

Title: PHARMACOKINETICS OF KETAMINE (K) IN INFANTS AND SMALL CHILDREN

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INTRODUCTION:

Little is known about the pharmacokinetics of K in infants and children (1). They noted a beta-phase half-life of 40-58 minutes for K (only) in children, 2-9 years, given 10 mg/kg K i.m. We were interested in determining the kinetics, distribution (including binding), and metabolism of K in infants and children. Our particular concern was the influence of temperature and cardiopulmonary bypass (CPB) on the beta-phase of K elimination and metabolism.

METHODS: Six infants and small children undergoing CPB for correction of ventricular septal defects were studied. This study was approved by the Institutional Review Board. All patients were medicated with morphine (0.1 mg/kg) one hour prior to surgery. Anesthesia was induced with IM K (7 mg/kg) or IV K (2 mg/kg) and maintained with nitrous oxide-morphine (1.5 mg/kg) in the 2 small children (Group A) and with fentanyl (50 µg/kg) in the 4 infants (Group B); the 4 infants subsequently had surface cooling to 28°C. Following induction of anesthesia, percutaneous arterial catheters were placed. Blood (1.0 ml) was drawn at 3, 5, 7, 12, 15, 30, 60 and 90 min following K and at 5 and 30 min following CPB. Plasma was collected in the presence of heparin in plastic syringes and test-tubes free of trisbutoxyethyl phosphate and 2-(2-hydroxyethyl mercapto) benzothiazole to avoid artifactual displacement of drug.

K and nor-K analysis was done by gas chromatography using nitrogen sensitive detection and bromo-K as the internal standard (2). Plasma was extracted at pH 8.5 with heptane. After evaporation, the residue was derivatized with heptafluorobutyric anhydride and solvent was evaporated. Column: Ultrabond 20M, Carbowax, carrier gas: N₂; temp.: 180°C, relative retention time: 0.75 and 0.60 for K and nor-K respectively. Sensitivity was 10 ng/ml; assays were made with as little as 0.2 ml plasma. Binding studies were carried out at pH 7.4 at 37°C unless otherwise indicated. We used K-3H prepared by the Wilzbach method (3) for studies with human alpha-1 acid glycoprotein (AAG), binding was studied in the range of 0.05-0.2% AAG.

RESULTS: Results in children are given in Table I. Children eliminate K about twice as fast as adults, in agreement with prior studies (1,4).

In a typical patient, plasma levels at 5, 7, 15, 30, 60 and 90 min were 1.38, 1.27, 0.72, 0.47, 0.33 and 0.20 µg/ml for K and 0.14, 0.19, 0.27, 0.28, 0.29 and 0.29 µg/ml for nor-K respectively. Thus nor-K levels in this and in other children exceeded K concentrations after about 1 hr. This is in contrast to observations in adults undergoing CPB (Group C). In this child, at 90 min CPB was initiated and plasma levels of K and nor-K at 95 min dropped to 0.14 and 0.12 µg/ml for K and

nor-K respectively; the levels remained at this level for at least another 25 min.

We studied the binding of K to plasma of adult and children. One of the children undergoing CPB exhibited 43.3% binding. In newborns (cord plasma, N=12) binding was 9.7%, range 4.5 - 21%. In mother (N=7) binding averaged 34.6% range 24.6 - 41.1%. We found that K binds not only to human albumin, but also to AAG. Since AAG is known to be low in cord blood (5), the low binding of K in the newborn is probably related to AAG concentrations. K binding is not altered in the temperature range 20-37°C, though it is pH dependent. The latter was expected in view of the pKa of 7.5; the pKa of nor K is 6.7.

The free fraction is about 20-30% greater in children than in adults; this could contribute to the shorter t_{1/2}. However, the small difference cannot account for the fact that t_{1/2} are more than twice in adults vs. children.

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TABLE I

	Typical (T) and Average (Av) Cases				7	
	GROUP A		GROUP B		GROUP C	
	T	Av	T	Av	T	Av
Beta t-1/2 min	74.4	59.9	60.7	52.3	129	108
AUC ug/ml /min	62.0	53.5	60.7	54.1	39.7	36.3
A ug/ml	1.50	1.34	1.56	1.52	7.70	6.82
B ug/ml	0.402	0.461	0.684	0.611	0.483	0.584