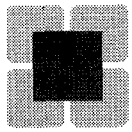

Mechanism of the anticonvulsant action of benzodiazepines

DAVID J. GREENBLATT, MD AND LAWRENCE G. MILLER, MD

BENZODIAZEPINE derivatives have been in clinical use throughout the world since 1960. Some benzodiazepines are used primarily in the treatment of anxiety and panic disorders and some as hypnotics.[1] A few have been used extensively in the treatment of seizure disorders. It is possible that these different patterns of clinical use reflect intrinsic neuropharmacological differences among the available benzodiazepine derivatives. However, it is more generally agreed that similarities among benzodiazepines are far more striking than differences and that the clinical development and marketing strategy has a major impact on usage patterns. We should emphasize that the officially labeled clinical indications, as approved by the Food and Drug Administration, do not necessarily correspond to the indications for which the drugs are actually used in clinical practice.

This paper reviews the biochemical and pharmacokinetic properties of the benzodiazepine derivatives in relation to their clinical anticonvulsant properties.

THE BENZODIAZEPINE RECEPTOR

Specific benzodiazepine binding sites in animal and human brain were first described in the 1970s. The $GABA_A$ receptor, to which benzodiazepines bind, has a complex structure with several functional subunits, which include binding sites for benzodiazepine, picrotoxinin, and GABA.[2,3] These sites in turn determine the frequency of opening of an associated chloride channel. Increased chloride channel permeability leads to neuronal hyperpolarization, which is presumed to mediate the sedative/hypnotic/anticonvulsant actions of benzodiazepines. The chloride channel action of benzodiazepines appears to be an indirect one mediated via GABA, i.e., benzodiazepine binding modulates GABA binding, which in turn causes the chloride channel to open. The reverse is also true—concentrations of GABA can influence benzodiazepine binding. The benzodiazepine and picrotoxinin binding sites are also related. Barbiturates, for example, appear to bind at the picrotoxinin binding site, facilitating the binding of benzodiazepines. The entire binding complex is presumed to be located on the postsynaptic surface of GABA-ergic neurons.

From the Division of Clinical Pharmacology, Tufts University School of Medicine and New England Medical Center, Boston, MA.
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DETERMINANTS OF CLINICAL ACTION

Affinity for the receptor

The benzodiazepine derivatives differ considerably in their intrinsic affinity for the specific binding site.[4] Quantitative affinities of several benzodiazepines used as anticonvulsants are shown in *Table 1*. The affinity constant (K_i) values can be understood as the molar concentration of drug necessary to produce occupancy of 50% of the receptors in cortex preparations in vitro. For drugs with relatively low K_i values, such as clonazepam, the amounts of drug needed to produce a given degree of receptor occupancy are smaller than those needed for drugs such as diazepam or nitrazepam, that have higher K_i values. That is, the intrinsic "potency" or receptor affinity of clonazepam is higher than that of diazepam; a difference reflected in the range of usual

TABLE 1
PROPERTIES OF BENZODIAZEPINES USED AS ANTICONVULSANTS

Drug	Receptor K_i (nM)*	Lipid solubility index†
Clonazepam	0.51	0.28
Lorazepam	1.64	0.48
Nitrazepam	7.88	0.29
Diazepam	9.57	1.00

* In vitro binding affinity constants are based on studies of rat cerebral cortex preparations. Lower numbers indicate greater affinity (data were generated in collaborative studies with Drs. Steven M. Paul and My Do Luu, National Institutes of Mental Health).

† Indexes are based on the liquid chromatographic retention relative to that of diazepam. Higher numbers indicate greater lipid solubility (data were generated in collaborative studies with Dr. Rainer M. Arendt, Klinikum Grosshadern, Munich).

effective clinical doses of the two drugs, which is smaller for clonazepam than for diazepam. Despite the quantitative differences in receptor affinity among the various drugs, little if any evidence supports a qualitative difference in the character of the drug-receptor interaction. In experimental models, the relation between the sedative-ataxic effect and the degree of in vivo receptor occupancy appears independent of the particular benzodiazepine interacting with the receptor.[5]

Access to the receptor

Before a benzodiazepine derivative can interact with its specific binding site, it must reach brain tissue itself —in particular, the extracellular fluid surrounding the binding site. The availability of drug to the binding site is governed by pharmacokinetic and physicochemical principles.[6] If a benzodiazepine is given intravenously, it reaches the capillary circulation of brain tissue within one circulation time. However, the drug must also diffuse out of the capillary circulation and through a lipoidal membrane system (the blood-brain barrier) before it can actually interact with its specific binding site. The time necessary for diffusion and equilibration varies depending on the lipid solubility of the benzodiazepine in question. For a highly lipophilic drug such as diazepam (*Table 1*), tissue equilibration and receptor occupation is extremely rapid;[7–9] the onset of clinical action after intravenous administration is correspondingly rapid.[7,10,11] For a less lipophilic benzodiazepine such as lorazepam, equilibration with brain tissue and receptor occupancy is much slower, requiring up to 30 minutes after intravenous administration for completion (*Figure 1*).[7,8] These differences explain the correspondingly slow onset of clinical effects of intravenous lorazepam. Although available experimental and clinical data for clonazepam are limited, clonazepam is even less lipophilic than lorazepam (*Table 1*), suggesting that for clonazepam the onset of clinical action may be as slow as or even slower than that for lorazepam.

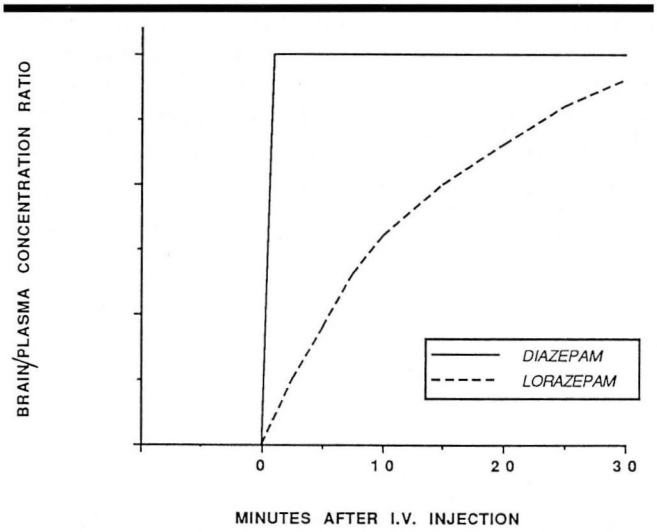

FIGURE 1. Schematic representation of the time-course of equilibration of diazepam and lorazepam with brain tissue (based on the brain: plasma concentration ratio) after intravenous injection. For diazepam, equilibration is almost immediate, whereas for lorazepam, equilibration may take up to 30 minutes.

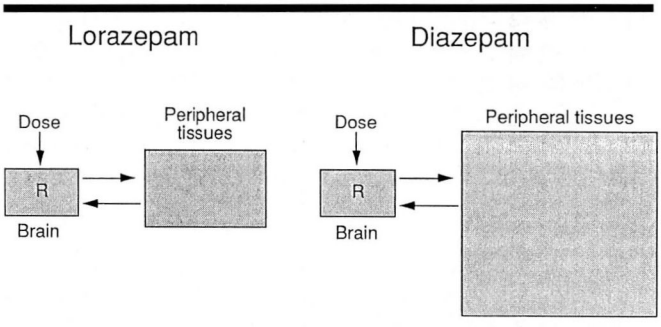

FIGURE 2. After intravenously administered lorazepam reaches its receptor site (R) in the brain, its duration of action will be relatively long because of the limited peripheral distribution of the drug. For diazepam, on the other hand, peripheral distribution is extensive, resulting in removal of drug from the receptor site and in a relatively short duration of action.

Termination of clinical action

After a benzodiazepine has equilibrated between blood and brain, has bound to the receptor, and has

produced its maximal clinical effect, its clinical action will start to wane as drug molecules leave the receptor. Available evidence strongly indicates that the rate of drug removal or disattachment from the receptor is directly determined by the rate of drug disappearance from brain tissue, which in turn depends entirely upon the rate of drug disappearance from systemic blood.[5,8,9,12] There is no evidence that any benzodiazepine "sticks" to the receptor or otherwise lingers in the brain longer than would be expected on the basis of its systemic pharmacokinetic profile.

Although clearance via hepatic metabolism will ultimately be responsible for irreversible elimination of benzodiazepines, systemic blood concentrations during the first few hours after an intravenous dose are influenced by drug distribution to "depot" tissues such as adipose tissue and muscle.[13] A highly lipophilic benzodiazepine such as diazepam will appear to have a relatively short duration of action after a single intravenous dose because of the extensive decline in plasma and brain concentrations in the first few hours after dosage.[7,10,11] These decreases are attributable to extensive distribution of lipophilic benzodiazepines to fat, muscle, and other peripheral tissues. Lorazepam, on the other hand, has less extensive peripheral tissue distribution, thereby leaving relatively large amounts of drug in brain and at the receptor site. In clinical terms, lorazepam will appear to have a somewhat longer duration of activity than diazepam (*Figure 2*).[7,10,11]

COMMENT

The clinical anticonvulsant action of benzodiazepines is determined by a combination of neurochemical, physicochemical, and pharmacokinetic factors. Anticonvulsant activity and other aspects of clinical action probably result from interaction of the benzodiazepine with the specific binding site in the brain, causing increased chloride channel permeability and neuronal hyperpolarization. Despite differences in intrinsic potency (on a milligram basis), benzodiazepines are similar in the qualitative character of the drug-receptor interaction. Apparent clinical differences among benzodiazepines in the time-course of action probably are the result of physicochemical and pharmacokinetic differences. Diazepam, being highly lipid soluble, will rapidly traverse the blood-brain barrier and have a rapid onset of action; however, its duration of action will be relatively short as a result of its extensive distribution to peripheral tissues. Lorazepam, being less lipid soluble, will reach brain tissue more slowly and have a slower onset of action but also a longer duration of action. Clonazepam is a relatively nonlipophilic benzodiazepine, but further studies will be needed to characterize its pharmacodynamic properties.

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DAVID J. GREENBLATT, MD
Division of Clinical Pharmacology
Box 1007
New England Medical Center
171 Harrison Avenue
Boston, Massachusetts 02111

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