

Reference ranges for antiepileptic drugs revisited: a practical approach to establish national guidelines

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Background and objective: Laboratories sometimes use different reference ranges for the same antiepileptic drug (AED), particularly for new and poorly investigated drugs. This may contribute to misunderstandings, concerns or inappropriate dose changes, which in turn may affect therapeutic effect, drug safety or treatment adherence. Therefore, the Norwegian Association of Clinical Pharmacology wished to update and harmonize the reference ranges for AEDs and establish national guidelines for Norway.

Methods: A working group collected information on the reference ranges used by Norwegian laboratories for all commonly used AEDs. These reference ranges were compared to recent recommendations by the International League Against Epilepsy, current literature, applicable clinical studies, reference ranges used by leading Northern European epilepsy centers outside of Norway, and routine data derived from Norwegian laboratory databases.

Results: Reference ranges varied between laboratories for four of 23 available AEDs (lamotrigine, valproate, eslicarbazepine and oxcarbazepine). For four AEDs (brivaracetam, perampamel, stiripentol and sulthiame), reference ranges had not previously been established. In total, 13 reference ranges were either harmonized, updated or newly established. No changes were applied to the remaining 10 AEDs.

Conclusion: Updated and harmonized reference ranges are now available for 22 of the 23 AEDs available in Norway. The exception is vigabatrin (reference range not applicable). Revision of reference ranges is an important part of pharmacovigilance of AEDs and must be a continuous process based on current literature and clinical experience.

Keywords: antiepileptic drug, serum concentration, reference range, therapeutic drug monitoring

Introduction

The use of antiepileptic drugs (AEDs) has been constantly increasing over many years, and the major part of this growth can be ascribed to psychiatric disorders and pain treatment.¹⁻³ In 2016, there were 127,138 registered users of AEDs in the records of the Norwegian Institute of Public Health, corresponding to 24 users per 1,000 inhabitants.³

Due to unfavorable pharmacokinetic properties, marked drug interaction potential and narrow therapeutic windows, therapeutic drug monitoring (TDM) of AEDs has traditionally been used to support and optimize epilepsy treatment.^{4,5} In Norway, TDM has been used as a part of the comprehensive care approach in epilepsy for 50 years.⁴ Reference ranges for first-generation AEDs (ie, introduced until 1984) are well established and almost uniform worldwide.⁵

In general, reference ranges for AEDs are as poorly documented as reference ranges for any medical drug. While there are some studies that have examined the

correlation between dose and clinical effect of AEDs, studies that examine the correlation between serum concentration and clinical effect are scarce. Fortunately, almost all AEDs exhibit linear pharmacokinetics, meaning that their dose correlates proportionally with their serum concentration. Moreover, many AEDs have been in use for 30 years or longer, and clinical experience has led to broadly accepted reference ranges, even if they have not been studied systematically. Where such clinical data or experience is lacking, preliminary reference ranges may be calculated from concentration/dose ratios derived from Phase I and II studies and doses used in Phase III studies. Reference ranges may also be derived from routine data, for example, the central 90% or 95% of accumulated routine serum concentration measurements, although this method is less reliable for various reasons.⁶

Since 1989, 15 new or second-generation AEDs have been introduced. For the oldest among them (eg, lamotrigine), reference ranges may be regarded as equally well established as for the first-generation AEDs. For the more recent ones, however, there is a general paucity of data. The Commission on Antiepileptic drugs of the International League Against Epilepsy (ILAE) has issued recommendations for TDM during drug development.⁷ Yet, even if TDM may be used during clinical studies of new AEDs, serum concentrations collected in such studies are only rarely published. Thus, clinical data that could form an appropriate basis to define reference ranges are usually not available until years of clinical experience and routine measurements have elapsed. Consequently, reference ranges used by laboratories and in scientific publications may differ.

The Norwegian Association of Clinical Pharmacology launched in February 2015 a web-portal for all pharmacologic and toxicologic analyses that are available in Norway (The Pharmacology Portal).⁸ One of the goals is the nationwide harmonization of reference ranges used by the laboratories represented. A working group was established with the task to update and harmonize reference ranges for AEDs. This paper describes the workflow and the results of this process.

Methods

Data collection

The working group started the harmonization process by gathering information on AED reference ranges used by the largest laboratories in Norway. The data were collected from The Pharmacology Portal, from the laboratories' official websites and from direct contact with the laboratories.

The standard practice for TDM of AEDs in Norway is to use drug-fasting blood samples (ie, 12–24 hours after the last dose) taken at steady state. Accordingly, reference ranges are

based on values from such samples. This ensures that serum concentration measurements and procedures are comparable in all parts of the country.

Evaluation of the reference ranges

Current reference ranges as shown in Table 1 were compared with guidelines for TDM of AEDs as proposed by the ILAE in 2008.⁵ Because this publication contains official ILAE recommendations, it was used as the main reference. Since 2008, several new AEDs have entered the market. A more recent review article that includes most of these new AEDs was used as another main reference.⁹ Additionally, other relevant primary and secondary literature was used (referenced in the Results section) following a systematic literature search in PubMed, with search terms including “antiepileptic drugs”, “concentration”, “reference range” and “therapeutic drug monitoring”.

Where the literature was inconclusive and where we found considerable differences between established/recommended reference ranges and the existing reference ranges in Norway, additional data were obtained from the routine TDM databases at St Olavs University Hospital (Trondheim), Haukeland University Hospital (Bergen), Oslo University Hospital (National Center for Epilepsy; Ullevål) and from the Filadelfia Epilepsy Hospital in Dianalund, Denmark. This included both published and unpublished data as well as personal communications. We also used information on reference ranges used by the laboratories of two leading German epilepsy centers, Bielefeld-Bethel and Kehl-Kork.

We then performed an overall assessment and evaluation of the available information for each individual AED, with emphasis on the degree of clinical evidence. Clinical studies on the correlation between dose or serum concentration and clinical effect were ranked highest, while retrospective, database-derived reference ranges were ranked lowest. The overall assessment also considered Scandinavian/Northern European treatment traditions and the fact that there is close collaboration and professional exchange between the Scandinavian countries. Care was taken to ensure that only data in accordance with Norwegian standards were used, that is, values from blood samples taken drug fasting and at steady state. All sources of information are referenced in detail for each AED.

Results and discussion

General

The Board of the Norwegian Association of Clinical Pharmacology approved the final report submitted by the

Table 1 Former and new reference ranges, given in molar units and mass units^a

Antiepileptic drug	Former reference range ^b		New reference range		Action performed
	μmol/L	mg/L	μmol/L	mg/L	
Brivaracetam	NA	NA	1–10	0.2–2	Newly established
Carbamazepine	15–45	4–11	15–45	4–11	None
Free carbamazepine	20%–30%				None
Carbamazepine-10,11-epoxide ^c	5%–15%				
Clobazam ^d	0.1–1	0.03–0.3	0.1–1	0.03–0.3	None
N-desmethyloclobazam ^d	1–10	0.3–3	1–10	0.3–3	
Clonazepam ^d	0.06–0.22	0.019–0.069	0.04–0.12	0.013–0.038	Updated
Eslicarbazepine	30–100 50–140 10–100 45–140	8–26 13–36 3–26 12–36	12–100	3–26	Harmonized and updated
Ethosuximide	300–600	42–85	280–700	39–99	Updated
Felbamate	125–250	30–60	125–250	30–60	None
Gabapentin	20–120	3–21	20–120	3–21	None
Lacosamide	10–40	3–10	10–40	3–10	None
Lamotrigine	10–50 10–60	3–13 3–15	10–50	3–13	Harmonized
Levetiracetam	30–240	5–41	30–240	5–41	None
Oxcarbazepine ^e	45–140 50–140	12–36 13–36	12–140	3–36	Harmonized and updated
Perampanel	NA	NA	0.25–2.85	0.1–1	Newly established
Phenobarbital	50–130	12–30	50–130	12–30	None
Phenytoin	40–80	10–20	40–80	10–20	None
Free phenytoin	≤10%				
Pregabalin	10–30	2–5	10–35	2–6	Updated
Rufinamide	20–130	5–31	15–130	4–31	Updated
Stiripentol	NA	NA	15–95	4–22	Newly established
Sulthiame	NA	NA	5–35	2–10	Newly established
Topiramate	15–60	5–20	6–30	2–10	Updated
Valproate	250/300–600/700	36/43–87/101	300–700	43–101	Harmonized
Free valproate	≤10%				
Vigabatrin ^f	NA	NA	NA	NA	None
Zonisamide	45–180	10–38	45–180	10–38	None

Notes: All serum concentrations apply to blood samples taken in drug-fasting and in pharmacokinetic steady state. Decimals rounded to nearest whole number except clobazam and perampanel. ^aTraditionally, serum concentrations of AEDs are given either in micrograms (μg/mL), milligrams (mg/L) or in micromoles (μmol/L). Clonazepam is usually given in nanograms (ng/mL) or nanomoles (nmol/L). Clonazepam has a minor role as an AED and is mostly used for psychiatric indications. As concentrations of most psychotropic drugs are given in ng/mL or nmol/L, we suggest that clonazepam concentrations continue to be stated in ng/mL or nmol/L. ^bFormer reference ranges were gathered from Norwegian laboratories using The Pharmacology Portal (www.farmakologiportalen.no).¹⁰ ^cConcentrations of carbamazepine-10,11-epoxide are usually not included in the reference range. ^dUsually stated in either nmol/L, μg/L or ng/mL. ^eReference range applies to the active metabolite licarbazepine (formerly called monohydroxy derivative, MHD). ^fVigabatrin is an irreversible enzyme inhibitor, and thus there is no direct correlation between serum concentration and effect.

Abbreviations: AED, antiepileptic drug; NA, not applicable.

working group. The new reference ranges are now officially acknowledged in Norway and The Pharmacology Portal has been updated.¹⁰ The medical community was informed through the Journal of the Norwegian Medical Association.¹¹

For most AEDs, the reference ranges used by Norwegian laboratories were either identical or similar. For some AEDs, considerable differences were found, most pronounced for eslicarbazepine and valproate (Table 1). Measurement of

serum concentrations was available for a total of 18 out of 23 AEDs. Some analyses are currently under development; they were, therefore, included in this work.

Most reference ranges were suggested to be kept unchanged, or with minor adjustments only. For some AEDs, however, more significant changes were recommended. This is accounted for below. An overview of old and new updated reference ranges is given in Table 1. Note that all reference

ranges are based on drug-fasting serum concentrations at pharmacokinetic steady state.

Brivaracetam

This is the most recently marketed AED. A method for measuring serum concentrations is currently under development at one of the laboratories represented in this paper. A reference range of 2.4–4.3 $\mu\text{mol/L}$ (0.5–0.9 mg/L) has recently been suggested.¹² Recommended daily doses are 50–200 mg. Postmarketing studies show that doses above 200 mg/d may be safely used in epilepsy and status epilepticus.^{13–15} Pharmacokinetic data suggest that a daily dose of 2×50 mg will result in an average steady-state serum concentration of about 3.3–3.8 $\mu\text{mol/L}$ (0.7–0.8 mg/L).¹⁶ Brivaracetam has linear kinetics and dose proportionality can be assumed.¹⁶ Thus, 50 mg/d would be expected to yield 1.4–1.9 $\mu\text{mol/L}$ (0.3–0.4 mg/L), while 200 mg would be expected to result in about 6.6–8.5 $\mu\text{mol/L}$ (1.4–1.8 mg/L). Pharmacokinetic–pharmacodynamic modeling based on five Phase II and Phase III trials predicts a 50% seizure reduction from about 0.9 $\mu\text{mol/L}$ (0.2 mg/L).¹⁷ Based on these data, we suggest a preliminary reference range of 1–10 $\mu\text{mol/L}$ (0.2–2 mg/L).

Carbamazepine

The reference range for carbamazepine of 15–45 $\mu\text{mol/L}$ (4–11 mg/L) has been applied in Norway for decades. ILAE's therapy commission (2008) states 17–51 $\mu\text{mol/L}$ (4–12 mg/L).⁵ This is in line with other epilepsy centers, with only minor deviations.^{18–20} Data from the routine databases at St Olavs University Hospital and the National Center for Epilepsy show that <6% of all serum concentrations are above 45 $\mu\text{mol/L}$ (11 mg/L), which even includes overdose cases and intoxications (unpublished data). We, therefore, recommend keeping today's reference range unchanged.

Carbamazepine has a pharmacologically active metabolite (carbamazepine-10,11-epoxide) that is separately measured in many laboratories. The concentration of the epoxide metabolite is highly variable, also dependent on the comedication, but generally 5%–15% of the parent drug.⁹ The epoxide metabolite is usually not included in the reference range.

Measurement of free (unbound) carbamazepine is available at some laboratories. Usually, carbamazepine is about 70%–80% protein-bound and concentrations of the unbound fraction range from 4 to 12.5 $\mu\text{mol/L}$ (1–3 mg/L).²¹

Clobazam

Clobazam is one of the older AEDs but has recently attracted more attention following the licensing of this drug in the USA.

The reference ranges of 0.1–1 $\mu\text{mol/L}$ (0.03–0.3 mg/L) for the parent substance and 1.0–10 $\mu\text{mol/L}$ (0.3–3 mg/L) for the active metabolite desmethyl-clobazam are well established and identical with the ILAE recommendations.⁵ Experience has shown that analysis of desmethyl-clobazam can be very useful. It fluctuates more than the parent compound and can indicate genetic mutations in CYP2C19.²² We recommend keeping these reference ranges unaltered.

Clonazepam

Clonazepam is marketed as an AED, but is also widely used for psychiatric indications. The former reference range in Norway for epilepsy was 60–220 nmol/L (20–70 ng/mL). This reference range has been used for many years, and is also currently recommended by ILAE.⁵ There are, however, clinical data supporting a lower reference range of 48–160 nmol/L (15–50 ng/mL).²³ The Filadelfia Epilepsy Hospital in Denmark uses 40–120 nmol/L (13–38 ng/mL) (J Borg Rasmussen, personal communication), and Bethel (Germany) 64–128 nmol/L (20–40 ng/mL).¹⁸ As clonazepam has a significant potential for misuse, our suggestion is changing the reference range to 40–120 nmol/L (13–38 ng/mL).

Eslicarbazepine

Patsalos and Berry suggest 12–139 $\mu\text{mol/L}$ (3–36 mg/L).⁹ This is identical to the suggested reference range for oxcarbazepine's active metabolite, licarbazepine (formerly called monohydroxy derivative, MHD). However, licarbazepine is a racemate consisting of 20% *R*-licarbazepine and 80% *S*-licarbazepine (eslicarbazepine), and most of the pharmacologic effect is ascribed to eslicarbazepine.²⁴ Thus, a 20% lower reference range would appear more appropriate. A recent clinical study by Svendsen et al that investigated the serum concentration/effect relation of eslicarbazepine proposes a reference range of 12–100 $\mu\text{mol/L}$ (3–26 mg/L).²⁵ This is in accordance with the results from pharmacokinetic/pharmacodynamic modeling,²⁶ and we suggest following their proposal.

Ethosuximide

Only two laboratories in Norway offer this analysis, and both used the same reference range of 300–600 $\mu\text{mol/L}$ (42–85 mg/L). ILAE suggests 283–708 $\mu\text{mol/L}$ (40–100 mg/L), based on two clinical studies that correlated serum concentrations with clinical effect.⁵ This range is also used by the two German epilepsy centers Bethel and Kork.^{18,20} In Denmark, 240–700 $\mu\text{mol/L}$ (34–100 mg/L) is used.¹⁹ Our recommendation is, therefore, to change the current reference range in Norway to 280–700 $\mu\text{mol/L}$ (39–99 mg/L).

Felbamate

Felbamate is infrequently prescribed, mainly because it may induce severe hepatotoxicity and bone marrow depression. Concentrations above 250 $\mu\text{mol/L}$ (60 mg/L) are associated with better therapeutic effect, but also with significantly higher prevalence of adverse effects.²⁷ The reference range used in Norway is 125–250 $\mu\text{mol/L}$ (30–60 mg/L), which is identical to the ILAE recommendation.⁵ Bethel uses an upper bound of 336 $\mu\text{mol/L}$ (80 mg/L), while Kork uses a range of 85–190 $\mu\text{mol/L}$ (20–45 mg/L).^{18,20} The available data are too ambiguous to justify a change; thus, we suggest keeping today's reference range.

Gabapentin

While some laboratories in Norway have used a reference range of 70–120 $\mu\text{mol/L}$ (12–20 mg/L), others have used 20–120 $\mu\text{mol/L}$ (3–21 mg/L), which is close to the values suggested by ILAE and the Bethel epilepsy center.^{5,18} The epilepsy center in Kork uses a lower upper limit of 60 $\mu\text{mol/L}$ (10 mg/L).²⁰ A recent study showed that 35% of 189 patients with epilepsy had serum concentrations below 20 $\mu\text{mol/L}$ (3 mg/L).²⁸ Preliminary data from the same center suggest that a large part of these low concentrations is most likely due to incomplete gastrointestinal absorption, a common phenomenon with gabapentin.²⁹ Although gabapentin is mostly prescribed for neuropathic pain, sufficient data to describe the correlation between serum concentration and degree of pain-relieving effect are not available. Still, a low serum concentration may be an indicator of poor clinical efficacy. As the current reference range of 20–120 $\mu\text{mol/L}$ (3–21 mg/L) is close to the ILAE recommendation, we suggest keeping this unchanged until more data are available to allow for a re-evaluation. It should also be indicated by laboratories that this reference range applies to treatment of epilepsy.

Lacosamide

A reference range of 10–40 $\mu\text{mol/L}$ (3–10 mg/L) has so far been used in Norway. Patsalos and Berry suggest 40–80 $\mu\text{mol/L}$ (10–20 mg/L),⁹ but this is based on blood samples taken 0–3 hours after intake.^{30,31} A Norwegian study with 344 patients and an Italian study with 75 patients found that nearly all patients with good therapeutic effect had drug-fasting serum concentrations within a range of 10–40 $\mu\text{mol/L}$ (3–10 mg/L).^{32,33} We, therefore, recommend that the current reference range remains unchanged.

Lamotrigine

A reference range of either 10–50 (3–13 mg/L) or 10–60 $\mu\text{mol/L}$ (3–15 mg/L) has been stated by laboratories

in Norway. ILAE (2008) recommends 10–60 $\mu\text{mol/L}$ (3–15 mg/L), based on several studies.⁵ This recommendation was maintained by Patsalos and Berry.⁹ A large, retrospective Norwegian register study with more than 12,000 serum concentrations found that 40% of all samples were below 10 $\mu\text{mol/L}$ (3 mg/L), and 90% of all samples were below 30 $\mu\text{mol/L}$ (8 mg/L).³⁴ This was a database study without information on clinical efficacy, and included patients with psychiatric disorders. On the other hand, a study from Australia found that 75% of all samples were 27 $\mu\text{mol/L}$ (7 mg/L) or above.³⁵ The two leading German epilepsy centers use 12–55 $\mu\text{mol/L}$ (3–14 mg/L; Bethel) and 8–40 $\mu\text{mol/L}$ (2–10 mg/L; Kork). In Denmark, 10–50 $\mu\text{mol/L}$ (3–13 mg/L) is used.^{18,20} We recommend keeping the reference range at 10–50 $\mu\text{mol/L}$ (3–13 mg/L).

Levetiracetam

The current reference range in Norway is 30–240 $\mu\text{mol/L}$ (5–41 mg/L). The lower limit is lower than that suggested by ILAE (70–270 $\mu\text{mol/L}$; 12–46 mg/L). The ILAE proposal is based on a retrospective database study that only included the highest doses used by each patient.³⁶ On the other hand, two studies showed that 45% of all samples were below 70 $\mu\text{mol/L}$ (12 mg/L), and 80% of all samples were between 30 and 150 $\mu\text{mol/L}$ (5 and 25 mg/L) ($n=353$ [A. Reimers, unpublished data] and $n=300$).³⁷ Hence, we recommend no changes until there are adequate clinical data available.

Oxcarbazepine

Oxcarbazepine is pharmacologically active and, thus, not a prodrug according to standard definition. Thus, increased serum concentrations of oxcarbazepine may cause toxicity. For instance, co-administration with perampanel may reduce the clearance of oxcarbazepine.³⁸ Usually, however, oxcarbazepine is rapidly biotransformed to its active metabolite licarbazepine (formerly called MHD).^{24,39} For that reason, the reference range applies to licarbazepine. In Norway, both 45 and 50 $\mu\text{mol/L}$ (12 and 13 mg/L) have been used as the lower limit, and 140 $\mu\text{mol/L}$ (35 mg/L) as the upper. ILAE recommends 12–140 $\mu\text{mol/L}$ (3–36 mg/L).⁵ This corresponds well with the findings from Norwegian routine TDM databases (unpublished data). Our recommendation is, therefore, to reduce the lower limit to 12 $\mu\text{mol/L}$ (3 mg/L).

Perampanel

Data from clinical studies show that after repeated administration of 4 or 8 mg per day, maximum serum concentrations (c_{max}) average around 1,064 and 2,008 nmol/L (370 and 690 ng/mL), respectively.⁴⁰ After 10–12 hours, distribution is

complete and concentrations have fallen to ~70% of c_{\max} . One would, therefore, expect drug-fasting serum concentrations of ~750–1,400 nmol/L (260 and 480 ng/mL). The Bethel epilepsy center uses 143–4350 nmol/L (50–1,500 ng/mL); this is classified as preliminary.¹⁸ The Epilepsy Hospital in Dianalund uses a preliminary range of 250–2,850 nmol/L (86–1,000 ng/mL; J Borg Rasmussen, personal communication). The Danish reference range is closer to the theoretically derived numbers. We suggest using this range until sufficient clinical data are available. As AED concentrations traditionally are given in $\mu\text{mol/L}$, we suggest using the same unit of measurement also for perampanel. The suggested reference range, thus, is 0.25–2.85 $\mu\text{mol/L}$ (86–1,000 ng/mL or 0.1–1 mg/L).

Phenobarbital

All laboratories in Norway state 50–130 $\mu\text{mol/L}$ (12–30 mg/L) as the reference range. ILAE (2008) and Patsalos and Berry suggest 43–172 $\mu\text{mol/L}$ (10–40 mg/L).^{5,9} ILAE points out, however, that sedation frequently occurs above 130 $\mu\text{mol/L}$ (30 mg/L). Data from the routine databases at St Olavs University Hospital, Haukeland University Hospital and the National Center for Epilepsy confirm that concentrations exceeding 130 $\mu\text{mol/L}$ (30 mg/L) are rarely seen. We suggest keeping the existing reference range.

Phenytoin

The current reference range of 40–80 $\mu\text{mol/L}$ (10–20 mg/L) is well established and has been used for decades. ILAE as well as Patsalos and Berry also state this reference range.^{5,9} Thus, we suggest no changes. Some laboratories offer measurement of free (unbound) phenytoin. Phenytoin is highly protein-bound, and only the unbound portion is pharmacologically active. Measurement of free phenytoin may be useful in situations where the serum concentration of total phenytoin does not correlate well with the clinical picture and where a higher-than-normal free proportion of phenytoin might be suspected, for example, in patients with albumin deficiency, or in case of suspected interaction with other highly protein-bound drugs. At common doses/serum concentrations, the free portion of phenytoin usually does not exceed 10% of the total phenytoin concentration.²¹

Pregabalin

The current reference range is 10–30 $\mu\text{mol/L}$ (2–5 mg/L). This range was derived from pharmacokinetic calculations based on doses used in clinical studies. We did not find recommendations in the literature. The Epilepsy Hospital

in Dianalund, Denmark, uses 10–35 $\mu\text{mol/L}$ (2–6 mg/L; J Borg Rasmussen, personal communication), while the epilepsy center in Bethel, Germany, uses 12.6–31 $\mu\text{mol/L}$ (2–5 mg/L).¹⁸ Indeed, the majority of patients have serum concentrations within these ranges, but in a Norwegian study ($n=167$), 18% of the patients had higher concentrations.²⁸

An estimated 95% of all pregabalin prescriptions are for neuropathic pain treatment where there is no tradition for TDM, but rather dosing according to effect or dosing schemes.^{1,41} There is no available clinical data allowing to establish a reference range. However, pregabalin clearly has a potential for misuse,^{42–44} and, thus, it is desirable to have a reference range. Our recommendation is to adjust the upper limit and use 10–35 $\mu\text{mol/L}$ (2–6 mg/L).

Rufinamide

The current Norwegian reference range is 20–130 $\mu\text{mol/L}$ (5–31 mg/L). The reference range used in Denmark is 15–90 $\mu\text{mol/L}$ (4–21 mg/L), mainly based on clinical experience (J Borg Rasmussen, personal communication) and in Germany, 21–126 $\mu\text{mol/L}$ (5–30 mg/L; Bethel).¹⁸ A review by Perucca et al, based on unpublished data from the manufacturer, reports that concentrations needed to reduce seizure frequency by 25%–50% range between 63 and 126 $\mu\text{mol/L}$ (15–30 mg/L).⁴⁵ Patients with Lennox–Gastaut syndrome seem to need concentrations up to 210 $\mu\text{mol/L}$ (50 mg/L). The authors state that a concentration of 126 $\mu\text{mol/L}$ (30 mg/L) is higher than most patients will reach in clinical practice. The above-mentioned numbers were not obtained by clinical observation, but by pharmacokinetic–pharmacodynamic modeling. We suggest a lower limit according to the Danish experience; hence, the (still preliminary) reference range would be 15–130 $\mu\text{mol/L}$ (4–31 mg/L).

Stiripentol

Stiripentol is a challenging AED because of saturation kinetics, 99% protein binding and various drug interactions.^{4,21} Patsalos and Berry cite one study that found therapeutic effect in the range of 17–94 $\mu\text{mol/L}$ (4–22 mg/L).⁴⁶ The Epilepsy Hospital in Dianalund, Denmark, uses 15–95 $\mu\text{mol/L}$ (4–22 mg/L; J Borg Rasmussen, personal communication), while the epilepsy center in Bethel, Germany, uses 4–43 $\mu\text{mol/L}$ (1–10 mg/L).¹⁸ We suggest 15–95 $\mu\text{mol/L}$ (4–22 mg/L), as supported by clinical data.

Sulthiame

Sulthiame was introduced in the 1960s and has been little or not used in most countries. However, in recent years, it

has gained popularity. In Germany, it has long been used as first-choice AED in children with self-limited epilepsy with centrotemporal spikes, and as a second choice in other focal epilepsies and in infantile spasms.²⁰ Bethel uses a reference range of 7–28 $\mu\text{mol/L}$ (2–8 mg/L), while in Kork, 3.5–10.5 $\mu\text{mol/L}$ (1–3 mg/L) and 17.5–35 $\mu\text{mol/L}$ (5–10 mg/L) are used, depending on the type of seizure.^{18,20} In Dianalund, 5–35 $\mu\text{mol/L}$ is used (2–10 mg/L; J Borg Rasmussen, personal communication). Our recommendation is 5–35 $\mu\text{mol/L}$ (2–10 mg/L), where the lower limit is identical to the Danish one, and between the two German ones.

Topiramate

All laboratories in Norway state 15–60 $\mu\text{mol/L}$ (5–20 mg/L) as the reference range, which is in accordance with the ILAE guideline.⁵ The Epilepsy Hospital in Dianalund, however, uses a somewhat lower range of 6–30 $\mu\text{mol/L}$ (2–10 mg/L). This is based on a clinical study by Christensen et al and routine TDM data (J Borg Rasmussen, personal communication).⁴⁷ The Bethel epilepsy center uses 6–24 $\mu\text{mol/L}$ (2–8 mg/L); also this is based on own clinical data.^{18,48} Routine TDM data from St Olavs University Hospital show indeed that the mid 80% of all serum concentrations fall between 7 and 38 $\mu\text{mol/L}$ (2–13 mg/L; unpublished data). Similar findings have been documented at the National Center for Epilepsy.³⁷ The ILAE guideline states that more recently, lower doses are used than immediately after introduction of topiramate.⁵ A lower limit of 6 $\mu\text{mol/L}$ (2 mg/L), therefore, appears adequate, while an upper limit of 30 $\mu\text{mol/L}$ (10 mg/L) would fall between the upper limit in Bethel and the 90 percentile from St Olavs Hospital. Our recommendation is, therefore, 6–30 $\mu\text{mol/L}$ (2–10 mg/L).

Valproate

In Norway, both 250 and 300 $\mu\text{mol/L}$ (36 and 43 mg/L) were used as the lower limit, while 600 and 700 $\mu\text{mol/L}$ (87 and 100 mg/L) were stated as the upper limit. Most international text books as well as review articles state 347 $\mu\text{mol/L}$ (50 mg/L) as the lower limit, and either 694 $\mu\text{mol/L}$ (100 mg/L) or 867 $\mu\text{mol/L}$ (125 mg/L) as the upper. Overdosing of valproate produces generally mild and quickly reversible symptoms such as tremor and sedation. We, therefore, recommend an upper limit of 700 $\mu\text{mol/L}$ (101 mg/L). A recent study showed that valproate's pharmacokinetic variability in women is extensive. The authors recommend that serum concentrations (both total and free valproate) should be monitored for improved safety in women.⁴⁹ Measurement of free (unbound) valproate is available at some laboratories.

It can be useful in situations where the serum concentration of total valproate does not correlate with the clinical picture, for example, in patients with albumin deficiency, during pregnancy or in case of suspected interaction with other highly protein-bound drugs. At common doses and serum concentrations, the free fraction of valproate usually does not exceed 10% of the total valproate concentration.²¹

Vigabatrin

At doses from 1,000 to 3,000 mg/d, serum concentrations ranging from 6 to 279 $\mu\text{mol/L}$ (0.8–36 mg/L) have been reported.⁵ This range demonstrates a very large pharmacokinetic variation (dose varies by a factor of 3, while serum concentration varies by a factor of 47). Being an irreversible inhibitor of the enzyme GABA-transaminase, vigabatrin is a hit-and-run drug. That means that its pharmacologic effect lasts longer than its plasma half-life would imply. For that reason, vigabatrin's clinical effect does not correlate with its serum concentration. It is, thus, neither possible nor suitable to state a reference range for vigabatrin.

Zonisamide

The current reference range in Norway is 45–180 $\mu\text{mol/L}$ (10–40 mg/L), which is identical with ILAE's proposal and close to the ranges used in Dianalund (J Borg Rasmussen, personal communication), Bethel and Kork.^{18,20} While the upper limits of the German centers are close to the ILAE recommendation, the lower limits are more divergent. We suggest keeping the current reference range unchanged, because the lower limit is in accordance with the ILAE guideline and between the values used by the two German centers.

Usefulness of TDM

The usefulness of TDM of AEDs has been discussed controversially for decades. Interestingly, an AED, phenytoin, was among the first drugs that made TDM popular, because of its dose-dependent kinetics.⁵⁰ Experience shows that TDM is most useful in given clinical situations.⁵ This means that the blood sample is taken with a certain question in mind that the serum concentration shall help to answer. Clinical situations where TDM can be useful include lack of therapeutic effect despite an adequate dose, adverse effect despite a low dose, altered pharmacokinetics due to pregnancy, liver or kidney disease, microbial infection, suspected drug interaction, known or suspected pharmacogenetic mutations, and more. The value of routine TDM without a clinical reason is indeed doubtful.^{4,51–53} It must also be emphasized that TDM is not the drug concentration

measurement only, as TDM in addition provides expert clinical interpretation.⁵⁴

Clinical experience shows that reference ranges are not always used the way they are supposed to, which may be one reason why there is a lack of studies that support the usefulness of TDM in epilepsy treatment.⁵² One of several common misconceptions is that a concentration within the reference range will always give the desired clinical effect.⁵⁵ Similarly, a serum concentration below the reference range is acceptable if the patient is seizure free. Arbitrary, outdated and divergent reference ranges for the same drug may cause misunderstandings, which may contribute to suboptimal use and reinforce the skepticism toward the concept of TDM.^{5,56}

Methodologic considerations and limitations

Due to a general lack of sufficient data, this report cannot consider all possible clinical consequences of polytherapy including pharmacodynamic and pharmacokinetic interactions. Clinical evaluation and observant follow-up of the patient must, therefore, be the leading element, as in all medical treatment.

Most suggested reference ranges are tentative and many are poorly documented. Several are supported by broad clinical experience and population-based data from pharmacologic laboratories, but only few are based on systematic investigations of correlations between clinical data and serum concentrations. A Cochrane review only found one randomized controlled trial comparing the outcomes of AED monotherapy guided by TDM with drug treatment without the aid of TDM.⁵³ All types of documentation are hampered by limitations, and further adjustments of reference ranges based on future studies must be anticipated. Moreover, seizure type, severity and frequency, as well as epilepsy syndrome, age, comorbidity and comedication may influence the efficacy and tolerability of AEDs in the individual patient. For example, clinical experience shows that patients with pre-existing cognitive deficits are often more vulnerable to cognitive side effects than other patients.^{57–60} Nevertheless, most individual therapeutic ranges should fall within the suggested population-based reference ranges.

Routine data from pharmacologic laboratories in Norway support many of the proposed reference ranges in this report, but these data include cases where TDM was performed because of loss of seizure control, adverse effects, suspected nonadherence or other adverse clinical circumstances.

Nonetheless, in cases where no sufficient clinical data are available, we believe that after cutting off the extreme values at both ends by using only the central portion, for example, the central 80% or 90% of the distribution curve, such routine data are robust enough to establish preliminary reference ranges, at least in the country where they have been collected. As the example of lamotrigine shows (Lamotrigine in Results section), different national treatment traditions may lead to different dosing and, thus, different average serum concentrations.^{34,35}

Significance

We found several AEDs with diverging reference ranges in Norway. Laboratories in different parts of Norway should not state different reference ranges, because treatment traditions and health care services are equal across the country. Discrepancies in reference ranges could confuse prescribers and lead to unnecessary, potentially harmful alterations in patient treatment. Harmonized reference ranges render the process of staying updated to a national concern and oblige every laboratory to share new information and research that could be of importance, and in turn lead to changes of AED reference ranges. In a small country like Norway, interlaboratory cooperation makes it possible to stay updated in a world where medical knowledge is subjected to rapid changes. Harmonizing reference ranges is the first step to create joint reference manuals for laboratories. These reference manuals provide information to clinicians and laboratory personnel on how to do sampling, and how to interpret analytic results. National reference manuals render the continuous work with updating information an interlaboratory collaboration – saving resources and being an assurance of quality of the information given. This also contributes to improve pharmacovigilance and facilitates the clinical implementation of TDM.

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Disclosure

All authors except EB work at state-owned laboratories that offer measurement of serum concentrations of drugs, including antiepileptic drugs. None of the authors are gaining any financial profit from this paper. The authors report no conflicts of interest in this work.

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