

Acute Tolerance to Triazolam during Continuous and Step Infusion: Estimate of the Effect Offset Constant.

Kroboth, Patricia D.; Bertz, Richard J.; Smith, Randall B. *Journ of Pharm and Exp Thera*. 1993. Vol 263(3):1047-1055.

Abstract

Although acute tolerance to selected effects of many benzodiazepines is known to occur, acute tolerance to triazolam has not been documented even in studies that have included pharmacodynamic modeling. The purpose of this investigation was to determine whether acute tolerance to triazolam occurs in humans, intravenous bolus doses of triazolam were used to individualize two subsequent intravenous infusions: one to achieve and maintain a constant triazolam concentration and one to achieve a series of incremental steady-state concentrations; a placebo treatment was also included. Ten healthy men completed the four single-dose treatments. Serial blood sampling and psychomotor and memory testing were done. In the constant infusion treatment, mean performance impairment was greatest at 1 h and then decreased rapidly despite maintenance of a mean triazolam concentration of 2.48 ng/ml for 9 h. Neither learning nor changes in free concentration account for the observations. Additionally, data from the step-infusion treatment indicate that the triazolam effect-concentration relationship after a single dose can be altered by rate of administration. Because tolerance develops, the administration of drug in small increments results in an increased effect at a lower concentration, with a blunted maximal response. Furthermore, our data suggest intersubject variability in the rate of development of acute tolerance. Patients who develop tolerance more slowly would experience a longer duration of effect. Further study regarding the rate of development of tolerance to specific effects and in different patient populations is warranted.