was achieved. Each animal was induced with either substance at no less than 24 h interval.

Blood concentrations

Blood for analysis of racemic, S- and R-ketamine and of norketamine was drawn at 1, 10 and 40 min after each bolus infusion of study drug. Drug concentrations were assayed in haemolysed blood by gas liquid chromatography (6).

Experimental design

To evaluate the experimental model designed for comparison of different drugs in the same animal, three identical iv 60-second bolus infusions of racemic ketamine were first given in each animal of the first series (part I, n=8), and the pharmacodynamic responses were compared. After that the racemate was compared to its two enantiomers in randomised order in each animal of the second series (part II, n=6).

The approximately 90-minute period of surgical preparation was followed by a 60-minute wash-out of desflurane. The three series of measurements in part I and in part II lasted for approximately 150 min (Fig. 1).

In the part I experiment, an iv bolus dose of racemic ketamine, $10.0 \text{ mg} \cdot \text{kg}^{-1}$, was given over 60 s with determinations of CBF and systemic haemodynamic variables at 1, 5, 10, 15 and 30 min after the start of infusion. A second and a third bolus dose of study drug were given and the effects studied accordingly after approximately 45 and 90 min, respectively, from the first infusion (Fig. 1).

In the part II experiment three infusions of racemic ketamine, $10 \text{ mg} \cdot \text{kg}^{-1}$, S-ketamine, $5 \text{ mg} \cdot \text{kg}^{-1}$, and R-ketamine, $20 \text{ mg} \cdot \text{kg}^{-1}$, were given in each animal in randomised order according to a predetermined schedule. The study drugs were given as iv bolus infusions over 60 s with determinations of cerebral and systemic haemodynamic variables at 1, 5, 10, 15, 25 and 40 min from the start of each infusion. The second and third bolus infusions were given 3-5 min after completion of the preceding measurement period (Fig. 1).

After each experiment the animal was given an iv overdose of pentobarbital, and adequate positions of all catheters were verified at autopsy.

Statistical considerations

Values in text and tables are given as median with 25th and 75th percentiles in parenthesis when not stated otherwise. Percentages were calculated from the mean values.

In part I, maximal (one-minute value) and average (area under curve) changes in CBF after each of the three bolus infusions were compared to detect any acute tolerance to repeated administration of racemic ketamine. Systematic and random errors were defined as the mean and standard deviation, respectively, of differences in CBF change between the second and first and between the third and second infusions.

Student's *t*-test was used for analysis of parametric data and the Mann-Whitney U-test was used for unpaired analysis of non-parametric data. One-way analysis of variance (ANOVA) with repeated design was used to detect differences in response over time of and between the study drugs. To avoid mass significance, posthoc analysis was made with correction according to Bonferroni, and no comparisons between study drugs at different time points were made. A *P*-value of 0.05 or less was considered as statistically significant.

Results

Part I

Blood concentrations of racemic ketamine and corresponding levels of the main metabolite norketamine are given in Table 1.

[TABLE 1 NEAR HERE]

Cerebral and systemic haemodynamics

The first, second and third bolus infusions of racemic ketamine (10 mg kg^{-1}) reduced CBF to 36 (33; 54), 40 (36; 52) and 42 (32; 46) $\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, respectively, at 1 min (Table 2), corresponding to a mean decrease by 40% from the 61 (58; 65) $\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ baseline level determined immediately before the first period of measurements.

Maximal effects on CBF did not differ significantly between the three bolus infusions of ketamine (Table 2), since the systematic errors were 0.2 (95% confidence interval -17.3–17.7; random error 18.9) $\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ between the second and first infusions, and 2.4 (-10.1–14.8; 13.4) $\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$ between the third and second infusions.

[TABLE 2 NEAR HERE]

Cerebral and systemic physiological effects of racemic ketamine were evaluated for all three bolus infusions together, since they did not differ significantly from each other.

Changes in CVRe were biphasic with a 1-minute increase by 7.0% and a 10-minute decrease by 33%, and the MAP was reduced by 38% at 1 min (Table 2).

Part II

Induction doses as determined by the lateral recumbency test were for S-ketamine 4.8 ± 0.4 mg \cdot kg⁻¹ and for R-ketamine 18 ± 2.3 mg \cdot kg⁻¹, corresponding to an S/R potency ratio of 3.8.

The duration of clinical effect, i.e. maintenance of lateral recumbent position, were for S-ketamine 9.7 ± 3.4 min and for R-ketamine 12 ± 4.6 min ($P=0.093$).

Accordingly, comparable iv induction doses of S-, racemic and R-ketamine were 5, 10 and 20 mg \cdot kg⁻¹ with respect to cerebral effects in this and previous (2) studies.

Blood concentrations of racemic ketamine, S-ketamine, R-ketamine and the main metabolite norketamine in part II are shown in Table 1.

Cerebral blood flow and vascular resistance

The effect on CBF over time was significant for S-ketamine ($P=0.036$) and racemic ketamine ($P=0.001$) but not for R-ketamine ($P=0.10$), with initial 22% decreases at 1 and 5 min for racemic ketamine, and a biphasic response pattern including a 19% decrease at 1 min followed by a 12% increase at 15 min for S-ketamine. The responses in CBF differed significantly between S- and R-ketamine ($P<0.001$) and between S- and racemic ketamine ($P<0.001$) but not between racemic and R-ketamine ($P>0.30$) (Fig. 2).

There was no significant effect on CVRe over time for any study drug (S-ketamine $P=0.16$, racemic ketamine $P=0.29$ and R-ketamine $P=0.083$), and no difference in effect between the study drugs ($P>0.30$).

No study drug increased the CavO₂ by more than 10% and there was no significant effect in CavO₂ over time for any study drug ($P>0.30$). Infusion of S-ketamine was associated with significantly lower CavO₂ than of R-ketamine ($P=0.016$) or racemic ketamine ($P=0.008$) but there was no difference in effect between R-ketamine and racemic ketamine ($P>0.30$) (Fig. 2).

[FIGURE 2 NEAR HERE]

Systemic haemodynamics

All three study drugs had significant effects on MAP over time (S-ketamine $P=0.005$, racemic ketamine $P<0.001$, R-ketamine $P<0.001$) with maximal reductions by 11% for S-ketamine and 18% for racemic ketamine at 5 min, and by 31% for R-ketamine at 1 min. The response in MAP to S-ketamine differed from those to R-ketamine ($P<0.001$) and racemic ketamine ($P<0.001$), but there was no difference in response between R-ketamine and racemic ketamine ($P>0.30$) (Fig. 2).

Other physiological variables

Median core temperature was 37.8 (37.1; 38.6)°C in part I and 38.5 (38.3; 38.6)°C in part II.

Discussion

Our main findings of smaller decreases in cortical CBF and systemic MAP by S-ketamine than by racemic or R-ketamine in equipotent anaesthetic doses – indicating more stable cerebral and systemic haemodynamics – have not been reported previously.

Earlier studies in volunteers and patients have shown similar systemic haemodynamic reactions to S-ketamine and to racemic ketamine at the same dosage ratio as used by us (7-11). A confounding factor in those studies could be the simultaneous administration of midazolam, which might have attenuated differences in effect between the ketamine compounds.

The initial depression of cerebral and systemic haemodynamics found here probably results from a direct effect of ketamine and its enantiomers and from attenuation of their norepinephrine-releasing effect by the continuous infusion of fentanyl. This experimental situation might resemble that of a severely traumatised or ill patient given ketamine for pain

relief or anaesthesia outside the hospital or in the emergency unit, where similar haemodynamic responses could be expected. In contrast, ketamine-induced increases in CBF reported in studies with no background anaesthesia could accordingly have resulted from lack of attenuation by other anaesthetic drugs (12, 13). Results obtained in experimental studies on subanaesthetic doses of racemic ketamine are contradictory, and increased (14, 15) as well as unaltered (4, 16) CBF values have been reported. Accordingly, anaesthetic doses have been reported to be associated with either increased (17-19) or decreased (2, 20-22) CBF or CBF velocity. Depressed cerebrovascular autoregulation with a pressure-dependent blood flow has been proposed to explain these diverging effects of ketamine on CBF, but recent studies show both static (23) and dynamic (24) cerebral autoregulation when racemic ketamine (23) or S-ketamine (24) is administered.

The maximal increase in $CavO_2$ at 10 min after the administration of racemic ketamine is in accordance with previous results obtained in the same model (4), but our finding of lower $CavO_2$ values after infusion of S-ketamine might indicate a potential advantage of S-ketamine over racemic and R-ketamine in equipotent doses.

Our model could be used to estimate the $CMRO_2$ from determinations of $CavO_2$ and CBF.

However, we report no such estimations, since $CavO_2$ values calculated from arterial and internal jugular venous blood samples reflect the balance between global cerebral demand and supply of oxygen, whereas CBF values obtained with the Kety-Schmidt method mainly reflect cerebrocortical regional flow. Our finding of no significant change in $CavO_2$ despite a decrease in CBF is in contrast to the ketamine-induced uncoupling between flow and metabolism of the brain reported in several previous studies. These findings are in accordance with a recent hypothesis that changes in CBF are determined by changes in the cerebral metabolic rate for glucose rather than in the $CMRO_2$ (25, 26).

The similarity in CBF response between the three injections of racemic ketamine in part I of the study implies lack of cerebral acute-tolerance to ketamine allowing repeated bolus doses

of racemic ketamine and its enantiomeres to be evaluated accordingly in part II. Although carry-over or order effects cannot be statistically excluded due to the limited number of animals, they are unlikely considering the randomised cross-over study design. In part I the CBF returned completely to the baseline level before the next injections of racemic ketamine, whereas the MAP did not, possibly because the time between injections was too short, particularly after injection of R-ketamine as further discussed below.

The doses are crucial when comparing effects of anaesthetic drugs. In the present experiments, the study drugs were compared in equianaesthetic doses obtained from the recumbency tests indicating a dose ratio of 1:3.8 between S- and R-ketamine. This ratio in the pig is close to that of 1:4 reported in humans in the early eighties (27, 28). Anaesthetic equipotency of these doses is further supported by their similar decreases in CBF at the one-minute measurements. This is also in conjunction with earlier work, where the NMDA receptor affinity of S-ketamine has been shown to be three to four times higher than that of R-ketamine in humans (5). These results are all in accordance with the theory of NMDA receptors as main cerebral targets of action for racemic ketamine and its enantiomeres (29). In contrast, the difference in initial effect on MAP between the study drugs in these doses indicates that systemic haemodynamic effects of ketamine and its enantiomers are non-specific and probably also involve receptors other receptors. The pharmacodynamic aspects of the ketamine compounds are complex, and they interact not only with NMDA receptors but also with i.a. glutamate, nicotinic and muscarinic cholinergic, mono-aminergic, sigma and opioid receptors (30). However, the affinity of ketamine and its enantiomers for these receptors is 10-20 times lower than for NMDA receptors. Differences in the duration of effects on CBF and on MAP of the study drugs might partly be explained by differences in target receptors between the cerebral and the systemic circulation.

The haemodynamic effects could also at least in part be due to differences in their pharmacokinetic properties, since differences in drug load, and hence in need for metabolising capacity, between racemic, S- and R-ketamine are two- to fourfold.

The concentration of R-norketamine, the main metabolite of R-ketamine, has been shown to be up to three times higher than that of S-norketamine in brain tissue after administration of the same doses of R- and S-ketamine (31). The main metabolite, norketamine, with a one-third to one-fifth potency of the racemate (30), was found to reach blood peak levels of $3 \mu\text{g ml}^{-1}$ with possible, but probably little, sustained influence on systemic and cerebral haemodynamics.

The relative plasma concentration ratio between study drug and main metabolite at 40 min was below 1:2 for S-ketamine and close to 1:1 for both racemic and R-ketamine.

Nevertheless, the 40-minute CBF value had returned to baseline for S-ketamine but not so for R- or racemic ketamine (Table 2). A difference in CBF level at 40 min between S- and R-ketamine could have resulted from the four times higher dose of R-ketamine considering the similar pharmacokinetic properties of the enantiomers (27, 28).

Conclusion

S(+)-ketamine was associated with less cerebral and systemic haemodynamic depression than racemic or R(-)-ketamine in equipotent doses in this experimental model. These findings indicate potential advantages of S-ketamine over racemic ketamine.

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Legends

Figure 1.

Study design for parts I and II.

Figure 2.

Effects of iv bolus infusions of $10 \text{ mg} \cdot \text{kg}^{-1}$ of racemic, $5 \text{ mg} \cdot \text{kg}^{-1}$ of S(+)- and $20 \text{ mg} \cdot \text{kg}^{-1}$ of R(-)-ketamine at 1, 5, 10, 15, 25 and 40 min on mean arterial pressure (MAP; mmHg), cerebral blood flow (CBF; $\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$) and cerebral arteriovenous difference in blood oxygen content (CavO_2 ; $\text{ml STPD} \cdot 100\text{ml}^{-1}$) in six normoventilated pigs anaesthetized with fentanyl and vecuronium. Data is shown as mean \pm 1 standard error of the mean (SEM).

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Table 1.

Blood concentrations of racemic ketamine, S-ketamine, R-ketamine and norketamine during part I (n=8) and II (n=6) in normoventilated pigs anaesthetized with fentanyl and vecuronium. Data is reported as median with 25th and 75th percentiles in paranthesis. Table 2.

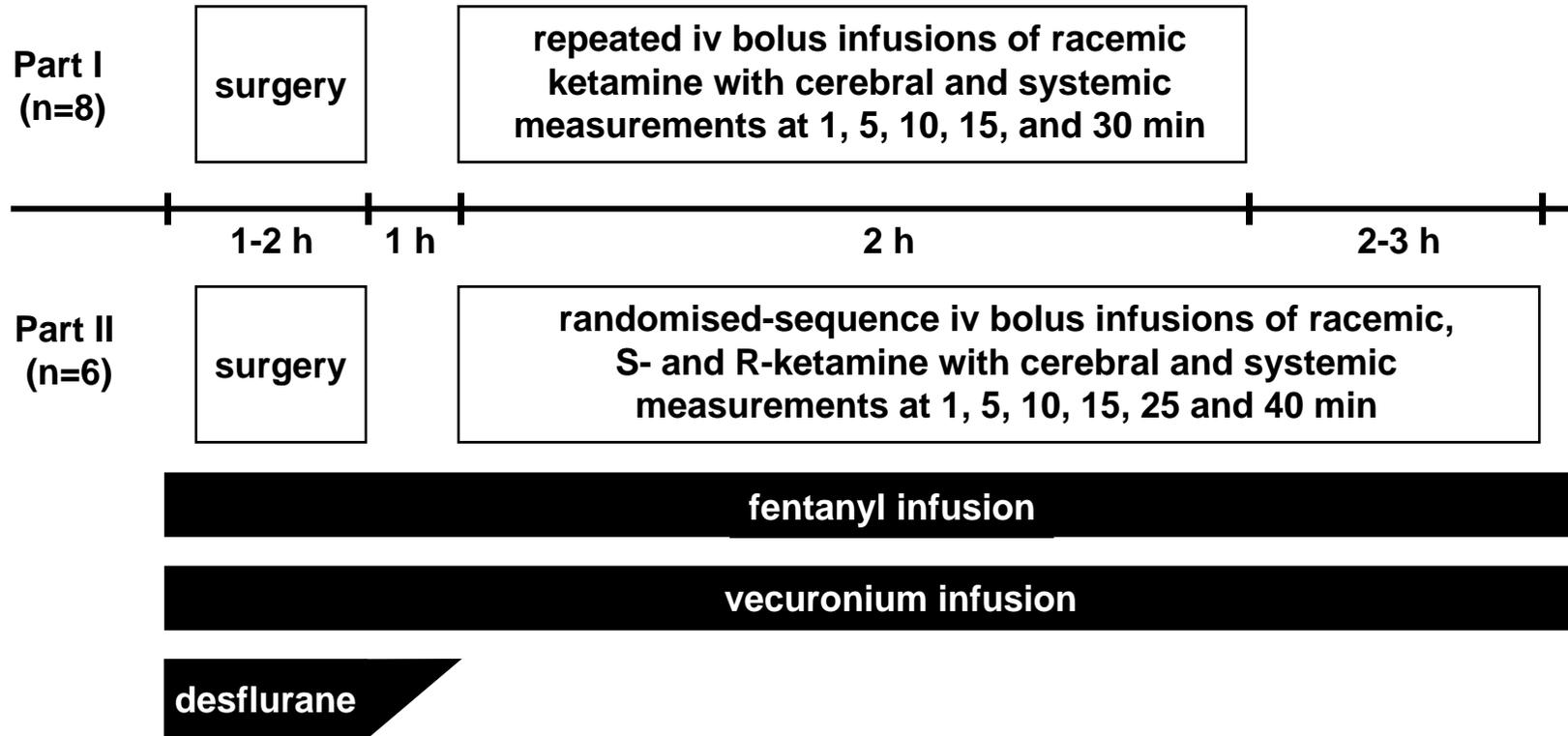
		Blood concentration (ug ml ⁻¹) at		
		1 min	10 min	40 min
Part I	Racemic ketamine	56 (50; 59)	4.3 (4.1; 4.8)	1.8 (1.6; 2.3)
	Norketamine after 1 st injection			1.5 (1.3; 1.5)
	Norketamine after 2 nd injection			2.2 (2.1; 2.4)
	Norketamine after 3 rd injection			2.9 (2.4; 3.1)
Part II	Racemic ketamine	89 (64; 112)	3.8 (3.1; 4.2)	1.5 (1.2; 1.6)
	Norketamine	1.6 (0.9; 2.3)	3.1 (1.9; 4.4)	2.0 (1.5; 2.8)
	S-ketamine	35 (33; 58)	1.3 (1.2; 2.4)	0.7 (0.4; 1.2)
	Norketamine	1.6 (1.4; 1.9)	2.0 (1.2; 2.8)	1.6 (1.0; 2.1)

R-ketamine	158 (141; 172)	6.8 (6.1; 7.6)	2.4 (1.9; 3.3)
Norketamine	1.2 (1.0; 1.8)	2.7 (1.7; 3.6)	2.8 (1.6; 3.2)

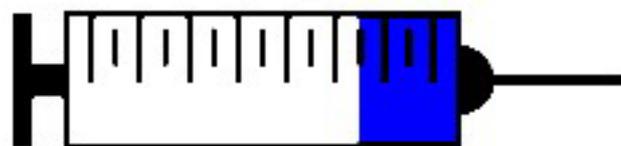
Table 2.

Part I. Effects of three consecutive intravenous bolus injections of 10 mg · kg⁻¹ of racemic ketamine on systemic and cerebral variables in eight normoventilated pigs anaesthetized with fentanyl and vecuronium. Individual pre-bolus values are mean values from two measurements and the remaining individual values are mean values from three measurements. The results are median with 25th and 75th percentiles in parenthesis.

	Pre-bolus	1 min	5 min	10 min	15 min	30 min
Mean arterial pressure (mmHg)	141 (135; 149)	104 (93; 112)	81 (64; 110)	94 (70; 125)	106 (78; 124)	122 (110; 133)
Estimated cerebral vascular resistance (mmHg·100g·min·ml⁻¹)	2.2 (2.1; 2.6)	2.4 (2.2; 2.8)	1.7 (1.4; 2.0)	1.6 (1.3; 1.8)	1.8 (1.4; 2.0)	2.1 (1.9; 2.2)
Cerebral blood flow (ml·100g⁻¹·min⁻¹)	61 (58; 65)	38 (33; 49)	50 (40; 59)	59 (47; 70)	58 (52; 68)	57 (51; 64)



S (+)



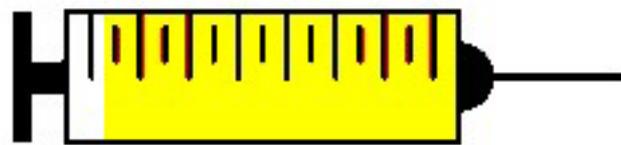
5.0 mg/kg

racemic



10 mg/kg

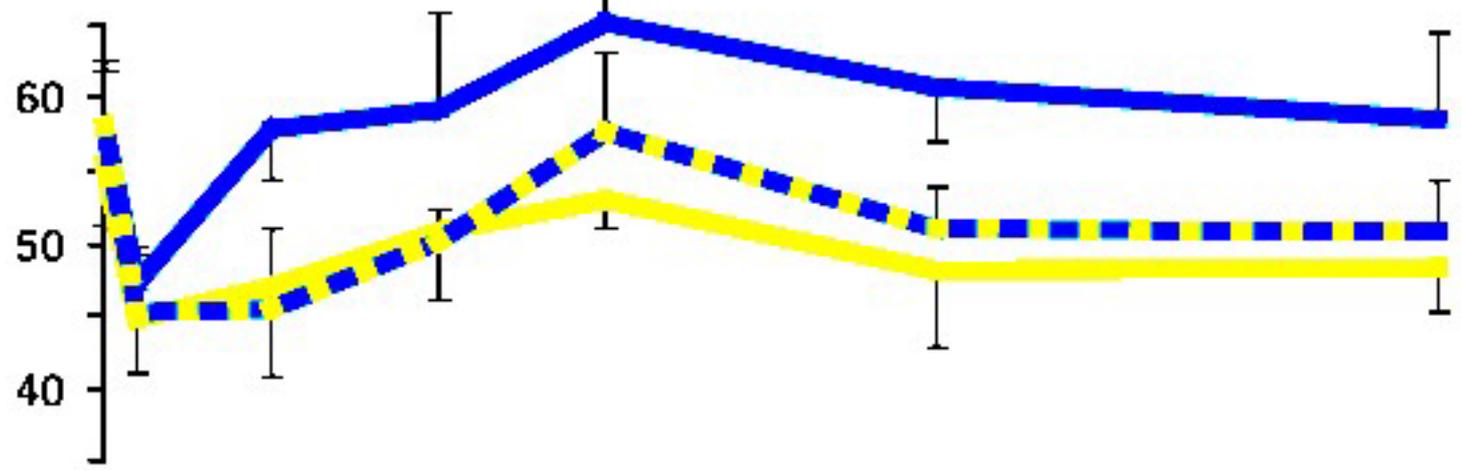
R (-)



20 mg/kg

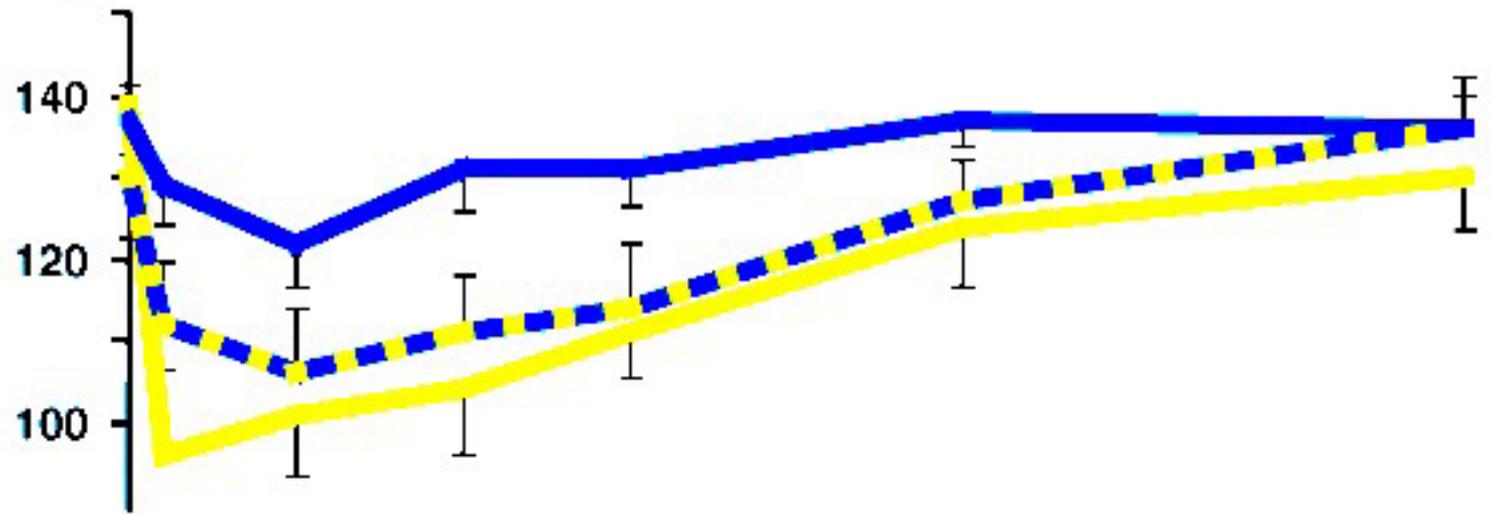
ml·100g⁻¹·min⁻¹

CBF ($\bar{x} \pm \text{SEM}$)



mm Hg

MAP ($\bar{x} \pm \text{SEM}$)



time (min)