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Lamotrigine therapeutic thresholds

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Summary

Purpose: To evaluate therapeutic drug monitoring (TDM) of lamotrigine (LTG) with establishment of individual therapeutic thresholds (TT) in outpatients of a tertiary epilepsy centre on monotherapy.
Methods: In the outpatient clinic of the Danish Epilepsy Centre, Dianalund, all patients treated in 2004 with LTG monotherapy were identified. Patients who had not reported seizures or adverse reactions in the last 6 months were considered seizure free and well-medicated on LTG monotherapy, and were further evaluated. Plasma levels from routine LTG TDM obtained by reversed-phase high-pressure liquid chromatography (HPLC) during up-titration were used to calculate the TT for each patient as the mean of the highest subtherapeutic and the lowest therapeutic level.
Results: Eighty-two patients undergoing LTG monotherapy were reported seizure free as defined above. In 34 the TT could not be calculated because they became seizure free on the first chosen dose. TTs of the remaining 48 patients ranged from 4.0 to 42.0 μmol/l. There were no differences between children and adults, and between generalized and localization-related epilepsies. The therapeutic levels of patients with undefined TT tended to be lower. The level—dose ratio in both groups varied only moderately indicating absence of major exogenous influences.
Conclusion: Even in patients of a tertiary referral centre only a minority had high TTs and needed therapeutic levels in a range where toxicity is increasingly observed. TDM appears useful in LTG treatment both for the establishment of individual reference ranges and for the identification of the individual level-to-dose ratio.

Introduction

The literature about the use of therapeutic drug monitoring (TDM) in lamotrigine (LTG) treatment is controversial. Kilpatrick et al.[1] and Bartoli et al.[2] indicated no clear-cut relationship between clinical response, toxicity and serum concentrations, and Chong and Dupuis[3] in a review concluded that "clear relationships between concentration and pharmacologic response (either efficacy or toxicity) have not been demonstrated". However, Perucca[4] and

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Johannessen and Tomson[5] proposed that TDM for LTG is useful because of its pharmacokinetic properties. Several studies suggested appropriate ranges of optimal serum concentrations and therapeutic intervals, based on determination of median concentrations among responders on moderate dose versus median concentrations among non-responders exhibiting side effects,[6,7] but a considerable overlap between responders and non-responders was found, as reviewed by Johannessen et al.[8] and Johannessen.[9]

The classic investigations that have established TDM as a tool for better treatment have used a different approach. They compared plasma levels in a period when the patient still had seizures with levels when seizure control was obtained. Likewise, in patients on high doses, plasma levels in the presence of signs and symptoms of overdose were compared with subtoxic levels. With these determinations, individual thresholds for sufficient therapeutic action and dose-dependent side effects can be identified. This was particularly important for Phenytoin whose non-linear kinetics and narrow therapeutic index limit the significance of doses, and therapeutic drug monitoring (TDM) introduces a much more reliable parameter.[10] Similar investigations have rarely been performed for the newer AEDs including LTG which have easier kinetics and a wider therapeutic range. Hirsch et al.,[11] however, have shown that the incidence of toxicity increased in clear relation to increasing LTG serum concentrations. At levels of 10–15 μg/ml (39–59 μmol/l) 24%, and above 20 μg/l (78 μmol/l) 59% of patients showed signs of toxicity whereas others required and tolerated levels above 20 mg/l to obtain full seizure control.

Sabers et al.[12,13] using plasma level monitoring have shown that co-medication of LTG with oral contraceptives impairs seizure control by induction of LTG metabolism. Without TDM this clinical important interaction could not have been detected, and it was followed up by the investigation of LTG during pregnancy[14] which is now considered an indication for TDM of LTG.[15] A long-term survey of LTG monitoring in an Australian Laboratory revealed a 2.9-fold increase of LTG assay requests over a 7-year period from 1996 to 2003, indicating a wide clinical use of LTG assays in clinical practice of today.[16]

In the Danish Epilepsy Centre, Dianalund, TDM is performed routinely with every dosage step in patients undergoing LTG therapy. In this paper we report findings with individual LTG therapeutic thresholds (TTs) as defined by longitudinal TDM in patients who were titrated to full seizure control with LTG in monotherapy.

Individual TTs are calculated values that are useful in the LTG treatment of patients undergoing stepwise titration. Individual TTs are not directly related to the general therapeutic index of any drug. They rather define the minimum level which creates seizure freedom in the individual patient. The TT is more accurate than the "therapeutic level" where seizure control was achieved because, if the therapeutic dose was not titrated, the therapeutic level may be considerably higher than needed for seizure control.

The TT alone also does not inform on the entire individual therapeutic range whose upper limit is defined by a toxic threshold. In successfully treated patients like those reported here this is only rarely reached.

Materials and methods

Patients

The files of all patients who in 2004 were seen in the outpatient clinic at the Danish Epilepsy Centre, Dianalund were screened to identify those who were treated with LTG monotherapy. Among these, the patients who had not reported seizures or adverse reactions related to the antiepileptic medication in the previous 6 months were identified. This group of patients was considered seizure free with well-tolerated LTG monotherapy. To define the individual therapeutic threshold (TT) for each of these patients, plasma levels found at routine LTG TDM during stepwise titration to seizure control were used. Only data from patients who had not fully responded to an initial LTG dose, but needed titration to a higher dose to become seizure free were used for the calculation of TTs. Plasma levels were included only if they were determined at a moment when the patient was on LTG monotherapy and could be considered free from possible pharmacokinetic interactions of present or previous co-medications. The only exception was one patient where the increase from the subtherapeutic to the individually therapeutic LTG level was due not to an increase of dose which remained the same, but to termination of hormonal contraception.

Therapeutic drug monitoring (TDM)

Plasma levels were morning trough levels. The LTG concentration was estimated by use of reversed-phase high-pressure liquid chromatography (HPLC) according to Croci et al.[17] in combination with UV detection at 306 nm of the elution solution followed by calculation of the area of the elution peak. Based

on correlation to standard curves the concentration of LTG was given in μmol/l with a cut-off value <1 μmol/l and linear correlation up to 125 μmol/l.

Therapeutic threshold (TT)

The TT cannot be determined directly, and there is no generally accepted method of defining it. In this investigation, TT was calculated as the mean of the highest plasma level where seizures still occurred, and the lowest level where they were controlled. Individually, the true TT may be closer to either the subtherapeutic level or the therapeutic level, but in a drug with linear kinetics no systematic bias is to be expected, and in the absence of precise measurements, this seems to be an adequate operational measure.[18]

Results

A total of 82 patients were seizure free with well-tolerated LTG monotherapy as defined above. Of these, 34 had become seizure free on the initial LTG dose. Their TTs could not be calculated because no highest subtherapeutic plasma levels exist. The individual TTs could be determined in the remaining 48 patients.

The characteristics of the 48 patients are given in Table 1. The ages ranged from 4 to 73 years, and 40 patients were diagnosed with localization-related epilepsy whereas 8 had generalized epilepsy. Among the localization-related epilepsies in adults, temporal lobe epilepsies covered over 50% (18 out of 32 cases) as expected from earlier reports on difficult-to-treat patients referred to tertiary centres.[19] The generalized epilepsies comprised cases of Juvenile myoclonic epilepsy (4) and idiopathic generalized epilepsy without specification (4).

Table 1 Patient overview

	Adults	Children
N	40	8
Age	16—73	4—14
Localization-related epilepsy	32	8
Temporal lobe	18	1
Occipital lobe	2	1
Idiopathic rolandic	0	4
Multifocal	0	2
Unidentified	12	0
Generalized epilepsies	8	0
Juvenile myoclonic	4	
Other idiopathic	4	

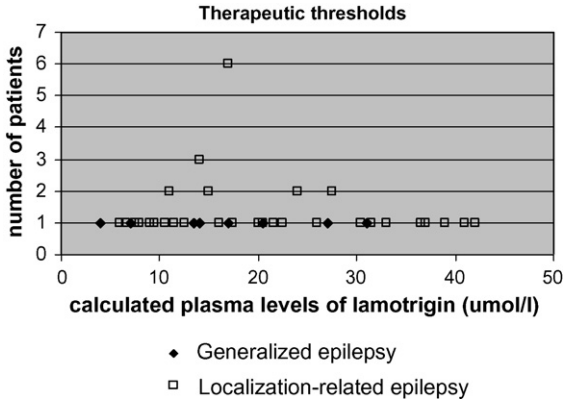

Figure 1 Distribution of therapeutic thresholds (TTs) in 48 patients who became seizure free during stepwise uptitration of LTG monotherapy in response to seizures, TTs were defined as mean of the highest subtherapeutic and the lowest therapeutic plasma level.

The calculated TTs of the 48 patients in monotherapy are presented in Fig. 1. They ranged from 4.0 to 42.0 μmol/l. Patients with localization-related epilepsies had TTs between 5.5 and 42.0 μmol/l, and patients with generalized epilepsies ranged from 4.0 to 31.0 μmol/l. In children, the TTs ranged from 7 to 26 μmol/l, and in adults from 4 to 42 μmol/l. Between the groups (localization-related vs. generalized epilepsies) there was no difference.

To compare plasma levels resulting in full seizure control in patients with and without defined TTs, we looked at the lowest therapeutic plasma levels in both groups (Fig. 2).

The mean therapeutic plasma level of the patients with defined TT was 23.2 μmol/l with S.D. ±10.60 μmol/l. In the patients who became seizure free with the first chosen dose, the respective values were 13.3 ± 7.27 μmol/l (Fig. 3). Thus, the apparent

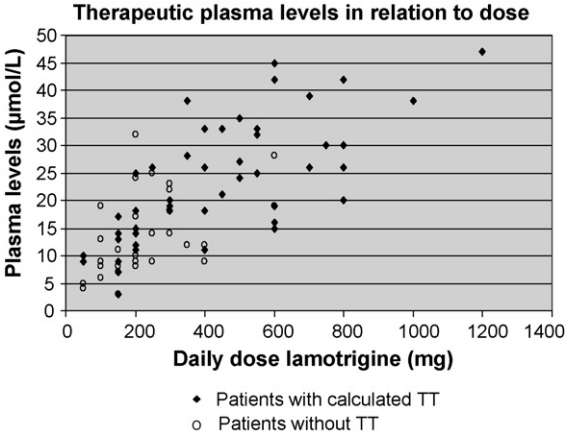

Figure 2 Level—dose ratio of the therapeutic levels (not thresholds) of 48 patients with known TTs and 34 patients who became seizure free with the first chosen dose of LTG in monotherapy.

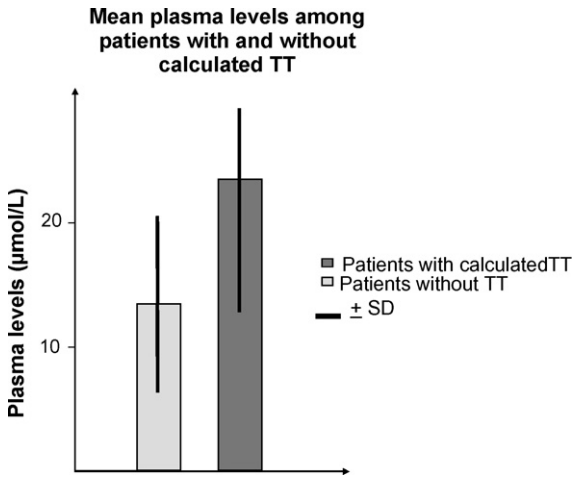

Figure 3 Comparison of therapeutic levels of the groups with and without identified TT. The patients responding to the first dose seem as a group to require lower plasma levels to be seizure free, but the difference is not significant due to large interindividual variability with some overlap of standard deviations.

clear difference between the two groups is not statistically significant due to the considerable interindividual variability with a slight overlap of standard deviations. Among the patients with a calculated TT, a dose of 1200 mg in one patient resulted in a plasma level of 47 μmol/l, which was the highest therapeutic and non-toxic level of LTG in the present study. The highest therapeutic level in a patient without known TTwas 32 at a dose of 200 mg. The therapeutic plasma levels of 8 of the 82 patients were 35 μmol/l or more, all with localization-related epilepsy (no significant difference from generalized epilepsy, Fisher's exact test).

The level—dose ratios (LDRs, Fig. 2) showed considerable interindividual variability but no systematic deviations from the mean, and did not differ between the two groups with and without defined TTs.

Discussion

The literature proposing that TDM for LTG is irrelevant because neither therapeutic nor toxic effects can be correlated with plasma levels,[3] is based on comparisons of plasma LTG levels in patient groups that were seizure free versus still having seizures. The plasma levels showed no group differences.

This, however, is not an adequate method to establish the use of therapeutic monitoring of an AED because it compares heterogeneous groups, i.e. drug-resistant patients with others who are well treatable. TDM is based upon the comparison of drug level determinations with subtherapeutic and therapeutic as well as subtoxic and toxic doses in individual patients.[10]

Our findings demonstrate that individual therapeutic thresholds can be defined in LTG and support the view of Fröscher et al.,[7] Hirsch et al.,[11] Johannessen,[9] Johannessen et al.,[8] Johannessen and Tomson[5] and Perucca[4] that TDM has a place in the management of epilepsy with this drug. This is further supported by the interindividual variability of LDRs which makes it impossible to relate the therapeutic effects directly to the doses. In spite of their individual variability, the LDRs for the whole cohort did not display any systematic deviations which would indicate major influences of confounding factors like frequent compliance problems or interactions with other medication like contraceptives[12,13] although both certainly occurred in individual cases. Nor did the distribution of LDRs differ in the two groups (Fig. 2). Obviously, the differences of the LDRs together with the titration scheme result in individual differences of the interval between the highest subtherapeutic and lowest therapeutic levels from which the TT is calculated, and its definition is the more accurate the narrower the interval. But even the less accurate TTs clearly provide a clinically more reliable orientation than an individual therapeutic level which was reached without titration.

The wide ranges of TTs and therapeutic levels reflect the variability of the patients' responses to treatment. It is remarkable that even in this sample of patients who are treated in a tertiary referral centre for epilepsy, the TTs for LTG of most patients are in a low to moderate range. Only a small minority have therapeutic levels above 40 μg/ml, i.e. in a range where toxicity is found in as much as one-fourth of patients.[11] These are the patients with an individually narrow reference range for a drug which in general is known for a broad therapeutic index.

Although there is a slight overlap of standard deviations between the groups with and without defined TTs, due to the high interindividual variation of therapeutic levels, these clearly tend to be lower in the group of patients who responded to the first chosen dose, which is consistent with the findings of Wolf et al.[18] and confirms that they represent a relatively benign segment of patients.

In the present study we looked at individual therapeutic thresholds as a tool to identify an individual medication scheme for each patient irrespectively of general therapeutic indexes. A "start low—go slow" titration allows the clinician to adjust long-term treatment to a dose which is just above the TT and minimizes the risk of toxicity.

Conclusion

Even in patients of a tertiary referral centre only a minority had high TTs and needed therapeutic levels in a range where toxicity is increasingly observed. TDM appears useful in LTG treatment both for the establishment of individual reference ranges and for the identification of the individual level-to-dose ratio. Seizure free patients were subsequently kept on LTG doses that gave TDM serum concentrations as low as possible above the calculated TT concentration in order to continue full seizure control and avoid developments of unacceptable adverse reactions.

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