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Title: THE PHARMACOKINETICS OF KETAMINE IN THE PEDIATRIC SURGICAL PATIENT

Authors: P.D. Allen, M.D., Ph.D., R.N. Reynolds, M.D., R.M. Maddi, M.D., P.J. Orsulak,Ph.D

Affiliation: Departments of Anesthesia, Affiliated Hospitals Center and Tufts New England Medical Center, and the Psychiatric Chemistry Laboratory, Boston, MA 02115

Introduction: Ketamine is used in the pediatric surgical patient for both induction and maintenance of general anesthesia. Clinical observations suggest that the effective dose of Ketamine is greater in children than in adults with the greatest difference seen in the neonate.

Methods: To explain this clinical difference we have examined the pharmacokinetics of Ketamine in 21 children, ASA I & II from age groups 0-6m, 6m-1y, 1y-5y, 5y-12y. Informed consent was obtained, as approved by the human studies committee, from the parents of all children. In the latter three groups, each child was pre-medicated with nebutal and scopolamine and brought to the OR. Anesthesia was induced with halothane, N_2O, O_2, and an indwelling venous and radial arterial cannula placed. After intubation with an appropriate size tube, assisted with succinyldicholine, anesthesia was maintained with N_2O-O_2 without halothane for 5 min. Infants under 6m were premedicated with atropine and intubated awake. They were anesthetized with halothane, N_2O, O_2, for line placement, then maintained with N_2O-O_2. Temperature, pulse, blood pressure and respiration were monitored throughout the studies. Ketamine 3mg/kg was given as an IV bolus in all patients and 2.5cc arterial samples were drawn according to one of two schedules (1,2,4,8,16,24,32 min. or 3,5,10,20,30,40,50,60 min.) into heparinized syringes. The plasma obtained from these samples was kept frozen prior to analysis. Samples were analyzed by a modification of the technique of Chang and Glazko,[1] using gas liquid chromatography with electron capture detector. Samples were analyzed for concentrations of Ketamine and its two major metabolites, Metabolite I and II. The results of this analysis were analyzed using a non-linear least squares analysis using a two-compartment open model. Apparent volume of distribution of the central compartment (VD_C) and the constants for the fast and slow phases ($t_{\frac{1}{2}\alpha,\beta}$) were determined.

Results: The results for the pharmacokinetics of ketamine in pediatric patients are seen in the following table.

Age group	VD_C (l/kg)	$t_{\frac{1}{2}\alpha}$	$t_{\frac{1}{2}\beta}$
0m-6m	0.931± 0.16#	3.20± 1.51	34.75± 28.25
6m-1y	0.592± 0.06*	4.047±0.009	28.05± 8.59
1y-5y	0.464± 0.042	4.18± 1.08	29.87± 9.99
5y-12y	0.357± 0.040	3.33± 0.72	32.82± 6.70

Mean ± S.E.

sig. diff. from all other group $p<0.05$,
* sig. diff. from groups 0-6m and 5y-12y, $p<0.05$.

Significant levels of metabolite I were seen within 8 min. and rose slowly to a peak at 30-40 min., equaling the concentration of ketamine at that time. Metabolite II was seen after 30 min. but in very low concentrations not exceeding 0.08μgm/ml at 60 min. There was a transient increase in both heart rate and blood pressure which subsided in 5-7 min. In most subjects there was a transient episode of apnea requiring controlled ventillation for 3-5 min. Patients required additional anesthesia with halothane depending on the surgical stimulus when the blood level was between 0.8 and 1.2μgm/ml, usually after 25-30 min.

Discussion: There were significant differences found in the pharmacokinetics of ketamine between the age groups studied in pediatric patients. All of the differences lie in the volume of distribution, which decreases rapidly as age increases. No differences were found in rate of distribution or elimination. This difference may explain the clinical findings seen with dose/kg and effect, and may be related to differences in body composition, protein binding, metabolism, distribution and excretion.

Supported in part by a grant from Warner Lambert-Parke Davis Co.

References

1. Chang T, Glazko AJ: A gas chromatographic assay for ketamine in human plasma, Anesthesiology, 36:401-404, 1972