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Should newly diagnosed epilepsy be treated with generics?

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In recent years, a fervent debate has been going on—at meetings more than in the literature—about possible risks related to the use of generic drugs in patients with epilepsy. This debate was summarized by Bialer,[1] who underlined that the concern is not about the quality of the generic preparations. There is broad consensus that generics are prescribable if they are accepted as bioequivalent by the relevant national authority (in North America and the European Union, bioequivalence is achieved when the 90% CIs of the average ratio between the generic and brand product for key pharmacological parameters fall within the range of 80–125%). Rather, the concern is about the interchangeability of antiepileptic drug (AED) preparations—both branded products and generics.

Unlike most other medical conditions, in epilepsy therapeutic success is generally of the all-or-nothing type; either a patient becomes seizure-free, or he or she does not. Mere reduction of seizure frequency is unsatisfactory, because someone whose seizures are fully controlled can lead a more or less normal life, whereas ongoing seizures result in handicaps and risks of complications in the physical, social and psychological spheres. With the presently available AEDs, about 70% of all patients with epilepsy can be seizure-free.[2] It was already discovered in the earliest period of therapeutic AED monitoring that, to maintain seizure control, the plasma level of a given AED needs to be kept above a threshold level, and that this level differs from person to person depending on the severity of the individual's epilepsy.[3] Patients with a high seizure propensity have a higher therapeutic threshold than those with a low or moderate seizure propensity. In consequence, those with a high seizure propensity might display a narrow *individual* therapeutic index for a drug that *in general* has a wide therapeutic index. The doses and plasma levels of an AED that effectively control a patient's seizures might be so close to the therapeutic threshold that the shift to a preparation with a lower bioavailability, within the accepted range of bioequivalence, could produce a seizure relapse. Of the patients at a tertiary referral center who became seizure-free with lamotrigine (a drug with a wide therapeutic index), about 10% did indeed have a high therapeutic threshold.[4]

A narrow individual therapeutic index that requires high doses also means that the patient is close to the individual toxic threshold of the drug, which can be exceeded by a shift to a preparation with higher bioavailability. In a comparative study of carbamazepine sustained-release preparations, Mayer *et al.*[5] found that 9 of 14 patients on subtoxic doses developed typical signs and symptoms of toxicity after being shifted to a product with a bioavailability that was higher than that of brand carbamazepine but within the accepted bioequivalence range (generic:brand ratio of the average area under the concentration–time curve [AUC]: 111.5%, 90% CI 105.6–117.8%; generic:brand ratio of the average maximum concentration reached [C_{max}]: 110.1%, 90% CI 100.4–117.0%]).

The risks of relapse and toxicity have led several national epilepsy societies to formulate recommendations for the use of generic AEDs (for Italy see Perucca *et al.*[6]) that caution against shifts between preparations, especially in patients who are seizure-free.

It could be argued that the above considerations do not matter at treatment onset, when the patient's individual response to a given drug is not known and the concern over possible loss of full seizure control does not yet apply. If the patient can continue with a specific generic preparation there is indeed no difference from treatment with a branded product. There are, however, concerns regarding the continuity of supply—some general, and some specific to certain countries.

Shifts between different generic preparations are more risky than shifts between a brand and a generic product (either way), because generics might not be bioequivalent to each other (e.g. one generic might have a higher bioavailability

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than the brand product, whereas the other generic might have a lower bioavailability, and the two 90% CIs for bioequivalence with the brand product might not overlap). A patient who is started on a generic product, therefore, must not be considered as being 'on generics' as opposed to 'on brand', but as being on one particular generic, which should not be changed without a specific reason. However, there is little awareness of this issue, and generic AEDs are often erroneously treated as a homogeneous group of interchangeable products, even by health-care personnel.

In addition, a series of circumstances can lead to the interruption of continuous treatment with a specific generic. For example, the distributor of a generic product might decide to leave the market or discontinue certain dosages. The distributor might change supplier, and as a result the product might differ from the original one although the name remains the same. Furthermore, the production process of a given product might be modified and this change might affect the drug's absorption parameters.

The above concerns also apply to brand products, and the argument is often heard that deviations in absorption between different preparations might not exceed the fluctuations that occur with continuous use of the same product. Evidence for this assumption is, however, missing, and there is an obvious need for clarification through controlled studies.

Another concern exists regarding the use of generics in newly diagnosed epilepsy: repetitive preparation shifts during dose titration could result in the erroneous assumption that the patient's seizures are resistant to the given drug. This scenario might happen when preparations with pharmacological parameters at the upper and lower ends of the bioequivalence range are used in alternation. A small dose increase might result in the serum level jumping from the subtherapeutic to the toxic range, so the individual therapeutic window will falsely appear too narrow to permit use of this drug (see also Supplementary Figure 1 online).

There are also concerns that are specific to certain countries. Legislation on the substitution of a prescribed brand AED for an appropriate generic equivalent varies throughout the world—there is at present no scientific evidence to either prove or disprove the assumption that shifts to preparations accepted as bioequivalent are safe for patients with epilepsy, so it is a political decision whether more weight is given to the interests of the public (considerations of cost) or to the interests of the patient (considerations of safety). In many countries it is the doctor's decision whether to allow substitution of a prescribed drug with a generic, but this is not the case everywhere. In Denmark, legal requirement for automatic substitution of a prescribed drug with the cheapest available preparation results in frequent and mandatory changes between generics; through political action the bioequivalence range for AEDs accepted for automatic substitution has, however, been reduced to 90–111%, and patients who require high AED doses can be exempt from substitution.[7] In some other countries, such as the USA, shifts occur not only because of mandatory substitution, but also because pharmacies get favorable prices for certain preparations, which they then dispense instead of the prescribed preparation (even if a generic product has been prescribed).

To conclude, newly diagnosed patients with epilepsy can be treated with generic AEDs provided that they can continue on the same preparation. Where local regulations preclude this possibility, political action is required to have the regulations improved. If the generic product disappears from the market, it is recommended that drug levels are monitored after a patient is changed to a new product and that the dose is adjusted if there is substantial deviation from the previous plasma level.

Supplementary information in the form of a figure is available on the *Nature Clinical Practice Neurology* website.

Competing interests
The author has declared associations with the following companies/organizations: Eisai, GlaxoSmithKline and UCB. See the article online for full details of the relationships.

References

1 Bialer M (2007) Generic products of antiepileptic drugs (AEDs): is it an issue? *Epilepsia* **48:** 1825–1832
2 Brodie MJ (2005) Response to antiepileptic drug therapy: winners and losers. *Epilepsia* **46 (Suppl 10):** S31–S32
3 Kutt H (1972) Relation of plasma levels to clinical control. In *Antiepileptic Drugs*, 211–218 (Eds Woodbury DM *et al.*) New York: Raven Press
4 Søndergaard Khinchi M *et al.* (2008) Lamotrigine therapeutic thresholds. *Seizure* [doi:10.1016/j.seizure.2007.11.023]
5 Mayer T *et al.* (1999) Clinical problems with generic antiepileptic drugs: comparison of sustained-release formulations of carbamazepine. *Clin Drug Invest* **18:** 17–26
6 Perucca E *et al.* (2006) Recommendations of the Italian League Against Epilepsy working group on generic products of antiepileptic drugs. *Epilepsia* **47 (Suppl 5):** S16–S20
7 Wolf P (2007) Generic antiepileptic drugs: political campaign in Denmark. *Epilepsia* **48 (Suppl 7):** S6–S7

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Comparative daily profiles with different preparations of lamotrigine: A pilot investigation

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ABSTRACT

Comparative pharmacokinetic data obtained with different preparations of lamotrigine (LTG) are reported for the first time. Nine outpatients reporting problems attributed to shifts in the preparation of LTG used were admitted to hospital. Patients were treated with proprietary LTG for at least 2 weeks prior to admission. Daily profiles (DPs) spanning 24 hours were obtained by blood sampling at 3- or 4-hour intervals on Day 3 after admission. A second DP was obtained under similar conditions after generic LTG therapy for at least 7 days. LTG concentrations were determined by HPLC, and DPs were generated to compare pharmacokinetic parameters. In five of nine patients, parameters deviated beyond ±10%. Even with the narrower bioequivalence requirements for mandatory substitution in Denmark, there are some patients who experienced serious clinical consequences (relapse in a seizure-free patient, status epilepticus, epidural hematoma due to ataxia with falls) in association with a change in preparation, and significant corresponding alterations in plasma levels could be demonstrated by comparative pharmacokinetic testing.

1. Introduction

Generics have become a part of antiepileptic drug (AED) treatment, and were the topic of the Presidential Symposium of the 27th International Epilepsy Congress [1–4]. Whereas quality-controlled generic AEDs should cause no serious problems [1] and could help to bring the newer AEDs to the developing world more rapidly [2], uncontrolled substitutions and continuity of supply are issues of concern [3] that have been addressed in national political actions [4]. Bioequivalence testing is performed in populations and does not preclude larger differences in individual patients. In the case of a narrow therapeutic index with either drug, individual patient, or both, larger differences between LTG preparations could cause relapses in seizure-free patients or toxic reactions. According to several reports [5,6], clinical problems of this kind have been encountered relatively frequently. However, objective data on the newer AEDs are lacking, and the question remains open whether the deviations that can be observed with generic substitutions exceed the day-to-day variations that occur without changes in preparation. Recently, Bialer [7] discussed the putative importance of individual rather than group bioequivalence data. In the present work, pilot data concerning the individual bioequivalence of lamotrigine (LTG) are reported.

Since April 2005, the legislature of Denmark has imposed on pharmacies the policy of delivering the cheapest of several preparations of any drug accepted as bioequivalent. The prices of drugs are monitored at 2-week intervals and change frequently. For those drugs for which many preparations exist, frequent shifts are experienced by patients in chronic AED treatment. Following political intervention during the preparation of the new legislature [4], the Danish Medicines Agency defined the bioequivalence standard that must be met by generic antiepileptic drugs accepted for automatic substitution: the 90% confidence interval for the average pharmacokinetic value must be within 90–111% of the reference (brand) pharmacokinetic value tested in a population of healthy controls [8].

Lamotrigine is the most frequently used AED in Denmark [9]. Numerous generics were introduced in mid-2005, and following mandatory substitution, many patients reported problems to their physicians, the Danish Epilepsy Association, and the public media. Some of these reports indicated breakthrough seizures resulting from reduced absorption of a substituted preparation; others indicated toxicity as a result of increased absorption; yet others were less clear. To exempt patients from mandatory substitution, the Danish Medicines Agency requests documentation of pharmacokinetic (PK) deviations. For complete PK documentation, we offer patients with such complaints the opportunity to undergo determination of their comparative daily profiles (DPs) of LTG plasma concentrations, to prove or disprove that their problems are

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due to shifts in the preparation used. Nine patients accepted this offer. The findings are reported here as a pilot investigation.

2. Methods

2.1. Patients

Nine patients on chronic LTG treatment underwent determination of their DPs. Eight patients spontaneously reported problems that they attributed to shifts in the preparation used and requested clarification of their individual bioequivalence data. One patient was afraid of changing the LTG preparation and requested the DP data to prepare for a change. Clinical and drug treatment data are summarized in Table 1. Eight patients were outpatients of the Danish Epilepsy Centre, and one was an outpatient of the epilepsy clinic of Copenhagen University Hospital Rigshospitalet.

Before admission, the patients had been on stable treatment with a proprietary LTG for at least 2 weeks. In both clinics the use of drug dispensers to ensure full drug intake is routine and recommended with regular reminders. All nine patients had requested clarification of a perceived problem with shifts in the LTG preparation used. The rationale behind determining the comparative DPs for this purpose and the procedures involved were explained to the patients in detail, and all fully understood the particular importance of absolute adherence to their drug regimen during the investigation period. Major compliance problems during the study were therefore unlikely. However, to adjust for possible deviations in intake before admission, DPs were determined after a delay of 3 days, at which time drug intake was supervised by experienced personnel. Thereafter, the patients were switched to the generic preparations with which they had reported problems. In one patient, the sequence was the reverse (proprietary drug after generic), and one patient who had received two generics was not entirely sure which one had caused the problem. The DP for comparison was obtained 7 to 15 days after beginning the generic preparation and followed the schedule applied earlier in comparative studies of sustained-release carbamazepine preparations [10,11].

Seven patients were on LTG monotherapy or on combinations without pharmacokinetic interactions (PKIs); one was on an enzyme-inhibiting (valproic acid, VPA) and one on an enzyme-inducing (phenobarbital, PB) combination. In the patient receiving PB, three different preparations were compared, and for one of these, DPs were obtained twice. In the remaining patients, two DPs were obtained: one while the patient was taking proprietary LTG and one while on the generic preparation. All patients were on twice-daily regimens: four with equal or approximately equal morning and evening doses at 8:00 and 19:00, and four with asymmetrical doses at the same times (Table 1).

2.2. Blood collection

Blood samples were taken at 3-hour intervals starting from a morning trough level and extending over 24 hours. The patient from Rigshospitalet had a different schedule with 4-hour intervals from morning to evening. The timing of evening drug intake and of blood sampling during the night turned out to be difficult to standardize in ward routine, and time differences of up to 1.5 hours between comparative DPs occurred. We therefore restricted the data analysis to the period from morning trough level to evening.

2.3. Serum concentrations

All LTG determinations were performed at the laboratory at The Danish Epilepsy Centre by HPLC according to the procedure described by Søndergaard Khinchi et al. [12].

2.4. Data analysis

The following PK parameters were identified and compared: morning trough level (MTL), maximum plasma concentration (C_{max}) of the DP, minimum plasma concentration (C_{min}) of the DP, time to reach observed maximum concentration (t_{max}). The area under the curve (AUC) was calculated for all DPs in the time interval from 7:30 to 16:30 as a measure of total drug absorption. The findings were referred to the accepted bioequivalence range for AEDs of 90–111% of the reference preparation as used by Danish legislation [8].

3. Results

The patients' complaints and pharmacokinetic findings are summarized in Table 2. Five of the nine patients (Nos. 1, 3, 4, 6, and 8) showed PK deviations beyond the limits set by the Danish Medicines Agency in at least one relevant parameter (Table 2). In three of these patients (Nos. 3, 6, and 8), several parameters deviated and were consistent with reports of serious consequences of a shift in preparation, that is, seizure relapse in one seizure-free patient, status epilepticus in another, and gait ataxia with falls, skull fracture, and epidural haematoma in the third (Table 2 and Figs. 1A and B). In patients 1 and 4 only one PK parameter deviated and this did not explain the complaint. In patient 9 co-medicated with VPA and with a 1-week interval between the DPs, changes in C_{max} and t_{max} were consistent with a spontaneous report of transient morning ataxia, even though C_{max} deviations between the LTG preparations were below 10% (Fig. 1C). Of the three remaining patients for whom the preparations were fully bioequivalent, one had made no complaints but asked for a prophylactic investigation, the second had made amorphous and clinically unconvincing complaints, whereas the third had convincingly reported an increase in seizures. However, she had received several generic preparations, and it is possible that the generic investigated was not the one that caused the problem.

4. Discussion

The ongoing debate about the safety of generic substitution of AEDs is hampered by a lack of scientific evidence. Toxicity resulting from a shift to a preparation with higher bioavailability has been clearly demonstrated for carbamazepine sustained-release [10,11] preparations but not for newer AEDs, although level-dependent side effects have been described with LTG [13]. Reports of seizure relapse caused by a change to a product with lower bioavailability and the subsequent fall in plasma levels below the individual therapeutic threshold [12] lack confirmation with comparative PK data. The present pilot investigation provides, for the first time, such data with different formulations of LTG.

Bioequivalence is defined by the 90% confidence interval of relevant PK parameters in a group of tested persons falling within a range of usually 80–125% of the reference product. In Denmark, this range has, for AEDs, been narrowed to 90–111%. These figures are not directly applicable to clinical conditions but suggest that the observed deviations in individuals would "normally" be within this range. The definition does not preclude sporadic larger deviations, and this is what we have observed. These deviations were consistent with reports of both seizure relapse and status epilepticus indicating lower bioavailability, and locomotor ataxia with the

Table 1
Patient overview

Patient	Diagnosis	Sex	Age	Co-medication	Lamotrigine schedule
1	Cryptogenic TLE[a]	F	45	VGB 2000 mg	300 + 350 mg
2	Absences with GTCS	M	52	None	300 + 300 mg
3	Epilepsy with focal and generalized seizures	M	25	None	300 + 200 mg
4	Childhood absence epilepsy with GTCS	F	35	LEV 1000 mg	400 + 550 mg
5	Epilepsy with focal and generalized seizures	M	49	None	400 + 400 mg
6	Mesial temporal lobe epilepsy	F	54	None	200 + 300 mg
7	Symptomatic TLE	M	40	TPM 800 mg	600 + 400 mg
8	Unclassified	M	57	TPM 300 mg, PB 150 mg, CLB 10 mg	400 + 600 mg
9	Juvenile myoclonic epilepsy	M	37	VPA 300 mg, LEV 1000 mg, ESM 500 mg	400 + 400 mg

[a] TLE, temporal lobe epilepsy; GTCS, generalized tonic–clonic seizures; CLB, clobazam; ESM, ethosuximide; LEV, levetiracetam; PB, phenobarbital; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid.

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Table 2
Comparative pharmacokinetic data on LTG in 9 patients with preparation shift

Patient	Complaint	Preparation (interval in days)	MTL	C_{min}	C_{max}	AUC (7:30–16:30)	Conclusion
1	Seizures and vertigo	Lamictal	33	32	52	390	AUC = −13%
		LTG Copyfarm (15)	34	32	52	345	
2	Vague	Lamictal	26	26	38	286	Full bioequivalence
		LTG Hexal (14)	25	23	35	267	
3	(Fig. 1A) Ataxia, falls	Lamictal	22	22	34	–[a]	C_{max} = +21%
		LTG Copyfarm (14)	30	30	41		
4	Increase in seizure frequency	Lamictal	44	38	61	453	C_{min} = +16%
		LTG Ratiofarm (10)	45	44	64	467	Complaint unconfirmed
5	Increase in seizure (but possibly with other generic)	Lamictal	26	26	39	291	
		LTG Ratiopharm (15)	24	24	38	296	Full bioequivalence
6	Relapse after 1.5 seizure-free years	LTG Actavis	23	22	34	254	C_{min} = −12%
		Lamictal (13)	28	25	41	276	C_{max} = −17%
							Complaint confirmed
7	No complaint but afraid of relapse with preparation shift, prophylactic	Lamictal	34	32	46	419	
		LTG 1A Farma (15)	42	29	48	443	Full bioequivalence
8	(Fig 1B) Status epilepticus	Lamictal	31	24	42	325	C_{min} = −17%
		LTG Actavis 1 (12)	26	20	37	273	AUC = −16%
		LTG Actavis 2 (9)	30	20	36	285	AUC = −12%
	None	LTG Copyfarm (9)	32	23	44	326	Complaint confirmed
9	(Fig. 1C) Temporary ataxia	Lamictal	41	39	51	435	Earlier t_{max}
		LTG Stada (7)	42	38	54	446	Higher C_{max}? DP's interval!

[a] Not calculated to due to the 4-hour blood sampling interval.

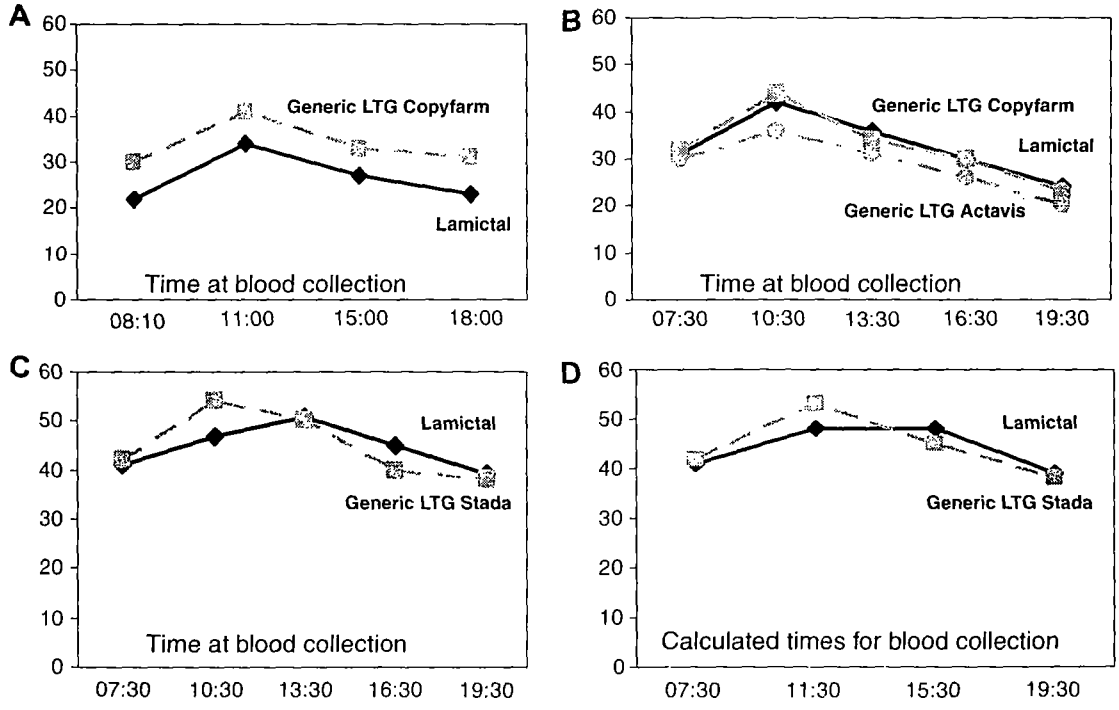

Fig. 1. Graphic presentations of daily profiles (DPs) of (A) patient 3, who experienced gait ataxia resulting in falls, a skull fracture, and an epidural haematoma; (B) patient 8, who experienced status epilepticus; (C) patient 9, who reported transient gait ataxia with generic LTG Stada starting ca. 1.5 hours after the morning dose; and (D) patient 9, for whom 3-hour-interval data (C) were extrapolated to the case of 4-hour blood sampling intervals.

consequence of severe head trauma indicating higher bioavailability. All generics used in this investigation passed tests claiming their bioequivalence with proprietary LTG according to the aforementioned definition. However, five of nine subjects manifested deviations greater than 10% in at least one PK parameter. In the three cases in whom more than one parameter exceeded this range, there was consistency with the clinical complaint that prompted the investigation.

It is unclear what causes these deviations. It is unlikely that they are due to the formulation of the generics as they have all passed the bioequivalence test. In this small group of patients, a particular generic preparation was bioequivalent in one patient, yet had a significantly higher bioavailability in another patient. These observations favor deviations being due largely to individual, currently undefined factors of absorption interacting with the formulation of the preparations.

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Because of plasma level fluctuations [14], deviations observed in the DPs were not necessarily apparent when only morning trough levels were compared. There are no standard methods for establishing DPs for AEDs. Ideally, blood sampling would have to take place at 30- to 60-minute intervals after drug intake, followed by increasing intervals until the next dose. Compromises are, however, necessary when blood sampling needs to be integrated into daily hospital routine. The 3-hour schedule used for the eight patients in the present study had previously been used with CBZ sustained-release preparations [10,11]. It appears to provide reasonably informative data although it may underestimate the C_{max} value. This was clearly the problem with the 4-hour schedule used in patient 3 which may fail to detect differences in t_{max}. This is illustrated for patient 9 for whom the 3-hour-interval data (Fig. 1C) are extrapolated into data that would have been obtained with 4-hour sampling (Fig. 1D). The 4-hour interval carries an additional risk of rather imprecise C_{max} measurements, on which derived calculations like $C_{max/min}$ and total absorption depend.

Care should always be taken to compare DPs under steady-state conditions. We may have failed to do this in patient 9, who had reported ataxia 2 weeks after a shift in preparation but was reinvestigated after 1 week, mainly to avoid his reexposure to toxicity. Because he was also taking valproic acid (VPA), his LTG half-life, according to the literature, was approximately 50 hours [15] and steady state was expected to be reached after 10–11 days, that is, 5 half-lives. Even if the shorter half-lives indicated by our findings [14] are assumed, the interval was probably too short.

Bioequivalence is generally tested by comparison of single doses of two preparations in a group of healthy volunteers. Our findings demonstrate that, under realistic clinical conditions, this does not exclude larger deviations in bioavailability. Two of the nine patients investigated experienced life-threatening complications after a shift in preparation, and their comparative DPs revealed PK deviations greater than the ±10% permitted in Denmark. If the usual bioequivalence range of 80–125% (defined by inclusion in the 90% confidence interval) were applied, the deviations related to these serious complications would be considered consistent with bioequivalence. Similarly, in the study of Mayer et al. [11], 8 of 13 patients on a subtoxic dose/level of CBZ developed ataxia when they were switched to another preparation although the bioequivalence range of 80–125% was not surpassed.

The argument is often heard that deviations in absorption between different products may not exceed the fluctuations occurring with continuous use of the same product. Evidence for this argument, however, is lacking and there is an obvious need for clarification by controlled studies. Our investigation includes repetitive DPs with the same preparation in one case. Here the two DPs were practically identical (see Fig. 1B).

5. Conclusions

5.1. Methodology of DPs

Comparative DPs provide differentiated information on the bioequivalence of different LTG preparations. A 3-hour sampling schedule may be adequate to elucidate suspected clinical problems. For a scientific study, more frequent sampling would be necessary, especially in the first phase after drug intake. To ensure investigation at steady state, 2 weeks of intake of a stable dose should be required before a DP is determined, and in the case of VPA co-medication, 3 weeks.

5.2. Bioequivalence and interchangeability

Serious complications following shifts in preparations could be confirmed by deviations in two relevant PK parameters greater than ±10% but not necessarily beyond the common international bioequivalence range of 80–125%.

The present investigation represents a pilot study documenting that serious problems arising from differences in individual bioavailability can occur with shifts in AED preparations fulfilling the accepted population parameters for bioequivalence. It does, however, not allow conclusions to be drawn concerning the magnitude of the problem. Our patients were retrospectively selected, which may have created a bias toward cases with deviant bioequivalence. Prospective randomized studies are necessary comparing day-to-day variations with unchanged preparations to variations after preparation shift.

Conflict of interest statement

K.A.N., M.D., and E.T. report no conflicts of interest. P.W. is on an advisory board of UCB, has conducted a clinical AED study for Neurosearch, and, as a speaker at professional meetings, has received sponsorship by various pharmaceutical companies.

Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

[1] Perucca E. Generic antiepileptic drugs: general overview [abstract]. Epilepsia 2007;48(s7):6.
[2] Dua T. Essential antiepileptic drugs and the treatment gap [abstract]. Epilepsia 2007;48(s7):6.
[3] Gidal BE. Generic substitution [abstract]. Epilepsia 2007;48(s7):6.
[4] Wolf P. Political campaign in Denmark [abstract]. Epilepsia 2007;48(s7):6.
[5] Andermann F, Duh MS, Gosselin A, Paradis PE. Compulsory generic switches of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia 2007;48:464–9.
[6] Krämer G, Steinhoff BJ, Feucht M, Pfäfflin M, May TW. Experience with generic drugs in epilepsy patients: an electronic survey of members of the German, Austrian and Swiss Branches of the ILAE. Epilepsia 2007;48:609–11.
[7] Bialer M. Generic products of antiepileptic drugs: is it an issue? Epilepsia 2007;48:1825–32.
[8] http://www.laegemiddelstyrelsen.dk/1024/visLSArtikel.asp?artikelID=6410.
[9] http://www.medstat.dk/MedStatDataViewer.php.
[10] Wolf P, May Th, Tiska G, Schreiber G. Steady state concentrations and diurnal fluctuations of carbamazepine in patients after different slow release formulations. Drug Res 1992;42:284–8.
[11] Mayer Th, May TW, Altenmüller D-M, Sandmann M, Wolf P. Clinical problems with generic antiepileptic drugs: comparison of sustained-release formulations of carbamazepine. Clin Drug Invest 1999;18:17–26.
[12] Søndergaard Khinchi M, Nielsen KA, Dahl M, Wolf P. Lamotrigine therapeutic thresholds. Seizure Eur J Epilepsy 2008, in press. doi:10.1016/j.seizure.2007.11.023.
[13] Hirsch LJ, Weintraub D, Buchsbaum R, et al. Correlating LTG serum concentration with tolerability in patients with epilepsy. Neurology 2004;63:1022–6.
[14] Nielsen KA, Dahl M, Tømmerup M, á Rogvi Hansen B, Erdal J Wolf P. Daily fluctuations of lamotrigine (LTG) plasma levels [abstract]. Epilepsia 2007;48(s7):42.
[15] Garnett WR. Lamotrigine, interaction with other drugs. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs. Philadelphia: Lippincott, Williams, & Wilkins; 2002. p. 380–8.

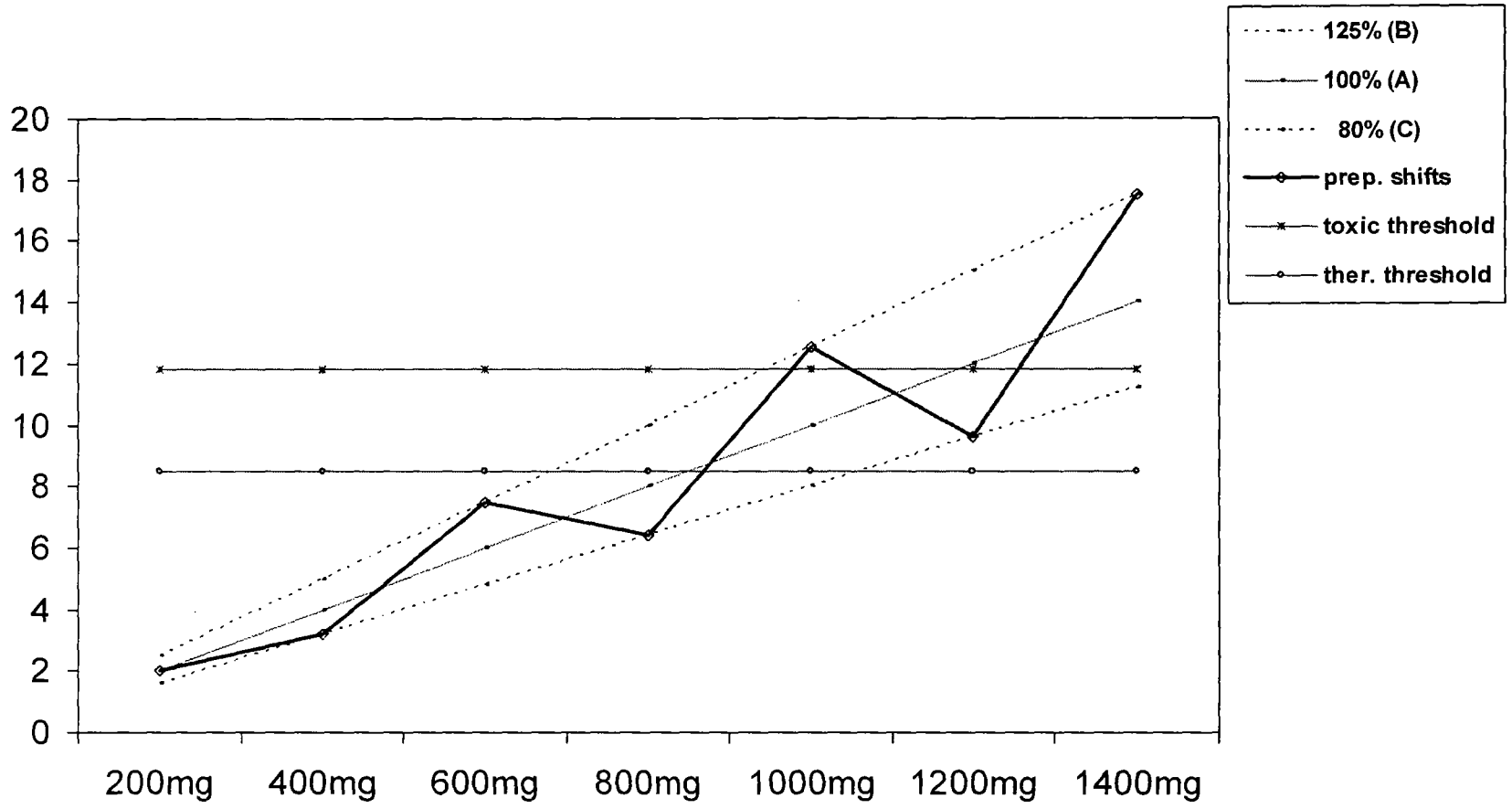
125% (B)
100% (A)
80% (C)
prep. shifts
toxic threshold
ther. threshold
20
18
16
14
12
10
8
6
4
2
0
200mg
400mg
600mg
800mg
1000mg
1200mg
1400mg

Figure 1: Drug plasma levels during dose titration with carbamazepine while switching between different drug preparations—a model case.

In this model patient, carbamazepine has a therapeutic threshold of 8.5 µg/ml and a toxic threshold of 11.8 µg/ml, and the reference product (generic A) has a level-dose ratio of 1:100. Generic product B has a bioavailability of 125% and generic C has a bioavailability of 80%, compared with the reference drug. A dose of 1,000 mg is therapeutic with generic A, toxic with B, and subtherapeutic with C. The therapeutic doses with generics B and C would be 800 mg and 1200 mg, respectively. Plasma drug levels rise in a linear fashion if only one of the preparations (generic A) is used, enabling determination of the therapeutic dose. When repeated preparation shifts occur during titration (generics B and C), the plasma levels of carbamazepine will rise in a zigzag fashion and might not come to lie within the therapeutic window. It might, therefore, not be discovered that this patient can actually be kept seizure-free with carbamazepine. This could happen even if plasma levels are measured during titration, because the doctor is most likely to ascribe the nonsensical plasma concentration values to noncompliance on the part of the patient.