Title: EFFECTS OF DIAZEPAM ON THE PHARMACOKINETICS OF KETAMINE IN MAN

Authors: E.P. Domino, M.D., S.E. Domino, B.S., L.E. Domino, M.D. and E.K. Zsigmond, M.D.

Affiliation: Departments of Pharmacology and Anesthesiology, University of Michigan, Ann Arbor, MI 48109 and Department of Anesthesiology, University of Illinois, Chicago, IL 60612

Introduction. A number of investigators have reported that benzodiazepines like diazepam given i.v. just prior to ketamine improve the quality of anesthesia. In view of the fact that there is some evidence of an increase in the plasma ketamine levels after diazepam, a detailed pharmacokinetic analysis was undertaken which is the subject of this report.

Methods. A double-blind, randomized, cross-over design was utilized. Eight healthy male volunteers were selected. Each subject received either diazepam or a 0.9% NaCl placebo before ketamine and the alternate combination 5 to 24 days later. Diazepam, 0.3 mg/kg, or placebo in equal volume was given i.v. at a rate not exceeding 5 mg/min, 10 min before ketamine. Ketamine was given i.v. over 1 min in a dose of 2.2 mg/kg. The subjects fasted the night before medication. The analysis of ketamine in plasma was performed using gas chromatography-mass fragmentography. A multicompartmen model of the data was obtained by weighted nonlinear least squares analysis using CSTRIP and NONLIN. Various standard pharmacokinetic parameters were calculated from the coefficients and exponents of the polyexponential equations. The Michigan Terminal System was used for the pharmacokinetic and the two tailed correlated "t" test programs.

Results. Mean plasma ketamine differences between placebo-ketamine and diazepam-ketamine were relatively small over the 24 hr period. For the clinical relevant period for anesthesia (0-30 min), diazepam-ketamine treatment resulted in higher plasma levels (P < .05) at some time points. The mean three exponential equation of best fit for the infusion placebo-ketamine data was

\[ Q_p = 1600000e^{-104t} + 3210e^{-8.88t} + 551e^{-391t} \]

where t is time in hr after ketamine infusion and Qp the ketamine concentration in ng/mL. After diazepam-ketamine

\[ Q_p = 204000e^{-100t} + 402e^{-6.53t} + 594e^{-0.298t} \]

After placebo-ketamine the t 1/2 = 24.0 sec, at 1/2 = 4.68 min, and t 1/2 = 1.77 hr. After diazepam-ketamine the t 1/2 = 25.0 sec, at 1/2 = 6.37 min and t 1/2 = 2.33 hr. Although the a and t 1/2 of ketamine were slightly prolonged by diazepam, this difference did not reach statistical significance. With placebo-ketamine the plasma clearance was .848 1/kg/hr and after diazepam-ketamine .719 1/kg/hr (P < .08). These findings are in agreement with the prolonged duration of anesthesia by diazepam pretreatment from 14.8 to 21.7 min (followed first command, P < .02) and 16.7 to 24.5 min (verbalized coherently, P < .04). However, there was no simple correlation with ketamine plasma levels and duration of anesthesia. The subjects' behavior while emerging from anesthesia did not differ appreciably between treatments, although twice as many subjects described the experience as favorable after diazepam-ketamine than after placebo-ketamine.

Discussion. The results of this study are in close agreement with previous literature. Most of the pharmacokinetic parameters of ketamine are not altered significantly by diazepam. Perhaps with a larger series of subjects more statistically significant differences would have been obtained. However, from a clinical point of view, the slightly increased plasma levels of ketamine and the slight prolongation of anesthesia by diazepam pretreatment are not particularly disadvantageous compared to the favorable reduction in circulatory stimulation and subject acceptance.

This study was supported in part by a grant from Warner Lambert and the Psychopharmacology Research Fund (Domino).

References