

Title: CHRONIC ALCOHOLISM ATTENUATES THE ANESTHETIC EFFECTS OF DIAZEPAM

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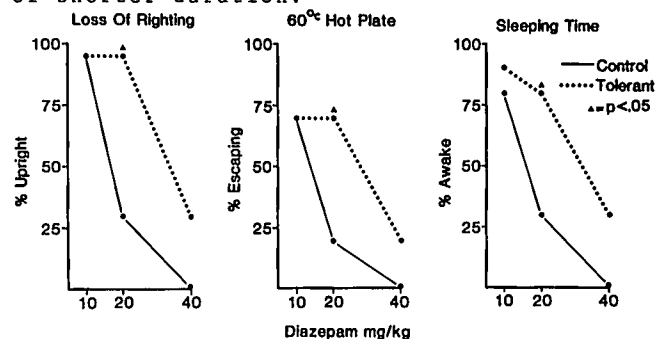
Introduction: Although it is "common knowledge" that chronic alcoholics, not acutely intoxicated, require increased doses of anesthetics, the data that support this notion are meager and incomplete. Published studies have dealt with only two of the three currently used inhalational anesthetics, and only analgesic effects were examined. The present work was designed to examine how chronic alcohol intake modifies diazepam anesthesia with regard to induction time (loss of righting reflex), analgesia (escape from a 60°C hot plate), and duration of action (sleeping time).

Methods: Male Sprague Dawley rats, housed two per cage, were allowed ad libitum access to a complete balanced liquid diet containing 6.54% ethanol as their only source of food and water for three weeks. Pair-fed controls were given the same diet except that dextrin was isocalorically substituted for the alcohol. Nine hours before testing, the diets were removed and the animals given free access to water. Ethyl alcohol 2.4, 3.2, and 4.0 gm/kg or diazepam 10, 20, and 40 mg/kg were injected intraperitoneally and the following observations made: whether or not righting reflex was lost, whether escape from a 60°C hot plate occurred within fifteen seconds, and whether the animals fell asleep. Sleep was considered to take place if the animals did not move from an 18 by 24 inch area within ten minutes. Ten rats were used at each dose for both experimental and control groups. The data were analyzed using the Fisher exact probability test; $p < .05$ was considered statistically significant. An additional group of ten rats were fed the alcohol-containing diet and venous blood samples, obtained by orbital puncture, were analyzed by gas chromatography for alcohol content. The samples were taken on the seventh day, at 9:00 A.M. and 4:30 P.M. on the fourteenth day and at midnight, 4:30 A.M., and 9:00 A.M. on the test day (day 21).

Results: Both experimental and control animals showed a significant weight gain over the three week feeding period, and the weights of the treated and control groups were not significantly different from each other at the time of the drug testing. The mean alcohol levels (in mg percent) were: 154.5 on day seven; 107.1 at 9:00 A.M. and 186.3 at 4:30 P.M. on day 14; 178.4 at midnight and zero by 4:30 A.M. on day 21.

The dose-response curves for the animals tested with ethyl alcohol demonstrated a shift to the right for the tolerant animals. The differences were statistically significant at 4.0 gm/kg for the loss of righting reflex and sleeping time and at 2.4 gm/kg for the hot plate escape. As shown in the figure, alcohol-tolerant rats were also less affected by diazepam than were their pair-fed controls. The differences were statistically significant at 20 mg/kg for all three behavioral measures.

Discussion The body weight and blood alcohol data indicate that the animals were consuming sufficient amounts of the diet to produce consistently elevated blood alcohol levels and at the same time support physical growth. That the levels were zero at the time of testing eliminates any possible effect from residual blood ethanol levels on the observed results. The rightward shift of the dose-response curve for ethanol verifies that tolerance was produced by the experimental paradigm. The significant shift of the dose-response curves for alcohol-tolerant rats given diazepam demonstrates cross tolerance between ethanol and diazepam for anesthesiologically relevant variables. Subject to the reservations of generalizing from rodents to man, the data suggest that alcoholic humans would in fact require more diazepam for the induction of anesthesia and for analgesia, and the effects of a given dose of diazepam would be of shorter duration.



Dose response curves for chronic alcoholic rats and pair fed controls given diazepam and tested for loss of righting reflex, escape from a 60°C hot plate, and sleeping time. The differences at 20 mg/kg were statistically significant on all three measures.