FACTORS INFLUENCING THE ACTIVITY AND FATE OF BENZODIAZEPINES IN THE BODY

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- 1 The clinical pharmacokinetics of the many benzodiazepines used to treat numerous and varied clinical conditions can be influenced by many factors.
- 2 Combinations of drugs efficacious in the central nervous system can change the onset, intensity and duration of effect as a result of pharmacological, physiological and pharmacokinetic actions.
- 3 Pharmacokinetic considerations indicate that short to medium long-acting benzodiazepines that depend on only glucuronidation for their major metabolic pathway are the drugs of choice in this category.

Onset, duration and intensity of pharmacological activity

THE pharmacological and therapeutic effects of the benzodiazepines depend on their route, frequency and duration of administration; their dosage form and size; and the particular drug's properties. Pharmacokinetic data should be considered when choosing a dosage regimen.

The most rapid onset of action follows intravenous injections. For about 30–60 min after administration, plasma concentration declines rapidly until it reaches pseudoequilibrium at the concentration it would have reached after intramuscular or oral administration. After pseudoequilibrium is established, plasma concentration decays at a much lower rate than before, and the drug's action persists much longer, provided that the same optimum therapeutic concentration range persists.

Diazepam 10 mg given intravenously to a patient weighing 55 kg (relative apparent volume of distribution 1.8 l/kg) produces a plasma concentration of $10/100 = 0.1$ mg/l after 30 minutes. This may be less than the effective concentration. In contrast, repetitive oral administration every 15–20 min may produce higher plasma concentrations of about 0.4 mg/l, sufficient to control anxious crises (Dasberg, van der Kleijn, Guelen & van Praag, 1974). Intravenous administration is indicated for such conditions as status epilepticus, anaesthesia, tetanus, preeclampsia and cardioversion.

Intramuscular injections produce maximal plasma concentrations 15–30 min after administration. They

require more skill and attention than is sometimes appreciated (Dundee, Gamble & Assaf, 1974) to produce sufficiently high, reproducible plasma concentrations and therapeutic effect. This route of administration is appropriate in patients with status epilepticus or tetanus. Diazepam injected in the shoulder for premedication may give a slightly more rapid onset of action than injection in the thigh or oral administration.

After oral administration, the pharmacological activity of diazepam lasts for about 4 h in patients with chronic epilepsy (Gastaut, Roger & Lob, 1967) and for about 5–6 h when critical flicker fusion threshold and auditory flutter fusion threshold are measured (Besser & Duncan, 1967; Besser, 1967). The accumulation of diazepam or chlordiazepoxide and their active metabolites in patients taking the drugs three or more times daily and their rather long biological half-lives suggest an extension of duration of activity after subchronic treatment, but objective and subjective tests have not confirmed this. Reaction times, the results of pencil and point tests, arithmetic tests and rod and frame tests, and observed behaviour did not differ in volunteers receiving diazepam 10 mg three times daily and in volunteers who received single doses (Hollister & Gillespie, unpublished data).

Prolonged pharmacological activity has followed administration of large diazepam and chlordiazepoxide doses, for example, after treatment of cardioversion, preeclampsia, delirium and intoxication and after long-lasting anaesthesia. One patient with preeclampsia received 1300 mg diazepam in 3 d, and diazepam could be detected for about 18 days. Its

Figure 1 Plasma concentrations of diazepam (continuous line; $t_{1/2}$ 40 h) and desmethyldiazepam (dotted line; $t_{1/2}$ 60 h) during and after intravenous infusion of diazepam (1300 mg over 3 days) in a near-term pregnant woman suffering from pre-eclamptic seizures. No enzyme saturation can be observed.

half-life was about 40 h (Figure 1). Twenty-eight days after therapy had begun, desmethyldiazepam could be detected; its half-life was 60 hours. Figure 2 illustrates the plasma concentrations measured in one patient who received diazepam orally for 8 d and then intravenously 1 week after the last oral dose. Sedation and ataxia have occurred for several days after 100 mg diazepam or chlordiazepoxide were administered intravenously. After subchronic treatment with chlordiazepoxide and related drugs, characteristic electroencephalographic changes (low voltage and fast beta activity) may persist for several days or even weeks after therapy has ended (Clark & Arrowsmith, 1968).

The preferential accumulation of drug and metabolites in myelin-containing nerve fibre structures may be responsible for the duration of action of benzodiazepines (van der Kleijn, van Rossum, Muskens & Rijntjes, 1971; van der Kleijn, Vree & Guelen, 1977). Very often the plasma concentrations required to produce the effects observed in experimental conditions are not maintained in general practice because of intake problems and rapid total body clearance of the drug. Ideally, physiological and psychological experiments and treatment should be monitored by regular plasma concentration determinations especially when the anticipated effect is not observed.

The effect of benzodiazepines on motor action may be susceptible to tolerance; feedback mechanisms may affect voluntary movements. Many epileptic patients' symptoms become refractory to clonazepam or diazepam after about 3 months' treatment. If

Figure 2 Plasma concentration of diazepam (●) and desmethyldiazepam (○) after a single 30 mg dose of diazepam, followed by three 10 mg doses daily for 7 d, followed by 1 week without drug, followed by a single intravenous injection. Note the differences in the concentration curves following the single and the subchronic doses.

benzodiazepine therapy is interrupted for about 3 months, it can be resumed, and pharmacokinetic patterns similar to the earlier patterns will appear.

Because the anticipated effect of a drug depends on many variables, defining and assessing a therapeutic plasma concentration is often difficult. Moreover, most benzodiazepines are metabolized at different rates to pharmacologically active metabolites which mask the intrinsic activity of the parent compounds. This masking has made determining the intrinsic therapeutic efficacy of medazepam, a precursor of diazepam, almost impossible. As metabolites with lower clearance rates than those of the parent drug accumulate, the concentrations of drug and metabolites change until a pseudosteady state has been reached.

Mean therapeutic concentrations with large variances have been established, however, with rating scales (Curry, 1974; Dasberg *et al.*, 1974) and from observations of the particular dosage schedule (mg daily or, preferably, mg/kg body weight daily) to which most patients respond. The concentration can be calculated from the equation: dose/dosage interval = concentration $\times$ clearance, provided that the average rate of the drug's clearance is known. This calculation appears to be meaningful only when no active metabolites are formed, as after oxazepam treatment.

Table 1 lists the benzodiazepine plasma concentrations required for anxiety relief. However, other drugs administered concurrently may strongly influence therapeutic efficacy and pharmacokinetic profile, no matter what the indication. Higher receptor sensitivity in the elderly may be responsible for their response to lower doses (Bender, 1967).

Sites and mechanisms of action

Many pharmacological properties attributed to the benzodiazepines have been deduced from observations in animals and must be attributed to man with caution. In addition to central depressant activity, the benzodiazepines apparently have some facilitory action, possibly reversing inhibition. The limbic system has been accepted as their site of action

(Schallek, Schlosser & Randall, 1972) and as the site of the emotions and feedback to the automatically innervated organs. This explains the immediate taming effect of the drugs as well as their complex effects on behaviour and their secondary benefits in social stress, situational neuroses and organ dysfunctions.

Mapping the sites of action from electrophysiological studies have seemed to implicate the brain stem, the limbic system, the hypothalamic region, and the cortex. The observation that the rage reaction induced by electrical stimulation of the hypothalamus in the cat and monkey is blocked by benzodiazepines has provided evidence that this region is involved (Hernandez-Peon & Rojas-Ramirez, 1966). Influence on the cortex was studied with electrocorticogram analysis. The power spectrum analysis technique appears to differentiate the benzodiazepines from the barbiturates (Schallek & Thomas, 1971).

The cerebellum may also be a site of action for the benzodiazepines. Purkinje cells in the cerebellum are known to inhibit several subcortical structures. Intravenous diazepam enhances electrical activity of Purkinje cells and, therefore, may suppress cortical epileptiform activity. Karkos (1973) has observed degenerative changes in the cerebellum following long-term treatment of rats with phenytoin, phenobarbital, ethosuximide or diazepam. The most characteristic morphological change was the swelling of white matter, particularly in the brain stem, primarily within the myelin sheaths. The swelling compressed and damaged ganglionic cells. The oedematous changes in brain were reversible. This toxic oedema associated with electrolyte transport may change electrical conductance.

Biochemical investigations

To correlate increase or decrease of particular biogenous substances in organs or regions with a locus of pharmacological activity is very difficult. Disinhibition and inhibition of the effector regions or structures and feedback makes the identification of specific sites of action difficult.

In the central nervous system, the loci of the sub-

Table 1 Human plasma levels of benzodiazepines for anti-anxiety effect

Drug	Mode	Therapeutic concentration (mg/l)	Reference
Chlordiazepoxide	Single dose	0.75	Gottschalk <i>et al.</i> (1973)
Diazepam	Subchronic	0.4	Dasberg <i>et al.</i> (1974)
Diazepam and metabolite	Subchronic	0.24	Curry (1974)
Desmethyldiazepam	Subchronic	0.43	Curry (1974)
Oxazepam	Single dose	0.5	Vessman <i>et al.</i> (1973)

strates responsible for the activity of benzodiazepines are difficult to distinguish. The drugs do not seem to have a particular and exclusive affinity for isolated neurotransmitter-receptor reactions associated with behaviour (van der Kleijn *et al.*, 1977). Chlordiazepoxide and diazepam impair oxidative phosphorylation (Davis, Gatz & Jones, 1971).

Taylor & Laverty (1973) have found that benzodiazepines decrease noradrenaline (NA) turnover in the thalamus-hypothalamus, midbrain, cortex and cerebellum. Benzodiazepines only inhibit slightly NA uptake into hypothalamic synaptosomes and dopamine (DA) uptake into the striatal synaptosomes. The drugs decrease DA turnover and antagonize DA turnover due to stress of electroshock, especially in the corpus striatum. The benzodiazepines prevent decrease of hypothalamic histamine elicited by restraint and cold exposure. The deposition of benzodiazepines in specific presynaptic nerve endings (for example, in the guinea-pig cerebral cortex) has been linked to changes in local electrolytes (Essmann, 1973). The drugs affect synaptosomal nucleic acid and acetylcholine in the cholinergic nerve endings. Other evidence indicates that the benzodiazepines block the cholinergic nervous system; however, this has not been substantiated by clinical observations.

Benzodiazepines, meprobamate and barbiturates can counteract stress-induced increases in NA turnover in the entire rat brain (Lidbrink, Corrodi, Fuxe & Olson, 1973). In unstressed rats, they affect only cortical NA turnover. They do not change NA turnover in the brain stem, but they reduce DA and 5-hydroxytryptamine (5-HT) turnover in the fore-brain and cerebral cortex.

5-HT may also be involved in the action of the benzodiazepines. In 5-HT-depleted animals, seizure thresholds are lower and benzodiazepine anticonvulsant effects are less marked than in animals with normal 5-HT concentrations. Diazepam can also alter 5-HT metabolism in rats (Lidbrink *et al.*, 1973).

By facilitating the action of γ -aminobutyric acid (GABA) on the synapses, benzodiazepines cause it to inhibit brain structures and functions postsynaptically (Guidotti, Toffano & Costa, 1978). Benzodiazepines seem to compete with an endogenous inhibitor of GABA binding to Na^+ -independent GABA recognition sites. The inhibitor, which has a molecular weight of about 15,000 seems to reduce the affinity of diazepam for its recognition site. Therefore, other substances influencing synthesis or metabolism of GABA will inhibit or stimulate activity of the benzodiazepines (Lidbrink *et al.*, 1973). Valproate, an anti-epileptic drug which increases GABA concentrations in animal brains (Godin, Heiner, Mark & Mandel, 1969) has, however, not been demonstrated to potentiate clonazepam or diazepam activity.

Diazepam enhances polysynaptic inhibition in the spinal cord, brain stem, and thalamus just as glycine

enhances glycine receptor-containing interneurons (Young, Zukin & Snyder, 1974). The order of the benzodiazepines is the same whether they are ranked according to their inhibition of strychnine binding on these receptors or according to their efficacy in animals and man. Although the effect of benzodiazepines on brain monoamines and indolamines is still not well defined qualitatively or quantitatively, and its relevance in humans has to be established, data seem to indicate that benzodiazepines contribute to the activity of the neuroleptics by stimulating inhibition and feedback of DA receptors in certain brain structures (Bartholini, Keller, Pieri, & Pletscher, 1973). The impact in human pharmacology still has to be determined.

Benzodiazepine receptors

Although the activity of benzodiazepines may resemble the activity of barbiturates and meprobamate, specific and non-specific receptors with a high and exclusive affinity for benzodiazepines probably exist in the brain (Squires & Braestrup, 1977). Their density seems to be highest in the central cortex, hippocampus and cerebellum. Barbiturates and meprobamate do not displace the benzodiazepines from these receptors. Only benzodiazepines with higher binding affinity displace those with lower affinity. Biochemical and electrophysiological studies have shown interactions between benzodiazepine receptors and GABA receptors, although they have not been proved to be in the same places (Young & Kuhar, 1979).

The subcellular distribution studies with [^3H]-flunitrazepam conflict with the results of whole body autoradiography. The data may conflict because the subcellular distribution studies and the whole body autoradiography were done at different times in the distribution process. The duration of distribution may be additionally responsible. We cannot draw any conclusions about other influences of agents on the activity of benzodiazepines at the subcellular level.

Distribution studies of benzodiazepines in several species at various intervals after intravenous and oral administration show large regional concentration differences which depend on the time elapsed after administration. One hour after infusion only the thin myelinated fibre structures of the squirrel monkey cerebellum and dentate and fastigial nuclei, brain stem and lateral thalamus took up 2-[^{14}C]-oxazepam. Low concentrations were found in the limbic nuclei, and higher concentrations were found in the connecting fibres. The concentration in the gray matter (that is, cortex) was low but higher than that in the white matter at the same interval after infusion.

After plasma concentrations of 2-[^{14}C]-desmethyldiazepam infused for about 21 h reach about 75% of

Figure 5 Whole-body autoradiograph squirrel monkey mother and child 20 min after intravenous infusion of [^{14}C]-2-diazepam and Caesarean section. White areas correspond to the presence of the drug. Note the rather large differences in brain distribution in the mother and the child.

the steady-state concentration in squirrel monkeys, low concentrations are found in the grey matter including the limbic nuclei (for example, caudate nucleus and hippocampus), and high concentrations are found in all white matter including peripheral nerves. This may explain why benzodiazepines inhibit generalized seizures and decrease other nerve-impulse conductance. The distribution differs from that of phenobarbital, which is rather uniformly distributed. The properties of desmethyldiazepam resemble those of diazepam and oxazepam.

Tissue distribution studies show that to reach complete distribution equilibrium may take much longer than observations of plasma concentrations and clinical effect suggest. General distribution studies of benzodiazepines and other anticonvulsant drugs have shown selective accumulation of drug in the elastin-containing ligaments, in particular, in the intervertebral yellow ligaments, but also in the white ligaments as well as in the myocardium, blood vessel walls and brain membranes (van der Kleijn *et al.*, 1971). Elastin is a protein rich in glycine. This observation supports the similarities that Young *et al.* (1974) reported in the interneurons.

Because of the conflicting distribution data for drug compounds as well as for biogenic amines and electrolytes at several levels of brain structure and the differences in qualitative and quantitative kinetics of metabolism and distribution, the differences in duration of activity among the various compounds have not been explained. Lipophilicity rank order and a similar order in brain-plasma concentration ratios can partly explain the differences among the various compounds. Differences in kinetics after single or multiple dosing so far have not helped to explain differences in degree and duration of activity. The sites and mechanisms of action have not yet been fully elucidated.

Protein binding

Many investigators have reported plasma protein binding of benzodiazepines (Table 2) (van der Kleijn, 1969; Müller & Wollert, 1973). Although high protein binding of drugs acidic at the physiological pH strongly influences distribution and excretion of drugs with lower binding capacity, this is not necessarily similar for lipophilic, amphoteric and basic compounds. The higher their lipophilicity, ordered by the partition coefficient between an immiscible organic solvent and water, the higher the partition ratio between tissue and plasma. Displacement from plasma proteins has not been observed, which indicates that a rather non-specific, reversible binding mechanism exists (van der Kleijn, 1969). Plasma binding or partitioning appears to increase as concentrations increase in the therapeutic range, but binding to tissue may differ. High concentrations of benzodiazepines are also found in the ligaments in the intervertebral connections, in the blood vessel walls, in the myocardium and in the brain membranes.

Effects of alcohol on benzodiazepines

The interaction of diazepam and ethanol had been best investigated in studies measuring plasma concentrations. However, changing the sampling periods would have improved the studies. Alcohol could trigger residual, latent pharmacological activity of diazepam and its metabolites. Performance on simple attention, concentration and calculation tests differed significantly depending upon whether the subjects had received alcohol or benzodiazepines alone or in some combinations (Lutze, Gelbke & Schmidt, 1979).

Psychomotor skills related to driving were addi-

Table 2 Half-lives of various benzodiazepines

Compound	Half-life (h)	Elimination by
Diazepam	30	N-demethylation
N-desmethyldiazepam	50	Hydroxylation
Oxydiazepam	10	N-demethylation + glucuronidation
Oxazepam	10	Glucuronidation
Lorazepam	10	
Nitrazepam	30	Reduction
Flurazepam (desalkyl metabolite)	100	N-dealkylation
Clonazepam	25	Reduction
Clorazepate (desmethyl diazepam)	50	Hydrolysis + hydroxylation + glucuronidation
Triazolam	4	Hydroxylation + conjugation

tively impaired in subjects who had ingested alcohol with diazepam or chlordiazepoxide (Linnoila & Mattila, 1973). In another study, the impairment appeared to be mainly attributable to the benzodiazepine (Polva & Linnoila, 1978).

Alcohol enhances the rate and extent of absorption of diazepam (Hayes, Pablo, Radomski & Palmer, 1977; MacLeod, Giles, Patzalek, Thiessen & Sellers, 1977), but it may acutely inhibit diazepam metabolism, increasing diazepam concentration in the brain. However, inhibition of metabolism of benzodiazepines with long half-lives may not be clinically important. Alcohol may also enhance the rate and extent of absorption of oxazepam with its low solubility and slow absorption. Formulation as an elixir could then make oxazepam a valuable hypnotic.

Diazepam concentration in rat brain increased six-fold when rats received alcohol before the drug (Whitehouse, Paul, Coldwell & Thomas, 1975). Whitehouse and his colleagues have attempted to correlate the additive effects of alcohol and diazepam with this increase. They have also observed increased diazepam distribution following concurrent ethanol ingestion. Concurrent therapy with other psychotropic drugs may change diazepam distribution in the brain.

Figure 3 Plasma concentration of diazepam (○) and desmethyldiazepam (□) in a woman before and after delivery of a baby and in the baby after delivery. Note the rather different profiles in mother and child.

Plasma clearance of diazepam was lower in chronic alcoholic patients who had received no alcohol than in normal subjects (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975).

Benzodiazepines and neuromuscular-blocking agents

Concurrent administration of benzodiazepines and neuromuscular-blocking agents used in anaesthesia reduce muscle fasciculation, significantly reduce the incidence of postoperative muscle pain, and decrease the usual increase of serum potassium concentration (Eisenberg, Balsley & Katz, 1979).

Factors influencing benzodiazepine clearance

Pregnancy

The clearance of several drugs increases during pregnancy. Diazepam is often prescribed at the end of pregnancy for anxiety. The drug has been detected in the child and in the mother following delivery. The child metabolizes the drug quite differently from the mother. Probably because the hydroxylation mechanism in the child has not yet matured, desmethyldiazepam appears at much higher concentration in the child than in the mother (Figure 3). In identical twins a difference between the concentrations in the two children has been measured (Figure 4). These findings show that the drug is completely transferred through the placenta following chronic ingestion in the mother. So far, no dramatic clinical impairment of functions of the children has been observed at therapeutic dosage regimen (van Geijn, 1980). Data from the squirrel monkey indicate that following acute administration for anaesthesia in obstetrics, the rate of placenta transfer seems so slow that no effect on the child can be expected as long as the drug has not been given too early before birth (Figure 5).

Other factors

Several other factors influence the benzodiazepine clearance. Food in the patient's stomach and lying down both decrease the rate and extent of absorption. The site of absorption can also influence its rate and extent. In general, diazepam plasma concentrations following oral administration exceeded those following intramuscular administration (Korttila & Linnoila, 1975).

Young children may eliminate antiepileptics including benzodiazepines at higher rates than adults (Guelen & van der Kleijn, 1978). The volume of distribution in young children is also larger than in adults. Although the sensitivity of children to benzo-

Figure 4 Plasma concentrations of diazepam (○) and desmethyldiazepam (□) in mother and identical twins immediately following delivery. Note the rather large differences in diazepam/desmethyldiazepam ratios.

diazepines may differ from that of adults, they require larger doses per kilogram of body weight to produce the same plasma concentration (Bender, 1967).

In the elderly the metabolic clearance appears to be reduced, more in men than in women (Klotz *et al.*, 1975).

Metabolism

Several drugs that depend for their metabolism on mixed function oxidases in the liver can increase the rate of their own metabolism as well as that of other compounds. The 7-chlorobenzodiazepines are mainly metabolized by N-dealkylation and C₃-hydroxylation followed by glucuronidation.

The rate at which these processes occur differs widely among individuals and at different times in individual patients. The rates differ for the discriminated processes. The variability is high and, therefore, the outcome is often unpredictable.

The metabolic pathways of diazepam have been described extensively. After administration of diazepam, desmethyldiazepam and substantial amounts of oxydiazepam, oxazepam and their corresponding conjugates can be found in human and laboratory animal plasma (Vree, Baars, Hekster, van der Kleijn & O'Reilly, 1979). Although animals metabolize diazepam at a higher rate than man, animal models can supply variable information for comparative studies.

Low concentrations of oxydiazepam and oxazepam

can now be measured. When oxydiazepam is given, oxydiazepam glucuronide forms rapidly with low concentrations of oxazepam and its glucuronide. When N-desmethyldiazepam is given, a large fraction of the oxazepam glucuronide forms with a low concentration of unbound oxazepam. When oxazepam is given, only the glucuronide forms and is found with the parent compound.

In the dog model, glucuronidation seems to be the most rapid process followed by N-demethylation and then C₃-hydroxylation. Because conjugation produces pharmacologically inactive compounds that are eliminated rapidly, 3-hydroxybenzodiazepines should be chosen to be ataractics, anxiolytics and hypnotics (Figure 6). For patients with sleep-induction problems, oxydiazepam seems to act more rapidly than oxazepam probably because oxydiazepam is more rapidly absorbed (Nicholson & Stone, 1978, 1977). Pharmaceutical reformulation or dissolution improvement in an alcoholic elixir may overcome oxazepam's poor solubility.

Enzyme stimulation

Phenobarbital has often been reported as a mixed function oxidase-stimulating agent in rodents and other animal models. In man the effect has never been very impressive, but it may change (probably increase) the rate of elimination of other drugs, including the benzodiazepines. Carbamazepine recently has been identified as a much more potent enzyme inducer (Pitlick, Levy, Troupin & Green, 1976).

Figure 6 Plasma concentration, urine flow and renal excretion rate for oxydiazepam (temazepam) and its metabolites in man after 17.8 mg daily. Note the rapid elimination of the parent compound compared with most of the ataractic and hypnotic benzodiazepines. Only little oxazepam is formed.

Cytochrome P450 metabolizes drugs by alpha-C-oxidation; N-oxidation, resulting in N-dealkylation or N-demethylation; aromatic ring hydroxylation; epoxidation; and aliphatic carbon hydroxylation. Phenobarbital does not stimulate all these pathways to the same extent.

To elucidate the mechanism whereby phenobarbital stimulates benzodiazepine metabolism, dogs weighing about 30 kg received diazepam and phenobarbital (Vree, Baars & van der Kleijn, unpublished data). The dogs were chosen because of their rapid metabolism of various drugs and because large numbers of small blood samples could be taken. One dog was infused for 7 h with diazepam 0.00448 mg/kg body weight per minute to produce a steady-state

concentration of diazepam and desmethyldiazepam. The half-life of diazepam in dogs is 1.5 hours. With the assumption that diazepam is converted much faster into desmethyldiazepam than into oxydiazepam and oxydesmethyldiazepam (oxazepam), the clearances of both diazepam and desmethyldiazepam were calculated.

After this baseline experiment, phenobarbital 240 mg daily was administered orally twice daily for 3 weeks to the same dog to produce a steady-state phenobarbital concentration. Every 4–6 d, the diazepam infusion was repeated with gradually higher infusion rates to compensate for the induced metabolism and to ensure plasma levels which could be measured accurately by high performance liquid

Figure 7 Increase of diazepam and desmethyldiazepam clearance in the dog during concomitant treatment with phenobarbital.

chromatography (Vree *et al.*, 1979). Calculating the clearance of diazepam and metabolite during the phenobarbital induction of the cytochrome P450 and plotting that against the duration of phenobarbital treatment showed that phenobarbital affects conversion of diazepam to desmethyldiazepam and clearance more readily than it affects the conversion of desmethyldiazepam to its oxidized products (Figure 7).

Knop & Edmunds (unpublished data) have studied the concomitant administration of phenobarbital and clonazepam, because of their frequent combined use in the treatment of epilepsy. As phenobarbital concentration increased, the elimination rate rather than distribution volume of clonazepam directly increased (Figure 8). Stimulation seems to be dose related at low doses but susceptible to saturation at doses above 200 mg phenobarbital daily. After discontinuation of phenobarbital, the original elimination rate of clonazepam returned much more slowly than the half-life had decreased at the onset of combined treatment.

Administering a combination of diazepam and phenytoin can have serious consequences (Rogers, Haslam, Longstreth & Lietman, 1977). Phenytoin is known for its enzyme-limited elimination characteristics which Michaelis-Menten kinetics can describe. Concurrent diazepam infusion severely impairs phenytoin elimination (Figure 9). Many patients with status epilepticus receive diazepam; and since high phenytoin concentration may elicit status epilepticus, careful diagnosis of its origin, possibly including measurement of phenytoin plasma concentration, would be ideal but difficult to do in practice.

We suggest that drugs with much shorter biological half-lives be investigated for intravenous administration to patients in status epilepticus although similar decreases of the K_M and V_{max} values for phenytoin, resulting in a much higher plasma concentration, a

Figure 8 Decrease of the elimination half-life of clonazepam in the dog during treatment with different doses of phenobarbital. Note the rapid and saturable induction of clonazepam metabolism and the rather slow recovery to the original state after discontinuation of the phenobarbital treatment. —●—, 100 mg daily; △, 200 mg daily; ▲, 300 mg daily; ○, 400 mg daily; ····●, blank.

much lower elimination rate and longer state of toxicity, are likely to occur with other drugs as well.

Renal function does not seem to affect the kinetics of benzodiazepines that are excreted unchanged but does influence the kinetics of those that are mainly excreted as glucuronides. Liver pathology has been reported to influence the kinetics of benzodiazepines (Klotz *et al.*, 1975).

Figure 9 Effect of intravenous administration of diazepam on the elimination rate of phenytoin. Note the extension of the non-linear elimination phase. It extends the toxic state of patient (Reprinted with permission from Rogers *et al.*, 1978).

Figure 10 Plasma concentration of oxydiazepam and its metabolites with and without concomitant N₄-acetylsulphamethoxazole administration after 36 mg and 405 mg respectively.

Figure 11 The left panel shows the relationships between the plasma concentrations of oxydiazepam glucuronide and N₄-acetylsulphamethoxazole and their respective urinary excretion rates. The right panel shows the correlation between the renal clearance of oxydiazepam and of N₄-acetylsulphamethoxazole. The correlation between the N₄-sulphamethoxazole clearance and the oxydiazepam glucuronide clearance suggests similarities in excretion mechanism.

Renal excretion of benzodiazepines

Only about 1% of a dose of diazepam and its metabolite, N-desmethyldiazepam, is excreted unchanged in the urine. Most of each dose is excreted as the glucuronide conjugates; more than 90% of oxydiazepam, oxazepam and lorazepam are excreted as the glucuronides.

The glomeruli filter the parent compounds, and the tubules reabsorb them. The renal clearance of the parent compound depends on the parameters of tubular reabsorption, that is urinary pH and urine flow. Urinary pH and urine flow do not influence the renal excretion rate and renal clearance of the benzodiazepine glucuronide. This suggests that active tubular secretion or just glomerular filtration as characterized by creatinine clearance (inulin clearance) are the mechanisms of excretion.

To determine which mechanism predominates, the renal clearance of the benzodiazepine glucuronide was correlated with the clearance of N₄-acetylsulphamethoxazole (half-life: 3.5 h), which is predominantly excreted by active tubular secretion (Vree, unpublished data). This compound was chosen to avoid the large discrepancies between the half-lives

of para-aminohippurate (PAH) (0.5 h) and benzodiazepine glucuronide (10–15 hours).

The subject took oxydiazepam 35 mg orally. The drug seems to be metabolized to oxazepam and glucuronidated to oxydiazepamglucuronide and oxazepamglucuronide, which are subsequently excreted into the urine. When the oxydiazepam had been absorbed completely 6 h after intake, the subject took N₄-acetylsulphamethoxazole 450 mg orally, and the excretion of the two compounds was followed simultaneously (Figure 10). The renal clearances of oxydiazepamglucuronide and of oxazepamglucuronide were calculated and plotted against urine flow, urinary pH, creatinine clearance, and the clearance of N₄-acetylsulphamethoxazole. The clearances of the two glucuronide compounds did not correlate with the tubular reabsorption parameters, urine pH or flow, or with creatinine clearance, a measure of glomerular filtration. The renal clearance of oxydiazepamglucuronide does correlate with the clearance of N₄-acetylsulphamethoxazole ($r=0.67$ in Figure 11), suggesting that tubular secretion is the predominant renal excretion mechanism of the glucuronides.

Table 3 lists the half-lives of various benzodiazepines.

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