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Clobazam Therapeutic Drug Monitoring: A Comprehensive Review of the Literature
with Proposals to Improve Future Studies

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Conflict of interest: Dr. de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentation, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, Dr. de Leon has received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007); from Roche Molecular Systems, Inc. (ended in 2007); and, in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). He has been on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005). His lectures have been supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006).

In the past 3 years, Dr. Spina has participated in speakers/advisory boards and lectured supported by AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, Lundbeck, Pfizer and Servier. In the past three years, Dr. Diaz had no conflict of interest.

Abstract:

Background: Clobazam was recently approved for Lennox-Gastaut syndrome in the US. There is no published review article focused on clobazam therapeutic drug monitoring (TDM) in English.

Methods: More than two hundred clobazam articles identified by a PubMed search were carefully reviewed for information on clobazam pharmacokinetics. Clobazam is mainly metabolized by a cytochrome P450 (CYP) isoenzyme, CYP3A4, to its active metabolite, N-desmethyclobazam. Then, N-desmethyclobazam is mainly metabolized by CYP2C19 unless the individual has no CYP2C19 activity (poor metabolizer, PM).

Results: Using a mechanistic approach to reinterpret the published findings of steady-state TDM and single-dosing pharmacokinetic studies, four different serum clobazam concentration ratios were studied. The available limited steady-state TDM data suggest that the serum N-desmethyclobazam/clobazam ratio can be useful for clinicians, including identifying CYP2C19 PMs (ratio >25 in the absence of inhibitors). There are three possible concentration/dose (C/D) ratios. The clobazam C/D ratio has the potential to measure the contribution of CYP3A4 activity to the clearance of clobazam from the body. The N-desmethyclobazam C/D ratio does not appear to be a good measure of clobazam clearance and should be substituted with the total (clobazam+N-desmethyclobazam) C/D ratio.

Conclusions: Future clobazam TDM studies need to use trough concentrations after steady-state has been reached (>3 weeks in normal individuals and several months in CYP2C19 PMs). These future studies need to explore the potential of clobazam and total C/D ratios. Better studies on the relative potency of N-desmethyclobazam compared to the parent compound are needed to provide weighted total serum concentrations that correct for the possible lower N-desmethyclobazam pharmacodynamic activity. Standardization and more studies of C/D ratios from clobazam and other drugs can be helpful to move TDM forward.

Key words: anticonvulsant; clobazam; CYP3A4; CYP2C19; drug monitoring.

INTRODUCTION

Clobazam is a benzodiazepine, but it is the only 1,5-benzodiazepine available on the market since all other benzodiazepines have a 1,4 structure. Its nitrogen atoms occupy the 1 and 5 position, a keto group is placed in the 4 position, and the remainder of the molecule is analogous to diazepam.¹ Benzodiazepines act mainly by binding to γ -aminobutyric acid (GABA)-A receptors and increasing their affinity to GABA, and are considered GABA-A allosteric modulators.² This action probably explains their antiepileptic properties.³

Clobazam was first approved in Australia in 1970 and then in France in 1974 for anxiety and epilepsy.⁴ Clobazam demonstrated clinical benefit in more than 50 European epilepsy studies which reported data on >3000 pediatric and adult patients, 300 of whom were diagnosed with Lennox-Gastaut syndrome.¹ This led to 2 multicenter randomized clinical trials (RCTs)^{5,6} for Lennox-Gastaut syndrome using a double-blind design, and to the subsequent marketing in the US in October of 2011 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome.

Bentué-Ferrer et al.⁷ published an excellent review article focused on clobazam therapeutic drug monitoring (TDM) in French, but there is no published clobazam TDM review article in English. In their very comprehensive review of the TDM literature on psychiatric drugs, Hiemke et al.⁸ provided very limited information on clobazam TDM, which is only listed in a table. In a TDM practice guideline for antiepileptic drugs, Patsalos et al.⁹ provided information on clobazam using the traditional TDM approach. The current review article is based on a comprehensive reading of old and recent literature and, more importantly, uses a mechanistic approach¹⁰⁻¹² to reinterpret the published findings, taking into account what we know about clobazam pharmacokinetics. Thus, pharmacokinetic knowledge based on the concept of concentration/dose (C/D) ratio¹³ is used to provide practical recommendations for clobazam TDM. Four different serum concentration ratios are used to interpret clobazam pharmacokinetics in TDM: The N-desmethyloclobazam/clobazam plasma concentration ratio, the

clobazam C/D ratio, N-desmethyloclobazam C/D ratio and the total (clobazam+N-desmethyloclobazam) C/D ratio.

METHODS

Articles for this review were obtained from a PubMed search completed in January 2012 and then updated in April 2012. The search had no time limit and used the word “clobazam”. The first author reviewed all abstracts and selected all relevant articles to be read. Moreover, all article bibliographies were carefully reviewed for additional important articles not found in the PubMed search. The first author completed this computer search in the context of developing a practical guideline for the use of clobazam in epilepsy as he has done with all antiepileptic drugs marketed in the US.¹⁴ Thus, the original computer search included all available clobazam articles, not only those focused on TDM or pharmacokinetics. More than two hundred clobazam articles were carefully reviewed. Only those relevant to TDM are included in this review article.

Clobazam pharmacokinetics is characterized by two peculiarities: 1) it has an active metabolite; and 2) it is mainly metabolized by two cytochrome P450 (CYP) isoenzymes, CYP3A4 and the polymorphic CYP2C19.

A drug plasma concentration-to-dose (C/D) ratio is calculated by dividing the drug trough steady-state concentration by the dose that the patient is taking. In the opinion of the authors, the C/D ratio may be extraordinarily helpful in moving TDM forward, but this concept has suffered from too little representation in the literature. There are no comprehensive reviews of the application of this concept to TDM. According to a PubMed search, it was first used in a published research article in 1975.¹⁵ The C/D ratio has frequently been used by researchers working in TDM. Unfortunately, although their research has been published in journals like this one, or others with an interest in TDM and/or pharmacokinetics, the C/D ratio concept is not usually described in pharmacological textbooks¹⁶ or in comprehensive textbooks focused on pharmacokinetics.¹⁷

The C/D ratio, which can be considered a proxy of drug clearance, is at the core of a new family of pharmacokinetic mathematical models whose empirical and theoretical adequacy has been demonstrated in a number of studies.^{18,19} Although there is no room in this article to describe these models, which are essentially statistical random-effects linear models of steady-state drug concentrations, computer simulations and statistical theory have shown that clinical procedures for drug dosage individualization designed with these models may outperform some traditional procedures used in TDM.¹⁸

The C/D ratio is inversely related to drug clearance; thus, a high C/D ratio indicates poor drug clearance and a low C/D ratio indicates rapid clearance. In addition, basic compartmental theory predicts that, for a fixed dose, the C/D ratio obtained from TDM studies is directly proportional to the area under the curve ($AUC_{0-\infty}$), the typical measure of drug exposure used in single-dose pharmacokinetic studies. Although empirical data are needed to better study this relationship, a high AUC should be associated with a high C/D ratio and a low AUC should be associated with a low C/D ratio, bearing in mind that comparing C/D ratios and AUCs requires comparable doses.

LITERATURE REVIEW

The information was classified into five major topics: clobazam metabolism, clobazam versus N-desmethyloclobazam activity, clobazam and N-desmethyloclobazam half-lives (Table 1), TDM issues (Table 2), and the use of serum concentration ratios to interpret clobazam pharmacokinetics in TDM. Four serum concentration ratios are used to interpret clobazam metabolism: the N-desmethyloclobazam/clobazam ratio (Table 3), which is the most established ratio in the literature, and three C/D ratios: clobazam C/D ratio (Table 4), N-desmethyloclobazam C/D ratio (Table 5), and the total clobazam C/D ratio (Table 6). The total clobazam C/D ratio is calculated by dividing the sum of plasma clobazam and N-desmethyloclobazam concentrations by the dose. These four sections reviewing serum ratios on steady state TDM studies are supplemented with the review of the analogous AUC ratios in single-dose studies (Table 7).

Clobazam metabolism

According to the prescribing information²⁰ and in vitro study,²¹ clobazam is mainly metabolized by N-demethylation through CYP3A4 and, to a lesser extent, by CYP2C19 and CYP2B6. Thus, for clinical purposes, one can consider that CYP3A4 is the demethylation pathway that is clinically relevant. Another minor clobazam pathway is hydroxylation by CYP2C18 and CYP2C19.²¹ The main metabolite, N-desmethyloclobazam (or norclobazam) is mainly hydroxylated by CYP2C19^{21,22} as long as this CYP is present, since a functional enzyme is absent in CYP2C19 poor metabolizers (PMs). In their in vitro study, Giraud et al.²¹ indicated that CYP3A4 may have a minor role in hydroxylation of N-desmethyloclobazam. Clobazam drug-drug interaction (DDI) studies using inhibitors and inducers allow exploring how changes in CYP3A4 and CYP2C19 activity influence different C/D ratios.

According to the prescribing information, mild and moderate hepatic impairment is not associated with relevant pharmacokinetic changes. However, clinicians should be careful by using lower initial dosing, slower titration and caution before reaching maximum doses.²⁰

Renal elimination. N-desmethyloclobazam and its metabolites comprise approximately 94% of the total drug-related components in urine;²⁰ thus renal impairment may have some effects on clobazam metabolite clearance. According to the prescribing information, the effect of renal impairment on clobazam pharmacokinetics was evaluated by administering multiple 20 mg/day doses of clobazam in six patients with mildly decreased (> 50 to 80 mL/min) and moderately decreased (30 to 50 mL/min) creatinine clearance, and six matching healthy controls. There were small increases in the AUC (<13% for clobazam or N-desmethyloclobazam) associated with these levels of renal impairment. Thus, no dose adjustment is required for patients with mild or moderate renal impairment. According to the prescribing information, there are no clobazam studies in patients with severe renal impairments or end-stage renal disease.²⁰ Roberts and Zoanetti²³ found that serum concentrations did not reach toxic levels in a patient with end-stage renal disease taking a low dose of 10 mg/day of clobazam.

CYP3A4. CYP3A4 is responsible for most CYP3A-mediated drug metabolism but the minor isoforms CYP3A5, CYP3A7 and CYP3A43 also can contribute.²⁴ Since there is no data indicating that the minor isoforms are relevant for clobazam metabolism, this section focuses only on CYP3A4. CYP3A4 is the most important CYP enzyme in the liver and gut; and there is limited understanding of how its different genetic variations contribute to its function. However, there is definitive agreement that there are no CYP3A4 PMs.^{25,26}

There is also definitive agreement that environmental factors such as inducers and inhibitors have major effects on CYP3A4 function. Some antiepileptic drugs (carbamazepine, phenobarbital and phenytoin) and rifampin are major CYP3A4 inducers.^{13,27} Erythromycin (and some related compounds), ketoconazole (and some related compounds) and nefazadone are major CYP3A4 inhibitors.^{13,27} A potential confounder in CYP3A4 studies is that CYP3A4 shares substrates, inhibitors and inducers with p-glycoprotein, making it difficult to distinguish the metabolic contributions of CYP3A4 and p-glycoprotein for a particular drug.

There is also information that personal characteristics such age, gender and pregnancy may influence CYP3A4 activity. Neonates and infants have lower CYP3A4 activity but children from 1 to 12 years of age have greater CYP3A4 activity than adults.²⁸ Geriatric age does not appear to decrease CYP3A4 activity.²⁹ On average, females may have 20-50% higher activity than males³⁰ but this may be explained by differences in p-glycoprotein rather in CYP3A4 activity.³¹ Pregnant women may have increased CYP3A4 activity.³²

Clobazam auto-induction. In vivo controlled studies indicate that clobazam increases the metabolism of the CYP3A4 substrate midazolam, since it: (1) decreases midazolam AUC by 27%, and (2) increases the AUC of the metabolite 1-hydroxymidazolam by 4-fold.³³ The prescribing information provides conflicting information on the clinical relevance of the CYP3A4 induction by clobazam since it states that “this level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4”, but then states that the addition of clobazam may be associated with the

loss of contraceptive efficacy, and non-hormonal forms of contraception are recommended when using clobazam.²⁰

If clobazam is both a mild CYP3A4 inducer and is metabolized by CYP3A4, then one can predict some auto-induction in patients not taking powerful CYP3A4 inducers. This happened in one study in healthy volunteers³⁴ (see subsection on auto-induction in the section on clobazam C/D ratio).

CYP2C19. The CYP2C19 gene encodes for S-mephenytoin hydroxylase. The most frequent allele is CYP2C19*1, which has normal enzyme activity.³⁵ The two most common allelic variants are CYP2C19*2 and CYP2C19*3, which result in a nonfunctional enzyme. The CYP2C19*2 allele is particularly frequent in East Asians; approximately 10%-25% of Asians are classified as CYP2C19 PMs with two nonfunctional alleles, while fewer than 5% of people from other ethnic backgrounds are classified as CYP2C19 PMs.³⁵ In a large US study,³⁶ CYP2C19 PM prevalence was 2.2% in Caucasians (95% confidence interval, CI, 1.6%-2.5%) and 4.0% in African Americans (CI 2.6%-6.1%). Being an East Asian with poor tolerance to usual diazepam doses may reflect a CYP2C19 PM genotype.^{37,38} A new CYP2C19 *17 allele has been described and may be associated with the ultrarapid metabolizer phenotype for CYP2C19 drugs.³⁹ In 146 Swedes, the prevalence of homozygous subjects (*17/*17) was 2.7%.³⁹ There are no published studies of the effects of this new CYP2C19 allele in clobazam metabolism.

According to the prescribing information, N-desmethyloclobazam AUC was approximately 3-5 times higher in CYP2C19 PMs and 2 times higher in subjects with only 1 active allele than in subjects with 2 active alleles.²⁰ The prescribing information makes two statements that may be somewhat contradictory: (1) systemic exposure of clobazam is similar for both CYP2C19 PMs and non-PMs, and (2) clobazam dosage in known CYP2C19 PMs may need to be adjusted. Their practical recommendation is that in adult patients known to be CYP2C19 PMs, the starting dose should be 5 mg/day instead of 10 mg/day, and dose titration should proceed slowly up to 20 mg/day and be based upon clinical response. An additional titration to the maximum dose of 40 mg/day may be started on day 21.²⁰

There is limited independent information on how CYP2C19 polymorphism influences clobazam

antiepileptic response. Seo et al.⁴⁰ published a retrospective Japanese study including 25 PMs, 44 subjects with only 1 active allele, and 41 subjects with 2 active alleles. The respective response rates (defined as seizure reduction $\geq 50\%$) were 65%, 47% and 33%. The odds ratio (OR) of response comparing PMs versus subjects with 1 active allele was 10.0 (95% CI, 2.5-39.6) and when comparing those with 1 active allele versus those with 2 active alleles it was 2.5 (0.88-7.3). Adverse drug reactions (ADRs) were increased in PMs, who had 64% versus 43% in those with 1 active allele and 39% in those with 2 active alleles, although these differences were borderline significant ($p=0.07$). This is consistent with clobazam's description as a drug with wide therapeutic range.¹⁰ Therefore, higher levels of N-desmethyloclobazam in CYP2C19 PMs may be associated with a better chance of response but some risk of increased ADRs. On the other hand, there are two published cases^{41,42} of severe signs of clobazam intoxication in CYP2C19 PMs (see Table 2). In these 2 patients, N-desmethyloclobazam had extraordinarily long-half lives. One of them still had serum N-desmethyloclobazam concentrations in the therapeutic range 20 days after clobazam discontinuation,⁴² and the other required complete clobazam discontinuation for 10 days to reduce serum concentrations by one-third.⁴¹ Both cases appear to have been treated with dosages in the usual recommended ranges, but they were too high for these specific patients, which may have led to saturation of N-desmethyloclobazam metabolism.

There is definitive agreement that environmental factors such as inducers and inhibitors have major effects on CYP2C19 function in those subjects who are not CYP2C19 PMs and who have some CYP2C19 activity present. In CYP2C19 PMs, inducers and inhibitors may have effects on drugs mainly metabolized by CYP2C19 isoenzyme by influencing other metabolic enzymes. Some antiepileptic drugs (carbamazepine, phenobarbital and phenytoin) and rifampin are considered CYP2C19 inducers.^{43,44} Fluconazole, fluvoxamine, isoniazid, omeprazole and ticlopidine are major CYP2C19 inhibitors.^{43,45} Among antiepileptic drugs,⁴⁴ felbamate is a potent CYP2C19 inhibitor (and CYP3A4 inducer) and topiramate and oxcarbazepine are weak CYP2C19 inhibitors (and weak CYP3A4 inducers). Phenytoin is a powerful CYP3A4 inducer but may also compete with drugs metabolized by CYP2C19. Phenytoin is metabolized by CYP2C9 and CYP2C19 and follows non-linear kinetics. When serum phenytoin

concentrations are high (close to 20 µg/mL), there is probably a particularly high risk of competitive inhibition. This may be relevant to clobazam prescription. According to in vitro studies, N-desmethyloclobazam is a weak CYP2C9 inhibitor³⁵ and competitive inhibition of CYP2C19 is possible, too. Haig et al.⁴⁶ tested N-desmethyloclobazam as an antiepileptic drug in 4 patients taking phenytoin. In 2 of these 4 patients, there was a 1.6-fold increase in phenytoin levels. Thus, it is not surprising that Zifkin et al.⁴⁷ described 3 cases of phenytoin toxicity after adding clobazam to phenytoin therapy in patients with relatively high phenytoin levels. As clobazam sometimes can competitively inhibit phenytoin metabolism, some articles suggest that phenytoin sometimes can competitively inhibit clobazam metabolism.⁴⁸

Personal characteristics such as age, gender and pregnancy may influence CYP2C19 activity. Neonates and infants have lower CYP2C19 activity but children from 1 to 12 years of age have CYP2C19 activity similar to that of adults.²⁸ Geriatric age does not appear to decrease CYP2C19 activity.²⁹ It is not clear whether there are gender differences in CYP2C19 activity.³⁰ Pregnant women may have decreased CYP2C19 activity.³²

Clobazam versus N-desmethyloclobazam activity

There is definitive agreement that N-desmethyloclobazam has antiepileptic activity.⁴⁶ What is not clear is how much of the clinical activity of clobazam is due to the presence of the metabolite in the body. The prescribing information²⁰ reported that the relative potency of N-desmethyloclobazam compared to the parent compound ranges from 1/5 to equal potency. This estimation was based on animal and in vitro receptor binding data but no studies were provided as reference.

To determine the clinical relevance of N-desmethyloclobazam one needs to know the differences between clobazam and N-desmethyloclobazam in: (1) pharmacodynamic activity, (2) brain entrance and (3) tolerance.

Two in vitro pharmacodynamic studies have been published.^{49,50} Using a whole-cell voltage-clamp recordings on cultured rat cerebral neurons, Nakamura et al.⁴⁹ found that the same concentration

of clobazam and N-desmethyloclobazam displayed approximately similar effects of increasing chloride currents. After obtaining cells that express recombinant GABA-A receptors, Fisher et al.⁵⁰ used whole-cell voltage-clamp recordings and found that clobazam had approximately twice the potency of N-desmethyloclobazam.

Any possible differences in brain entrance between clobazam and N-desmethyloclobazam may produce differences between the N-desmethyloclobazam/clobazam concentration ratios in brain and serum. If there are no differences in the abilities of clobazam and N-desmethyloclobazam to cross the blood-brain barrier, the serum N-desmethyloclobazam/clobazam ratio should be the same as that of the brain. There are no published studies on clobazam brain entrance. From a theoretical point of view, the ability of a compound to cross the blood-brain barrier is influenced by the drug's physicochemical properties, which determine passive diffusion and/or actions of transporters such as the p-glycoprotein.⁵¹ Particularly in the benzodiazepines, brain uptake may be more closely related to lipophilicity.⁵² According to prescribing information, clobazam and N-desmethyloclobazam are p-glycoprotein substrates²⁰ but data on their affinity is not provided. P-glycoprotein affinity for clobazam and its metabolite may be important, since p-glycoprotein affinities explain differences in other psychiatric drugs. A relevant drug is risperidone, in which the high affinity of p-glycoprotein for the main risperidone active metabolite may explain why the metabolite has lower ability than risperidone to penetrate the brain and lower activity level.⁵³ Laux et al.⁵⁴ studied serum and cerebrospinal fluid (CSF) concentrations in 2 patients taking repeated doses of clobazam and found that, similar to what is observed in serum, there were greater CSF concentrations of N-desmethyloclobazam than clobazam. The N-desmethyloclobazam/clobazam ratios in serum and CSF were roughly similar in each patient. One patient had serum and CSF ratios of 10.7 and 8.6, respectively, and the other of 3.3 and 2.7. These limited data from 2 patients suggest that the CSF follows the same pattern as serum, and that both compounds may have roughly similar brain entrance rates.

As different species have different metabolic activity and different clobazam metabolites,⁵⁵ in vivo animal studies cannot provide definitive conclusions about the relative contribution of clobazam and

N-desmethyloclobazam to clobazam antiepileptic activity in humans. N-desmethyloclobazam is a minor metabolite in rats but is important in mice and guinea pigs.⁵⁶ Animal studies attempting to extrapolate the antiepileptic contributions of clobazam and N-desmethyloclobazam to humans need to account for differences in metabolism and brain entrance between humans and other species.

Haigh et al.⁴⁶, based on their limited clinical experience⁴⁶ with N-desmethyloclobazam administration and an animal study⁵⁷, proposed that N-desmethyloclobazam may be less prone to cause tolerance. To avoid the contamination of human pharmacodynamic studies by a difference in tolerance between clobazam and N-desmethyloclobazam, these studies should be completed when the maximum tolerance has been acquired.

Once the relative pharmacodynamic activity under conditions of maximal tolerance and brain entrance of clobazam and N-desmethyloclobazam are better established, an attempt can be made to calculate weighted serum concentrations to better predict clinical response.⁵⁸ For example, let us assume that clobazam has 3 times as much ability to penetrate the blood-brain barrier and is 2 times more potent in pharmacodynamic activity. This means that clobazam will be 6 times more potent at brain GABA-A receptors (3 times due to greater brain entrance, multiplied by 2 times due to its pharmacodynamic activity at the receptors). Therefore, weighted total clobazam serum concentrations should be calculated by adding clobazam to one-sixth of N-desmethyloclobazam concentrations and may better reflect clobazam clinical activity. Obviously, this total serum clobazam concentration would reflect average effects since it is possible that genetic, environmental and personal factors may differentially influence clobazam and N-desmethyloclobazam brain entrance and/or action at the GABA-A receptors in different individuals.”

Clobazam and N-desmethyloclobazam half-lives

According to the prescribing information, the estimated mean elimination half-lives of clobazam and N-desmethyloclobazam were 36-42 hours and 71-82 hours, respectively.²⁰ No details were given on how these estimations were obtained. Recent half-life estimations from single and repeated dose studies,³³ required for marketing clobazam in the US, are described in the upper panel of Table 1.

Nine prior studies^{34,59-67} estimated half-lives in healthy volunteers after single doses of clobazam. All 9 studies provided half-lives in non-elderly adults lower than the lowest limit (36 hours) described by the package insert, which probably reflects the difficulties of using single-dose studies to estimate half-lives, and that different methods of calculating half-lives may provide different results. These studies did not report subject races. However, all studies were probably done with Caucasians since all were done in the US or European countries. In Caucasians, one should expect a low prevalence (around 2%) of CYP2C19 PMs. The recent pharmacokinetic studies by the manufacturer³³ excluded CYP2C19 PMs. The 9 prior studies included a total of 82 individuals, which may incorporate 1 or 2 CYP2C19 PMs. Only 1 study⁶² included an individual with a very long N-desmethyloclobazam half-life, 131 hours, which is consistent with a CYP2C19 PM profile.

One study³⁴ provided data from both healthy controls and patients (Table 1). Patients had lower clobazam half-lives. No data on co-medications in patients was provided, but the results in patients were probably contaminated by inducers. In a single-dose study, Monjanel-Mouterde et al.⁶⁰ demonstrated differences in clobazam half-lives between volunteers and patients with hepatic impairment, but N-desmethyloclobazam was not studied.

Clobazam is taken by epileptic patients in repeated doses; thus, studies using repeated dosing provide a better idea of what the half-lives of clobazam and N-desmethyloclobazam are in a clinical environment. Pharmacokinetic textbooks usually state that 5 half-lives provide approximately 95% of steady-state concentrations and 7 half-lives provide 99% of them.⁶⁸ Most TDM articles consider 5 half-lives⁶⁹ to be required before reaching steady state but if one is a strict pharmacologist, one would ask for 7 half-lives to reach steady state. As a matter of fact, the graphic representation of clobazam TDM in two studies suggested that it may take up to 7 half-lives to reach a plateau. The two studies included one by Rupp et al.^{64,65} who gave 20 mg/day (10 mg twice daily) of clobazam for 28 days to 10 Indian subjects and one by Ochs et al.⁶¹ who gave 10-mg/day clobazam doses for 22 days (5 mg twice a day) to 13 healthy volunteers. In the first study,^{64,65} it was obvious that clobazam reached a steady state within 1 week in the average patient, but reaching N-desmethyloclobazam steady-state took more than 3 weeks.

Assuming that 7 half-lives are needed to reach a steady state, if clobazam reached steady state within 1 week but N-desmethyloclobazam required more than 3 weeks, then clobazam behaves with a mean half-life < 1 day (<24 hours) in a clinical environment, although clobazam may have a mean half-life > 3 days (>72 hours). In the second study,⁶¹ on average, clobazam concentration reached a plateau in less than 7 days while N-desmethyloclobazam did not appear to reach a plateau until 3 weeks had passed. In this second study, the clobazam accumulation half-life was about 24 hours.

Ochs et al.⁶¹ provided gender stratification. The arithmetic mean clobazam accumulation half-life was 24.5 hours in 6 males (range, 23.0-35.3) and 24.0 hours in 7 females (range, 21.6-27.4). The arithmetic mean N-desmethyloclobazam accumulation half-life was 106 hours; according to these long half-lives, 3 weeks may be needed to reach steady state of both the compound and active metabolite. In this second study, some gender differences appeared to be present in N-desmethyloclobazam half-lives, with 79.2 hours in 6 males (range, 39.0-108.0) and 128.6 hours in 7 females (range, 44.0-289.0). It is possible that female subjects may have included at least 1 CYP2C19 PM with a very long-half life of 289 hours after repeated dosing.

The above half-life estimations are from patients not taking CYP2C19 inhibitors. It is not clear how much these estimations are contaminated by rare individuals with a CYP2C19 PM phenotype. If one assumes that a patient without CYP2C19 activity due to genetic reasons or complete inhibition has N-desmethyloclobazam half-lives of 130 hours (or >5 days) in a single-dose study and of 289 hours (or >12 days) in a repeated-dose study, then the patient requires more than 1 month to reach steady-state.

In a single-dose study, Greenblatt et al.⁵⁹ demonstrated differences in clobazam half-lives between elderly and young male adults. They⁷⁰ completed a repeated-dose study of the same patients which supported the concept that elderly males have higher clobazam and desmethyloclobazam half-lives (Table 1), with an average of 326 hours (>13 days) for elderly males. If this estimation is correct, elderly males may need months to reach steady-state under clobazam.

Relevance of half-lives for interpreting clobazam DDI studies. Data from the manufacturer³³ comparing a 40-mg single dose versus 40 mg once a day for 15 days in 18 healthy volunteers suggest the inadequacy of single-dose studies. When moving from a single dose to repeated dosing for 2 weeks, the drug exposure (AUC) increases by 2.5- to 4.5-fold for clobazam and by 20- to 60-fold for N-desmethyloclobazam. This statement from the company probably undervalues the level of underestimation of N-desmethyloclobazam AUC by single-dose studies, since 2 weeks is probably not enough to reach a steady state of serum N-desmethyloclobazam concentrations. Thus, any DDI study using single clobazam doses carries a major risk of seriously underestimating DDI effects on clobazam metabolism, particularly on serum N-desmethyloclobazam concentrations.

Relevance of half-lives for interpreting lack of clobazam sedation in single-dose studies. Several neuropsychological studies using single doses to study healthy controls indicate that clobazam seems no different than placebo and produces less impairment than other benzodiazepines.⁷¹⁻⁷⁷ However, in anxiety RCTs that used repeated clobazam dosing and allowed for N-desmethyloclobazam accumulation, it was not clear that clobazam was better than other benzodiazepines regarding drowsiness.⁷⁸

Pharmacokinetic studies using single and repeated doses indicate that single-dose experiments allow elucidating clobazam action but lead to little accumulation of N-desmethyloclobazam. Ochs et al.⁶¹ provided a graphic representation of sedation in 9 healthy volunteers who took 10-mg/day clobazam doses (5 mg twice a day) for 22 days, after which clobazam was discontinued. The maximum average score in a sedation scale was not reached after day 22. In summary, only single-dose studies conclude that clobazam is less sedating than other benzodiazepines. These studies did not last at least 3-4 weeks and, therefore, did not allow for N-desmethyloclobazam reaching steady-state. If one wants to inform clinicians about clobazam sedating properties under real-world situations, one should complete studies with durations of at least 3-4 weeks.

Dosing. In spite of the relatively long clobazam and N-desmethyclobazam half-lives, the prescribing information for epilepsy recommends dosing clobazam twice a day.²⁰ The literature does not explain why twice a day may be needed since a clobazam half-life of 36 hours would allow for once-a-day dosing.

In their review of anxiety RCTs, Brogden et al.⁷⁹ recommended dosing clobazam 2 or 3 times a day for anxiety. They also described a preliminary study indicating that greater decreases in anxiety corresponded to clobazam peak values. Thus, it possible that administering clobazam twice a day, which provides 2 peaks, will determine potentially greater anti-anxiety effects which occur in the peaks.

TDM issues

Therapeutic window. Steady-state serum clobazam and N-desmethyclobazam concentrations are described as linearly related to dose.^{9,20} There are no studies of kinetic linearity in CYP2C19 PMs.

There is limited information regarding the clobazam therapeutic concentration window or range for controlling seizures. A large naturalistic study in children⁸⁰ provided evidence that clobazam has a wide therapeutic window. In a comprehensive review, Patsalos et al.⁹ stated that (1) because tolerance tends to develop to ADRs and sometimes to the therapeutic effects of clobazam, there is no clear relationship between efficacy and serum concentrations of either clobazam or N-desmethyclobazam; and (2) therapeutic clobazam doses were associated with serum concentrations of 30–300 ng/mL for the parent drug and 300–3000 ng/mL for N-desmethyclobazam. In another review, Neels et al.⁸¹ recommended a clobazam therapeutic range of 100–400 ng/mL, but provided no range for N-desmethyclobazam. In a sample of 11 consecutive patients (including many with DDIs), Contin et al.²² described median serum concentrations of 200 ng/mL (range, 80-560) for clobazam and 1370 ng/mL (range, 200-5000) for N-desmethyclobazam. In 39 adults, Guberman et al.⁸² reported that all 6 patients who had ADRs that appeared to be dose-related had plasma concentrations >900 ng/mL for N-desmethyclobazam.

Table 2 describes 6 reports of clobazam intoxication,^{41,42,83-86} including 2 deaths^{85,86} that occurred at elevated serum concentrations. Four of these cases^{41,42,84,85} had N-desmethyclobazam concentrations

>3000 ng/mL; 3 cases^{41,42,85} had concentrations > 4 times 3000 ng/mL, including 1 case⁸⁵ >10 times 3000 ng/mL. N-desmethyloclobazam concentrations were not measured in 2 cases,^{83,86} but their clobazam concentrations were >3000 ng/mL or 10 times higher than the upper recommended limit of 300 ng/mL.

Trough versus peak concentrations. Most studies of TDM in antiepileptic drugs tend to use trough levels after reaching steady-state to standardize measures. Clobazam literature is contaminated by the use of non-trough TDM in many studies. No systematic studies compare trough and peak clobazam concentrations in TDM, but Ochs et al.⁶¹ provided a graphic representation of clobazam serum concentrations of a healthy volunteer after 22 days under 10 mg/day. The trough clobazam concentration was approximately 270 ng/mL, and a peak of approximately 400 ng/mL was obtained in less than 2 hours after clobazam intake at day 22. Three hours after this intake, the concentration decreased to approximately 330 ng/mL. The trough N-desmethyloclobazam concentration was approximately 500 ng/mL, with no obvious change in the 3 hours after the last intake at day 22. After 12 hours, it reached a level of approximately 570 ng/mL. This means that N-desmethyloclobazam increases less than 15% from trough and peaks during the day, but clobazam increases up to 48% from trough to peak during the 2 to 3 hours after clobazam intake.

Serum concentration ratios to interpret clobazam TDM

We propose 4 possible ratios for serum concentrations that may help to interpret clobazam concentrations in TDM studies. The N-desmethyloclobazam/clobazam ratio has been studied a few times in the literature. The other 3 ratios are different ways of examining C/D ratios. The clobazam C/D ratio and the N-desmethyloclobazam C/D ratio have occasionally been calculated in published articles. No article was found that described the use of the total C/D ratio.

Tables 3 to 6 provides data on these 4 ratios extracted from published TDM studies. The footnote b of Table 4 provides a clarification regarding units for C/D ratios. Table 7 reviews additional information obtained from studies computing AUCs that complements TDM studies (see footnote a for details).

N-desmethyloclobazam/clobazam ratio

As clobazam is mainly metabolized by CYP3A4, and N-desmethyloclobazam by CYP2C19, the N-desmethyloclobazam/clobazam ratio is influenced by the activity of both CYP enzymes. Therefore, a high N-desmethyloclobazam/clobazam ratio can indicate: (1) the presence of a CYP2C19 PM or the co-prescription of a potent CYP2C19 inhibitor, (2) the co-prescription of a CYP3A4 inducer, or (3) both. Table 3 presents a comprehensive review of the few published studies reporting data on the N-desmethyloclobazam/clobazam ratio.^{21,22, 40,41, 48, 61,64, 69,87-91} The data suggest that: (1) very high ratios (>25) indicate that the patient is a CYP2C19 PM, or is taking a drug which is a CYP3A inducer and a CYP2C19 inhibitor, such as felbamate; (2) ratios of 10-25 are compatible with the patient taking a CYP3A inducer; and (3) ratios <10 are compatible with “normal” patients [who are: (a) not taking CYP3A inducers, (b) not taking CYP2C19 inhibitors, and (c) not CYP2C19 PMs]. These ratio ranges are rough approximations calculated by reviewing the limited available studies, which were not designed to study this ratio. In fact, none of the articles explored whether there are differences in the N-desmethyloclobazam/clobazam ratio between children and adults.

CYP3A4 and CYP2C19 inhibitors. There are no steady-state TDM studies on the effects of CYP3A4 or CYP2C19 inhibitors on the N-desmethyloclobazam/clobazam ratio. Table 7 describes a single-dose study by the manufacturer³³ that provided mean AUCs after 6 days on ketoconazole (CYP3A4 inhibitor) and on omeprazole (CYP2C19 inhibitor). This limited data indicated that ketoconazole mildly decreased this ratio (by 24% or multiplying by a factor of 0.76) and omeprazole mildly increased it (by 18% or multiplying by a factor of 1.18), which is consistent with pharmacological knowledge. It is possible that, under steady-state conditions of both inhibitors and clobazam, these effects may be larger and clinically relevant.

Clobazam C/D ratio

The clobazam C/D ratio may be mainly a measure of CYP3A4 activity. Table 4 presents a comprehensive review of the few published studies that provided data either peak or trough concentrations (see footnote a) that can be used to calculate clobazam C/D ratio.^{22,41,48,61,69,88-91}

If the clobazam C/D ratio is a measure of CYP3A4 activity the following predictions can be made, it should: 1) be lower in patients taking inducers than in normal controls; 2) change with time if clobazam auto-induces its metabolism; 3) be lower in children 1-12 years than in adults; 4) be higher in patients taking CYP3A4 inhibitors; and 5) not be influenced by CYP2C19 inhibitors.

Inducers. Table 4 indicates that normal subjects appear to have clobazam C/D <30 while patient taking inducers show clobazam C/D ratios <10, which is consistent with greater CYP3A4 activity.

The average clobazam concentration decreased by 62% (from 354 to 136 ng/mL)⁹¹ in the only well-controlled study of induction. This study used subtherapeutic doses of carbamazepine (400 mg/day) and a too short (2 weeks) duration to reach maximal induction. Naturalistic studies indicate: 1) patients taking phenytoin or carbamazepine had significantly lower C/D ratios corrected by weight;³⁴ 2) trough weight-corrected clobazam C/D ratio appeared to be 10 times higher in the volunteers than in adult patients presumably taking inducers;³⁴ and 3) no significant differences in clobazam peak concentrations were observed before and after carbamazepine administration, but N-desmethylclobazam concentration increased significantly.³⁴ In a single-dose study⁹² measuring AUCs, clobazam clearance was increased by carbamazepine and phenytoin (Table 7).

Auto-induction. Bun et al.^{34,88} compared peak and trough weight-corrected clobazam C/D ratios from 6 healthy volunteers and 17 patients (6-32 years) with co-medications. In patients who were presumably taking inducers, there was a very small increase from day 2 to day 21. It is interesting that in healthy volunteers both peak and trough weight-corrected clobazam C/D ratios increased from day 2 to day 7, and then decreased to day 21. In healthy volunteers at day 7, when steady state has not been reached, one

would expect that all C/D ratios, clobazam C/D, N-desmethyloclobazam C/D and total C/D ratios, should be lower than those at day 28. However, it is striking that 5 of 6 patients had clobazam C/D ratios that were 20-30% higher at day 7 than at day 28. This is consistent with self-induction, which is manifested by decreased clobazam concentrations at day 28 compared to day 7.

In a pharmacokinetic study using 10 mg/day of clobazam for 22 days, focused on 12 young and 12 elderly adults, no signs of self-induction in clobazam metabolism were observed.⁷⁰

Age. Adults are treated with proportionally lower clobazam doses than children on a weight-normalized basis (e.g. mg/kg).^{40, 65} When studying adult and children dosages, clobazam articles frequently quote a study by Tedeschi et al.,⁶⁶ who compared 16 children with 14 adolescents or adults who had respective trough clobazam C/D ratios of 0.078 ± 0.01 and 0.147 ± 0.02 (units were not provided). However, this comparison does not take into account the metabolism of N-desmethyloclobazam and did not correct for the effects of inducers. In a naturalistic study,³⁴ trough weight-corrected clobazam C/D ratios in children appeared to be half those in adults.

CYP3A4 and CYP2C19 inhibitors. There are no steady-state TDM studies on the effects of CYP3A4 or CYP2C19 inhibitors on clobazam C/D ratios. Table 7 describes a single-dose study by clobazam maker³³ using ketoconazole (CYP3A4 inhibitor) and omeprazole (CYP2C19 inhibitor) that indicates they have small effects but it is possible that under steady-state conditions of both the inhibitors and clobazam, these effects may be larger and clinically relevant.¹²

In summary, the limited data on clobazam C/D ratio and clobazam AUC suggest that the clobazam C/D ratio may have reasonable potential for being a good measure of CYP3A4 activity. Children and patients taking inducers appear to have lower clobazam C/D ratios. Patients on CYP3A4 inhibitors should have higher clobazam C/D ratios. As most epileptic patients taking clobazam are on powerful inducers, one should not expect clobazam C/D ratios to be influenced by auto-induction. Auto-induction may be mild and only seen in individuals not taking powerful inducers.

N-desmethyloclobazam C/D ratio

Bun et al.³⁴ found that peak weight-corrected N-desmethyloclobazam C/D ratios were very mildly elevated when compared with trough weight-corrected N-desmethyloclobazam C/D ratios. This is compatible with the findings that 1) N-desmethyloclobazam has a very long half-life and 2) there are small differences between studies using peaks or trough N-desmethyloclobazam measures. Table 5 presents a comprehensive review of the few published studies^{22,41,48,61,69,88-91} that provided data for the N-desmethyloclobazam C/D ratio.

The N-desmethyloclobazam C/D ratio has been described by some studies. However, it is not a good measure because it is influenced by both CYP3A4 and CYP2C19 activity and may not solely reflect clobazam clearance. There is no consistent pattern for the N-desmethyloclobazam C/D ratio in Table 5. Other studies indicate how inducers, age, CYP3A4 inhibitors, CYP2C19 inhibitors and CYP2C19 PM phenotype may influence N-desmethyloclobazam C/D ratio.

Inducers. In 414 patients from 9 months to 40 years of age, Bun et al.³⁴ measured peak concentrations three hours after clobazam morning dose and calculated an N-desmethyloclobazam C/D ratio corrected for weight. They found that those taking phenytoin or carbamazepine had significantly higher values. In a subsample of 10 patients, there were significant differences in N-desmethyloclobazam peak concentrations before (727 ng/mL) and after (1720 ng/mL) carbamazepine administration (the concentration more than doubled). Another study in the same article focused on the comparison of 6 healthy volunteers with 17 patients (6 -32 years) with co-medications. The trough weight-corrected N-desmethyloclobazam C/D ratio appeared to be more than twice as high in healthy volunteers as in adult patients. The co-medications were not described.

Contin et al.⁸⁹ found that felbamate was associated with 5 times higher weight-adjusted N-desmethyloclobazam C/D ratios. Jawad et al.⁹² compared 6 adult controls with 6 adult epileptic patients who took a single dose of clobazam on stable phenytoin or carbamazepine doses for 3 months. N-desmethyloclobazam AUC increased by a factor of 5.24 on phenytoin versus a factor of 1.66 on

carbamazepine (Table 7). In a study administering N-desmethyloclobazam 30 mg/day for 2 weeks, Pullar et al.⁶³ compared 8 healthy controls, 5 female patients and 3 male patients. The male controls had median N-desmethyloclobazam C/D ratios of 40.5 (ng × mg)/(mL × day) (range 36.7-55). The 5 female patients had slightly elevated ratios with a median of 63.3 (ng × mg)/(mL × day) (range 40.3-76.7). All 3 male patients were taking phenytoin and had ratios twice as high, with a median of 82.3 (ng × mg)/(mL × day) (range 77.6-95.0).

Age. Bun et al.³⁴ provided graphic results for trough weight-corrected N-desmethyloclobazam C/D ratios, which appeared to be roughly twice as high in adult as in child patients. Co-medication was not described and the study included only 17 patients. In a larger sample of 414 patients, trough weight-corrected N-desmethyloclobazam C/D ratios were significantly lower in children than in adults.

CYP3A4 and CYP2C19 inhibitors. There are no steady-state TDM studies on the effects of CYP3A4 or CYP2C19 inhibitors on the N-desmethyloclobazam C/D ratio. Table 7 describes a single-dose study³³ by clobazam maker using ketoconazole (CYP3A4 inhibitor) and omeprazole (CYP2C19 inhibitor). This limited data indicated that there were almost no increases in the N-desmethyloclobazam AUC on ketoconazole (12% or multiplied by a factor of 1.12), but there was an important increase on omeprazole (65% or multiplied by a factor of 1.65). Under steady state conditions for omeprazole and clobazam these effects may be larger.

CYP2C19 PMs. Table 4 describes a few cases with the CYP2C19 PM phenotype who had very high N-desmethyloclobazam C/D ratios. According to the prescribing information,²⁰ CYP2C19 PMs had a 5-fold increase in N-desmethyloclobazam AUC.

In summary, the limited data on desmethyloclobazam C/D ratio and desmethyloclobazam AUC do not show a clear pattern that clearly informs clinicians regarding possible ranges. As expected, the CYP2C19 PM phenotype and taking CYP2C19 inhibitors should increase the desmethyloclobazam C/D

ratio. The limited available information suggests that phenytoin may behave as a CYP2C19 inhibitor in some patients, probably due to competitive inhibition with N-desmethyloclobazam metabolism.

Total C/D ratio

Table 6 presents a comprehensive review of the few published studies that provided data pertaining to total C/D ratios.^{22,41,61, 69,88, 91} Although little can be concluded from this limited information, most normal subjects appear to have total C/D ratios < 100. CYP2C19 PMs appear to have total C/D ratios >200.

CYP3A4 and CYP2C19 inhibitors. There are no steady-state TDM studies on the effects of CYP3A4 or CYP2C19 inhibitors on the total C/D ratio. Table 7 describes limited data from a single-dose study³³ by clobazam maker using ketoconazole (CYP3A4 inhibitor) and omeprazole (CYP2C19 inhibitor). There were small increases in the total AUC on ketoconazole (26% or multiplied by a factor of 1.26), but there was an important increase on omeprazole (54% or multiplied by a factor of 1.54). Under steady state conditions for these inhibitors and clobazam, it is possible that these effects may be larger. Based on pharmacogenetic data, the prescribing information²⁰ states that strong (e.g., fluconazole, fluvoxamine, and ticlopidine) and moderate (e.g., omeprazole) CYP2C19 inhibitors may result in up to 5-fold increases in exposure to N-desmethyloclobazam. Thus, clobazam dosage adjustment may be necessary when co-administered with strong or moderate CYP2C19 inhibitors, including omeprazole.

Jawad et al.⁹² compared 6 adult controls with 6 matched adult epileptic patients who had taken stable doses of phenytoin or carbamazepine for 3 months and received clobazam single doses. After adding clobazam and N-desmethyloclobazam AUCs, there were 2 patients taking phenytoin who clearly had increased N-desmethyloclobazam levels and total AUCs increased by a factor of 3.3, while carbamazepine was associated with a very small increase in total AUC (Table 7).

In summary, no prior study has calculated total C/D ratios. The limited data on total C/D ratios and total AUCs suggest that the total C/D ratio may have reasonable potential for being a good measure

of total clobazam clearance. The CYP2C19 PM genotype and possibly powerful CYP2C19 inhibitors may be associated with increased total C/D ratios. There are very limited data on how CYP3A4 inhibitors may influence total C/D ratios. The data on inducers are complex. Phenytoin appears to reduce serum clobazam concentrations but may increase N-desmethyloclobazam concentrations in some patients, more dramatically than the reduction in clobazam concentrations. It is not clear whether carbamazepine decreases total C/D ratio or not.

DISCUSSION

The need for standardization in future clobazam TDM studies

The first conclusion drawn from this literature review is that the available pharmacokinetic literature on clobazam is limited by the lack of standardization. Future clobazam TDM studies need to use both steady-state and trough concentrations. As N-desmethyloclobazam has a very long half-life, 3 weeks are needed to reach steady-state in normal subjects. Trough concentrations are fundamental to properly interpret clobazam TDM. It does not appear prudent to try to use peak concentrations since, according to the limited information available,⁶¹ serum clobazam concentrations vary substantially between 2-3 hours after a dose. Some published studies have used blood drawn within 3 hours of administering clobazam but these studies cannot determine if each collection corresponds to the time of peak concentration (at approximately 2 hours) or after the peak. Moreover, using peak concentrations requires accounting for the fact that food does not influence the extent of clobazam absorption but may slow the absorption rate.^{93,94}

Clobazam versus N-desmethyloclobazam activity

Better studies on the relative potency of N-desmethyloclobazam compared to the parent compound are needed.⁹⁵ This is a major requirement to make clobazam TDM a better instrument in the prediction of response and ADRs. Unfortunately, it is not easy to study this issue in a definitive way. In vivo human studies combining TDM and brain imaging of GABA receptors after maximal tolerance has been acquired

may be needed to definitively explore this issue. Studies combining TDM and brain imaging may provide information on the GABA-A binding activity of clobazam and N-desmethyclobazam which would allow the establishment of weighted total serum concentrations⁵⁸ for the average individual and initial exploration of interindividual variability. Considerable research studies or even new research approaches will be required to personalize clobazam pharmacokinetics and pharmacodynamics according to the genetic, environmental and personal characteristics of each individual.

CYP2C19 PM

CYP2C19 PMs may require much higher periods to reach a steady state than normal individuals. They may take several months to reach this state. Therefore, dose increases in these subjects should be extraordinarily slow. The limited data available from a few intoxicated patients suggest that it is possible that CYP2C19 saturation may occur in these subjects when high but therapeutic doses are prescribed. Clobazam TDM may be crucial in identifying these subjects. In the absence of CYP2C19 inhibitors, an N-desmethyclobazam/clobazam ratio >25 may be suggestive of a CYP2C19 PM genotype.

Therapeutic window

The lack of good prospective studies limits our information on clobazam therapeutic range. The lack of publication of TDM data from recent RCT trials^{5,6} on Lennox-Gastaut is a major limitation. Tolerance to efficacy and ADRs may also decrease the value of TDM. There is no definitive agreement on the relevance of tolerance for clobazam response. Older reviews provide estimations of tolerance development ranging from 1/3⁷⁸ to 89%.⁹⁶ Some recent reviews comment that the problem of tolerance may have been overestimated.^{97,98}

Currently, the best approximation to a therapeutic window or range is that of Patsalos et al.⁹ They described therapeutic clobazam doses as those associated with serum concentrations of 30–300 ng/mL for the parent drug and 300–3000 ng/mL for N-desmethyclobazam. If a patient on TDM has concentrations within these ranges and has not responded, then the patient is not likely to respond to clobazam treatment.

Clobazam probably has a wide therapeutic window, making only very high concentrations relevant to help diagnose toxicity. If there are symptoms consistent with clobazam intoxication, the presence of very high concentrations (>3000 ng/mL for clobazam and/or >12,000 ng/mL for N-desmethyloclobazam) probably confirm clobazam intoxication.

N-desmethyloclobazam/clobazam ratio

The available limited data suggest that the N-desmethyloclobazam/clobazam ratio can be useful for clinicians. This review suggests that: (1) very high ratios (>25) indicate that the patient is a CYP2C19 PM or taking a CYP3A4 inducer and CYP2C19 inhibitor such as felbamate; (2) ratios of 10-25 are compatible with the patient taking a CYP3A4 inducer; and (3) ratios <10 are compatible with “normal” patients who are: (a) not taking CYP3A4 inducers, (b) not taking CYP2C19 inhibitors, and (c) not CYP2C19 PMs.

Although there are no definitive data to support it, phenytoin may frequently behave as felbamate, acting simultaneously as a CYP3A4 inducer and CYP2C19 clinically-relevant inhibitor. If this is correct, phenytoin may be associated with N-desmethyloclobazam/clobazam ratios >25. Based on pharmacological knowledge, it is reasonable to predict that potent or moderate CYP2C19 inhibitors such as fluconazole, fluvoxamine, isoniazid, omeprazole and ticlopidine may be associated with N-desmethyloclobazam/clobazam ratios >25.

Future clobazam TDM studies need to examine the effects of topiramate and oxcarbazepine on the N-desmethyloclobazam/clobazam ratio. These two drugs are both weak CYP2C19 inhibitors and weak CYP3A4 inducers. Unfortunately, the actions of these drugs are not easy to study since the dosing level may be significant. It is believed⁴⁴ that only high doses of oxcarbazepine (≥ 1500 mg/day) or topiramate (≥ 400 mg/day) may cause CYP3A4 induction. In low and average doses, only their CYP2C19 inhibitory properties may be evident.

Total C/D ratio

The previously published literature does not describe the total C/D ratio. Future studies should explore whether it is a good measure to distinguish individuals according to their drug clearance ability. From the available knowledge on pharmacological mechanisms, using this ratio may be more reasonable than using the N-desmethyloclobazam C/D ratio. It is possible that renal impairment associated with aging, particularly in males,⁷⁰ may be associated with high total C/D ratios.

Clobazam C/D ratio

The clobazam C/D ratio has potential to measure the contribution of CYP3A4 activity to the clearance of clobazam from the body. If this is correct, children (ages 1-12 years) will have decreased clobazam C/D ratios after weight correction. Similarly, individuals taking inducers (carbamazepine or phenytoin) will have decreased C/D ratios. Patients taking potent CYP3A4 inhibitors (erythromycin or ketoconazole and some related compounds) will have increased clobazam C/D ratios.

CONCLUSION

This comprehensive review of the clobazam literature found a lack of standardization. Future clobazam TDM studies need to use both steady-state and trough concentrations. As N-desmethyloclobazam has a very long half-life, three weeks are needed to reach steady-state in normal subjects while months may be needed in CYP2C19 PMs and elderly males.

Using a mechanistic approach to reinterpret the published findings, four different serum concentration ratios were studied to interpret clobazam pharmacokinetics in TDM. The available limited data suggest that the N-desmethyloclobazam/clobazam ratio can be useful for clinicians. This review suggests that: (1) very high ratios (>25) indicate that the patient is a CYP2C19 PM, or taking a drug which is a CYP3A inducer and CYP2C19 inhibitor such as felbamate (or possibly phenytoin); (2) ratios of 10-25 are compatible with the patient taking a CYP3A inducer; and (3) ratios <10 are compatible with “normal” patients.

There are 3 possible C/D ratios. The clobazam C/D ratio has potential to measure the contribution of CYP3A4 activity to the clearance of clobazam from the body. The N-desmethyloclobazam C/D ratio does not appear to be a good measure of clobazam clearance and should be substituted by the total (clobazam + N-desmethyloclobazam) C/D ratio. Better studies on the relative potency of N-desmethyloclobazam compared to the parent compound are needed to provide weighted total serum concentrations that appropriately correct for the possible lower N-desmethyloclobazam pharmacodynamic activity at the GABA-A receptors. Standardization and more studies of C/D ratios from clobazam and other drugs can be helpful to move TDM forward.

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Table 1. Clobazam pharmacokinetic studies providing half-life estimations.

Reference	Sample size	Dose mg/d	Half-life (hours)	
			Clobazam	N-desmethylclobazam
RECENT STUDIES BY COMPANY IN HEALTHY ADULT VOLUNTEERS (probably Caucasians)				
SINGLE DOSE				
³³ Walzer et al. ^a	18	10	37.5 (17-69)	67.5 (33-133)
REPEATED DOSE (15 days)				
³³ Walzer et al. ^a	18	40	32	57
OTHER SINGLE-DOSE STUDIES IN HEALTHY ADULT VOLUNTEERS (probably Caucasians)				
³⁴ Bun et al. ^b	6	Unknown	24 ($\pm 7^c$)	57($\pm 33^c$)
⁵⁹ Greenblatt et al.	7♂ young	20	16.6 (11-23) ^d	Not studied
	8♀ young	20	30.7 (18-46) ^d	Not studied
	7♂ elderly	20	47.7 (29-77) ^d	Not studied
	6♀ elderly	20	48.6 (23-72) ^d	Not studied
⁶⁰ Monjanel- Mouterde et al.	6♂	20	22 ($\pm 6^c$) ^e	Not studied
⁶¹ Ochs et al.	7♂	20	22.3(13.6-35.2) ^f	Not studied
	9♀	20	26.0(19.1-33.0) ^f	Not studied
⁶² Pullar et al.	6♂	30	31 (13-44) ^g	70(20-131) ^g
⁶³ Pullar et al.	8♂	30	30 ($\pm 6.3^c$) ^g	64 ^h ($\pm 4.3^c$) ^g
^{64,65} Rupp et al.	10♂	15-30	18 (9.7-30.3)	Not studied ⁱ
⁶⁶ Tedeschi et al.	6	10	25 (10-57.9) ^j	Not studied
⁶⁷ Vallner et al.		10 ^k	18.4	Excluded contribution ^k
		20 ^k	18.3	Excluded contribution ^k
		40 ^k	17.3	Excluded contribution ^k
		average ^l	23	Excluded contribution ^k
SINGLE-DOSE STUDY IN PATIENTS TAKING ANTIEPILEPTIC DRUGS (probably Caucasians)				
³⁴ Bun et al. ^b	Adults ^m		12 ($\pm 6^c$)	49 ($\pm 38^c$)
	Children ^m		16 ($\pm 3^c$)	15 ($\pm 2^c$)
SINGLE-DOSE STUDY IN PATIENTS WITH HEPATIC IMPAIRMENT (probably Caucasians)				
⁶⁰ Monjanel- Mouterde et al.	6 Acute hepatitis	20	47 ($\pm 18^c$) ^e	Not studied
	9 Cirrhosis	20	51 ($\pm 21^c$) ^e	Not studied
REPEATED-DOSE FOR 22 DAYS IN HEALTHY ADULT VOLUNTEERS (probably Caucasians)				
⁷⁰ Greenblatt et al.	7♂ young ⁿ	10	22.6 (11-29) ^o	48.4 (23-92) ^o
	8♀ young ⁿ	10	35.5 (24-45) ^o	71.5 (39-116) ^o
	6♂ elderly ⁿ	10	72.7 (39-106) ^o	326.0 (67-831) ^o
	6♀ elderly ⁿ	10	52.0 (20-76) ^o	68.7 (33-107) ^o

^aTerminal half-lives were calculated using noncompartmental methods.

^bHalf-lives were calculated by computer program (APIS).

^cRanges were not provided but standard deviations were described.

^dThese are elimination half-lives calculated using iterative non-linear least-squares regression techniques.

There were no differences in clearance between young ♂ and ♀ suggesting that greater half-lives in ♀ were explained by greater volume of distribution.

^eHalf-lives were calculated by linear regression analysis of the terminal parts of the log plasma concentrations versus time curves.

^fThe terminal (smallest) exponent was used to calculate the apparent half-life of elimination.

^gElimination half-life was calculated from the terminal portion of the \log_{10} serum concentration curves.

^hThe authors also studied the same healthy controls after administering 30 mg of N-desmethyloclobazam. This provided an N-desmethyloclobazam half-life of 46.5 (± 5.5) hours.

ⁱThe authors also studied three healthy controls after administering 40 mg of N-desmethyloclobazam. This provided N-desmethyloclobazam half-lives of 36-46 hours.

^jClobazam pharmacokinetics were fitted to a tri-exponential equation associated with a two-compartmental model using a non-linear regression program.

^kPatients were randomly assigned to 10-, 20- or 40-mg doses at 3 different times. Authors calculated a half-life from the terminal phase of the individual curves “after excluding the contribution of the N-desmethyloclobazam”.

^lThe authors used a two-compartment model for calculating the average.

^mThe patient sample included 17 patients (numbers of children and adults were not specified).

ⁿThe same subjects who took part in the single-dose study.⁵⁹

^oThese are wash-out half-lives.

Table 2. Clobazam therapeutic drug monitoring in cases with intoxication signs.

Reference	Serum concentration (ng/mL)		Type of study	Description
	Clobazam	N-desmethyl-clobazam		
⁴¹ Aylett et al.	Up to 100	Up to 14400	Case report ^a	Ataxia & abnormal movements
⁸³ Montenegro et al.	3900	Not described	1/251 patients ^b	Respiratory depression
⁸⁴ Naccarato et al.	Up to 423 ^c	Up to 3,302 ^c	Case report ^d	Ataxia and dysarthria
⁴² Parmeggiani et al.	190	14700	Case report ^e	Severe somnolence
⁸⁵ Pok et al.	720 ^f	36000 ^f	Overdose case ^g	Death
⁸⁶ Proença et al.	3900 ^f	Unknown ^h	Overdose case ⁱ	Death

^aA 4-year-old male developed intoxication signs after adding 15 mg/day (0.75b mg/kg/day) of clobazam to lamotrigine. The patient had repeated serum concentration measures and was interpreted as an N-desmethylclobazam poor metabolizer (PM). Clobazam was discontinued for 10 days and restarted with a dose of 7.5 mg/day.

^bIn a US epilepsy center 251 patients were treated with clobazam. One of them was described as suffering from clobazam intoxication; no data is provided on dose or co-medications.

^cThe conversion of $\mu\text{mol/L}$ to ng/mL (for clobazam $1.0 \mu\text{mol/L}=333 \text{ ng/mL}$ and for N-desmethylclobazam $1.0 \mu\text{mol/L}=349 \text{ ng/mL}$) was based on Patsalos et al.⁹

^dA 44-year-old male developed intoxication signs after adding an antiretroviral agent, etravirine, which is a CYP3A4 inducer and CYP2C19 inhibitor, to antiepileptic treatment of clobazam and valproate.

^eA 10-year-old female developed severe somnolence with increased weight and enuresis. She was initially treated with 0.6 mg/kg/day (20 mg/d) and then her dose was decreased to 0.4 mg/kg/day (12 mg/d). The patient was thought to be an N-desmethylclobazam PM, possibly a CYP2C19 PM due to the presence of a CYP2C19 inactive allele (*2) and possibly a rare undetected CYP2C19 inactive allele. Twenty days after discontinuation, she had N-desmethylclobazam concentrations of 6,500 ng/mL while clobazam was below the level of detection (<10 ng/mL). This patient appears also to be case report 2 in another article.²²

^fAccording to Proença et al.⁸⁶ there is no tissue redistribution after death; thus postmortem blood concentrations reflect well the concentrations before death.

^gA 70-year-old French woman was found dead. The contribution of other drugs was eliminated by the toxicology report.

^hUnable to quantify due to lack of standard.

ⁱA 49-year-old Caucasian Portuguese female was found dead after an overdose. She also had bronchopneumonia, possibly associated with the respiratory depression caused by clobazam. The contribution of other drugs was eliminated by the toxicology report.

Table 3. Review of articles providing clobazam concentrations: N-desmethyloclobazam/clobazam ratio

Reference	Normal	Inducers ^a	Felbamate ^b	CYP2C19 PM
	N-desmethyloclobazam/clobazam ratio			
⁴¹ Aylett et al. ^c				246
⁸⁷ Bardy et al.	4-5 ^d	20 ^d		
⁸⁸ Bun et al. ^e	4.6 (N=6) range 2.3-8.4			
⁸⁹ Contin et al. ^f	3 (N=22) None >20	13 (N=28) One >20	29 (N=16) One <20	
²² Contin et al.	8 (N=11) ^g			207.5 (N=1) ^h & 77.4 (N=1) ⁱ
²¹ Giraud et al.	3 (N=18) ^j 6 (N=4) ^j None >10			
⁷⁰ Greenblatt et al. ^k	1.5 (N=7♂young) 4.3 (N=8♀young) 13.8 (N=6♂elderly) 5.0 (N=6♀elderly)			
⁹⁰ Kosaki et al. ^l	5-10 (N=7)	10-25 (N=6)		25-35(N=3)
⁹¹ Levy et al. ^m	2.3 (N=6) range 1.5-3.1	9.4 (N=6) low dose range 5.3-16.7		
⁶¹ Ochs et al.	1.9 (N=6♂) ⁿ 2.5 (N=7♀) ⁿ			
^{64,65} Rupp et al. ^o	8 (N=10)			
⁴⁸ Sennoune et al. ^p	3 (N=10) ^q	10-13 (N=22) ^r		
⁴⁰ Seo et al. ^s	8-10 (N=38) ^t			36 (N=12) ^u

^aBoth carbamazepine and phenytoin induce many metabolic enzymes, but it is believed that they increase the N-desmethyloclobazam/clobazam ratio by inducing CYP3A4. Phenytoin may sometimes behave as a competitive inhibitor of N-desmethyloclobazam metabolism. Phenobarbital may not be an inducer of clobazam metabolism (see footnote ^r).

^bFelbamate is a CYP3A inducer and CYP2C19 inhibitor.

^cThis is an English boy. First TDM values were used in ratio calculations.

^dRatio ranges were not provided. These are Finnish children. The mean N-desmethyloclobazam/clobazam ratio was 4.2 in patients not taking other antiepileptic drugs (N= 7). The mean ratio was 5.0 in patients taking non-inducing antiepileptic drugs (sample size was not described). The mean ratio was 19.9 in patients taking inducing antiepileptic drugs (sample size is not described).

^eThese are French volunteers who received 20 mg/day for 28 days. The ratios were calculated using concentrations described for day 28. The N-desmethyloclobazam/clobazam ratio values were 2.3, 3.0, 3.1, 3.9, 6.9 and 8.4.

^fThese are Italian children and adults. The table describes mean ratios and, for the upper panel, patients who were outliers are described in the line below.

^gRatio ranges were not provided. These are Italian children or adults. Three of 11 controls were taking inducers. Eight of the controls had 2 active CYP2C19 alleles and 3 had only 1 active allele.

^hItalian child who was a CYP2C19 PM.

ⁱItalian child who appeared to be a CYP2C19 PM due to the presence of a CYP2C19 inactive allele (*2) and possibly a rare undetected CYP2C19 inactive allele. This patient also appeared to be published as an individual case report in another article.⁵⁷

^jCYP2C19 genotyping was completed in 22 French children taking valproate and clobazam. There were 18 with 2 active CYP2C19 alleles and 4 with only 1 active allele. All patients with 2 active alleles had N-desmethyloclobazam/clobazam ratios <7.5. All 4 patients with 1 active allele had N-desmethyloclobazam/clobazam ratios <10.

^kUS volunteers.

^lJapanese patients who were not CYP2C19 PMs by genotype. Normals were patients who were not CYP2C19 PMs and were not taking inducers. The serum concentrations were not trough concentrations. Ranges of the N-desmethylclobazam/clobazam ratio are provided.

^mThese are 6 US volunteers who received 20 mg/day for 29 days. A carbamazepine dose of 400 mg/day was given from day 16 to day 29. The dose and duration will not allow viewing the induction seen in patients taking clinical doses. In the 6 subjects, the baseline versus carbamazepine N-desmethylclobazam/clobazam ratios were 2.4 vs. 8.5, 1.5 vs. 5.9, 3.1 vs. 10.9, 2.9 vs. 16.7, 1.6 vs. 5.3, and 2.2 vs. 9.3.

ⁿData calculated from an article table. After 22 days on 10 mg/day clobazam, 6 US males had a mean trough clobazam concentration of 191 ng/mL and N-desmethylclobazam concentration of 368 ng/mL, providing an estimated N-desmethylclobazam/clobazam ratio of 1.9 (368/191=1.9). The article table describing 7 US females shows a mean trough clobazam concentration of 253 ng/mL and a mean trough N-desmethylclobazam concentration of 637 ng/mL providing an N-desmethylclobazam/clobazam ratio of 2.5 (637/253=2.5).

^oRatio ranges are not provided. These are Indian volunteers who received 20 mg/day of clobazam for 28 days.

^pFrench adults. The serum concentrations were not trough; the blood samples were drawn within three hours after clobazam dose intake.

^qThese include 9 patients on monotherapy with a mean ratio of 3.3 ± 2.0 . This line of the table does not include 15 patients on valproate with a mean ratio of 4.2 ± 2.5 .

^rRatio ranges are not provided. The number is based on 17 patients on carbamazepine with a mean ratio of 10.3 ± 5.3 , and 5 patients on phenytoin with a mean ratio of 12.8 ± 5.6 . There were 17 patients on phenobarbital with a mean ratio of 6.2 ± 2.3 who are not included in this line of the table.

^sJapanese adult and child patients who were genotyped. It is not clear how much the data was influenced by inducers. The serum concentrations were not trough. For each patient, 1 concentration was randomly selected from the patient's available concentrations. Blood samples were drawn within 3-5 hours after clobazam dose intake.

^tRatio ranges were not provided. The number is based on 16 patients with 2 active alleles with a mean ratio of 7.6 ± 4.6 , and 22 patients with 1 active allele with a mean ratio of 9.8 ± 7.9 .

^uRatio ranges were not provided. The number is based on 12 patients with no active alleles with a mean ratio of 35.7 ± 16.7 .

Table 4. Review of articles providing clobazam concentrations (peak or trough^a): Clobazam C/D ratio^b

Reference	Normal	Inducers ^c	Felbamate ^d	CYP2C19
	Clobazam C/D ratio			
⁴¹ Aylett et al. ^e x kg				66.7
70 kg ideal				0.96
⁸⁸ Bun et al. ^f	12.1 (N=6) range 9.8-14.6			
⁸⁹ Contin et al. x kg ^g	600 ^h (N=22)	300 ^h (N=28)	200 ^h (N=16)	
70 kg ideal	8.6	4.3	2.9	
²² Contin et al. x kg	200-1100 (N=11) ⁱ			85.3 (N=1) ^j & 370.5 (N=1) ^k
70 kg ideal	12-66			1.2 5.3
⁷⁰ Greenblatt et al. ^l	11.1 (N=7♂ young) 16.6 (N=8♀ young) 28.4 (N=6♂ elderly) 20.2 (N=6♀ elderly)			
⁹⁰ Kosaki et al. ^m x kg	<1000 (N=7)	<1800 (N=6)		<700(N=3)
70 kg ideal	<14.3	<25.7		<10
⁹¹ Levy et al. ⁿ	17.7 (N=6) range 9.9-24.6	6.8 (N=6) low dose range 4.4-11.1		
⁶¹ Ochs et al.	19.1 (N=6♂) ^o range 15.6-23.3 25.3 (N=7♀) ^o range 18.7-28.1			
⁴⁸ Sennoune et al. x kg	1030(N=9) ^p	492-497 (N=22) ^q		
70 kg ideal	14.7	7.0-7.1		

^aTable 4 includes studies with trough and peak concentrations. The study by Ochs et al.⁶¹ suggested major variations (by 48%) between clobazam trough and peak concentrations. Similarly, Bun et al.³⁴ presented clobazam C/D ratios corrected by weight at trough and peak (3 hours after clobazam dose) points on the 21st day of clobazam treatment from 6 healthy volunteers and 17 patients (6-32 years old) taking co-medications. The peak weight-corrected clobazam C/D ratio appeared to be roughly twice as high as the trough C/D ratio in both healthy volunteers and patients. Therefore, the use of either peak or trough concentrations in different studies may seriously contaminate comparisons of C/D ratios data in this table.

^bMost TDM articles use ng/mL to measure clobazam levels. When using ng/mL for concentration and mg/day for dosing, C/D ratio units are (ng × day)/(mL × mg). This is a reasonable approximation and an easy measure for clinicians. In strict pharmacological terms, it would be better to transform the clobazam concentration to μmol/L and the daily dose to μmol/day. This would make calculations more accurate but much harder for clinicians to estimate. According to Patsalos et al.⁹ 1.0 μmol/L is equivalent to 333 ng/mL for clobazam, and 1.0 μmol/L is equivalent to 349 ng/mL for N-desmethyloclobazam. This is a minor difference of 5% (349/333=1.05) between both molar transformations on N-desmethyloclobazam versus clobazam. A 5% error is made when the differences in molecular weights between N-desmethyloclobazam and clobazam are disregarded by calculating C/D ratios using ng/mL. This increases the weight of serum N-desmethyloclobazam concentrations by 5% more than would be the case if molar concentrations were used. Thus avoiding the tedious (and probably confusing for clinicians) molar transformations makes a reasonable error of only 5%. When clobazam TDM studies focus only on adults, using this (ng × day)/(mL × mg) unit for C/D ratios is reasonable. When the studies include children, there is a need to correct the dose by weight using mg/kg × day, and to make the unit for C/D ratios (ng × day×kg)/(mL × mg). Tables 4-6 use an additional way to compare children and adults by transforming weight-corrected C/D ratios in children to standardized values in a standard 70-kg individual.

^cBoth carbamazepine and phenytoin induce many metabolic enzymes but it is believed that they increase the N-desmethyloclobazam/clobazam ratio by inducing CYP3A4. Phenytoin may sometimes behave as a

competitive inhibitor of N-desmethyloclobazam metabolism. Phenobarbital may not be an inducer of clobazam metabolism (see below footnote r).

^dFelbamate is a CYP3A inducer and CYP2C19 inhibitor.

^eThis is an English boy. First TDM values were used in ratio calculations.

^fThese are French volunteers who received 20 mg/day for 28 days. The ratios were calculated using concentrations described for day 28.

^gThese are Italian children and adults.

^hCalculations were made by adding approximations taken from figures.

ⁱRatio ranges were not provided. These are Italian children or adults. Three of 11 controls were taking inducers. Eight of the controls had 2 active CYP2C19 alleles and 3 had only 1 active allele.

^jItalian child who was a CYP2C19 PM.

^kItalian child who appeared to be a CYP2C19 PM due to the presence of a CYP2C19 inactive allele (*2) and possibly a rare undetected CYP2C19 inactive allele. This patient also appeared to be published as an individual case report in another article.⁴²

^lUS volunteers.

^mJapanese patients who were not CYP2C19 PMs by genotype. Normals were patients who were not CYP2C19 PMs and were not taking inducers. The serum concentrations were not trough concentrations.

ⁿThese are 6 US volunteers who received 20 mg/day for 29 days. A carbamazepine dose of 400 mg/day was given from day 16 to day 29. The dose and duration will not allow viewing the induction seen in patients taking clinical doses.

^oData calculated from an article table. After 22 days on 10 mg/day clobazam, 6 US males provided a mean trough clobazam concentration of 191 ng/mL (range 156-233) with a clobazam C/D of 19.1 (15.6-23.3), and 7 US females provided a mean concentration of 253 ng/mL (range 187-281) with a C/D of 25.3 (18.7-28.1).

^pThese include 9 patients on monotherapy. There were 15 patients on valproate with a mean clobazam C/D ratio of 699 (ng ×kg/ml)/(mg/day) that corresponds to 9.99 (ng /ml)/(mg/day) in a hypothetical person of 70 kg, which is not included in this line of the table.

^qThese include 17 patients on carbamazepine with a mean clobazam C/D ratio of 492 (ng ×kg/ml)/(mg/day) that corresponds to 7.0 (ng /ml)/(mg /day) in a hypothetical person of 70 kg; and 5 patients on phenytoin with a mean clobazam C/D ratio of 497 (ng ×kg/ml)/(mg/day) that corresponds to 7.1 (ng /ml)/(mg/day) in a hypothetical person of 70 kg. There were 17 patients on phenobarbital with a mean clobazam C/D ratio of 373 (ng ×kg/ml)/(mg/day) that corresponds to 5.3 (ng /ml)/(mg/day) in a hypothetical person of 70 kg, which is not included in this line of the table.

Table 5. Review of articles providing clobazam concentrations: N-desmethylclobazam C/D ratio^a

Reference	Normal	Inducers ^b	Felbamate ^c	CYP2C19 PM
N-desmethylclobazam C/D ratio				
⁴¹ Aylett et al. ^d x kg				16400
70 kg ideal				234
⁸⁸ Bun et al. ^e	58.1 (N=6) range 28.1-122.1			
⁸⁹ Contin et al. ^f x kg	2000 ^g (N=22)	3000 ^g (N=28)	7000 ^g (N=16)	
70 kg ideal	28.6	42.9	100	
²² Contin et al. x kg	200-10000 (N=11) ^h			17707 (N=1) ⁱ & 28865 (N=1) ^j
70 kg ideal	2.9-143			253 409.5
⁷⁰ Greenblatt et al. ^k	16.4 (N=7♂ young) 71.5 (N=8♀ young) 393.2 (N=6♂ elderly) 101.7 (N=6♀ elderly)			
⁹⁰ Kosaki et al. ^l x kg	<4000 (N=7)	<13000 (N=6)		8000-17000(N=3)
70 kg ideal	<57.1	<185.7		114.3-242.9
⁹¹ Levy et al. ^m	42.5 (N=6) range 14.8-77	61.3 (N=6) low dose range 25.9-88.1		
⁶¹ Ochs et al.	36.8 (N=6♂) ⁿ range 26.8-63.5 63.7 (N=7♀) ⁿ range 29.0-118.6 ^o			
⁴⁸ Senoune et al. x kg	2974(N=9) ^p	5066-5830 (N=22) ^q		
70 kg ideal	42.5	72.4-82.3		

^aSee footnote b on table 4 for clarification about units.

^bBoth carbamazepine and phenytoin induce many metabolic enzymes but it is believed that they increase the N-desmethylclobazam/clobazam ratio by inducing CYP3A4. Phenytoin may sometimes behave as a competitive inhibitor of N-desmethylclobazam metabolism. Phenobarbital may not be an inducer of clobazam metabolism (see below footnote r).

^cFelbamate is a CYP3A inducer and CYP2C19 inhibitor.

^dThis is an English boy. First TDM values were used in ratio calculations.

^eThese are French volunteers who received 20 mg/day for 28 days. The ratios were calculated using concentrations described for day 28. The N-desmethylclobazam/clobazam ratio values were 2.3, 3.0, 3.1, 3.9, 6.9 and 8.4.

^fThese are Italian children and adults. This line of the table describes mean ratios.

^gCalculations were made by adding approximations taken from figures.

^hRatio ranges were not provided. These are Italian children or adults. Three of 11 controls were taking inducers. Eight of the controls had 2 active CYP2C19 alleles and 3 had only 1 active allele.

ⁱItalian child who was a CYP2C19 PM.

^jItalian child who appeared to be a CYP2C19 PM due to the presence of a CYP2C19 inactive allele (*2) and possibly a rare undetected CYP2C19 inactive allele. This patient also appeared to be published as an individual case report in another article.⁴²

^kUS volunteers.

^lJapanese patients who were not CYP2C19 PMs by genotype. Normals were patients who were not CYP2C19 PMs and were not taking inducers. The serum concentrations were not trough concentrations.

^mThese are 6 US volunteers who received 20 mg/day for 29 days. A carbamazepine dose of 400 mg/day was given from day 16 to day 29. The dose and duration will not allow viewing the induction seen in patients taking clinical doses.

ⁿData calculated from an article table that described that after 22 days on 10 mg/day clobazam, 6 US males provided a mean trough N-desmethylclobazam concentration of 368 ng/mL (range 268-635) with

an N-desmethylobazam C/D of 36.8 (26.8-63.5), and 7 US females provided a mean concentration of 637 ng/mL (range 290-1186) with a C/D of 63.7 (29.0-118.6).

^oThis high range in US female subjects may be compatible with at least one of the females being a CYP2C19 PM.

^pThese include 9 patients on monotherapy. There were 15 patients on valproate with a mean N-desmethylobazam C/D ratio of 2638 (ng ×kg/ml)/(mg/day) that corresponds to 37.7 (ng /ml)/(mg/day) in a hypothetical person of 70 kg, which is not included in this line of the table.

^qThese include 17 patients on carbamazepine with a mean N-desmethylobazam C/D ratio of 5066 (ng ×kg/ml)/(mg/day) that corresponds to 72.4 (ng /ml)/(mg /day) in a hypothetical person of 70 kg; and 5 patients on phenytoin with a mean clobazam C/D ratio of 5830 (ng ×kg/ml)/(mg/day) that corresponds to 82.3 (ng /ml)/(mg/day) in a hypothetical person of 70 kg. There were 17 patients on phenobarbital with a mean N-desmethylobazam C/D ratio of 2037 (ng ×kg/ml)/(mg/day) that corresponds to 29.1 (ng /ml)/(mg/day) in a hypothetical person of 70 kg, which is not included in this line of the table.

Table 6. Review of articles providing clobazam concentrations: Total C/D ratio^a

Reference	Normal	Inducers ^b	Felbamate ^c	CYP2C19 PM
Total (clobazam+N-desmethylclobazam) C/D ratio				
⁴¹ Aylett et al. ^d x kg 70 kg ideal				16467 235
⁸⁸ Bun et al. ^e	70.2 (N=6) range 39.2-136.7			
²² Contin et al. x kg 70 kg ideal				1792 (N=1) ^f & 29036 (N=1) ^g 254 415
⁷⁰ Greenblatt et al. ^h	27.5 (N=7♂ young) 88.1 (N=8♀ young) 421.6 (N=6♂ elderly) 121.9 (N=6♀ elderly)			
⁹¹ Levy et al. ⁱ	60.2 (N=6)	68.1 (N=6) low dose range 24.7-102		
⁶¹ Ochs et al.	55.9 (N=6♂) ^j 89.0 (N=7♀) ^{j,k}			

^aSee footnote b on table 4 for clarification about units.

^bBoth carbamazepine and phenytoin induce many metabolic enzymes but it is believed that they increase the N-desmethylclobazam/clobazam ratio by inducing CYP3A4. Phenytoin may sometimes behave as a competitive inhibitor of N-desmethylclobazam metabolism. Phenobarbital may not be an inducer of clobazam metabolism (see footnote ^r).

^cFelbamate is a CYP3A inducer and CYP2C19 inhibitor.

^dThis is an English boy. First TDM values were used in ratio calculations.

^eThese are French volunteers who received 20 mg/day for 28 days. The ratios were calculated using concentrations described for day 28.

^fItalian child who was a CYP2C19 PM.

^gItalian child who appeared to be a CYP2C19 PM due to the presence of a CYP2C19 inactive allele (*2) and possibly a rare undetected CYP2C19 inactive allele. This patient also appeared to be published as an individual case report in another article.⁴²

^hUS volunteers.

ⁱThese are six US volunteers who received 20 mg/day for 29 days. A carbamazepine dose of 400 mg/day was given from day 16 to day 29. The dose and duration will not allow viewing the induction seen in patients taking clinical doses.

^jData calculated from an article table describing that, after 22 days on 10 mg/day clobazam, 6 US males had a mean trough clobazam concentration of 191 ng/mL and a mean N-desmethylclobazam concentration of 368 ng/mL, providing a mean total C/D ratio of 55.9 [(191+368)/10=55.9]. Seven US females had a mean trough clobazam concentration of 253 ng/mL and a mean trough N-desmethylclobazam concentration of 637 ng/mL, providing a mean total C/D ratio of 89.0 [(253+637)/10=89.0].

^kThis high range in US female subjects may be compatible with at least 1 of the females being a CYP2C19 PM.

Table 7. Review of articles providing clobazam area under the curve (AUC) values.^a

Reference	Control	Ketoconazole	Omeprazole	Carbamazepine	Phenytoin
N-desmethylclobazam AUC/clobazam AUC					
⁹² Jawad et al. ^b	1.5 range 1.0-8.8			6.2 range 4.3-8.8	18.8 range 16.6-20.9
³³ Walzer et al. ^c	1.60	1.22 ^d			
³³ Walzer et al. ^e	1.31		1.55 ^f		
Clobazam AUC (µg/l)×h					
⁹² Jawad et al. ^b	14,226			5,916 ^g	5,941 ^h
³³ Walzer et al. ^c	4,360	6,432 ⁱ			
³³ Walzer et al. ^e	4,239		5,938 ^j		
N-desmethylclobazam AUC (µg/l)×h					
⁹² Jawad et al. ^b	21,227			35,241 ^k	111,413 ^l
³³ Walzer et al. ^c	6,987	7,851 ^m			
³³ Walzer et al. ^e	5,549		9,176 ⁿ		
Clobazam+N-desmethylclobazam AUC (µg/l)×h					
⁹² Jawad et al. ^b	35,453			41,157 ^o	117,355 ^p
³³ Walzer et al. ^c	11,347	14,283 ^q			
³³ Walzer et al. ^e	9,788		15,114 ^r		

^aThis AUC data from single-dose studies with different designs cannot be compared across studies, but AUC parameters from each study can be used to provide ratios reflecting drug clearance. Single-dose studies describing clobazam and N-desmethylclobazam AUCs can be used to estimate an N-desmethylclobazam AUC/clobazam AUC ratio that supplements information from the N-desmethylclobazam/clobazam ratio from TDM studies. Single-dose studies describing clobazam AUC can help to supplement information on the clobazam C/D ratio from TDM studies. Single-dose studies describing N-desmethylclobazam AUC can help to supplement information on the desmethylclobazam C/D ratio from TDM studies. And single-dose studies describing both clobazam and N-desmethylclobazam AUCs can help to supplement information on the total C/D ratios from TDM studies.

^bThis study compared clobazam after a single dose in 6 controls with 6 adult epileptic patients on stable medication for 3 months. Four of the 6 patients were taking only carbamazepine and 2 were taking both carbamazepine and phenytoin.

^cThis study in 17 patients taking 10 mg/day of clobazam provided a baseline AUC and an AUC after 400 mg/day of ketoconazole for 6 days.

^dThe ratio between ketoconazole and baseline was $1.22/1.60=0.76$ or a 24% decrease.

^eThis study in 18 patients taking 10 mg/day of clobazam provide a baseline AUC and an AUC after 40 mg/day of omeprazole for 6 days.

^fThe ratio between omeprazole and baseline was $1.55/1.31=1.18$ or an 18% increase.

^gThe ratio between carbamazepine and controls was $5916/14226=0.42$ or a 58% decrease.

^hThe ratio between phenytoin and controls was $5941/14226=0.42$ or a 58% decrease.

ⁱThe ratio between ketoconazole and baseline was $6432/4360=1.48$ or a 48% increase.

^jThe ratio between omeprazole and baseline was $5938/4239=1.40$ or a 40% increase.

^kThe ratio between carbamazepine and controls was $35241/21227=1.66$ or a 66% increase.

^lThe ratio between phenytoin and controls was $111413/21227=5.24$ or a 424% increase

^mThe ratio between ketoconazole and baseline was $7851/6987=1.12$ or a 12% increase.

ⁿThe ratio between omeprazole and baseline was $9176/5549=1.65$ or a 65% increase.

^oThe ratio between carbamazepine and controls was $41157/35453=1.16$ or a 16% increase.

^pThe ratio between phenytoin and controls was $117355/35453=3.31$ or a 231% increase.

^qThe ratio between ketoconazole and baseline was $14283/11347=1.26$ or a 26% increase.

^rThe ratio between omeprazole and baseline was $15114/9788=1.54$ or a 54% increase.