

Comparative daily profiles of various Lamotrigine preparations.

Marit Dahl¹, Peter Wolf^{1,2}

¹Danish Epilepsy Centre, Kolonivej 1, DK-4293 Dianalund, Denmark

²Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen Ø. Denmark

Rationale: Generic substitution of all drugs by the pharmacies is now compulsory in Denmark, and the bioequivalence range for AEDs has been set to 90 – 111 % of the original product. Patient complaints about serious problems following substitution of Lamotrigine (LTG) have prompted us to investigate comparative daily profiles in view of obtaining detailed pharmacokinetic data for comparison including C_{max} , C_{min} , t_{max} , $C_{max/min}$ and C_x . Until now, six patients have been investigated.

Case 1: 37 year old male with JME.

Regimen: LTG 800 mg, VPA 300 mg, LEV 1000 mg + ESM 500 mg

Complaint: 2 weeks after shift of preparation vertigo, nausea and inability to walk starting ca. 1 hour after intake and lasting 2 – 3 hours.

Clinical conclusion: Ataxia related to high LTG levels with preparation of higher bioavailability.

Profiles: brand followed by change to same generic and control after one week on a day without complaints.

Finding: higher bioavailability of generic confirmed.

Case 2: 45 year old female with cryptogenic TLE

Regimen: LTG 650 mg + VGB 2000 mg.

Complaint: after change to generic, relapse of complex focal sz. after 8 years, together with vertigo, nausea

Clinical conclusion: Contradictory report of both level-dependent side effects and sz breakthrough.

Profiles: brand followed by change to same generic and repetition after 15 days.

Finding: no notable difference.

Case 3: 52 year old male with absence epilepsy and rare GTCS.

Regimen: LTG mono 600 mg.

Complaint: After 6 years without sz and change to generic LTG, symptoms which he was afraid indicated recurrence of seizures.

Clinical conclusion: no indication of epileptic seizures.

Profiles: brand followed by shift to same generic and control after 2 weeks.

Finding: no notable difference.

Case 4: 25 year old moderately handi-capped male with focal and generalized sz.

Regimen: LTG mono 500 mg.

Complaint: after shift to generic, increased instability of gait, repeated falls, one leading to skull fracture and epidural hematoma.

Clinical conclusion: ataxia with preparation of higher bioavailability.

Profiles: brand followed by shift to same generic and control after 2 weeks.

Finding: substantially higher bioavailability of generic consistent with drug-induced ataxia.

Case 5: 35 year old female with absences and GTCS since childhood

Regimen: LTG 950 mg +LEV 1000 mg

Complaint: after shift to generic seizure relapse after 15 years.

Clinical conclusion: unconvincing; had not been completely seizure free before preparation shift.

Profiles: brand followed by change to same generic and control after 10 days

Finding: no notable difference.

Case 6: 57 year old slightly handicapped male with cryptogenic localised-epilepsy and GTCS

Complaint: History of a night with uncountable seizures spontaneously ending in the morning, followed by drowsiness and apathy for 24 hours, few days after shift to generic LTG.

Clinical conclusion: strong suspicion of status epilepticus due to change to preparation with lower bioavailability.

Profiles: brand followed by shift to same generic and repetition after 12 + 22 days. After demonstration of lower bioavailability, shift to different generic, 4th profile taken again after 12 days.

Finding: lower bioavailability of first generic. Clinical observation: on day 8 after shift, status-like series of numerous mild complex focal, then tonic seizures, necessitating 2x 20 mg Clobazam. With second generic, almost no difference from brand, but also here one series of seizures requesting CLB administration, no drug levels that day.

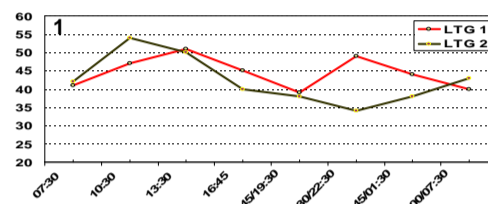
Discussion

Bioequivalence: Although the release of new AED preparations in Denmark requires bioequivalence studies respecting a range of 90 – 111%, larger deviations connected with serious morbidity could be observed with continuous medication. These were not necessarily apparent when only morning trough levels were compared but required the determination of daily profiles.

Monitoring scheme: The monitoring schedules are compromises due to adaptation to the practical situation on the wards. Blood sampling at 3 hr intervals over 24h was feasible in the Danish Epilepsy Centre, Dianalund, whereas the situation at the Copenhagen University Hospital (case 4) allowed only for 4 samples at 4 hr intervals. Shorter intervals especially in the first 3 – 4 hours following drug intake would give more precise information especially in cases with short LTG half-life. The four hour schedule may fail to detect differences in t_{max} and carries a risk of imprecise C_{max} measurements from which other calculations depend. Nonetheless, relevant information was obtained in the presented cases.

Relation of level to last drug intake: In the practice on a ward, precise timing of drug intake and blood sampling is more difficult to organize in the evening than in the morning. Thus the evening C_{max} may be less reliable; the night curve may be influenced by this especially in cases with enzyme-inducing comedication and consequent short half-life (see cases 1 + 6)

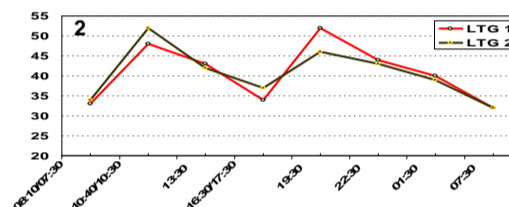
Intervals, and proof of principle: The intervals between two investigations should be considered in relation to co-medication and half-life. In case 1 with enzyme-inhibiting comedication the difference in bioavailability is not striking, but it must be noted that the ataxia, reported after 2 weeks with previous preparation shift, was not present when the 2nd profile was taken after 1 week. However, there is proof of principle.



LTG 1: Lamictal
LTG 2: Ltg Stada

	LTG 1	LTG 2	difference
Morning trough	41	42	+ 2.5%
C_{max}	51	54	+ 6.0%
C_{min}	39	34	- 14.0%
$C_{max/min}$	1.31	1.59	+ 21.5%
C_x	44.5	42.4	- 4.7%

LTG 400 + 400 mg
VPA 300 mg
LEV 1000 mg
ES 500 mg



LTG 1: Lamictal
LTG 2: LTG copyfarm

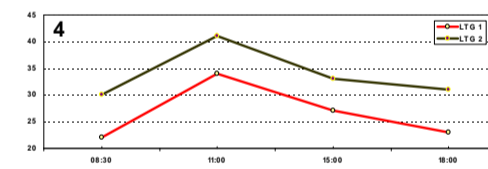
LTG 300 + 350 mg
VGB 1000 + 1000 mg



LTG 1: Lamictal
LTG 2: Ltg Hexal

	LTG 1	LTG 2	difference
Morning trough	26	25	- 4.0%
C_{max}	38	35	- 8.0%
C_{min}	25	23	- 8.0%
$C_{max/min}$	1.52	1.52	0
C_x	29.75	27.9	- 6.0%

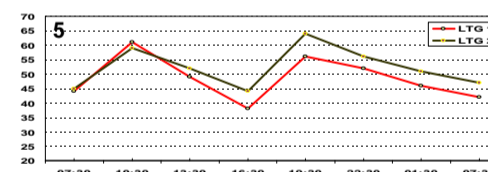
Monotherapy
LTG 300 + 300 mg



LTG 1: Lamictal
LTG 2: Ltg Copyfarm

	LTG 1	LTG 2	difference
Morning trough	-	-	-
C_{max}	34	41	+ 21.0%
C_{min}	22	30	+ 37.0%
$C_{max/min}$	1.55	1.37	- 12.0%
C_x	26.5	33.8	+ 27.0%

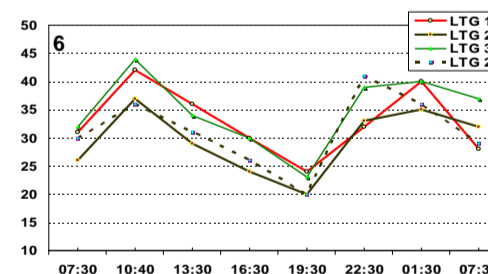
Monotherapy
LTG 300 + 200 mg



LTG 1: Lamictal
LTG 2: Ltg Ratiopharm

	LTG 1	LTG 2	difference
Morning trough	41	42	+ 2.5%
C_{max}	51	54	+ 6.0%
C_{min}	39	34	- 14.0%
$C_{max/min}$	1.31	1.59	+ 21.5%
C_x	44.5	42.4	- 4.7%

LTG 400 + 550 mg
LEV 500 + 500 mg



LTG 1: Lamictal
LTG 2 & 2B: Ltg actavis
LTG 3: Ltg Copyfarm

	LTG 1	LTG 2	LTG 3	2/1	3/1	3/2
C_{max}	42.0	37.0	44.0	-12.0%	+4.7%	+19.0%
C_{min}	24.0	20.0	23.0	-17.0%	-4.2%	+15.0%
C_x	32.9	30.3	34.9	-8.0%	+6.0%	+15.4%
$C_{max/min}$	1.75	1.9	1.9	+5.7%	+9.3%	+2.7%

LTG 400 + 600 mg
TPM 150 + 150 mg
PB 0 + 150 mg
CLB 5 + 5 mg