Therapeutic Drug Monitoring of Clobazam and Its Metabolite—Impact of Age and Comedication on Pharmacokinetic Variability

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Background: Clobazam (CLB) has been used as an antiepileptic drug for several decades. There is still insufficient data regarding its pharmacokinetic variability in clinical practice. The purpose of this study was to investigate pharmacokinetic variability of CLB with emphasis on the impact of age and comedication in patients with epilepsy.

Methods: Serum concentration measurements of CLB and its metabolite N-desmethylclobazam (NCLB), as well as demographic and clinical data were retrieved from the routine therapeutic drug monitoring service at the National Center for Epilepsy, Norway, 2009–2013. NCLB/CLB and total (CLB + NCLB), CLB and NCLB concentration/dose (C/D) ratios were calculated.

Results: 550 patients (296 women/254 men), average age 27 years (range 1–86), were included. The interindividual pharmacokinetic variability was extensive, as illustrated by a 100-fold variability in serum concentration compared with dose (total C/D ratio 0.03–3.29 µmol L⁻¹•mg⁻¹). The CLB C/D ratio was 36% lower in young children (2–9 years) than in adults (18–64 years), reflecting a higher clearance. In patients receiving phenytoin, felbamate, stiripentol, oxcarbazepine or eslicarbazepine acetate, valproate, phenobarbital, zonisamide or carbamazepine one or more of the calculated ratios were significantly different from that in patients receiving no or neutral comedications. The mean values for the different groups were in the order of 20%–230% of C/D ratios in the neutral group and 200%–950% of the NCLB/CLB ratio.

Conclusions: The pharmacokinetic variability of CLB and its metabolite NCLB in clinical practice is extensive, and is influenced by drug–drug interactions, age, and pharmacogenetics. Therapeutic drug monitoring of CLB and NCLB is therefore valuable in patient management.

Key Words: antiepileptic drugs, clobazam, epilepsy, N-desmethylclobazam, therapeutic drug monitoring (TDM)

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INTRODUCTION

Clobazam (CLB) is a 1,5-benzodiazepine acting as a GABAA agonist, potentiating inhibitory neurotransmission.¹ It is recently approved in the US (2011) for use in Lennox-Gastaut syndrome, but with a long tradition of use in Europe in epilepsy and anxiety. In Norway CLB is not licensed, but has been used as an antiepileptic drug (AED) for several decades. Based on the Norwegian Prescription Database, which provides data from all Norwegian pharmacies, on average 664 patients have been prescribed the drug each year in Norway in the period 2009–2014.² CLB and N-desmethylclobazam (NCLB) are metabolized through CYP3A4 and CYP2C19 (Fig. 1). This makes CLB prone to both drug–drug interactions and to pharmacogenetic variability. Patients with epilepsy need individualized treatment, and the implementation of therapeutic drug monitoring (TDM) may therefore be useful to correct for pharmacokinetic variability.³⁶ CLB is used in many “difficult-to-treat” epilepsies, including Lennox-Gastaut syndrome.⁷⁻⁹ These patients may use up to 5 concomitant AEDs, and 20%–30% also use other psychotropic drugs that might be involved in interactions.¹⁰⁻¹² A number of other AEDs have the potential to affect the metabolism of CLB,¹³ but the resulting effects on serum levels of CLB are not fully understood. Some patients, especially those of Asian ancestry (20%–25%), may be poor metabolizers (PM) in the last metabolic step through CYP2C19, which can result in an accumulation of the metabolite and potential for adverse effects.¹⁴⁻¹⁵ Genotypes resulting in increased enzyme activity, such as CYP3A5*1 and CYP2C19*17, could be assumed to increase the capacity of the first and second step in CLB metabolism. Whether this leads to decreased levels of CLB and NCLB, respectively, has not been studied.

There is incomplete knowledge about the pharmacokinetic variability of CLB in clinical practice, and a recent review about the use of TDM for CLB called for further research in this area.⁸ The purpose of this study was to investigate pharmacokinetic variability of CLB in clinical practice with emphasis on the impact of comedication and age in patients with epilepsy.
Clobazam

\[ \text{CYP3A4, CYP2C19, CYP2B6} \]

N-desmethyl-clobazam

\[ \text{CYP2C19} \]

Inactive metabolites

**FIGURE 1.** Metabolism of CLB. The figure depicts the main pathway for metabolism of CLB and NCLB. CLB is mainly metabolized to the active metabolite NCLB by CYP3A4, and to a lesser extent by CYP2C19 and CYP2B6. NCLB is further metabolized by CYP2C19 to inactive metabolites.

**MATERIAL AND METHODS**

**Study Material**

Serum concentration measurement of CLB and NCLB, as well as demographic and clinical data, including the use of other AEDs, were retrieved retrospectively from a routine TDM database at the National Center for Epilepsy in Norway, from the period 2009 to 2013. All blood samples were drawn drug fasting in the morning. The most recent measurement, at assumed steady-state conditions, was included for every patient, and data regarding sex, age, weight, utilization of AEDs, dose and serum concentration were collected. Inclusion criteria were at least 1 serum concentration measurement of CLB and NCLB during 2009–2013 and that information regarding dosage was available. Patients with nonfasting blood samples were excluded (n = 1). All data were anonymized before further processing. The study was approved by the Regional Committee for Medical and Health Research Ethics, Norway.

**CLB and NCLB Analysis**

Measurements were performed using high-pressure liquid chromatography with ultraviolet detection (Ultimate 3000 HPLC-UV). A ZORBAX Eclipse Plus C18 (4.6 × 30 mm, 3.5-micron) column was used, and the mobile phase consisted of 71/29% phosphate buffer/acetonitrile. The measuring range for CLB and NCLB was 0.03–3.0 and 3.0–30.0 μmol/L, respectively. The calibration curves were linear with \( R^2 = 0.99 \). Flunitrazepam was used as internal standard. 100 μL serum-standard/control, 50 μL internal standard, and 5 mL ethylacetat/hexan solution (1 + 4) were mixed well for 10 minutes, centrifuged for 5 minutes, the upper layer was transferred and evaporated at 60°C with N\(_2\) and dissolved in 300 μL mobile phase. The injection volume was 20 μL, flow 1.0 mL/min, and CLB and NCLB were detected at 230 nm. The accuracy variation coefficient for the method was ≤10%.

**Age Groups**

The patients were divided into age groups for relevant pharmacokinetic comparisons: <2, 2–9, 10–17, 18–64 and >64 years.\(^6,16\)

**Comedication**

Information on comedication was retrieved from the accompanying request form and/or concurrent serum concentration measurements. To examine the effect of comedication on the pharmacokinetics of CLB, the patients were divided into groups according to coprescribed drugs. Based on published data,\(^8,12,13,16–23\) we decided to further examine patients receiving carbamazepine, felbamate, oxcarbazepine or eslicarbazepine acetate, phenobarbital, phenytoin, stiripentol, sulthiame, valproate or zonisamide, and grouped them accordingly. Patients in each of these groups could also receive other medications (including AEDs from the other groups). A neutral group served as the reference population. This group included patients receiving monotherapy or coprescribed drugs (AEDs or non-AEDs) not documented to be strong inducers/inhibitors of CLB metabolism (based on published data,\(^8,12,13,16\) and Summaries of Product Characteristics). An overview of drugs included and excluded in the groups is presented in Table 1.

**Calculations**

Four ratios that may help interpret CLB concentrations were calculated: (1) NCLB/CLB, (2) total (CLB + NCLB) concentration/dose (C/D) ratio, (3) CLB C/D ratio, and (4) NCLB C/D ratio. The C/D ratios were used as expressions for pharmacokinetic variability. The C/D ratio is inversely proportional to clearance based on the following equation: CL/F (mL·kg\(^{-1}\)·min\(^{-1}\)) = daily dose (mg/kg)/\( C_{ss} \) (mg/L × 1000) × 1440 as in a previous publication,\(^6\) where oral clearance is CL/F; CL is clearance, F is oral bioavailability, \( C_{ss} \) is the serum concentration at steady-state, and 1440 is the number of minutes per 24 hours. Daily dose of CLB was adjusted for a 70 kg individual in patients <18 years, to enable comparisons with adults (where weight was most often not listed). Patients <18 years of age where there was no information on weight were excluded from C/D ratio calculations. The ratios were compared with the neutral group for each group of co-administered drugs.

Serum concentration measurements, ratios, and doses are presented as mean (median) values, and range is used to express variability.

The measured serum concentrations are given as μmol/L. The conversion factor (F) to mg/L is 3.33 for CLB and 3.49 for NCLB (μmol/L = F × mg/L).\(^5\)

For statistical analyses, IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL) was used. One-way Anova post hoc test by Dunnett was used to compare each age group (as defined above) with the group of adults aged 18–64 years, because these were considered the most relevant comparisons.

Students two-sided t test with unequal variance was used to calculate significant differences between each concomitant drug ratio as compared with the neutral group. A significance level of \( P < 0.05 \) was chosen for all analyses.
RESULTS

Patient Characteristics and the Utilization of AEDs

In total, 550 patients (296 women/254 men) were included in the study. Details on age distribution and information on indication for TDM are shown in Table 2. In 49% (n = 271) of the cases, patients were from the National Center for Epilepsy, whereas the remaining were from hospitals and medical practices throughout the whole country. For 13% (n = 71) of patients, there were no information/serum measurements of other AEDs. In the others, CLB was combined with a wide range and number of AEDs. As many as 48% (263) of patients used 3 or more AEDs, pointing to a difficult-to-treat population with refractory epilepsy.

Serum Concentrations of CLB, NCLB, and Ratios

Prescribed doses, serum concentrations of CLB and NCLB, and calculated ratios for different age groups are presented in Table 3. The CLB serum concentration was between 0.1–1.0 μmol/L in 77% of the patients (n = 426), whereas 63% (n = 347) of the patients also had NCLB concentrations between 1.0–10.0 μmol/L, i.e. both concentrations within the suggested reference range.5

The pharmacokinetic variability was extensive for both CLB and NCLB, as demonstrated by more than 100-fold variability in the C/D ratios of the 2 substances. Figure 2A–D depicts the prescribed dose and corresponding serum concentration of CLB and NCLB in adult patients (>18 years) and for patients <18 years of age (dose adjusted for 70 kg individuals). In the overall material, median (mean) NCLB/CLB ratio was 11.7 (5.8). The NCLB/CLB ratio was >10 in 80 patients (40 women/40 men), and >25 in 46 patients (30 women/16 men).

To elucidate the impact of pharmacogenetic variability, 3 patients known to be CYP2C19 PMs are presented: The NCLB/CLB ratios were 28, 55, and 112. Patient 1 used oxcarbazepine and lamotrigine, patient 2 no other AEDs, and patient 3 used zonisamide in addition to CLB. C/D ratios were available for patient 1 and 3 (patient 2 was under 18 years of age, and no information on weight was provided): Total C/D ratios were 3.29 and 1.68, CLB C/D ratios 0.11 and 0.01, and NCLB ratios 3.17 and 1.66 μmol·L⁻¹·mg⁻¹.

TABLE 1. Patients Grouped According to Comedication

| Group                        | N Total (N When Patients <18 Years of Age Without Information on Weight Are Excluded) | Included Drugs | Excluded Drugs/Conditions |
|------------------------------|------------------------------------------------------------------------------------|----------------|---------------------------|
| Neutral                      | 170 (132)                                                                          | AEDs: Clonazepam, diazepam, ethosuximide, gabapentin, lactosamide, lamotrigine, levetiracetam, nitrazepam, perampanel, pregabalin, retigabine, tiagabine, vigabatrin Non-AEDs: Alimemazine, cetirizin, metylphenidate, zuelopenthixol | AEDs: Carbamazepine, eslicarbazepine acetate, felbamate, liscantine, oxcarbazepine, phenobarbital, phenytoin, rufinamide, stiripentol, sulthiame, topiramate, valproate, zonisamide Non-AEDs: Erythromycin, esomeprazole, fluoxetine, onemprazole 1 pregnant woman, 1 CYP2C19 PM |
| Stripentol                   | 13 (8)                                                                            | All other drugs |                           |
| Phenytoin                    | 16 (14)                                                                           | All other drugs |                           |
| Felbamate                    | 6 (5)                                                                             | All other drugs |                           |
| Valproate                    | 172 (134)                                                                         | All other drugs |                           |
| Carbamazepine                | 51 (47)                                                                           | All other drugs |                           |
| Phenobarbital                | 11 (8)                                                                            | All other drugs |                           |
| Sulthiame                    | 8 (5)                                                                             | All other drugs |                           |
| Oxcarbazepine/eslicarbazepine acetate | 69 (62)                        | All other drugs | 1 known CYP2C19 PM |
| Zonisamide                   | 47 (40)                                                                           | All other drugs | 1 pregnant woman |

Included and excluded drugs according to their potential to affect the serum concentration of CLB or NCLB based on Refs. 8,12,13,16–23. PM, Poor metabolizer.

TABLE 2. Age Distribution and Indication for TDM

| Included Patients n = 550: 296 Women/254 Men |
|---------------------------------------------|
| Age distribution: Average 27 years (1–86)    |
| <2 yrs n = 1 (0 with weight)                 |
| 2–9 yrs n = 80 (37 with weight)              |
| 10–17 yrs n = 117 (47 with weight)           |
| 18–64 yrs n = 341                            |
| >64 yrs n = 11                               |
| Indication for TDM                          |
| Routine control 26.9% (n = 148)              |
| Dosage adjustments 6.7% (n = 37)             |
| Therapy failure 6.2% (n = 34)                |
| Adverse effects 0.7% (n = 4)                 |
| Acute intoxications 0.2% (n = 1)             |
| Not listed 59.3% (n = 326)                   |
TABLE 3. CLB Dose, Serum Concentrations and Calculations

| Age   | Number of Patients | Dose, mg*, Mean [Median], (Range) | CLB Concentration, μmol/L, Mean [Median], (Range), Reference Range 0.1–1.0 μmol/L† | NCLB Concentration, μmol/L, Mean [Median], (Range), Reference Range 1.0–10.0 μmol/L‡ |
|-------|--------------------|----------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| All   | 550                | 26.0 [12.2] (1.56–103.7)         | 0.68 [0.58] (0.03–2.62)                                                          | 5.5 [3.5] (0.3–57.4)                                                               |
| 2–9   | 80 (37 with weight)| 35.1 [30.2] (1.6–103.7)         | 0.57 [0.48] (0.06–1.65)                                                          | 5.9 [3.5] (0.6–57.4)                                                               |
| 10–17 | 117 (47 with weight)| 23.6 [21.2] (4.3–53.0)        | 0.69 [0.58] (0.03–2.18)                                                          | 5.6 [2.8] (0.3–56.7)                                                               |
| 18–64 | 341                | 21.2 [20] (1–50)                | 0.71 [0.60] (0.03–2.62)                                                          | 5.5 [3.9] (0.3–41.6)                                                               |
| >64   | 11                 | 14.5 [10] (5–40)                | 0.59 [0.55] (0.03–1.66)                                                          | 4.2 [2.6] (0.8–16.8)                                                               |

The clobazam C/D ratio mainly reflects CYP3A4 activity, whereas the other ratios are influenced by both CYP3A4 and CYP2C19 activity.³

*Dose is calculated as mg/70 kg for patients <18 years of age. Weight adjusted doses (70 kg) for patients <18 years of age are used in calculating C/D ratios, and patients <18 years of age without information on weight excluded form these calculations.

†Reference ranges from Patsalos et al.⁴

‡Significantly lower than in 18–64 years age group (P < 0.001).

The Impact of Age
Table 3 compares the NCLB/CLB and C/D ratios in the different age groups, irrespective of comedication. CLB C/D ratio was 36% lower in young children (2–9 years) than in adults (18–64 years). There were no other significant differences in the ratios between the groups.

The Impact of Comedication
The “neutral” group contained 171 patients. Table 1 lists coprescribed medications causing patients to be excluded from this group and medications permitted. Three patients who were known to be CYP2C19 pm, and 2 patients who were known to be pregnant, were excluded from further analysis, so that these conditions would not influence the comparisons.

Figure 3A, B depicts the percentage of the mean value for ratios in the neutral versus other groups of drugs. As depicted, the coadministration of several relevant AEDs influenced the various ratios: The mean NCLB/CLB ratio was significantly increased compared with the neutral group in patients receiving stiripentol, phenytoin, carbamazepine, phenobarbital, oxcarbazepine/eslicarbazepine acetate, and zonisamide (200%–950% of the mean in the neutral group). For groups of patients receiving stiripentol, felbamate, phenytoin and zonisamide, there was a high mean NCLB (130%–230% of mean in neutral group) and/or mean total C/D ratio (160%–200% of neutral group). Patients receiving phenytoin, valproate, carbamazepine and phenobarbital had lower CLB C/D ratios than those in the neutral group (20%–70% of mean in neutral group).

DISCUSSION
The pharmacokinetic variability of CLB was extensive. CLB C/D ratio was lower in children than in adults, and several coadministered medications seem to affect the metabolism of CLB, and some to a large extent, which will be discussed in detail.

Serum Concentrations/Ratios
Extensive pharmacokinetic variability of CLB in clinical practice—both overall, and within different age groups has been demonstrated in the present study. CLB is rapidly and extensively absorbed after oral administration, and the bioavailability of CLB is thus regarded as a constant. The CLB C/D ratio mainly reflects CYP3A4 activity, whereas the other ratios are all influenced by both CYP3A4 and CYP2C19 activity.⁵ A recent review suggested to explore whether the total C/D ratio is a useful measure of CLB clearance ability.⁶ In the present study, this ratio does not show the magnitude of all interactions with other AEDs; in fact none of the 4 ratios alone reflected all relevant drug–drug interactions. This is in agreement with the fact that the ratios reflect different aspects of CLB clearance, as detailed above. Furthermore, although there is agreement that NCLB has antiepileptic activity, it is not clear how much of the clinical activity of CLB is attributable to this metabolite.⁷ Relative potency of 1/5 to 1/1 has been suggested based on animal and in vitro data but remains to be confirmed in humans in clinical practice.⁵,²⁴ This makes it difficult to evaluate the value of each C/D ratio for research purposes and when evaluating patients with serum measurements outside the suggested reference range(s). The question should be further studied by combining pharmacokinetic with clinical data on effect and tolerability. In clinical practice, the NCLB/CLB ratio is a useful measure, and is frequently used in our own laboratory to distinguish high serum levels due to excessive dose from those due to interactions or pharmacogenetics.
Impact of Age

Because of age-related changes in physiological function (kidney and liver) and alterations in blood flow, clearance of many AEDs is increased in children and decreased in the elderly. The C/D ratios can thus be expected to be lower in children, reflecting a higher clearance. In the present study, this was only demonstrated for the CLB C/D ratio. It is important to note, however, that the results may be influenced by differences in comedications between age groups. The neutral comedication group only contained a total of 26 children 2–17 years with information on weight-adjusted doses, and could thus not be used to make meaningful comparisons of the ratios.

It has previously been suggested that both CLB and NCLB C/D ratios are lower in children, reflecting higher clearance. Some mechanisms thought to lead to increased drug clearance in children (such as increased blood flow) would affect both metabolic steps equally. Our finding that only the CLB C/D ratio was significantly lower in young children seems contradictory to this. However, it has been indicated that in young children higher weight-corrected doses compared with adults are needed for drugs eliminated by CYP3A4, but not for drugs metabolized by CYP2C19. For CLB, it has been suggested that no age related dose (mg/kg) is required for children 2 years of age, because of the increase in active metabolite.

As a limited number of patients ≥64 years of age (n = 11) were included in the study, it is not possible to draw any firm conclusions as to the impact of advancing age on CLB pharmacokinetics.

Impact of Comedication

A number of AEDs have previously been reported to influence serum concentrations of CLB/NCLB, and our finding of several significant interactions is in agreement with this. However, authors of 2 recent studies concluded that there were no clinically relevant drug–drug interactions with selected AEDs, based on a pharmacokinetic modeling approach with grouped comedication. However, the methodology of studies on interactions between CLB and other drugs varies to an extensive degree. Important factors to consider include sampling time, drugs included in the comparison.

FIGURE 2. A-D, Doses and serum concentrations of CLB and NCLB. The figure depicts serum concentrations of CLB (A and C) or NCLB (B and D) plotted against prescribed dose (adjusted for 70 kg individuals in patients <18 years of age, C and D). D, *Child 13.5 kg receiving clobazam 20 mg/d.
group, and CYP2C19 polymorphisms in the studied ethnic groups.

In the present study, the comediations that seemed to affect the metabolism of CLB tended to increase NCLB/CLB ratios, total and NCLB C/D ratios, and decrease CLB C/D ratios, pointing to induction of CYP3A4 and, even more pronounced, inhibition of CYP2C19 as the predominant mechanisms of significant interactions. Carbamazepine, phenobarbital, and phenytoin are known to induce the activity of CYP3A4 (and phenytoin thought to possibly inhibit CYP2C19) whereas felbamate, oxcarbazepine, and eslicarbazepine acetate may inhibit CYP2C19 and induce CYP3A4. This is consistent with the demonstrated effects on CLB pharmacokinetics. The effects of valproate and zonisamide on the CYP enzymes are less clear. In our study, the total and NCLB C/D-ratios and the NCLB/CLB ratio were significantly increased compared with the neutral group for patients receiving zonisamide, whereas the CLB C/D-ratio was reduced in patients taking valproate. It is

![Diagram](image)

**FIGURE 3.** Impact of comedication on the C/D ratios (A) and on the NCLB/CLB ratio (B). Figure A depicts the % of mean C/D ratios in the neutral group for each coprescribed drug. Mean total C/D ratio = 0.29, CLB C/D ratio = 0.047, NCLB C/D ratio = 0.24 in neutral group (n = 132). Figure B depicts the % of the mean NCLB/CLB ratio in the neutral group for each coprescribed drug. Mean NCLB/CLB ratio in the neutral group = 7.23 (n = 171). *Statistically different from neutral group. Ox-/eslicarbazepine = oxcarbazepine or eslicarbazepine acetate.
possible that the observed changes are related to effects on CYP2C19 and/or 3A4. Valproate has been demonstrated in vitro to upregulate CYP3A4, and a weak inhibitory effect on CYP2C19 has been shown for zonisamide in vitro. More data are required for any conclusions to be drawn on the mechanisms behind the interaction that has been observed with CLB.

Some patients in each group also received several other drugs, and it cannot be assured that all coadministered medications were listed on the request form for all patients. Thus, the exact magnitude of change for each drug should be interpreted with caution. The results show, however, that a number of drug combinations have the potential to affect the pharmacokinetics of CLB. In these patients, serum concentration measurements of both CLB and NCLB in addition to a clinical evaluation of effect and tolerability would be valuable as a basis for the consideration of possible dosage adjustments.

Methodological Considerations

A substantial number of the patients prescribed CLB in Norway are monitored through our TDM service, which is the only laboratory in the country offering this analysis. In contrast to other studies where a limited group of patients or a single AED is studied, the present work reflects the complexity of clinical practice, and enables different age groups and the influence of complex AED polytherapy to be assessed. However, some important limitations need to be considered. The established practice is a standardized sampling time, drug fasting before the morning dose at steady state, but it cannot be assured that this is complied with at all times. Because of the long half-life of NCLB, it may take more than 3 weeks to reach steady state, and it is therefore possible that some samples have been collected before steady state of NCLB is reached. Because this could be the case in all the compared groups, it is unlikely that this would have significant impact on the results of the study. Poor adherence cannot be controlled for in a naturalistic setting. Incomplete data provided on the TDM request forms may result in lack of information on concomitantly used AEDs or other drugs for some patients. When examining the effect of comedication, the use of other interacting medications in each drug group (other than in the neutral group) can have affected the results. However, because 48% of the included patients used 3 or more AEDs, “cleaning” these groups would exclude a large number of patients, and the grouping presented (Table 1) would better reflect clinical practice. Owing to the limited number of patients using some drugs, lack of statistically significant changes does not rule out relevant effects. Because the laboratory database and not medical records was used, the serum concentration measurements could not be matched with seizure control, and the indications for TDM were often lacking.

CONCLUSIONS

The pharmacokinetic variability of CLB and its metabolite NCLB in clinical practice is extensive, and is influenced by drug-drug interactions, age, and pharmacogenetics. Multiple relevant AEDs used in combination with CLB affects the pharmacokinetics of CLB and NCLB. TDM of CLB and NCLB is therefore valuable in patient management.

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