Pharmacokinetic-Pharmacodynamic Relationships For Benzodiazepines

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Summary

This article reviews the literature on the plasma concentration-effect relationships for benzodiazepines, in humans and in experimental animals. Only literature that explicitly links pharmacokinetics to pharmacodynamics is included. The following questions are evaluated.

• Can concentration-effect relationships be demonstrated?
• If so, are these relations stable?
• Are the influences of specific factors such as age and disease on these relationships established?
It is clear that, when studies are conducted and interpreted appropriately, relations can be found for a wide range of benzodiazepine effects. These include objective measures such as electroencephalography, semisubjective measures such as psychomotor performance, and subjective measures such as mood/sedation scales. A generally applicable model of the relationship which will allow prediction of effect is, however, not yet established. The relationship appears to be dependent on route and rate of administration, because of factors such as distributional delay, formation of active metabolites and, probably, acute tolerance. Furthermore, intra- and interindividual variability is considerable, probably due to varying experimental conditions and intrinsic interindividual differences.

The limited data available on factors influencing the plasma concentration-effect relationships for benzodiazepines demonstrate clear changes in the pharmacodynamics after multiple doses, suggesting the development of tolerance, and a subsensitivity in patients with panic disorder. The influence of factors such as age, disease and drug interactions on the pharmacokinetic-pharmacodynamic relationship remains less clear.

1. Introduction

The benzodiazepines are widely prescribed drugs,[1] Their main clinical applications include roles as sedative-hypnotics, anticonvulsants and anxiolytics, but the full list of clinical uses is much longer and is still growing.[2] The present article reviews the literature on the pharmacokinetic-pharmacodynamic (PK-PD) relationship of benzodiazepines. In the last 5 to 10 years, improvements have been made in methods for measuring effect, study design and modelling techniques, making it possible to obtain adequate data necessary to describe this relationship. The many studies that describe either pharmacokinetics or pharmacodynamics alone, or include both without an attempt to link them, are not included in this review.

1.1 Concentration-Effect Relationships

Pharmacokinetics is the application of mathematical models to describe and predict the time course of drug amounts and concentrations in body fluids; pharmacodynamics describes the time course and intensity of drug effect. The next step in evaluating drug action is the relation between concentration and effect, which (at least initially) removes time as a variable. The ultimate relation is the one between the concentration at the receptor site and the in vivo effects.

Repeated measurement of the drug concentration at the effect site during 1 experiment in 1 individual (or even animal) is generally not possible, particularly for CNS-acting drugs. Therefore, mathematical models must be developed which allow inference of the effect-site concentrations based on plasma concentrations. A further complication is plasma protein binding, since the unbound (free) drug in plasma is presumed to represent that which is available for diffusion to an extravascular effect site.[3]

What are the potential implications and applications of the PK-PD relationship? Some examples, as pointed out in reviews on PK-PD modelling of CNS drug effects,[4-8] are as follows.

(i) It allows more complete understanding of the determinants of drug action, including phenomena such as distributional delay of effect, formation of active metabolites, and acute tolerance.

(ii) It provides a rationale for monitoring drug plasma concentrations as an indicator of clinical efficacy or toxicity. Plasma concentration monitoring is of considerably lower value when no relation between plasma concentration and effect is established. Similarly, knowledge of this relation is necessary to evaluate the clinical implications of situations in which the pharmacokinetics of a drug are...