Pharmacotherapeutics of epilepsy: use of lamotrigine and expectations for lamotrigine extended release

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Abstract: The goal in managing patients with epilepsy is complete seizure freedom. Pharmacotherapeutic management of epilepsy is complicated by multiple syndromes, inter-individual differences in drug sensitivities, inter-individual differences in drug disposition, and drug interactions. Most anti-epileptic drugs (AEDs) have a therapeutic window with only a 2- to 3-fold concentration range. Extended release formulations offer advantages over their immediate release counter parts with less fluctuation in the serum concentration vs time curve and improved compliance. However, missed doses are more likely to result in prolonged "sub-therapeutic serum concentrations". Best clinical outcome may sometimes require twice daily dosing of extended release formulations even though approved for once daily dosing, as this optimally balances pharmacokinetics against compliance. Lamotrigine (LTG) is a broad spectrum AED with efficacy in partial and generalized epilepsy syndromes and good tolerability. Its metabolism is affected by co-medications which may be inducing, neutral or inhibiting of hepatic glucuronidation. Furthermore, though the average half-life in monotherapy is about 24 hours, there is a large inter-individual variation that may, including the extremes, approach a range of 10-fold. LTG-XR is expected to decrease fluctuation of serum concentration in the presence of hepatic inducing or neutral drugs. However, optimal clinical benefit in some patients may require twice daily dosing when metabolism is rapid.

Keywords: lamotrigine, antiepileptic drugs, extended release, epilepsy, pharmacokinetics

Introduction to management issues in epilepsy

Epilepsy is a common neurologic disorder affecting about 1% of the population (Hauser et al 1993). Pharmacotherapy with anti-epileptic drugs (AEDs) remains the major treatment modality for epilepsy. Management of epilepsy differs from the treatment of other chronic diseases in that a single breakthrough event has a major negative effect on quality of life (Gilliam 2002). Complete control of seizures is necessary as a single seizure impacts negatively on patient quality of life and independence. As an example, a single seizure usually limits driving privileges for a minimum of 3 months. Management of epilepsy is further complicated by variables such as: multiple epilepsy syndromes with varied pharmacosensitivities, inter-individual differences within a syndrome, and inter-and intra-individual differences in AED disposition.

This review will sequentially overview: therapeutic management issues in epilepsy, role of extended release formulations, clinical outcomes with currently available extended release formulations, lamotrigine (LTG) and LTG extended release (-XR) pharmacokinetics, LTG efficacy in epilepsy syndromes, LTG safety and tolerability, LTG impact on quality of life, and a summary of the place of LTG- XR in epilepsy management.

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Management issues in epilepsy

Epilepsy syndromes

Epilepsy is actually a group of disorders sharing the occurrence of unprovoked seizures. Over 30 epilepsy syndromes were described by the Commission on Classification and Terminology of The International League Against Epilepsy (1989) with varied seizure expression, age of onset, pharmacologic sensitivity, and prognosis. The initial categorization usually begins with determination of partial (focal) or generalized (simultaneous bihemispheric) onset. Generalized epilepsies may be idiopathic with a good prognosis and include the syndromes of childhood absence, juvenile absence, and juvenile myoclonic epilepsy (Valentin et al 2007). These syndromes are genetically based and to date underlying alterations of ion channels and neurotransmitter receptors that modulate synaptic transmission have been identified as the underlying cause (Helbig et al 2008). Generalized epilepsies may be symptomatic due to a broad range of genetic or catastrophic cerebral insults with a poor overall prognosis and include syndromes such as infantile spasms, Lennox-Gastaut, and progressive myoclonic epilepsies (Duchowny and Harvey 1996). Partial epilepsies have focal onset of seizures usually from the temporal or frontal lobes and less commonly from the parietal or occipital lobes. Etiologies of partial epilepsies are varied including mesial temporal sclerosis, cortical dysgenesis, vascular malformations, tumors, and in a minority primary genetic defects.

AEDs may be effective in select syndromes or may even worsen certain epilepsy syndromes and then are termed "narrow spectrum" (Genton 2000). Others are likely to be effective in many epilepsy syndromes and are often referred to as "broad spectrum". Management is further complicated in that our knowledge of syndromes remains quite superficial and in therapeutics for a single epilepsy syndrome a drug might work for one individual but another drug may be required for seizure freedom in another. To date, there is no way to pre-identify an individual's AED sensitivity. Serum concentrations needed for seizure control also vary significantly across individuals (Schmidt and Haenel 1984) which has led to the term "individual therapeutic reference concentration" (Johannessen and Tomson 2006).

Epilepsy pharmacotherapeutics

Currently, more than 12 AEDs are available with mechanism(s) of action very incompletely understood. Most have been approved in the last decade. Use-dependent voltage-dependent sodium channel blockade is a common action of numerous AEDs including early drugs such as phenytoin and carbamazepine (Rogawski and Löscher 2004; Perucca 2005a). LTG is often simply categorized as a sodium channel blocker (Lang et al 1993). Inconsistent with this mechanism of action, LTG has a broad spectrum of activity in animal models and in current clinical use. LTG actions on high voltage activated calcium currents (Hainsworth et al 2001), hyperpolarization activated inward current (I h) (Poolos et al 2002), potassium currents (Huang et al 2004), and even nicotinic receptor channels are reported (Valles et al 2007). Many of the AEDs marketed over the last 15 years have had multiple sites of action identified (Rogawski and Löscher 2004; Perucca 2005a).

Most patients with epilepsy, nearly two-thirds, respond to the first drug or second AED tried (Kwan and Brodie 2000). However, the pivotal clinical trials leading to initial approval of an AED are done in highly intractable adult patients with partial epilepsy and a severe seizure burden (about one seizure per week) and who have failed multiple AEDs. Post-approval studies are then extended to include children with a similar spectrum of epilepsy. Monotherapy trials in Europe study the more typical patient with non-intractable epilepsy. These studies have failed to show differences in efficacy across AEDs, with most subjects becoming seizure free at low doses. However, AEDs have differed in terms of tolerability in this study design (Kwan and Brodie 2003). Few controlled trials of AEDs for other specific epilepsy syndromes exist.

In choosing an AED for a patient the major considerations are the triad: ease of use, efficacy, and tolerability. Ease of use considerations includes rapidity of titration rate, lack of serious idiosyncratic reactions, and lack of potential drug interactions. Efficacy includes consideration of the underlying epilepsy syndrome, and in situations of uncertainty regarding the specific syndrome, broad spectrum AEDs have advantages. Required serum concentrations of AEDs are often lower for generalized epilepsy syndromes when compared to partial (Schmidt and Haenel 1984). Tolerability includes dose-dependent side effects common to AEDs as a therapeutic class, such as dizziness, fatigue, unsteadiness, decreased concentration, and visual blurring. Side effects may be specific to an AED and may be beneficial, ie, weight loss, or harmful, ie, impaired memory.

Epilepsy pharmacokinetic parameters

The pharmacokinetic parameters of an AED impact on both efficacy and tolerability. Most AEDs have a small therapeutic window so that with a two to three fold change in serum concentration, seizures may become controlled but adverse events appear (Johannessen et al 2003).

Trough serum concentrations (C_{min}) may put individuals at increased risk of seizures whereas AED peak serum

concentrations (C_{max}) may lead to adverse events. A clear goal of therapy would be to maintain the AED serum concentration vs time curve in a narrow range without fluctuations. This scenario is also described as a flat serum concentration time curve. Integration of the time curve gives the area under the curve (AUC) that measures overall drug exposure. Of course, the AED concentration time curve in serum may not be super imposable upon cerebrospinal fluid or extracellular brain concentration vs time curves and this type of data is usually quite limited .

Half-life is an important pharmacokinetic variable. Drugs with short half-lives need to be taken 2, 3, or even 4 times per day to maintain peak and trough serum concentrations within a therapeutic window. Regimens with frequent daily dosing are very inconvenient and are associated with increased medication non-adherence. Non-adherence is inversely related to the number of daily doses. Claxton et al (2001) reviewed 76 studies and found a mean compliance of 71% for all dosing regimens combined that declined as the number of doses per day increased: 1 dose = 79%, 2 doses = 69%, 3 doses = 65%, and 4 doses 51% adherence. The difference between once and twice daily did not reach statistical significance though the difference between once and three times and once and four times per day did. Cramer et al (2002) showed that 72% of epilepsy patients missed doses and 45% reported having a seizure after a missed dose.

Finally, medication non-adherence (Osterberg and Blaschke 2005) and seizures result in increased health care utilization and cost. Begley et al (1994) detailed a model of the cost of epilepsy, including medical care and time lost from work, based on incidence and prognosis. Cost in 1990 dollars per patient was lowest for patients with remission after diagnosis and treatment, US $4,272, and highest for persons with intractable and frequent seizures, US $138,602 (Begley et al 1994). Population based studies from Europe have shown average annual health care costs of US $100 to US $2,000 for inactive cases, US $900 to US $3,000 for active cases and a 2- to 7-fold increase in cost for active cases with frequent seizures compared with active cases with few (Begley and Beghi 2002). A recent retrospective analysis of a managed care population revealed that 39% of patients were non-adherent based on AED refills and that this was associated with increased emergency room and in-patient hospital stays costing US $260 and US $1,799, respectively, per patient per year (Davis et al 2008).

Role of extended release formulations

The goal of extended release formulations is to take drugs with short half-lives and develop formulations with a "pseudo-long half-life" that allow once or twice daily dosing with near constant (flat) serum concentration vs time curves compared with the rapid release formulation, thus resulting in improved management. Firstly, the decreased peak serum concentration seen with use of extended release formulations is expected to decrease dose-dependent side effects that are often maximal several hours after an oral dose. Secondly, in theory the increased trough concentration should lead to improved seizure control. Thirdly, seizure control might be improved with extended release formulations by allowing increase of dose, bringing the mean steady state serum concentration closer to the peak value previously achieved with the immediate release formulation. Fourthly and finally, compliance is expected to improve with once or twice daily dosing as discussed in the preceding paragraph (Sommerville 2006; Verotti et al 2007). Patients often prefer once daily doing. One potential shortcoming of once daily dosing is that a missed dose may be more likely to result in a seizure. This is because the missed dose will result in a rapid decline in serum concentration based on the unmasking of the true short half-life of the AED (Table 1) (Levy 1994; Bialer 2007). For this reason, it has been argued that dosing extended release formulations, that are "approved" for once daily dosing, twice daily in many situations offers the highest probability of long-term seizure control based on improved therapeutic coverage that outweighs the modest decline of adherence (Bialer 2007). The increased compliance should be weighed against the impact of omitted dose(s) (Levy 1994). From a (theoretical) pharmacokinetic perspective, unless magnitude of non-compliance is reduced by more than two-thirds when a medication regimen is taken from three times a day to once a day dosing (assuming half-life of 12 hours), the increased compliance is unlikely to be advantageous and may actually be counter-productive in minimizing the occurrence of sub-therapeutic drug concentrations (Levy 1994). Non-adherence and subthreshold AED serum concentrations do relate to the

Table 1 Comparison of extended release to immediate release formulations

Potential benefits
Lower maximum blood concentration → improved tolerability
Increase minimum blood concentration → improved seizure control
Increase dose → improve seizure control
Patient preference for simplified dosing
Improved medication adherence (benefit may be offset by impact of a missed dose)
Potential harm
Impact of missed doses on serum concentration → seizure breakthrough

occurrence of breakthrough seizures. A recent observational study of AED post-ictal serum concentration, found a level less than half of the individual baseline serum concentration of AED in 44.3% of seizures (Specht et al 2003).

The development of extended release formulations is driven by the above described potential clinical benefit as well as the potential for patent extensions and marketing advantages. AEDs are also often used for psychiatric indications where once a day dosing may be especially critical for medication adherence (Rogawski and Löscher 2004; Johannessen Landmark 2008). Extended release formulations currently exist for phenytoin, carbamazepine, and valproic acid. Extended release formulations of lamotrigine, oxcarbazepine, and levetiracetam are under development. Successful development requires demonstration that the compounds are therapeutically equivalent (Sommerville 2006).

Outcomes with currently released extended formulations

Clinical outcome measures comparing extended release to immediate release formulations have included pharmacokinetic variables to assess bioequivalence and clinical measures of seizure frequency, adverse event frequency, patient preference, and quality of life measures. Two extended release formulations of carbamazepine indicated for twice daily dosing are marketed in the US: a capsule with three bead types each having a different rate of release (Carbatrol®; Shire) and an osmotic-release delivery system (Tegretol® XR; Novartis). Clinical development included testing in double-blind crossover studies demonstrating pharmacokinetic bioequivalence and no significant differences in seizure frequency but with improvements in adverse events, 55% for immediate release vs 13% for extended release, and patient preference for decreased dosing (Canger et al 1990; Tegretol OROS Study Group 1995). Pharmacokinetic benefit also probably came from flattening the serum concentration time curve of the shorter half-life carbamazepine active metabolite, carbamazepine 10,11 epoxide (McKee et al 1993). Subsequent unblinded, open-label studies have also observed decreased adverse events (Miller et al 2004, Ficker et al 2005), improved quality of life (Mirza et al 1998; Ficker et al 2005) and a statistically significant decrease in the rate of seizures (Hogan et al 2003; Ficker et al 2005). The ability to modestly increase total daily dose using the extended release formulation was also demonstrated (Canger et al 1990; Miller et al 2004).

Divalproex extended release (Depakote® ER; Abbott), approved for once daily doing, is a tablet of sustained release hydrophilic matrix technology with sustained release over more than 18 hours controlled by the erosion of water soluble polymer (hydroxypropyl methyl cellulose) from the matrix. Divalproex ER was approved in 2000 for the indication of migraine. The epilepsy indication was held up for two years as divalproex ER is not bioequivalent to divalproate delayed release (DR) (Depakote®; Abbott). A meta-anlysis of 5 multiple dose studies (Dutta and Zhang 2004) with 82 healthy volunteers and 83 epilepsy patients compared different divalproex dosing regimens (2, 3, or 4 times per day) and meal conditions (fasting, low, medium, and high calorie meals). Fasting and food with varied caloric content had a less than 10% effect on divalproex ER availability. The estimated ratio of divalproex ER to divalproex DR and 95% confidence intervals for AUC, C_{max}, and C_{min} was 0.89 (0.85–0.94), 0.79 (0.74–0.84), 0.96 (0.90–1.02), respectively. When changing from divalproex to divalproex ER the recommendation was to increase the dose by 1/0.89 or 12%, to compensate for the overall decrease in AED exposure indicated by the difference in AUC. Thus, the recommendation for an 8%–20% increase in dose when changing to the ER formulation, the amount of increase determined by the nearest tablet size. A pooled analysis from 9 non-blinded, open label studies (5 epilepsy and 4 psychiatry) showed improved tolerability with divalproex ER with significant reductions of tremor, weight gain, gastrointestinal symptoms, and hair loss. Two of the open label epilepsy trials reported a significant reduction of seizures (Smith et al 2004).

The half-life of the routine divalproex formulation is about 14 hours in the absence of inducing drugs and decreases to about 9 hours in the presence of hepatic inducing drugs. The effects of concomitant enzyme-inducing AEDs on bioavailability was investigated comparing divalproex DR dosed tid vs divalproex ER dosed 8%–20% higher as a single daily dose with the following effect on AUC, C_{max}, C_{min}: 1539 vs 1551 mg/L, 92.6 vs 83.3 mg L, and 44.8 vs 45.8 mg/L. The difference in peak serum concentration was significant. Thus, while the overall bioavailability of once daily divalproex ER is comparable with that achieved with thrice daily dosing of divalproex, the peak concentration achieved is less and there was a 64% peak to trough fluctuation (Sommerville et al 2003). The setting of concomitant inducing drugs may be where twice daily dosing of divalproex ER results in a flatter serum concentration time curve with better tolerability and potential seizure control (Dutta and Reed 2006a, b). This is further supported by derivation of the "functional half-life" of divalproex ER which was 40 hours in the absence of hepatic inducers but decreased to 27 hours with concomitant

inducers, resulting in an approximate 50% reduction (absence of inducer) and 75% reduction (presence of inducer) from baseline trough serum concentration if one dose is missed and the next dose occurs 48 hours after the last dose (Dutta and Reed 2006a, b).

To summarize current experience with AED XR formulations, they offer better tolerability. Improvement of seizure control has been demonstrated only in non-controlled, open-label clinical trials. Choosing to dose a sustained release formulation approved for once daily dosing twice daily, may be more "forgiving" if a medication dose is missed and better tolerated in terms of adverse events, especially in the presence of concomitant enzyme inducers.

Lamotrigine and lamotrigine XR pharmacokinetics

LTG, with a chemical name of 3, 5-diamino-6-(2, 3-dichlorophenyl)-1,2,4-triazine, is a broad spectrum AED first approved in Ireland in 1990 and the United States in 1994 and now having over 5 million worldwide patient exposures. The immediate release formulation typically achieves a peak concentration 1.4–4.8 hours after oral dose. It has near complete bioavailability (98%). Protein binding is weak at about 55%. Drug interactions are essentially unidirectional with other drugs affecting the rate of LTG metabolism but not vice versa. In adult healthy volunteers and patients on LTG monotherapy mean half-life is about 24 hours after some autoinduction. Metabolism is affected by concomitant drugs. Half-life is shortened to a mean of 12.6 hours in the presence of hepatic inducing drugs, such as phenytoin, carbamazepine, phenobarbital, and primidone, and less so by oxcarbazepine, and lengthened to a mean of about 60 hours in the presence valproic acid. Other drugs inducing LTG metabolism include synthetic estrogens and progestins, HIV protease inhibitors such as lopinavir and rotinavir, rifampin, sertraline, escitaloprim, risperidone, and gingko. Oral contraceptives have been shown to decrease LTG serum concentrations nearly 50% in a controlled study (Sabers et al 2003; Christensen et al 2007). Concomitant administration of hepatic inducers and inhibitors produces a "pseudo-monotherapy" state, again a half-life of about 24 hours. Clearance is age-dependent, up to 2-fold faster in children compared with adults and slower in infants.

Metabolism is predominantly hepatic via glucuronidation with 75%–90% recovered in urine as a 2-N-glucuronide derivative and minor additional metabolites, a 5-N-glucuronide, an N-2 methylated derivative, unidentified metabolites, and unchanged drug (Doig and Clare 1991; Sinz and Remmel 1991). Glucuronidation reactions are catalyzed by UDP-glucouryltransferase (UGT).

The UGTs exist as a super family of 117 enzymes divided into 4 families (UGT1, UGT2, UGT3, and UGT8) (Mackenzie et al 2005). UGTs conjugate a variety of substrates of endogenous, ie, bilirubin, steroid hormones, thyroid hormones, bile acids and fat soluble vitamins, and exogenous, drugs. UGT1A4 and UGT2B7 have major roles in N2-glucuronidation of LTG (Rowland et al 2006). Inter-individual variability of glucuronidation would be expected to be at least 10-fold (Burchell et al 2001). Data from healthy volunteers and epilepsy patients supports a 5- to 10-fold inter-individual variability in lamotrigine clearance based on concentration to dose ratio (Armijo et al 1999; Hirsch et al 2004; Bootsma et al 2008; Tompson et al 2008).

LTG-IR is usually dosed twice daily except in the presence of valproic acid where dosing may be once a day. In the absence of inducing agents the trough to peak ratio for immediate release LTG would on average be 0.75 (t1/2~24 hours) and in the presence of inducing agents 0.5 (t1/2~12 hours). Minimal fluctuation would be expected in the presence of the inhibitor valproic acid.

An extended release formulation of LTG has been developed and is currently being studied. LTG-XR tablets contain a modified release eroding matrix formulation (DiffCORE) designed to produce a steady dissolution rate over 12–15 hours (Tompson et al 2008).

The pharmacokinetic profile of LTG-XR in patients with epilepsy was recently published (Tompson et al 2008). Patients had a diagnosis of epilepsy, complex partial or generalized seizures) and were already on a stable dose of LTG-IR (immediate release) prior to enrollment. The study had an open-label crossover design beginning with a 2-week baseline on LTG-IR, followed by 2 weeks on LTG-XR, and then 1 week follow-up back on LTG-IR. Forty-four subjects were enrolled with 3 equal groups of patients based on concomitant AED effects on hepatic metabolism: neutral (n = 15), inducing (n = 15) or inhibiting (n = 14) LTG metabolism. Pharmacokinetic measures were steady state 24 hour serum concentration vs time curves (AUC (0–24)), C_{max}, C_{min}, T_{max} (time to maximal serum concentration after oral dose), and fluctuation index. Fluctuation index measures flatness of the concentration time curve and is defined as ($C_{max} - C_{min}$) divided by the average serum concentration (C_{avg}). Data are given as the geometric mean (individual values are multiplied and then the nth root of the product is taken). Data variation was described by coefficient of variation defined as the

standard deviation divided by the mean and then reported as a percentage by multiplying by 100. Coefficient of variation is a dimensionless number allowing comparison between datasets with wildly different means.

LTG daily doses, mean and range, were 400 mg (200–600 mg), 600 mg (200–1200 mg), and 200 mg (50–800 mg) for the neutral, induced, and inhibited groups respectively. LTG-IR was given every 12 hours and compared with once daily dosing of LTG-XR. Median serum LTG concentration-time profiles over 24 hours for the two LTG formulations are shown in Figure 1. For the neutral and especially for the induced groups, the LTG-XR formulation produced marked flattening of the serum concentration-time curves, slower absorption rate and decreased fluctuation. There

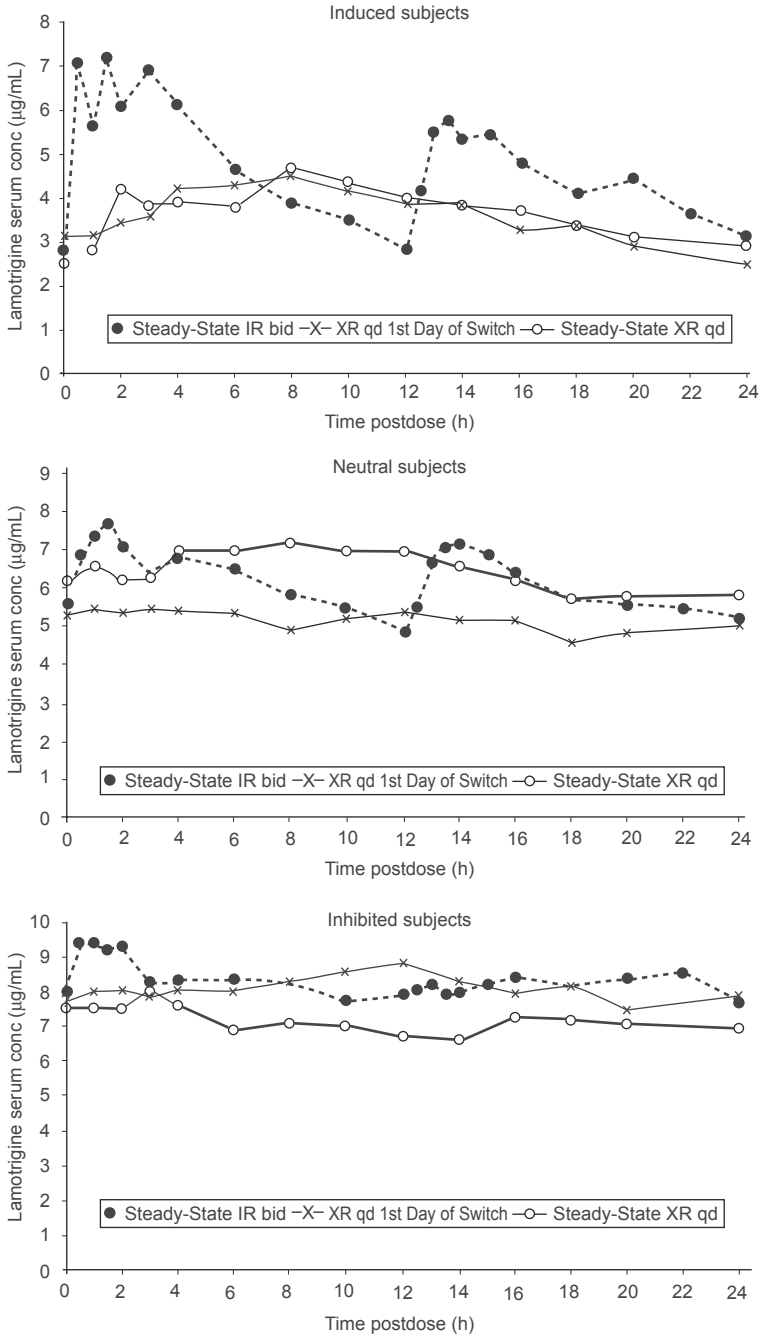

Figure 1 Median serum lamotrigine concentration—time profiles for steady-state LTG-IR on first day of switch (Day 15) and steady-state XR once-daily (Day 28 for (**A**) induced subjects. (**B**) neutral subjects, and (**C**) inhibited subjects. Bid, twice-daily, qd, once-daily.

was no decrease of C_{min} even on the first day of transition to LTG-XR. The effect was minimal for the inhibited group.

The time to maximal serum concentration, T_{max}, for LTG-IR was typically 1–1.5 hours for the three groups ranging from 0.5 to 6.13. T_{max} was prolonged by LTG-XR for the neutral group to ten hours (range 0.00–24.00). Similar T_{max} prolongation was noted for the inhibited group (mean 9.08, range 2.88–24.00 hours) but was somewhat shorter for the induced group (mean 6.00, range 0.00–23.85 hours). AUC (0–24) was similar for the two LTG formulations with the exception of the group on concomitant inducers where it was reduced on average 21% lower for the XR formulation with 90% confidence interval between 10% and 31%. Steady-state C_{max} on LTG-XR compared with LTG-IR was on average 29% lower for the induced group compared to about 11% decrease for the neutral and inhibited groups. In contrast C_{min} for the three groups was similar for both LTG preparations. As would be expected, the fluctuation index during baseline on LTG-IR was lowest for the group on inhibitors (0.318), intermediate for the neutral group (0.545), and highest for the induced group (0.986). The fluctuation index at steady-state LTG-XR was 0.209 for the inhibited, 0.341 for the neutral but 0.817 for the induced group. A dose normalized statistical analysis comparing the primary pharmacokinetic parameters showed that both AUC (0–24) and C_{max} for the induced group was outside the 90% confidence interval relative to the neutral and inhibited groups (Tables 2, 3). The small study did not observe a reduction of adverse events or improvement of seizure outcome in transitioning from LTG-IR to LTG-XR. However, over two-thirds (69%) of subjects reported a preference for LTG-XR and 17% reported no preference leaving only 14% with a preference for twice daily dosing.

Efficacy for LTG-XR for partial seizures was demonstrated against placebo in an add-on blinded study design (Naritoku et al 2007). The study included 238 patients (118 LTG-XR, 121 placebo) with a minimum of eight partial seizures during the 8-week baseline while on 1–2 baseline AEDs. Concomitant AEDs for the LTG-XR and placebo groups were carbamazepine (43% vs 42%), valproic acid (23% vs 35%), topiramate (16% vs 14%), oxcarbazepine (9 % vs 18%), phenytoin (14% vs 13%), and levetiracam (13% vs 11%). LTG-XR titration rate and target dose was adjusted to the presence of valproic acid (200 mg/day), enzyme-inducing AEDs (500 mg/day), and 300 mg for metabolically neutral drugs. Eighty percent of subjects randomized to LTG-XR compared with 87% to placebo

Table 2 Summary of serum lamotrigine pharmacokinetic parameters (geometric mean and % CVb)

	Formulation		
Serum LTG PK parameter	**LTG-IR (day 14)**	**LTG-XR (day 15)**	**LTG-XR (day 28)**
Induced			
AUC (0–24) (μgh/ml)	100 (85.9%)	92.0 (75.9%)	79.0 (100%)
Cmax (μg/ml)	6.71 (80.5%)	5.49 (64.1%)	4.77 (85.9%)
Cmin (μg/ml)	2.66 (100%)	2.51 (79.1%)	2.10 (131%)
Fluctuation index	0.986 (40.1%)	0.780 (31%)	0.817 (50.0%)
Tmax (h)	1.01 (0.50–298)[a]	6.00 (0.00–23.85)[a]	4.00 (0.00–24.00)[a]
Inhibited			
AUC (0–24) (μgh/ml)	208 (59.7%)	198 (62.8%)	167 (48.1%)
Cmax (μg/ml)	10.2 (57.5%)	9.37 (58.3%)	7.77 (49.0%)
Cmin (μg/ml)	7.44 (53.9%)	7.41 (57.6%)	6.32 (47.1%)
Fluctuation index	0.318 (27.0%)	0.240 (44.3%)	0.209 (16.4%)
Tmax (h)	1.00 (0.50–6.13)[a]	9.08 (2.88–24.00)[a]	11.00 (0.00–24.00)[a]
Neutral			
AUC (0–24) (μgh/ml)	142 (43.4%)	114 (44.3%)	138 (40.8%)
Cmax (μg/ml)	7.82 (39.3%)	5.80 (38.7%)	6.83 (38.6%)
Cmin (μg/ml)	4.57 (46.6%)	3.31 (66.4%)	4.87 (41.0%)
Fluctuation index	0.545 (29.5%)	0.470 (62.2%)	0.341 (40.6%)
Tmax (h)	1.50 (0.50–3.02)[a]	10.00 (0.00–24.00)[a]	6.00 (0.00–24.00)[a]

[a]Tmax is presented as geometric mean and range.

Table 3 Summary of statistical analysis of dose normalized steady-state lamotrigine parameters

	Geometric least squares mean ratio (90% CI)		
Serum LTG PK parameter	**Induced**	**Inhibited**	**Neutral**
AUC (0–24)	0.79 (0.688, 0.899)	0.94 (0.810, 1.084)	1.00 (0.882, 1.140)
Cmax	0.71 (0.613, 0.823)	0.88 (0.750, 1.030)	0.89 (0.775, 1.026)
Cτ	0.99 (0.894, 1.094)	0.99 (0.884, 1.101)	1.14 (1.033, 1.252)

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completed the study. During maintenance phase, 61.3% of subjects on LTG-XR vs 42.2% on placebo achieved at least a 50% reduction in seizure frequency. Adverse event rates were similar with 69% vs 62% reporting at least one adverse event except for dizziness (18% LTG-XR vs 5% placebo). Seventy-one percent reporting dizziness were on carbamazepine. This association has been previously reported. There were no differences between LTG-XR and placebo on health outcomes questionnaires (Profile of Mood States, Epidemiologic Depression Scale, Quality of Life in Epilepsy-31-P, Liverpool Adverse Experience Profile, Seizure Severity Questionnaire, and the Epworth Sleepiness Scale).

In summary, the pharmacokinetic data show similar parameters for AUC (0–24), C_{min}, and C_{max} for LTG-XR and LTG–IR in the presence of the inhibitor valproic acid or the absence of concomitant inducing AEDs. In the presence of inducing AEDs, the AUC and C_{max} were reduced 20%–30% and the fluctuation index, 0.817, was high compared with the absence of inducers, 0.341. Therefore, in the presence of inducing drugs, LTG-XR twice daily dosing should be considered, especially in patients more difficult to control. The achieved more stable-serum concentration time curve may outweigh the modest increase of medication adherence. The "average" patient on LTG-XR in the absence of inducing AEDs is likely to do very well. With the average 24 hour half-life of LTG, even missing a single dose is unlikely to be catastrophic in most patients. However, LTG clearance rate is highly variable, and patients who are rapid metabolizers, identified by dose to concentration ratio, may also benefit from the decreased fluctuation of the serum concentration time curve achieved with twice daily dosing and the "forgiveness" of a missed dose. Children with their rapid metabolism may also benefit from twice daily dosing.

In terms of benefits in seizure and tolerability, no differences were found in a small pharmacokinetic study directly comparing LTG-XR and LTG-IR. Therefore, no direct statement can be made though extrapolation to experience with divalproex and carbamazepine XR formulations anticipates benefit.

Lamotrigine indications and uses in epilepsy syndromes

LTG-IR was initially indicated as add-on therapy in partial epilepsies in adults and later in children above the age of two. A recent study has demonstrated efficacy below two years of age down to one month of age (Piña-Garza et al 2008). In the pivotal clinical trials in adults, daily dosages between 200 and 500 mg were studied. As most subjects were on concomitant enzyme-inducing AEDs, trough serum concentrations of only 1–4 μg/mL were achieved (Messenheimer et al1994). More recent data suggest that serum concentrations of at least 15 μg/mL are generally well tolerated (Froscher et al 2002; Hirsch et al 2004; Morris et al 2004b). A pharmacodynamic interaction of lamotrigine with valproate to improve seizure control when combined has been reported for partial seizures (Pisani et al 1999) and generalized seizures (Ferrie and Panyiotopoulos 1994).

LTG is also approved in the treatment of generalized seizures in Lennox-Gastaut (Motte et al 1997). It is also approved for conversion to monotherapy (Gilliam et al 1998). With initiation of therapy, the slow upward titration has prohibited approval as initial therapy for epilepsy.

AEDs often have uses outside of epilepsy (Rogawski and Löscher 2004; Johannessen Landmark 2008). LTG has psychiatric indication with controlled studies showing efficacy in the treatment of bipolar disorder (Calabrese et al 2008).

LTG-XR has been shown to have efficacy, compared with placebo, in partial epilepsies in adults to date. This is the initial indication submitted to the FDA. Ongoing studies are evaluating efficacy in primary generalized tonic-clonic seizures (Biton et al 2008) and conversion to monotherapy. There is no reason to expect a different spectrum of activity than for the immediate release formulation.

Most AEDs have rarely been formally studied in controlled, blinded designs of most specific epilepsy syndromes. LTG-IR has been described as having efficacy in a number

of generalized epilepsy syndromes in non-controlled designs (Gericke et al 1999). Open-label studies have reported efficacy in childhood absence (Frank et al1999) and juvenile myoclonic epilepsy (Morris et al 2004a). LTG may worsen myoclonus in a subset of juvenile myoclonic epilepsy (Biraben et al 2000; Carrazana et al 2001). LTG has been reported to potentially worsen severe myoclonic epilepsy of infancy (Guerrini et al 1998).

Lamotrigine safety and tolerability

General tolerability

Overall LTG-IR was well tolerated compared to placebo in a meta-analysis of clinical trials with the odds ratio for withdrawal of 1.19 (CI 95%: 0.79, 1.79). Review of data from placebo-controlled add-on studies showed the following adverse events occurring a minimum of 3% more on LTG than on placebo: dizziness (35–5 = 20), diplopia (25–6 = 19), ataxia (20–6 = 14), nausea (19–9 = 10), blurred vision (13–4 = 9), somnolence (13–7 = 6), vomiting (10–5 = 5), abnormal coordination (6–2 = 4), tremor (5–1 = 4), insomnia (6–3 = 3), and rhinitis, (11–8 = 3). (Messenheimer et al 1998). Ataxia, diplopia, dizziness, and nausea occurred statistically more commonly with LTG treatment. Rash was noted in 10% on LTG and 5% in controls.

Rash

Rash was the most common serious adverse event observed in both the add-on and monotherapy clinical trials occurring in 42 of 3071 subjects (1.4%) and 2 of 443 (0.5%). Most rashes were simple morbiliform. Rash leading to hospitalization occurred in 11 (0.3%) and 4 were Stevens-Johnson Syndrome (0.1%). Toxic-epidermal necrolysis and hypersensitivity syndrome have been reported.

Rash almost always occurs in the first 8 weeks after the start of LTG therapy. In the epilepsy trials, rash incidence was related to the effects of the concomitant AEDs on LTG metabolism: highest in the presence of the inhibitor valproic acid (12.2%), lowest in the presence of inducing AEDs (2%) and with metabolically neutral AEDs (3%). These data suggest a concentration dependent effect. This was confirmed by review of rash incidence in trials of all indications with initial LTG dose and rash rate as follows: 25 mg (~1%), 50 mg (~9%), 100 mg (~12%), and 200 mg (38%). The rate of upward titration also affects rash rate: at week five, LTG dose 62.5 had a 1.5% incidence compared with 12% at 375 mg/day. These results led to the manufacturer's recommendation as to starting dose and upward titration rates for LTG in the presence of valproic acid, inducing AEDs, and neutral AEDs (Lamotrigine package insert 2007).

Decreasing the rate of initial titration was recommended by the manufacturer in 1993 and has dramatically decreased the incidence of rash, both benign (Hirsch et al 2006; Arif et al 2007) and serious (Kanner 2005; Mockenhaupt et al 2005). A German population-based study, using an academically run registry to ascertain all hospitalized cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis combined with identified total and new users of lamotrigine via review of prescriptions claimed through the general health insurance plan covering 85% of the population, showed an incidence 5 cases per 4,450 exposures in 1993, 2 of 7,610 exposures in 1994, and 3 of 17,648 exposures in 1999. The rates of both benign and serious rash rate with initiation of LTG is now comparable to phenytoin, carbamazepine, phenobarbital, and zonisamide (Zonisamide package insert 2008).

Pregnancy: teratogenesis and management

Until recently, counseling patients regarding the effects of AEDs on pregnancy outcome has relied on retrospective data that indicated a 2- to 3-fold increased risk in the incidence of major malformations with the older AEDs (Holmes et al 2001; Perucca 2005b; Battino and Tomson 2007) with increasing risk on polytherapy, especially with valproic acid. The newer AEDs released since 1990 arrived with no data available to counsel women planning pregnancies. Therefore, multiple prospective registries have been established to fill this gap in information: national registries as the Swedish Medical Birth Registry and in Finland, independent academic registries as the North American Pregnancy registry, United Kingdom Register, European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and the Australian Register, and pharmaceutical company registries. GlaxoSmithKline (GSK) began a pregnancy registry for women on LTG in 1992. More data are currently available for LTG than for any other new AED.

The GSK Lamotrigine pregnancy registry (2008) has accumulated 1155 outcomes involving first trimester monotherapy exposure and identified 31 major malformations for a rate of 2.7% (95% CI: 1.9%–3.8%) compared with an estimated general population risk of 1.62% (95% CI 0.9%–2.3%) identified by the Brigham and Women's Surveillance program and Metropolitan Atlanta Congenital Defects Program. The registry is currently powered to detect a 1.6-fold increase in monotherapy associated

risk (The Lamotrigine Pregnancy Registry Interim Report 1 September 1992 through 30 September 2007). Similar malformation rates are reported in the UK registry (3.2%, n = 647, 95% CI: 2.1%–4.9%) and North American registry (2.3%, n = 684, 95% CI: 0.9%–3.8%) (Holmes et al 2008).

The UK pregnancy registry suggests a dose-dependent effect of LTG seen by 200 mg/day or more (Morrow et al 2008). Dose-dependence has not been confirmed by the GSK registry in daily doses up to 400 mg with insufficient data at higher doses (Cunnington et al 2007) or for the North American registry (Holmes et al 2008).

An increased occurrence of facial cleft has been reported in two registries. The Swedish Medical Birth Registry found a cleft palate rate in 90 first trimester LTG monotherapy exposures of 9.9 per 1000 compared to an expected rate of 2 per 1000; relative rate 4.5% (95% CI: 2.7%–7.1%). The North American Pregnancy Registry also identified a specific increase in non-syndromic cleft palates with LTG: in 684 outcomes there were three isolated cleft palates, one cleft lip, and one cleft palate plus cleft lip for a combined rate of 7.3/1000 compared to a rate in the comparison population of 0.7/1000 (Holmes et al 2008). The comparator group was historical and taken from the Active Malformations and Surveillance Program at Brigham and Women's Hospital in Boston with 206,224 infants and elective pregnancy terminations accumulated between 1972–1974 and 1979 and 2000. The rates of facial cleft were 1 in 647 outcomes for a rate of 2/1000 in the UK registry (Morrow et al 2006), 2 in 707 for a rate of 3/1000 in the GSK International Registry, 0 in 128 outcomes in the Australian Pregnancy Registry, and 0 of 51 outcomes in the Danish Multicentre Registry (Holmes et al 2008).

Overall multiple registries have power to exclude a 2- to 3-fold increase in major malformations by LTG. An increase in specific defects can not be excluded and several registries have noted an increased rate of facial clefts. There are major differences in the design of the registries that may account for differences in outcome (Tomson et al 2007; French et al 2008). Firm conclusions will require identification of similar outcomes across registries. Studies of the effects of neonatal AED exposure on cognition are ongoing (Meador et al 2006; Tomson and Battino 2008).

LTG has been associated with increased frequency of seizures during pregnancy. This observation has been attributed to increased clearance of LTG with declining serum concentrations during pregnancy. The increase in LTG clearance is substantial with reports ranging from about 94% to 250% (Öhman et al 2008; Pennell et al 2008).

Quality of life

About 30% of patients complain of medication side effects, most commonly tiredness and cognition (Gilliam et al 1997, Fisher et al 2000). Specific complaints in decreasing order of report were problems of cognition, energy level, school performance, childbearing, coordination, and sexual function (Fisher et al 2000). Mood is also a strong predictor of health assessment in patients with epilepsy.

LTG has been compared to phenytoin, carbamazepine, valproic acid, and topiramate in double-blind, controlled trials of intractable epilepsy, new onset epilepsy or healthy volunteers. These studies have consistently found better cognitive status based on objective measures as well as improved quality of life and mood on subjective inventories (Cohen et al 1985; Gillham et al 2000; Sackellares et al 2002; Meador et al 2005; Blum et al 2006; Meador 2006). Similar observations are noted in open label trials. LTG has also been associated with improved sexual function in women and men (Gil-Nagel et al 2006).

Conclusions

LTG is a broad spectrum AED that is typically dosed twice a day with good overall tolerability. In the presence of valproic acid which inhibits metabolism via glucuronidation, LTG may easily be dosed once per day. LTG-XR is an improved formulation that will be approved for once daily dosing. Extrapolating to experience with other extended release formulations, this should lead to improved tolerability, patient preference, compliance, and possibly seizure control. However, in patients with rapid metabolism or on concomitant hepatic inducing drugs, there is significant serum concentration fluctuation plus a lack of forgiveness for a missed dose of medication. Twice daily dosing in these patients may improve therapeutic coverage outweighing the modest decline of adherence. Overall, LTG XR is a welcome agent to our AED armamentarium.

Disclosures

The author has no conflicts of interest to disclose.

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