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CLINICAL COMMENTARY

Effect of variations in treatment regimen and liver cirrhosis on exposure to benzodiazepines during treatment of alcohol withdrawal syndrome

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Abstract

Purpose: Benzodiazepines (BDZs) are the drugs of choice to prevent the symptoms of alcohol withdrawal syndrome (AWS). Various treatment protocols are published and have been shown to be effective in both office-managed and facility-managed treatment of AWS. The aim of this scientific commentary is to demonstrate the differences in the expected exposure to BDZs during AWS treatment using different treatment regimens available in the literature, in patients with or without alcoholic liver cirrhosis.

Methods: Diazepam and lorazepam AWS protocols were examined and reviewed in the literature, and blood plasma levels were examined and compared, respectively.

Results: Considerable variation in the blood levels with the different dosing schedules was found. Because the drugs are metabolized differently, we have also shown that liver disease affects the blood levels of diazepam, but not of lorazepam.

Conclusions: Differences in treatment regimens, the choice of BDZ, as well as the presence of liver cirrhosis can substantially alter the exposure of patients to drugs used for AWS treatment. Outpatient treatment of AWS has been shown to be relatively safe and effective for the treatment of AWS but patients should be carefully monitored.

Keywords: benzodiazepines, alcohol withdrawal, cirrhosis, pharmacokinetics, clearance, area under curve, metabolism, outpatients.

Abbreviations: AUC, area under the curve; AWS, alcohol withdrawal syndrome; BCMA, British Columbia Medical Association; BDZ, benzodiazepine.

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Introduction

Alcohol withdrawal syndrome (AWS) can be a serious medical problem because approximately 5% of patients progress to grand mal seizures and delirium tremors with symptoms such as disorientation, elevated body temperature, insomnia, visual and auditory hallucinations, hypertension, and paranoia. There can be a 5–15% mortality rate associated with these symptoms, which occur on the third to fifth day of AWS [1]. Benzodiazepines (BZDs) are considered to be the drugs of choice in treating AWS [2]. The choice of a BZD is argued in the literature, but in general, with the exception of alprazolam and triazolam, BZDs with an intermediate (such as lorazepam) or long (such as diazepam) half-life are the drugs of choice based on the guidelines of the British Columbia Medical Association (BCMA) [3]. Many dosing regimens are available in the literature, most of which use a fixed dose schedule. However, it has been demonstrated [4,5] that symptom-triggered dosing of BZD resulted in a shorter withdrawal period and a decreased total dose of BZD. Most treatments of AWS take place outside a facility. Guidelines for conducting the office-based management of AWS have been established [3,6] along with warnings as to when BZD treatments should take place only in a medical facility.

Because guidelines for treatment dosing and timing vary quite widely, it is perhaps not apparent to the physician what the rationale and the BZD drug levels will be at any given time after the initiation of treatment. In addition, BZD drugs that are used for AWS are metabolized differently (Phase I oxidative

metabolism *vs* conjugation), and therefore the presence of alcoholic liver cirrhosis will affect the drug levels of BDZs with Phase I oxidative metabolism but not those with conjugation metabolism [7–9].

Therefore, the aim and the novelty of this scientific commentary is to demonstrate the differences in the expected exposure to BDZs during AWS treatment using different treatment regimens available in the literature, in patients with or without alcoholic liver cirrhosis, using as an example two frequently used BDZs with different metabolic pathways: diazepam (oxidative metabolism) and lorazepam (conjugation).

Materials and Methods

Treatment regimens

Diazepam- and lorazepam-based alcohol withdrawal treatment protocols were obtained from the literature. Each protocol discussed in this work in fact represents a range of treatment regimens. For simplicity, only maximal (highest-dose) treatment regimen from each protocol has been analyzed and simulated in this work. The treatment protocols that were analyzed and simulated in this work are described in Table 1.

Pharmacokinetic simulation

The simulation of the predicted plasma concentration-time profiles of diazepam and lorazepam in healthy individuals compared with patients affected by alcoholic liver cirrhosis was performed using ADAPT 5 software (Biomedical Simulations Resource, University of Southern California). The pharmacokinetics of diazepam and lorazepam was assumed to follow a two-compartmental model. The initial pharmacokinetic parameters (CL, Vd, ka) for healthy 70 kg individuals were obtained from the literature [8,13–15]. Alcoholic liver cirrhosis has been reported to decrease the clearance of diazepam twofold [16]. Therefore, in patients who suffer from alcoholic liver cirrhosis, hepatic clearance of diazepam was assumed to be reduced by half (750 *vs* 1500 mL/h in healthy individuals), while the clearance of lorazepam was assumed to be unchanged in alcoholic liver cirrhosis patients. The predicted plasma concentration-time profiles were obtained for healthy individuals and patients with alcoholic liver cirrhosis during multiple-dose treatment protocols.

Results

The predicted area under the curve (AUC), T_{max}, and C_{max} of diazepam in healthy individuals compared with patients

Table 1. Diazepam and lorazepam AWS treatment protocols.

Diazepam protocols	**Dosing regimen**
Journal of Family Practice [10]	4 doses of 20 mg every 6 hours, followed by 8 doses of 10 mg every 6 hours
Journal of Family Practice modified [10]	10 mg 4 times on day 1, followed by 5 mg 4 times/day
American Family Physician mild withdrawal [11]	10 mg every 6 hours for 3 days
American Family Physician moderate withdrawal [11]	20 mg 4 times/day on days 1 and 2, 15 mg 4 times/day on day 3, 10 mg 4 times/day on day 4, 5 mg 4 times/day on day 5
2012 BCMA guidelines rigid [3]	10 mg 4 times/day on day 1, 10 mg 3 times/day on day 2, 10 mg 2 times on day 3, followed by 10 mg one dose on day 4
2012 BCMA guidelines flexible [3]	10 mg every 4 hours on day 1, 10 mg every 6 hours on day 2, 10 mg every 12 hours on day 3, 10 mg one dose on day 4
2012 BCMA guidelines front end loading [3]	Day 1: 20 mg at 0, 2, 6, and 10 hours; Days 2 and 3: 10 mg at 0, 4, 8, and 12 hours
Lorazepam protocols	**Dosing regimen**
Theriaque [12]	2 mg/day for 2 days, then 4 mg/day for 8 days (0.5 mg morning and noon, 1 mg supper)
Journal of Family Practice [10]	4 mg every 6 hours for 4 doses, then 2 mg every 6 hours for 8 doses
American Family Physician mild withdrawal [11]	2 mg every 6 hours for 3 days
American Family Physician moderate withdrawal [11]	4 mg every 6 hours for 2 days, then 2 mg every 6 hours for 2 days, then 1 mg 2 times for 1 day
Modified protocol which is a tailored version of American Family Physician protocol [11] prescribed for a patient to improve nighttime sleep on the first day of withdrawal treatment	5 mg at 0 and 6 hours; 3 mg at 13, 19, and 25 hours; 2 mg at 31, 37, 43, 49, 61, 67, and 73 hours

Table 2. Predicted area under plasma concentration-time of diazepam (exposure) at different treatment regimens in healthy individuals and liver cirrhosis patients.

	Healthy individuals			Liver cirrhosis patients		
Protocol	**AUC_{inf} (hour·µg/mL)**	**T_{max} (hour)**	**C_{max} (µg/mL)**	**AUC_{inf} (hour·µg/mL)**	**T_{max} (hour)**	**C_{max} (µg/mL)**
Journal of Family Practice [11]	106.6	67.8	0.87	213.3	68.2	1.12
Journal of Family Practice modified [10]	53.3	67.7	0.44	106.6	68.2	0.56
American Family Physician mild [11]	80.0	67.7	0.71	160.0	68.2	0.87
American Family Physician moderate [11]	186.6	67.8	1.26	373.3	91.6	1.68
BCMA guidelines rigid [3]	66.6	62.2	0.52	133.3	62.2	0.65
BCMA guidelines flexible [3]	86.6	49.8	0.70	165.9	74.0	0.88
BCMA guidelines front end loading [3]	93.3	61.6	0.81	186.6	62.0	1.01

Table 3. Predicted area under plasma concentration-time of lorazepam (exposure) at different treatment regimens in healthy individuals and liver cirrhosis patients.

	Healthy individuals and liver cirrhosis patients		
Protocol	**AUC_{inf} (hour·µg/mL)**	**T_{max} (hour)**	**C_{max} (µg/mL)**
Theriaque [12]	12.11	182.1	0.06
Journal of Family Practice [10]	9.70	20.0	0.14
American Family Physician mild [11]	7.88	73.8	0.10
American Family Physician moderate [11]	7.88	43.7	0.09
Modified from American Family Physician protocol [11]	9.99	27.0	0.13

affected by alcoholic liver cirrhosis during treatment are shown in Table 2. The table includes the predicted pharmacokinetic parameters during the following regimens: Journal of Family Practice protocol, Journal of Family Practice modified protocol [10], American Family Physician mild withdrawal protocol, American Family Physician moderate withdrawal protocol [11], 2012 BCMA guidelines rigid protocol, 2012 BCMA guidelines flexible and front end loading protocols [3]. In all treatment regimens, predictions show substantially higher AUC of diazepam, higher C_{max}, and longer T_{max} in patients affected by alcoholic liver cirrhosis compared with healthy individuals. In addition, there is considerable variability in the exposure to diazepam between different protocols even within the same patient population category (healthy individuals or alcoholic liver cirrhosis patients).

The predicted pharmacokinetic parameters of lorazepam during the alcohol withdrawal treatment regimens (Theriaque protocol [12], Journal of Family Practice [10], American Family Physician mild withdrawal [11], American Family Physician moderate withdrawal [11] and a slightly modified protocol) are shown in Table 3. These profiles are predicted to be nearly identical in healthy individuals and alcoholic liver cirrhosis patients. However, similar to diazepam protocols, there is a substantial variability in exposure to lorazepam between different protocols.

Discussion

The simulated plasma concentration-time profiles have demonstrated substantial differences in the extent and timing of the exposure to BDZs during AWS treatment in different treatment centers and using different treatment regimens. Both the diazepam and lorazepam exposures show profound differences in the extent of exposure (AUC), as well as C_{max} and T_{max} associated with these profiles (Tables 2 and 3).

Moreover, while the predicted exposure in normal individuals compared with patients who suffer from alcoholic cirrhosis in the case of lorazepam is identical, diazepam exposure is expected to be profoundly higher in cirrhosis patients. The predicted plasma concentration-time profiles of diazepam show elevated plasma concentration of diazepam in patients who are affected by alcoholic liver cirrhosis compared with healthy individuals in all treatment regimens tested. Patients who suffer from chronic alcoholism but do not have

Table 4. The British Columbia Medical Association (BCMA) Guidelines' [3] recommendations for conducting outpatient withdrawal.

Start on a Monday or Tuesday unless weekend coverage is available.
See the patient daily for the first three to four days and be available for phone contact.
Have the patient brought to the office by a reliable family member or caregiver.
Prescribe thiamine (Vitamin B1) 100 mg daily for 5 days.
Encourage fluids with electrolytes, mild foods and minimal exercise.
Ask the patient to avoid natural remedies, caffeine or any activity that increases sweating (e.g., hot baths, showers and saunas/sweat lodges).
Assess vital signs, withdrawal symptoms, hydration, emotional status, orientation, general physical condition, and sleep at each visit.
Encourage the patient to call local (including health authority/municipal) Alcohol and Drug or Employee Assistance Programs and attend Alcoholics Anonymous (AA) meeting on day 3.
Monitor for relapse, explore cause, and correct if possible. If unable to address cause, refer to inpatient detox.

morphological and functional liver changes should not be treated in the same way as patients suffering from alcoholic liver cirrhosis. Alcohol has three phases of effect on drug metabolism. Phase 1 is acute consumption in which the metabolism of BZDs is inhibited [9,17–19]. However, the acute consumption phase is not relevant for the current study that deals with chronic alcoholism. Phase 2 is chronic alcoholism but without hepatocellular changes. This phase will exist for many years, and probably the majority of alcoholic individuals under alcohol withdrawal treatment will be in this phase. Clearance of BZD will not be decreased in that phase. In fact, clearance could be enhanced in phase 2 (ethanol is classed as a microsomal enzyme inducer) [17,18]. As a result, a patient in phase 2 will have the same or slightly lower levels of diazepam comparing with a normal individual on the same regimen. Phase 3 is a phase of alcoholic liver cirrhosis. Patients in this phase will have reduced clearance of BZD that undergo oxidative hepatic metabolism. Diazepam undergoes oxidative metabolism in liver (mainly by CYP 2C19 and 3A4) and therefore is prone to impaired metabolic rate in patients who suffer from alcoholic liver cirrhosis [7–9].

Treatment regimens that involve lorazepam as a treatment agent have been also reviewed in this study. However, lorazepam is metabolized by conjugation (glucuronidation) rather than by oxidative reaction. It has been shown that glucuronidation is not or minimally affected in the states of alcoholic liver cirrhosis or liver cirrhosis from other etiologies. Therefore, it is unlikely that concentrations of lorazepam or other BDZs that are metabolized by conjugation would be different in liver cirrhosis compared with healthy individuals [1,7,9]

The dosing schedules selected from the literature all use front end loaded dosing. That is, they start with a relatively high dose and then taper off over a several-day period. The plots presented demonstrate that drug concentration levels are quite variable among the regimes used. It should also be noted that lorazepam is five to ten times more potent than diazepam, and this is reflected in the blood levels shown in this study.

The BCMA guidelines' [3] list of conditions for conducting outpatient withdrawal is shown in Table 4. Notable in these guidelines is the statement that the patient should be seen by the physician daily for the first 3–4 days and should be brought in by a reliable family member or other responsible person. Not stated, but important, is that a reliable family member or other responsible person should have daily supervisory contact with the patient. Daily contact with the patient provides opportunities to decrease or increase the dose of BZD. Supervision of the patient can ensure that the patient takes the drug as directed, does not consume alcohol or drive a vehicle, and can receive medical attention if required.

The pharmacological actions of alcohol and BZD have considerable overlap and this forms the basis for the use of BZD in AWD. The longer half-life of BZD and the gradual decrease in blood levels over a period of days allows the central nervous system to accommodate to the effects of the decreased drug concentration and prevents symptoms of AWD from occurring or at least lessens their severity of the withdrawal [20]. Persons using large amounts of alcohol do develop tolerance to its effects and to at least some of the effects of BZD [20,21]. It is often assumed that the tolerance of a high-dose alcohol user results in tolerance to all of the effects of BZD. Barbee [20] has reviewed the literature and concludes that prolonged alcohol use does result in tolerance to the sedative and psychomotor effects of BZD but that tolerance to the amnesic effect of BZD does not develop to the same extent. Both BZD and alcohol can produce anterograde amnesia; however, BZD, even in low doses, can have considerably more of an amnesic effect than alcohol. When alcohol and BZD are used together, an enhanced amnesic effect can occur. Amnesia of events that occur prior to BZD intake does not happen; the drugs do not affect the

retrieval of such information. Following drug administration, memory deficits do occur and are believed to be due to the fact that the memory of events following the BZD administration is not stored in long-term episodic storage. Alcohol can also produce this effect, which can account for so-called alcohol-induced blackout [20]. Patients taking BZD may carry out actions that they cannot later recall due to the effect on memory retention. Thus, patients taking BZD need to be monitored to prevent possible inappropriate behavior, which the patient may not be able to remember at a later time. The combination of alcohol and BZD increases the chance of amnesia [20,21].

It should be noted that it is unknown whether the differences in exposure to BDZs and their pharmacokinetic profiles will lead to altered clinically relevant pharmacological effects. However, the expected profound differences in concentrations and the lack of information in the literature about the clinical significance of these alterations suggest that detailed comparison of clinical effects associated with these treatment regimens should be performed.

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Study Group

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