

## DRUG INTERACTIONS WITH DIAZEPAM

Zoran Bojanić<sup>1</sup>, Novica Bojanić<sup>1</sup>, Vladmila Bojanić<sup>2</sup> and Marko Lazović<sup>3</sup>

Diazepam is a benzodiazepine derivative with anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, antitremor, and amnesic activity. It is metabolized in the liver by the cytochrome P (CYP) 450 enzyme system. Diazepam is N-demethylated by CYP3A4 and CYP2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyl-diazepam and temazepam are both further metabolized to oxazepam. Concomitant intake of inhibitors or inducers of the CYP isozymes involved in the biotransformation of diazepam may alter plasma concentrations of this drug, although this effect is unlikely to be associated with clinically relevant interactions.

The goal of this article was to review the current literature on clinically relevant pharmacokinetic drug interactions with diazepam.

A search of MEDLINE and EMBASE was conducted for original research and review articles published in English between January 1971. and May 2011. Among the search terms were drug interactions, diazepam, pharmacokinetics, drug metabolism, and cytochrome P450. Only articles published in peer-reviewed journals were included, and meeting abstracts were excluded. The reference lists of relevant articles were hand-searched for additional publications.

Diazepam is substantially sorbed by the plastics in flexible containers, volume control set chambers, and tubings of intravenous administration sets. Manufacturers recommend not mixing with any other drug or solution in syringe or solution, although diazepam is compatible in syringe with cimetidine and ranitidine, and in Y-site with cisatracurium, dobutamine, fentanyl, hydromorphone, methadone, morphine, nafcillin, quinidine gluconate, remifentanyl, and sufentanyl. Diazepam is compatible with: dextrose 5% in water, Ringers injection, Ringers injection lactated and sodium chloride 0.9%. Emulsified diazepam is compatible with Intralipid and Nutralipid.

Diazepam has low potential for pharmacokinetic drug interactions. Although interactions with diazepam may be predictable in specific circumstances, when diazepam is used with: analgesics, anesthetics, anticonvulsants, antipsychotics, anxiolytics/sedatives, barbiturates, hypnotics, MAO inhibitors, narcotics, sedative antihistamines, phenothiazines and other antidepressants, careful consideration is needed. *Acta Medica Medianae* 2011;50(2):76-82.

**Key words:** diazepam, drug interactions, drug metabolism

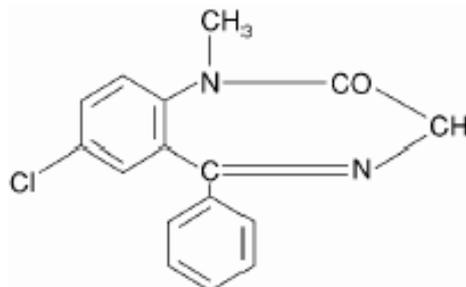
Institute of Pharmacology, Faculty of Medicine, University of Niš, Serbia<sup>1</sup>  
Institute of Pathophysiology, Faculty of Medicine, University of Niš, Serbia<sup>2</sup>  
Faculty of Medicine, University of Niš, Serbia<sup>3</sup>

Contact: Zoran Bojanić  
Institute of Pharmacology, Faculty of Medicine  
18000 Niš, Serbia  
E-mail: bojaniczoran@gmail.com

### Introduction

Diazepam is a benzodiazepine derivative. This is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The empirical formula of diazepam is C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O and the molecular weight is 284.75. It is colorless to light yellow crystalline powder, practically odourless. Soluble 1 in 333 of water, 1 in 16 of alcohol, 1 in 2 of

chloroform, and 1 in 39 of ether. A melting point of diazepam is 131.5 to 134.5 °C. The structural formula is as follows:



In addition to the active ingredient diazepam, each tablet contains the inactive ingredients: anhydrous lactose, corn starch, pregelatinized starch and calcium stearate.

### Mechanism of action

Diazepam is a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnesic properties. Its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain. Diazepam binds non-selectively to alpha1, alpha2, alpha3 and alpha5 subunits containing GABAA receptors at a site that is distinct from the binding site of the endogenous GABA molecule (1).

### Pharmacokinetics

Diazepam is administered orally, rectally, and parenterally: intravenously (needs to be diluted, as it is painful and damaging to veins) and intramuscularly.

After oral administration, diazepam is readily and almost completely (>90%) absorbed from the gastrointestinal tract. The peak plasma concentrations occur within about 30 to 90 minutes of oral administration. Absorption is delayed and decreased when administered with a fat meal. Diazepam is rapidly absorbed after administration as a rectal solution and the peak plasma concentrations are achieved after about 10 to 30 minutes.

Intramuscular administration is followed by unpredictable absorption which is characterized with obtained lower peak plasma concentrations compared with those following oral administration.

Diazepam and its metabolites are highly bound to plasma proteins (>95%). The volume of diazepam distribution at steady-state in young healthy males is 0.7 to 2.6 L/kg. Diazepam has a biphasic half-life with an initial rapid distribution phase (a half-life of approximately one hour) followed by a prolonged terminal elimination phase of 1 or 2 days. The action of diazepam is further prolonged by the even longer half-life of 2 to 5 days of its principal active metabolite, desmethyldiazepam (also known as nordiazepam or nordiazepam). The plasma elimination half-life of diazepam and/or its metabolites is prolonged in neonates, in the elderly, and in patients with liver disease. Diazepam accumulates upon multiple dosing. It is highly lipid soluble and passes rapidly into the brain and other well-perfused organs, and is afterwards redistributed to muscle and adipose tissues. Diazepam and its metabolites crosses placental barriers and are also present in breast milk in concentrations approximately one tenth of those in maternal plasma.

Diazepam is N-demethylated by CYP3A4 and CYP2C19 to the active metabolite N-desmethyldiazepam, and further hydroxylated by CYP3A4 to the active metabolite temazepam. Both N-desmethyldiazepam and temazepam are then metabolized to oxazepam. Temazepam and oxazepam are largely conjugated with glucuronide, and are excreted primarily in the urine.

### Indications

Diazepam is used for the short-term treatment of severe anxiety, panic attacks and states of agitation, as a sedative for pre-/postoperative sedation, anxiolysis and/or amnesia, as a hypnotic in the short-term management of insomnia, as an anticonvulsant (status epilepticus and febrile convulsions), for the control of muscle spasm, and for the management of alcohol, opiate and benzodiazepine withdrawal symptoms.

### Contraindications

Diazepam should be avoided in patients with pre-existing CNS depression or coma, respiratory depression, acute pulmonary insufficiency, myasthenia gravis, or sleep apnea. It should be carefully used in those with chronic pulmonary insufficiency.

### Interactions with diazepam in vitro

Diazepam is substantially sorbed by the plastics in flexible containers, volume control sets, chambers, and tubings of intravenous administration sets. Only a small part of diazepam may remain in the infused solution (2), because of the drug adsorption onto the walls of polyvinylchloride infusion sets. Administration sets should contain the minimum length of polyvinylchloride tubing and should not contain a cellulose propionate volume-control chamber. Diazepam solutions are stable in glass containers. Lack of sorption of the diazepam to polyolefin semi-rigid containers makes these alternatives acceptable (3). Suitable materials for infusion containers, syringes, and administration sets for administration of diazepam are: glass, polyolefin, polypropylene, and polyethylene.

Manufacturers recommend not mixing with any other drug or solution in syringe or solution, although diazepam is compatible in syringe with cimetidine and ranitidine, and in Y-site with cisatracurium, dobutamine, fentanyl, hydromorphone, methadone, morphine, nafcillin, quinidine gluconate, remifentanyl, and sufentanyl. Diazepam is compatible with: dextrose 5% in water, Ringers injection, Ringers injection lactated and sodium chloride 0.9%. Emulsified diazepam is compatible with Intralipid and Nutralipid.

### Interactions with diazepam in vivo

#### Analgesics

Coadministration of dextropropoxyphene had no influence on diazepam volume of distribution. Diazepam elimination half-life was longer during the dextropropoxyphene trial compared to the control trial and total metabolic clearance was less, without statistically significant differences in healthy subjects (4).

Paracetamol produced no significant change in plasma concentrations of diazepam or its major metabolite (5).

Diazepam may be used with opioid analgesics in anaesthetic or analgesic regimens. An additional sedative effect is to be expected. Pretreatment with morphine or pethidine has decreased the rate of oral absorption of diazepam. This has been attributed to the effect of opioid analgesics (morphine and pethidine) on delay of gastric emptying so that the rate of absorption of diazepam is reduced (6).

#### Antacids

The concomitant use of aluminium hydroxide or sodium citrate hastened the onset of the soporific effect of diazepam marginally, while magnesium trisilicate tended to delay it. The estimation of plasma diazepam concentrations over 90 min showed that the absorption of diazepam was increased significantly by the use of aluminium hydroxide (7). No adverse effect of any clinical importance is likely during the treatment with antacids and diazepam together.

#### Antibiotics

Ciprofloxacin causes the increased AUC (area under curve) in healthy subjects by 50%, reduced clearance by 37%, and doubled half-life of diazepam. These pharmacokinetic changes cause no significant changes in the performance of a number of psychometric tests (8).

Erythromycin increased the AUC of diazepam by 15%, but psychomotor effects of diazepam were not changed significantly. The interactions of erythromycin with diazepam are slight and of limited clinical significance (9).

Rifampicin increased the clearance in healthy subjects to 300% and desmethyl- and 3-hydroxydiazepam metabolic clearance to 400% (10). The mean half-life of diazepam was significantly shorter (14 hr) in patients with tuberculosis treated with rifampicin than in healthy control subjects treated only with diazepam (58 hr) (11). Rifampicin is a very potent liver enzyme-inducing drug which increases the metabolism of diazepam by the liver. In patients with tuberculosis who take isoniazid (an enzyme inhibitor) and rifampicin, the enzyme-inducing effect predominates.

#### Antiepileptics

Carbamazepine, phenobarbital, and phenytoin are all inducers of hepatic drug-metabolising enzymes. The metabolism of diazepam may be enhanced in patients receiving long-term therapy with these drugs, and decrease in serum levels of diazepam is present (12).

The clearance of diazepam is about threefold increased by carbamazepine and half-life shorter than in healthy subjects (13).

Diazepam has an unpredictable effect on phenytoin serum concentration. Metabolism of

phenytoin may be altered by diazepam influencing CYP2C9 or CYP2C19. In some cases, diazepam significantly increases phenytoin concentrations and induces toxic effect of this antiepileptic drug (14-16), but in other cases it decreases phenytoin serum concentrations (17,18).

Sodium valproate increased the serum levels of diazepam approximately twofold. It also induces a significant increase in apparent volume of distribution and plasma clearance of diazepam. Valproic acid displaces diazepam from plasma protein binding sites and inhibits its metabolism (19).

#### Antituberculotics

Ethambutol does not interact with diazepam (11).

Isoniazid did not alter diazepam volume of distribution or protein binding, but prolonged mean elimination half-life ( $t_{1/2}$ ) from 34 to 45 hr, and reduced total clearance from 0.54 to 0.40 ml/min/kg (11). Inhibition of CYP3A isoforms is the likely mechanism by which isoniazid slows the elimination of coadministered diazepam. Slow acetylators of isoniazid have greater risk for adverse drug interactions, because the degree of inhibition is concentration-dependent.

#### Anticoagulants

Free concentrations of diazepam and desmethyl-diazepam increase immediately after intravenous administration of heparin (20).

Anticoagulant effect of warfarin is not affected by diazepam (21).

#### Antidepressants

Nefazodone raised plasma level of desmethyl-diazepam 87%. Insomnia was significantly improved by combination of nefazodone with a diazepam (22).

#### Antifungals

Both voriconazole and fluconazole considerably increase the exposure to diazepam. After voriconazole the area under the plasma concentration time curve of diazepam was increased 2.2-fold and a prolongation of the mean elimination half-life was two fold. After the fluconazole the AUC of diazepam was increased 2.5-fold, and the  $t_{1/2}$  was prolonged from 2.5-fold. Recurrent administration of diazepam increases the risk of clinically significant interactions during voriconazole or fluconazole treatment, because the elimination of diazepam is significantly impaired (23).

#### Atropine

Atropine does not affect absorption or the sedative effects of diazepam (24).

### Beta blockers

Clinically unimportant pharmacokinetic interactions occur between diazepam and beta blockers. Only metoprolol increases AUC of diazepam by 25% (25).

### Calcium channel blockers

No significant drug interactions between diazepam and diltiazem (26), felodipine (27) or nimodipine (28) have been registered.

### Ethanol

Acute ethanol ingestion may potentiate the CNS effects of diazepam. Alcohol increases the absorption and raises the serum levels of diazepam. Tolerance may develop with chronic ethanol use. This is explained by decreased clearance of the diazepam because of CYP450 hepatic enzyme inhibition. The cognitive deficits induced by diazepam may be increased in patients who chronically consume large amounts of alcohol.

### Grapefruit

Grapefruit juice markedly improved the bioavailability of diazepam – increased the AUC of diazepam 3.2 fold and the maximum serum levels were increased 1.5 fold (29).

### H2 blockers

Cimetidine increased plasma concentrations of diazepam plus desmethyldiazepam by 57%, but reaction times and other motor and intellectual tests remained unaffected (30).

Famotidine (31), nizatidine (32), ranitidine (32) and roxatidine do not interact with diazepam (33).

Interaction a diazepam with H2 blockers (even a cimetidine) has a little or no clinical importance.

### Levodopa

The therapeutic effects of levodopa can be reduced or abolished in some patents by the concomitant use of diazepam (34). Some authors suggested administration of diazepam for sleep induction and maintenance in patients on levodopa (35).

### Metoclopramide

Intravenous but not oral metoclopramide increases the rate of absorption (peak levels by 30 instead of 60 min) of diazepam and raises its peak plasma levels by 38% (6). The clinical importance of this interaction is small.

### Metronidazole

Metronidazole does not significantly inhibit the oxidative drug metabolism of diazepam because there is no changes in total plasma clearance, plasma t<sub>1/2</sub> and volume of distribution of diazepam (36).

### Oral contraceptives

Oral contraceptives may inhibit the biotransformation of diazepam by oxidation and can increase the effects of diazepam (37).

Diazepam can possibly increase the incidence of break-through bleeding (38). Psychomotor impairment due to oral diazepam was greater during the menstrual pause than during the 21-daily oral contraceptive cycle. This may have been due to an effect of oral contraceptives on diazepam absorption (39).

### Penicillamine

Phlebitis associated with intravenous diazepam resolved with local heat but recurred on two separate occasions after oral penicillamine (40).

### Proton pump inhibitors

Long-term treatment with a therapeutic dose of lansoprazole does not interfere with the metabolism of diazepam (41).

After repeated oral administration of 40 mg omeprazole over 7 days a prolongation of the elimination half-life (by 130%) and a concomitant decrease of the clearance of diazepam (by 54%) were registered. Omeprazole did not affect the volume of distribution and the plasma protein binding of diazepam (42). This effect was only present in omeprazole extensive metabolizers who represent the majority (95%) of the Caucasian population (43).

Pantoprazole and diazepam may be administered concomitantly without dose adjustment even when high doses of pantoprazole are required (44).

Rabeprazole does not interact with diazepam (45).

Interaction of diazepam with proton pump inhibitors has no clinical importance and only administration of omeprazol increases plasma concentration and elimination of diazepam half-life.

### Tobacco smoking

Drowsiness as a side-effect of diazepam is less frequently found in smokers than in non-smokers (46). Reduced clinical sensitivity to diazepam among cigarette smokers is not directly related to alterations in diazepam pharmacokinetics because differences in volume of distribution, elimination half-life, total AUC, total clearance, and free fraction did not approach significance (47).

## Xantines

The aminophylline given intravenously reversed the sedation from intravenous diazepam (48,49). The aminophylline-treated patients showed a significantly more rapid reversal of sedation, but after 30 minutes there was no difference between the two groups. The aminophylline antagonizes the sedative effect of benzodiazepine, but in routine diazepam sedation, aminophylline will not shorten the necessary observation period after sedation (50). Blockade of adenosine receptors by aminophylline is a possible mechanism of this interaction (51).

The coadministration of caffeine with diazepam resulted in a 22% reduction in diazepam plasma levels (52).

Xanthine-containing beverages (tea or coffee) may be expected to decrease the incidence of diazepam-induced drowsiness due to both their CNS-stimulating effects and hepatic drug-metabolising enzymes induction. Drowsiness is reported less frequently in patients who are heavy coffee users, smoking less than or equal to 1 pack of cigarettes/day, while drowsiness is reported more frequently in patients who are heavy coffee users, smoking more than 1 pack of cigarettes/day. Similarly, drowsiness occurs less frequently among heavier smokers drinking less than or equal to 2

cups of coffee/day, while drowsiness occurs more frequently among heavier smokers drinking more than 2 cups of coffee/day (53).

## Conclusions

Diazepam is substantially sorbed by the plastics in flexible containers, volume control set chambers, and tubings of intravenous administration sets. Manufacturers recommend not mixing with any other drug or solution in syringe or solution, although diazepam is compatible in syringe with cimetidine and ranitidine, and in Y-site with cisatracurium, dobutamine, fentanyl, hydromorphone, methadone, morphine, nafcillin, quinidine gluconate, remifentanyl, and sufentanyl. Diazepam is compatible with: dextrose 5% in water, Ringers injection, Ringers injection lactated and sodium chloride 0.9%. Emulsified diazepam is compatible with Intralipid and Nutralipid.

Diazepam has low potential for pharmacokinetic drug interactions. Although interactions may be predictable in specific circumstances, use of diazepam need careful consideration with analgesics, anesthetics, anticonvulsants, anti-psychotics, anxiolytics/sedatives, barbiturates, hypnotics, MAO inhibitors, narcotics, sedative antihistamines, phenothiazines, and other anti-depressants.

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## INTERAKCIJE LEKOVA SA DIAZEPAMOM

Zoran Bojanić, Novica Bojanić, Vladmila Bojanić i Marko Lazović

Diazepam je derivat benzodiazepina sa anksiolitičkim, antikonvulzivnim, hipnotičkim, sedativnim, antitremorskim, amnezijskim i miorelaksantnim delovanjem na skeletne mišiće. Diazepam se metaboliše u jetri pomoću citohroma P (CIP) 450 enzimskog sistema. Diazepam N-demetilišu CIP3A4 i CIP2C19 do aktivnog metabolita N-dezmetildiazepama, a pomoću CIP3A4 se hidrosilira do aktivnog metabolita temazepama. I N-dezmetildiazepam i temazepam se dalje metabolišu u oksazepam. Istovremeni unos inhibitora ili induktora CIP izoenzima uključenih u biotransformaciju diazepama može da promeni plazmatske koncentracije tog leka, mada je malo verovatno da se taj efekat ispolji klinički relevantnim interakcijama.

Cilj ovog rada je da se revijski prikažu klinički relevantne farmakokinetičke interakcije sa diazepamom.

Izvršena je pretraga originalnih istraživanja i članaka objavljenih na engleskom jeziku u periodu između januara 1971. i maja 2011. godine na MEDLINE i EMBASE bazama podataka. Za pretragu su korišćeni termini: interakcije lekova, diazepam, farmakokinetika, metabolizam leka i citohrom P450. Uključeni su samo članci objavljeni u stručnim časopisima sa recenzijom, a apstrakti sa kongresa nisu uzimani u obzir. Ručnom pretragom referentnih lista relevantnih tekstova tražene su dodatne publikacije.

Diazepam znatno apsorbira mekana plastika od koje se pravi ambalaža, setovi za kontrolu volumena protoka leka i cevi setova za intravensku infuziju. Proizvođači preporučuju da se diazepam ne meša ni sa jednim drugim lekom u rastvoru ili špricu. Ipak, diazepam je kompatibilan sa cimetidinom i ranitidinom u špricu, a u Y sistemu za infuziju kompatibilan je sa cisatracurijumom, dobutaminom, fentanilom, hidromorfonom, hinidin glukonatom, metadonom, morfinom, nafcilinom, remifentanilom i sufentanilom. Diazepam je kompatibilan sa 5% vodenim rastvorom dekstroze, injekcijama Ringerovog rastvora i injekcijama laktatnog Ringera, kao i 0,9% rastvorom natrijum hlorida. Emulgovani diazepam je kompatibilan sa Intralipidom i Nutralipidom.

Diazepam ima slab potencijal za farmakokinetičke interakcije lekova. Iako se interakcije lekova sa diazepamom mogu predvideti u specifičnim okolnostima, primenu tog leka treba pažljivo razmotriti pri davanju sa: analgeticima, anksioliticima/sedativima, antikonvulzivima, antipsihoticima, barbituratima, fenotiazinima, hipnoticima, MAO inhibitorima, narkoticima, sedativnim antihistaminicima i drugim antidepresivima. *Acta Medica Mediana* 2011;50(2):76-82.

**Ključne reči:** diazepam, interakcije lekova, metabolizam lekova