Comparative daily profiles of Lamotrigine

Marit Dahl[1], Kirsten A. Nielsen[1] & Peter Wolf[1,2]

[1]Danish Epilepsy Centre, Kolonivej 1, DK-4293 Dianalund, Denmark, and [2]National Hospital, Neurocentre, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

Objective: To discuss the purpose and methodology of comparative daily profiles of Lamotrigine (LTG).

Rationale: Many patients on LTG treatment in Denmark report problems following preparation shifts. These are common since legislature imposes on the pharmacies always to deliver the cheapest preparation, and the prices change frequently. In six of these patients we have compared the daily profiles (DPs) of LTG levels with different preparations to quantify deviations of relevant pharmacokinetic (PK) data including morning trough level (MTL), Cmax, Cmin, tmax and Cmax/min.

Material and methods: LTG determinations were performed with HPLC. Blood samples were taken at 3-hour intervals from MTL over 24 hours. One patient had a deviant schedule with 4-hour intervals from morning to evening. The first DP was determined with stable chronic medication of branded LTG, and the DP for comparison after one to two weeks following shift to a generic preparation. All patients were on a b.i.d. schedule (Table 1), three with symmetric and three with asymmetric dosing. The timing of evening drug intake and of blood sampling during the night turned out to be difficult to standardize, and deviations of up to 1:15 hrs occurred. The analysis of the results was therefore restricted to the sequence from morning to evening trough levels.

Table 1: Patient overview

Pat	Diagnosis	Sex	Age	Co-medication	LTG schedule
1	Cryptogenic TLE	f	45	VGB	300 + 350 mg
2	Absences with GTCS	m	52	none	300 + 300 mg
3	Ep with focal a. gen. sz.	m	25	none	300 + 200 mg
4	CAE with GTCS	f	35	LEV	400 + 550 mg
5	unclassified	m	57	TPM, PB, CLB	400 + 600 mg
6	JME	m	37	VPA, LEV, ESM	400 + 400 mg

Results: Although the Danish Medicines Agency has set the bioequivalence range of AEDs for automatic preparation shift to ±10% of the original, three of the patients showed deviations beyond these limits of at least one PK parameter (Tab. 2), and in two cases this deviation confirmed reports of serious consequences of a preparation shift, gait ataxia with falls, skull fracture and epidural haematoma in one (Fig.1 and status epilepticus in the other (Fig. 2). In one patient with a one-week interval between the DPs, changes of Cmax and tmax were consistent with a report of transient morning ataxia (Fig. 3a) but the Cmax deviation was below 10%. In the two remaining cases, the findings did not support the patients' complaints which also clinically were unconvincing.

Table 2: Comparative pharmacokinetic data of LTG in 6 patients with preparation shift

Pat. and complaint	Preparation (interval days)	MTL	C_{min}	C_{max}	$C_{max/min}$	Conclusion
1 sz *and* vertigo	Lamictal LTG copyfarm (15)	33 34	32 32	52 52	1.63 1.63	full bio-equivalence
2 vague	Lamictal LTG hexal (14)	26 25	26 23	38 35	1.46 1.52	full bio-equivalence
3 (Fig. 1) ataxia, falls	Lamictal LTG copyfarm (14)	22 30	22 30	34 41	1.55 1.37	C_{max} +21%
4 increased sz frequency	Lamictal LTG ratiofarm (10)	44 45	38 44	61 64	1.60 1.45	C_{min} +16% complaint unconfirmed
5 (Fig. 2) none stat. epilepticus	Lamictal LTG copyfarm (12) LTG actavis 1 (12) LTG actavis 2 (14)	31 26 30 32	24 20 20 23	42 37 36 44	1.75 1.85 1.80 1.91	C_{min} -17%
6 (Fig.3) temporary ataxia	Lamictal LTG stada (7)	41 42	39 38	51 54	1.31 1.42	earlier t_{max}, higher C_{max}? DP's interval!

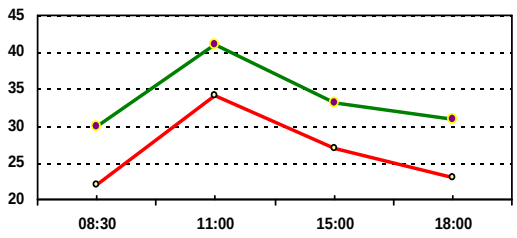

Fig 1: Comparative DPs of patient 3 with ataxia, falls, skull fracture and epidural haematoma. Red: branded LTG, green: generic LTG "copyfarm".

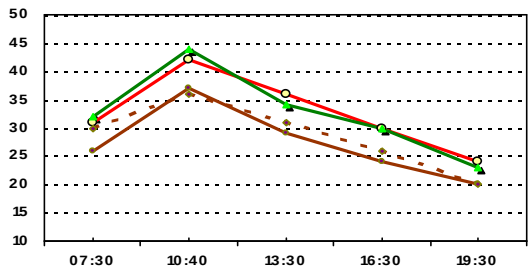

Fig 2: DPs of patient 5 on co-medication with TPM, PhB and CLB, asymmetric dose. Status epilepticus at shift from branded LTG (red) to generic LTG "actavis" (brown) which at two occasions shows lower bioavailability whereas LTG "copyfarm" (green) that caused toxicity in patient 3 does not differ from brand in this case.

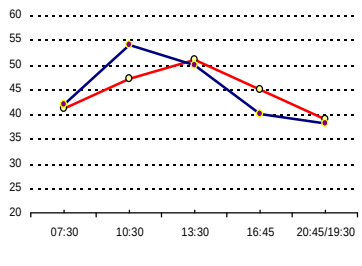

Fig. 3a: Comparatíve DPs of patient 6 on co-medication with VPA. Transient gait ataxia with generic LTG "stada" (blue) 1 ½ hrs after dose. Comparison with generic before steady state and without ataxia. Deviation of Cmax is within bio-equivalence limits. Earlier tmax fits with complaint and indicates more rapid absorption of generic.

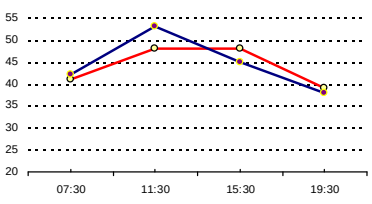

Fig. 3b: Blood sampling in case 6 transformed by interpolation into a 4 hr. schedule. The information about this patient's uncommonly slow absorption of branded LTG disappears.

Discussion (1): Sampling schedule

As the deviations observed were not necessarily apparent in the MTLs, comparisons of bioavailability in chronic treatment need to be based upon DPs. There are no standard methods to establish these in clinical conditions. Ideally, blood sampling would have to take place at 30 – 60 min intervals after drug intake, followed by increasing intervals until the next dose. But compromises are necessary because blood sampling needs to be integrated into daily hospital routine. The three-hour schedule appears to provide reasonably informative data, whereas a four-hour schedule may fail to detect differences in tmax as demonstrated in fig. 3b. It also carries a risk of rather imprecise Cmax measurements from which other calculations like Cmax/min or total absorption depend.

Discussion (2): Intervals

Care should be taken always to compare DPs in steady state conditions. We failed this in patient 6 who had reported ataxia 2 weeks after preparation shift but was re-investigated after 1 week, mainly to avoid re-exposing him to toxicity. As he is on co-medication with Valproic Acid (VPA), his LTG half-life is app. 50 hrs and steady state expected after 10 – 11 days, i.e. 5 half-lives.

Discussion (3): Clinical bioequivalence

Bioequivalence is tested by comparison of a single dose of two preparations in a group of healthy volunteers. Our findings demonstrate that this does not exclude larger deviations in bioavailability in realistic clinical conditions. Two of our patients experienced life-threatening complications after preparation shift, and their comparative DPs showed PK deviations beyond the 10% permitted in Denmark. If the usual bioequivalence range of 80 – 125% were applied, the deviations related to these serious complications would even be considered as consistent with bioequivalence.

Conclusions: Comparative DPs provide differentiated information on the bioequivalence of different LTG preparations which can be missed when only morning trough levels are considered. Serious complications following preparation shifts could be confirmed by deviations in relevant PK parameters beyond the nationally accepted ± 10%. If the usual international range of ± 20% were used, these deviations would even be considered as unproblematic.

To prevent similar complications, bioequivalence limits for AEDs should generally be set at 90 – 111% of the reference preparation.

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