

## THE USE OF BENZODIAZEPINES IN CLINICAL PRACTICE

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### Summary

- 1 The pharmacokinetic characteristics of the six benzodiazepine anxiolytic drugs available in the United States are reviewed.
- 2 Concern over the abuse potential of the benzodiazepine class of drugs is discussed.

### Introduction

AFTER almost 20 years benzodiazepine derivatives remain as the most commonly prescribed anti-anxiety agents in world-wide clinical practice. Six benzodiazepine anxiolytics are currently prescribed in the United States, and additional ones are available in other parts of the world. All anxiolytic benzodiazepines have similar properties—they reduce anxiety, produce sedation and sleep, have anti-convulsant effects, and can produce muscle relaxation. The clinician may well ask how best to make a rational choice among the available derivatives. Despite similarities, there are differences of clinical value among benzodiazepines in patterns of absorption, distribution, and elimination by the human body. This clinically oriented review will summarize pertinent pharmacokinetic characteristics of benzodiazepine anti-anxiety agents available in the United States and highlight some aspects of the growing concern with their abuse potential.

### Chlordiazepoxide

Chlordiazepoxide, the first available benzodiazepine, is generically available and offers the possibility of cost savings in some countries. The metabolic pathway of chlordiazepoxide in humans is complex, involving transformation into a series of pharmacologically active metabolites. Following oral administration, chlordiazepoxide is rapidly and completely absorbed from the proximal small bowel. Elimination proceeds with an apparent half-life ranging from 5 to 30 hours. Disappearance of chlordiazepoxide from blood is mirrored by appearance of its first pharmacologi-

cally active metabolite, desmethylchlordiazepoxide. Demoxepam, desmethyldiazepam and clocazepam are then formed, and with chronic administration all contribute to the net clinical effect.

An early lesson learned from kinetic research was that chlordiazepoxide given intramuscularly probably precipitates at the injection site. Intramuscular absorption can therefore be slow, erratic, and sometimes incomplete (Greenblatt *et al.*, 1974; Greenblatt, Shader, MacLeod, Sellers, Franke & Giles, 1978a). Oral use in the fasting state provides much more prompt and reliable clinical action, and intravenous infusion at a relatively slow rate is also effective. The metabolic clearance of chlordiazepoxide is reduced in elderly males and in patients with liver disease (Shader, Greenblatt, Harmatz, Franke & Koch-Weser, 1977; Roberts, Wilkinson, Branch & Schenker, 1978; Sellers, Greenblatt, Giles, Naranjo, Kaplan & MacLeod, 1979). This may partly explain the increased sensitivity of such individuals to the effects of the drug.

### Diazepam

Diazepam is still the most widely used benzodiazepine. It has a pharmacokinetic profile somewhat similar to that of chlordiazepoxide. The major metabolic pathway of diazepam in humans involves N-demethylation, yielding its pharmacologically active major metabolite, desmethyldiazepam. After intravenous injection of diazepam, distribution of the parent compound is rapid and very extensive, and this may lead to rapid termination of the action of the parent com-

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