KETAMINE: PHARMACOKINETICS AND ANALGESIC ACTIVITY IN MAN

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Intravenous ketamine (2 mg kg^{-1}) produces rapid anaesthesia in man which lasts 10-20 min. Disposition is described by a 2-compartmental model with a terminal plasma half-life in patients of 2.5h. (Wieber et al, 1975). Intramuscular injection is the favoured route of administration to children but the pharmacokinetics have not been reported. In smaller doses (< 0.5 mg kg^{-1} I.V.) ketamine has analgesic activity but the extent of analgesia has not been measured previously in volunteers.

We have given ketamine (as the hydrochloride salt) to volunteers on separate occasions (a) as a bolus I.V. injection (0.25 mg kg^{-1} and 0.125 mg kg^{-1}) and (b) as an intramuscular injection (0.5 mg kg^{-1}) and as an oral solution (0.5 mg kg^{-1}). Concentrations of ketamine and two metabolites were measured (as heptafluorobutyryl derivatives) by g.l.c. with electron-capture detection (Chang & Glazko, 1972). Concurrently the pain of ischaemic exercise was measured (Harrison and Bigelow, 1943) and the extent of analgesia calculated from pain scores recorded during the exercise period. Both studies were carried out in fasted subjects in a cross-over design with a suitable control; the order of administration was randomised and was on a "single-blind" basis.

After I.V. injection (5 subjects) ketamine disposition was rapid and fitted a two-compartmental model; mean disposition half-times during the fast and slow phases were 16 and 180 min respectively and clearance was 17.7 ml min^{-1} kg^{-1}. Pharmacokinetic values were independent of the administered dose. The short period of analgesia (5 to 10 min, 0.25 mg kg^{-1}; < 5 min, 0.125 mg kg^{-1} dose) corresponded to a plasma ketamine concentration of > 100 ng ml^{-1}.

Absorption was rapid and extensive after I.M. injection and concentrations rose above 100 ng ml^{-1} within 10 min. In contrast, oral administration produced low concentrations and the extent of absorption was small (Table). Concentrations of norketamine and dehydronorketamine were higher after oral than after I.M. administration and this suggests that extensive first-pass metabolism occurs. After I.M. injection analgesia was seen over the interval 15 to 45 min; at 60 min 3 of 4 subjects showed no analgesia, and the concentration had fallen to 120 ng ml^{-1} (range 100 to 150 ng ml^{-1}). No analgesic effect was found after oral administration at this dosage level.

Table: I.M. and oral administration of ketamine (0.5 mg kg^{-1})

Subject	I.M. injection				Oral solution		
	C_{max}	t_{max}	F	K_A	C_{max}	t_{max}	F
DB	230	30	85.1	0.033	30	45	14.5
JC	140	30	85.5	0.037	30	30	16.3
DL	330	15	88.7	0.115	-	-	-
WN	230	20	78.5	0.112	70	20	24.5
Mean	232		84.4				

C_{max}: apparent peak plasma ketamine concentration (ng ml^{-1}) at t_{max} (min)
F: fraction (%) absorbed; K_A: rate constant for absorption (min^{-1})

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