Distinguishing a benzodiazepine agonist from a nonagonist anxiolytic (buspirone) by electroencephalography: Kinetic-dynamic studies.

Greenblatt, David J.; Harmatz, Jerald S.; Gouthro, Terry A.; Locke, Jenifer; Shader, Richard I. *Clin Pharm & Therap*. Vol 56(1) 100-112.

Background and objectives: Benzodiazepine agonists and azaperone derivatives are used clinically as anxiolytics but have different neuroreceptor mechanisms of action. This study evaluated clinical pharmacodynamic approaches to distinguishing these two classes of compounds.

Methods: Healthy volunteers received single oral doses of placebo, the benzodiazepine agonist triazolam (0.25 mg) or the azaperone anxiolytic buspirone (20 mg), in a double-blind, three-way crossover study. Ratings of mood and sedation, performance on the digit symbol substitution test (DSST), and quantitative measures of electroencephalographic (EEG) beta activity (13 to 31.75 cycles/sec) determined by fast-Fourier transform were obtained at multiple times after dosage.

Results: Triazolam significantly increased self- and observer-rated sedation, impaired DSST performance, impaired recall, and increased EEG beta activity. Pharmacodynamic changes were significantly intercorrelated; all effects were maximal 1 to 2 hours after dosage but were indistinguishable from placebo by 8 hours. Buspirone did not alter the EEG or DSST performance but did increase self-ratings of sedation and feeling "spacey" and impaired memory function; these effects generally were quantitatively less than with triazolam. Peak plasma triazolam concentrations preceded maximum pharmacodynamic effects; the mean plasma effect site equilibration half-life was 9.4 minutes. Kinetic-dynamic modeling procedures yielded significant relationships between hypothetical effect site triazolam concentrations and pharmacodynamic changes.

Conclusions: Quantitative analysis of the EEG clearly distinguishes a typical benzodiazepine agonist from a nonagonist anxiolytic, in clinically relevant dosage, whose pharmacodynamic actions do not involve benzodiazepine receptor occupancy. EEG effects associated with triazolam are intercorrelated with other pharmacodynamic measures. (CLIN PHARMACOL THER 1994;56:100-11.)