Bioavailability File: Lamotrigine

Lamotrigine (LTG) is a phenyltriazine class anticonvulsant that shows efficacy against partial and generalized epilepsies. It exerts its antiepileptic effects by blocking voltage-sensitive sodium channels and inhibiting the release of excitatory neurotransmitters, particularly glutamate and aspartate. LTG is well absorbed with bioavailability approaching 100%. There is negligible first-pass effect. It is widely distributed to all organs and tissues. The volume of distribution is between 0.87 and 1.2 L/kg in healthy volunteers. Protein binding is about 55%. The half-life of LTG is between 24.1 and 31.2 hours after single oral doses in healthy volunteers, but it may be altered by enzyme-inducing and -inhibiting drugs. Age and disease states play important roles in LTG pharmacokinetics and dosage adjustment. The physicochemical properties, analytical methods, pharmacokinetics, bioavailability and pharmacology of LTG are discussed in this review.

Key Words: Lamotrigine, pharmacokinetics, bioavailability, pharmacology.

Received : 02.10.2007
Revised : 15.01.2008
Accepted : 31.01.2008

INTRODUCTION

Lamotrigine (LTG)(CAS 84057-84-1) is a new generation antiepileptic of the phenyltriazine class that is chemically unrelated to any established antiepileptic drug (AED). Its chemical name is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine; its molecular formula is C$_9$H$_7$Cl$_2$N$_5$, and its molecular weight is 256.09. It appears to exert its antiepileptic effects by blocking the voltage-sensitive sodium channels and inhibiting the pathological release of glutamate$^{1-3}$. Its chemical structure is shown in Figure 1.

Figure 1. The chemical structure of the triazine derivative LTG.
It has been shown to have efficacy in a wide range of partial and generalized seizure types\textsuperscript{4,5}. LTG is also approved for use in patients with seizures associated with the Lennox-Gastaut syndrome\textsuperscript{6,7}. Recently, LTG has been investigated for efficacy in bipolar disorder. Evidence from well-designed trials suggests efficacy for acute management and prophylaxis of bipolar depression\textsuperscript{8}.

The pharmacokinetics of LTG have been studied in single- and multiple-dose studies in animals, normal volunteers and patients with epilepsy.

**PHYSICOCHEMICAL PROPERTIES**

LTG is a white-to-pale cream colored, chemically stable powder that is poorly soluble in both water and ethanol. The solubility in water is 0.17 g/L at 25°C; in 0.1 M HCl, 4.1 mg/ml at 25°C, and in ethanol is approximately 1 g/L\textsuperscript{9,10}. LTG crystallizes from isopropanol. Its melting point is 216-218°C. The drug has a pK\textsubscript{a} of 5.7\textsuperscript{3}.

**ANALYTICAL METHODS**

In biological fluids, LTG can be determined by chromatographic methods [high-performance liquid chromatography (HPLC), gas chromatography (GC)] and immunoassays. Normal-phase HPLC methods\textsuperscript{11,12} and reverse-phase HPLC methods\textsuperscript{12-22} for the determination of LTG in human plasma and/or urine have been described in clinical reports. Sinz and Remmel\textsuperscript{23} reported on the assay of LTG and LTG-2N-glucuronide, its major human metabolite, in guinea pig blood and urine by reverse-phase ion-pairing LC. In published HPLC methods, liquid-liquid extraction\textsuperscript{11-16}, solid-phase extraction\textsuperscript{17-20} or protein precipitation\textsuperscript{21,22} have been used for the separation of LTG from endogenous compounds in the samples, prior to HPLC analysis. The lower limits of detection vary from 100-200 ng/ml. The wavelength used in these methods varies from 205 to 310 nm for detection. Published methods for measurement of LTG in human fluids are almost exclusively based on HPLC. Two reports have described the determination of LTG in serum or plasma, based on GC with nitrogen-phosphorus detection\textsuperscript{24,25} and GC/mass spectrometry\textsuperscript{26,27}. However, the limits of quantification for these assays\textsuperscript{24,25} are 150 and 500 ng/ml, respectively. Capillary electrophoresis assays\textsuperscript{28-30} can be used for determination of LTG in human plasma and serum. Determination by radioimmunoassay and immunofluorometric assay was also described in the literature\textsuperscript{31,32}.

**PHARMACOLOGICAL PROPERTIES**

LTG was initially synthesized as an antifolate agent, under the premise that folate acts as a proconvulsant, but it was subsequently discovered that the very weak antifolate activity of LTG could not be responsible for its antiepileptic properties\textsuperscript{33}. Current evidence suggests that LTG stabilizes presynaptic neuronal membranes by blockade of voltage-dependent sodium channels, thus preventing the release of excitatory neurotransmitters, particularly glutamate and aspartate\textsuperscript{34,35}. The principal fast excitatory transmitter in the brain is glutamate, although aspartate and various analogues of the dicarboxylic acids share similar properties. Similar to phenytoin (PHT) and carbamazepine (CBZ), LTG inhibits pentylenetetrazole-induced and maximal electroshock-evoked seizures in animal models, which explains its efficacy in partial and generalized tonic-clonic seizures. At high doses, LTG increases the latency time for pentylenetetrazole-induced clonus, suggesting possible protection against absence seizures\textsuperscript{36}. It also reduces the duration of electrically induced after-discharges in various species after focal, cortical, and hippocampal stimulation. LTG inhibits veratrine-evoked release of glutamate in vitro, when a threshold depolarizing concentration of 4 µg/ml is used, and aspartate release at higher concentrations (10 µg/ml)\textsuperscript{37}.

More recently, it was proposed that LTG also inhibits high voltage-activated Ca\textsuperscript{2+} currents, interacting consequently with the vesicular release of transmitters\textsuperscript{38}.

LTG also has weak affinity for the 5-HT\textsubscript{3} receptor. It has been shown to be an effective maintenance therapy for patients with bipolar disorder\textsuperscript{39,40}. The mechanism
of action of the drug in the treatment of patients with bipolar disorder is not fully understood, but may be related to the inhibition of sodium and calcium channels in presynaptic neurons and subsequent stabilization of the neuronal membrane. In addition, LTG has demonstrated neuroprotective effects in animal models. It lacks appreciable in vitro affinity for dopaminergic, adrenergic, muscarinic, opioid and adenosine receptors at clinically relevant concentrations, but binds weakly to serotonin 5-HT\textsubscript{3} receptors. It also down-regulates cortical 5-HT\textsubscript{1A} receptor-mediated adenyl cyclase responses in an animal model\textsuperscript{41}.

LTG shows efficacy against partial and secondarily generalized tonic-clonic seizures, either as adjunctive treatment in patients with refractory epilepsy or when received as monotherapy\textsuperscript{42,43}. Actually, LTG exhibits a relatively broad spectrum of efficacy against some common seizure types, such as partial (with or without secondary generalization), primarily generalized tonic-clonic seizures, absence seizures, drop attacks and seizures associated with the Lennox-Gastaut syndrome\textsuperscript{36,44}. In children, LTG monotherapy is effective for typical absence seizures, and it has significant antiepileptic activity when added to the standard therapy of children with refractory epilepsy\textsuperscript{45,46}.

LTG has been approved by the Food and Drug Administration (FDA) for three new indications in 2003: as adjunctive therapy for partial seizure in pediatric patients (age 2 years and older); as monotherapy in adults with epilepsy, when converting from valproic acid (VA); and for maintenance treatment of adults with bipolar disorders. Studies are currently being conducted to determine the efficacy of LTG in treating primary generalized epilepsy, neuropathic pain and central pain. Comparative studies are being conducted to determine its effect on cognition\textsuperscript{47}.

A therapeutic serum concentration range of 1-4 µg/ml was initially proposed, based on preclinical data, but subsequent observations have indicated that some patients may require much higher therapeutic concentrations between 3 and 14 µg/ml without clinical toxicity\textsuperscript{48}.

Initial dosing of LTG is dependent on concomitant AED treatment. If LTG is to be started and carried out in patients receiving an enzyme-inducing AED, 50 mg/day is the dose for two weeks, increasing to 100 mg/day for an additional two weeks. Typical maintenance doses range between 300 to 500 mg/day. For patients whose AED regimens include VA, drug introduction should be slower and more cautious. Initial doses of 25 mg every other day for two weeks followed by an increase to 25 mg daily for an additional two weeks is recommended. Usually, maintenance doses of LTG in these patients range between 100 and 400 mg/day. In patients receiving valproate alone, typical maintenance doses range between 100 and 200 mg/day\textsuperscript{49}.

**ADVERSE EFFECTS**

Although LTG is usually well tolerated, adverse behavioral effects, including irritability and aggression, may be encountered\textsuperscript{50}. These behavioral problems may be an expression of adverse effects resulting from a pharmacodynamic interaction with other AEDs, such as CBZ. Alternatively, it may represent an unmasking of behaviors previously suppressed with a more sedating medication\textsuperscript{49}. Side effects include rash, headache, nausea, insomnia, vomiting, dizziness, diplopia, ataxia, and tremor\textsuperscript{51}. Rash, including serious rash, has been reported with this agent. While the exact incidence of serious rash, such as Stevens-Johnson syndrome, is difficult to determine, a review of clinical data suggests that the incidence in adults and pediatric patients is approximately 0.3 and 1.0%, respectively\textsuperscript{49}. Important risk factors for the development of serious rash appear to include high initial doses and rapid dose escalation\textsuperscript{52}. The clinical impact of pharmacokinetic interactions between LTG and enzyme-inducing AEDs or valproate can be minimized by adhering to recommended dose-escalating schedules with demonstrated reliability in clinical trials and clinical practice. Likewise, adhering to recommended dosing guidelines can minimise the risk of LTG-associated rash\textsuperscript{53}. Concomitant use of VA also appears to be a risk factor for the development of rash. Most cases of life-threatening rash have occurred within two to eight weeks of treatment initia-
tion, although isolated cases have occurred after prolonged treatment. The appearance of rash is an indication for immediate discontinuation of LTG. Results of pregnancy outcome following exposure to LTG have revealed a rate of major birth defects of 3% for the first trimester monotherapy. The findings are consistent with the frequency of major malformations reported for women with epilepsy on AED monotherapy (3.6-9.6%). Overall, single LTG oral load of 6.5±2.7 mg/kg was well tolerated.

Overdoses with LTG up to 15 g have been reported with some fatalities. Signs and symptoms of overdose include ataxia, nystagmus, increased seizures (in patients with epilepsy), delirium, coma and intraventricular conduction delay. Appropriate supportive care is indicated. Up to 20% of LTG may be removable by hemodialysis.

PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

LTG is available for oral administration as 25, 100, 150 and 200 mg tablets and 2, 5 or 25 mg chewable/dispersible tablet formulations.

LTG is well absorbed in a range of species including humans; there is negligible first-pass effect and bioavailability is virtually 100%. The bioavailability of LTG is affected by food. A statistically significant decrease in rate and extent of absorption was observed with diet. The absolute bioavailability was examined in a combined intravenous (I.V.) infusion and oral study in eight healthy adult volunteers. They were aged 21-48 years and each received LTG orally (75 mg base in capsule) and by I.V. infusion (mean dose 67.8 mg base) over 30 min, using an open balanced crossover design. Both oral and I.V. data were best fitted with a one-compartment open model. The following values (mean±SD) were obtained after oral and I.V. dosing, respectively: Peak plasma concentrations (C_{max}) 1.00 (±0.16) and 1.01 (±0.17) µg/ml; plasma clearance (Cl_{p}) 0.53 (±0.16) and 0.56 (±0.26) ml/min/kg; apparent volumes of distribution (V_{d}) 1.14 (±0.11) and 1.11 (±0.13) L/kg; and a plasma disposition half-life (t_{1/2}) 26.7 (±6.7) and 26.0 (±8.9) h. Mean (±SD) urinary recovery of LTG (parent drug plus glucuronide) was 72.9% (±6.1) oral and 73.1% (±11.2) I.V.; recovery as conjugate was 90% (±2.6) oral and 89% (±4.0) I.V. Absolute bioavailability of the oral formulation calculated using the t_{1/2} correction method was 0.976 (±0.048), indicating that LTG is completely bioavailable with negligible first-pass effect. Oral and I.V. infusion administration showing complete bioavailability can be seen in Figure 2.

![Figure 2. Oral and intravenous administration showing complete bioavailability](image-url)

LTG is rapidly absorbed from the gastrointestinal tract. After an oral dose, C_{max} occurs within 1 to 3 hours in healthy individuals. Time to reach C_{max} (t_{max}) does not change significantly with different doses.

Cohen et al. investigated the pharmacokinetics of LTG in three studies in healthy volunteers: The first study with LTG in humans, examined escalating doses in five healthy volunteers with open conditions. Doses of LTG 240 mg produced a C_{max} of approximately 3 µg/ml, and no important side effects were observed. These concentrations were equivalent to those effective in protecting rodents in the maximal electroshock test and by analogy with other AEDs were likely to be effective in clinical trials. Both area under the curve (AUC) and C_{max} had a linear relationship to dose over the range of 30-240 mg in healthy volunteers (Fig. 3). Plasma profiles for a representative subject are shown in Figure 4.
Some pharmacokinetic parameters of ascending doses are given in Table 1.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>t_{max} (h)</th>
<th>C_{max} (µg/ml)</th>
<th>AUC (µg/ml h)</th>
<th>t_{1/2} (h)</th>
<th>V_{darea/F} (L/kg)</th>
<th>Cl/F (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.9±1.0</td>
<td>0.4±0.04</td>
<td>16.32±3.46</td>
<td>28.8±9.6</td>
<td>0.87±0.09</td>
<td>31.7±6.1</td>
</tr>
<tr>
<td>60</td>
<td>1.7±0.6</td>
<td>0.8±0.04</td>
<td>33.96±3.84</td>
<td>29.3±5.4</td>
<td>0.88±0.08</td>
<td>29.7±3.1</td>
</tr>
<tr>
<td>120</td>
<td>2.1±0.9</td>
<td>1.6±0.22</td>
<td>66.0±5.14</td>
<td>29.1±6.0</td>
<td>0.90±0.02</td>
<td>30.5±2.5</td>
</tr>
<tr>
<td>240</td>
<td>3.1±1.0</td>
<td>3.1±0.56</td>
<td>152.2±18.9</td>
<td>35.0±11.3</td>
<td>0.92±0.10</td>
<td>26.6±3.2</td>
</tr>
<tr>
<td>Average</td>
<td>2.2±1.0</td>
<td>3.0±8.2</td>
<td>50.3±3.4</td>
<td>29.6±4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.7±4.5</td>
<td>0.7±1.0</td>
<td>20.7±3.3</td>
<td>22.4±3.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In a second study, 10 volunteers received LTG 120 mg. The mean t_{1/2} ±SD was 24.1±5.7 hours; the mean volume of distribution adjusted for bioavailability (V_{darea/F}) was 1.20±0.12 L/kg, and mean oral clearance (Cl/F) was 41.7±10.3 ml/min (2.50±0.62 L/h) (Table 2). In a third study, the kinetics of repeated administration were studied. Fifteen subjects were randomized to LTG (n=10) or placebo (n=5) and received multiple doses over seven days. The overall t_{1/2} calculated from this data during seven days was 25.5±10.2 hours. Observed pharmacokinetics on multiple administrations obeyed closely those predicted from the single-dose experiment, suggesting the absence of autoinduction of metabolism. No clinically important side effects or changes in central nervous system or cardiovascular system variables, hematology, biochemistry, or urinalysis occurred during this period.

Ramsay et al. studied pharmacokinetics of LTG in eight patients receiving stable regimens of AEDs. AUC values increased linearly with dose. Mean t_{1/2} (13.5 hours), V_{darea} (1.36 L/kg) and clearance (Cl) (1.27 ml/min/kg) did not change with increasing dose. The findings indicate that LTG pharmacokinetics can be described by the one-compartment open model and that the drug has linear kinetics. It seemed that the drug did not induce its own metabolism in patients receiving concomitant AEDs.

In a second peak may occur between 4 and 6 hours after oral and I.V. dosing, suggesting enterohepatic recycling. This may be due to salivary excretion and
reabsorption in the stomach\textsuperscript{61,62}.

There is minimal individual variability in absorption\textsuperscript{12}. LTG tablets have been shown to be bioequivalent to the gelatin capsules\textsuperscript{62}.

A radiolabeled study confirmed complete oral absorption with no first-pass effect. Six volunteers received LTG 240 mg orally, containing 15 \( \mu \text{Ci} \) of \( ^{14}\text{C} \) tracer. Over the next 168 h, 94\( \pm \)2\% of radioactivity was found in urine and only 2.0\( \pm \)0.5\% in feces\textsuperscript{58}. Absorption is also reported to be complete and linear in patients with epilepsy, receiving doses up to 400 mg/day\textsuperscript{62}.

Yau et al.\textsuperscript{63} designed a study to evaluate the dose proportionality of LTG at single oral doses of 50, 200, and 400 mg in 20 subjects. They also compared a 200 mg tablet to 2X100 mg tablets. The four-fold increase in dose from 50 to 200 mg resulted in a 3.72-fold increase in AUC and a 3.93-fold increase in \( C_{\text{max}} \). The two-fold increase in dose from 200 to 400 mg resulted in a 1.93-fold increase in AUC and a 2.00-fold increase in \( C_{\text{max}} \). The AUC for the 2X100 mg dose and the 1X200 mg doses were 111.6\( \pm \)40.0 and 109\( \pm \)37 \( \mu \text{g.h/ml} \). The Cl/F and \( t_{\text{max}} \) were also comparable. The results of this study indicate that the pharmacokinetics of LTG are dose-proportional following a single dose over the dosage range of 50-400 mg and that the 100 and 200 mg tablets are bioequivalent. These doses were well tolerated\textsuperscript{63}.

Subsequent studies showed that this linear relationship between dose administration and both \( C_{\text{max}} \) and AUC extended to 450 mg in volunteers and 700 mg at steady-state dosing in patients\textsuperscript{61}.

**Distribution**

LTG is widely distributed to all organs and tissues, including brain tissue, with a remarkably constant \( V_d \) of 1.1 L/kg in healthy volunteers. It ranges between 0.87 and 1.2 L/kg\textsuperscript{60}. \( V_d \) in patients with epilepsy and receiving concurrent antiepileptic therapy is reported to be between 1.25 and 1.47 L/kg. It is also found to be independent of dose and the duration of the therapy\textsuperscript{60}.

A mean brain:serum ratio of 2.8 was found in 11 patients with brain tumors who had received LTG 100-400 mg/day from one day to 17 months\textsuperscript{41}. Such a good distribution of LTG in the brain is certainly a result of the basic and lipophilic properties of the molecule, which permits it to cross the blood-brain barrier easily and have high affinity to the brain tissue\textsuperscript{48}. A study assessed the ability of LTG and its glucuronide metabolite to penetrate the blood-brain barrier in a 10-year-old epileptic patient, who underwent a frontal topectomy to remove seizure-causing foci in the cerebral cortex, approximately four hours after the last dose. The concentration of LTG in the brain was higher than the unbound concentration in plasma. On the other hand, concentrations of LTG glucuronide were very low in the brain\textsuperscript{62}. In another study, the 14 volunteer plasma concentrations of LTG were fit to a two-compartment pharmacokinetic model (Fig. 5)\textsuperscript{64}. The drug appears to fit this model according to several goodness of fit criteria that can perhaps explain the good transport of the drug to the brain\textsuperscript{41,48,62}.

Subsequent studies showed that this linear relationship between dose administration and both \( C_{\text{max}} \) and AUC extended to 450 mg in volunteers and 700 mg at steady-state dosing in patients\textsuperscript{61}.

![Figure 5](image-url)
salivary LTG concentration measurement appears to be a practical approach to therapeutic drug monitoring. This has significant implications for the elucidation of pharmacokinetics of LTG in the pediatric population. Incecayir et al. found that LTG showed a moderate degree of protein binding of 57.5±15.1% (mean±SD) in 14 healthy volunteers when calculated from saliva concentrations. The mean fraction of saliva to plasma concentrations was reported to be 0.426±0.153 (mean±SD).

The results of this study demonstrated significant correlations between saliva and plasma concentrations of LTG in healthy volunteers. This is depicted in Figures 5 and 6.

Table 3 shows the pharmacokinetic parameters from noncompartmental analysis following 200 mg single oral doses of LTG administration to healthy volunteers.

LTG crosses the placenta, with fetal and/or placental concentrations similar to those in maternal plasma. Concentrations in breast milk are 40-80% of those in maternal blood. Rambeck et al. investigated the transfer of LTG in pregnancy and during lactation from a mother on LTG treatment to her child. In the child, LTG serum concentrations (up to 2.8 μg/ml) comparable to those usually achieved in active treatment with LTG were found, not only after birth, but also during lactation. A considerable amount of LTG (2-5 mg per day) was excreted in breast milk. No adverse effects were seen in the child. However, the transfer of LTG taking place during pregnancy and lactation should not be neglected. In this case, the child should be thoroughly observed for potential adverse effects.

Table 3. Pharmacokinetic parameters from noncompartmental analysis following 200 mg single oral doses of LTG administration to healthy volunteers [69]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (μg·h/ml) a</td>
<td>123</td>
<td>14</td>
</tr>
<tr>
<td>AUMC (μg·h²/ml) b</td>
<td>5930</td>
<td>1130</td>
</tr>
<tr>
<td>C max (μg/ml) c</td>
<td>2.91</td>
<td>0.26</td>
</tr>
<tr>
<td>t max (h) d</td>
<td>2.4</td>
<td>0.7</td>
</tr>
<tr>
<td>MRT (h) e</td>
<td>47.3</td>
<td>4.7</td>
</tr>
<tr>
<td>t 1/2(h) f</td>
<td>32.3</td>
<td>4.0</td>
</tr>
<tr>
<td>k d (h⁻¹) g</td>
<td>0.0230</td>
<td>0.0036</td>
</tr>
<tr>
<td>Cl (ml/h) h</td>
<td>1710</td>
<td>210</td>
</tr>
<tr>
<td>V darea/FF* (L) i</td>
<td>78.5</td>
<td>13.0</td>
</tr>
</tbody>
</table>

a: Area under the curve of concentration versus time from zero to infinity. b: Area under the curves of the product of time and concentration versus time from zero to infinity. c: Maximum plasma concentration. d: Time to reach C max. e: Mean residence time. f: Disposition half-life. g: Disposition rate constant. h: Total clearance. i: Apparent volume of distribution.

Metabolism and Elimination

LTG is a weak base that is extensively metabolized primarily by the action of uridine 5’-diphosphate (UDP)-glucuronosyl transferases. Glucuronide conjugation can occur at both heterocyclic nitrogen atoms to form a quaternary amine glucuronide, with the 5-N and 2-N glucuronide metabolites accounting for the majority of the dose recovered in urine. Approximately 70% of a single oral LTG dose is recovered in the urine, of which 75 to 90% is in the form of a glucuronide conjugate identified as the 2-N-glucuronide.

Sinz and Remmel isolated and characterized a quaternary ammonium-linked glucuronide of LTG from human urine. The structure of the compound was found to be L TG 2-N-glucuronide by mass spectroscopy and nuclear magnetic resonance spectroscopy, along with chemical and enzymatic hydrolysis studies. The remainder of the LTG dose retrieved in the urine is excreted as the parent compound, accounting for about 10% of the dose.
and as a 5-N-glucuronide detectable in smaller amounts. Only 2% is excreted unchanged in feces. The metabolites are not thought to be pharmacologically active. At steady-state following multiple oral doses, 43 to 87% of the dose was excreted over 24 hours; about 95% of this being present as the 2-N-glucuronide metabolite and 5% as unchanged LTG. The 2-N-glucuronide metabolite was undetectable in plasma.

When defined using urinary excretion data, the elimination profile of the 2-N-glucuronide metabolite of LTG is similar to that of the parent compound, suggesting that glucuronidation is the rate-limiting step in the elimination of LTG.

After single oral dose administration in healthy young volunteers, total clearance (Cl) values of LTG of 0.021 to 0.035 L/h/kg doses have been reported by most investigators. Much higher Cl values were found in epileptic patients maintained on enzyme-inducing drugs. Total Cl of LTG after a single dose as monotherapy is 0.026±0.078 L/h/kg in volunteers, but after multiple doses in patients taking VA, this may be reduced to 0.015 L/h/kg, and increased to 0.066 L/h/kg in the presence of enzyme-inducing drugs. Drug Cls (per kg) in children under 5 years old are approximately twice those in adults under similar circumstances.

The t1/2 of LTG has been reported as 24.1 to 31.2 hours following single oral doses in healthy adults.

Steady-state values of t1/2 are reduced compared with single-dose values. In multiple dose studies, the mean t1/2 was 13 hours. It is decreased to about 15 hours during concomitant administration of enzyme-inducing antiepileptics such as CBZ and PHT, and is greatly increased to 59 hours in the presence of VA, necessitating dosage modification. Figure 7 shows the effects of VA and CBZ on the normal t1/2 of LTC.

There is minimal autoinduction of LTG metabolism, reducing serum t1/2 by about 25%. On commencing therapy, this is complete, while the plasma levels of LTG are still rising to steady-state; thus, no subsequent decline in LTG concentration is seen. It was shown that it was not clinically significant.

Ramsay et al. did not demonstrate any evidence of autoinduction in patients with epilepsy. The early clinical trials on the efficacy of LTG also did not show any evidence of Michaelis-Menten kinetics or saturable metabolism. At the doses given clinically, the metabolism of LTG appears to be linear and proportional to dose. The kinetics also appear to be linear at steady-state within a dose range of 100 to 700 mg/day.

### Table 4. Summary of LTG kinetics after single-dose administration to patients (data supplied by Glaxo Wellcome)

<table>
<thead>
<tr>
<th>Parameter and study group</th>
<th>Age (in years)</th>
<th>Patients taking enzyme-inducing AEDs</th>
<th>Patients taking enzyme-inducing AEDs plus valproate</th>
<th>Patients taking valproate only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>0.17-5</td>
<td>3.0</td>
<td>5.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Children</td>
<td>5-10</td>
<td>3.1</td>
<td>3.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Adults</td>
<td>18-65</td>
<td>2.3</td>
<td>3.8</td>
<td>4.7</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>0.17-5</td>
<td>7.7</td>
<td>19.0</td>
<td>44.9</td>
</tr>
<tr>
<td>Children</td>
<td>5-10</td>
<td>7.0</td>
<td>19.7</td>
<td>65.8</td>
</tr>
<tr>
<td>Adults</td>
<td>18-65</td>
<td>14.4</td>
<td>28.7</td>
<td>58.9</td>
</tr>
<tr>
<td>Clsp (L/h/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>0.17-5</td>
<td>0.22</td>
<td>0.072</td>
<td>0.03</td>
</tr>
<tr>
<td>Children</td>
<td>5-10</td>
<td>0.16</td>
<td>0.054</td>
<td>0.001</td>
</tr>
<tr>
<td>Adults</td>
<td>18-65</td>
<td>0.066</td>
<td>0.003</td>
<td>0.016</td>
</tr>
</tbody>
</table>

AEDs: Antiepileptic drugs. Clsp: Renal clearance. t1/2: Apparent biological half-life. tmax: Time to reach maximum concentration.
Table 4 summarizes LTG kinetics after single-dose administration to patients (mean pharmacokinetic parameters)\(^9\).

**Effects of Age and Diseases on LTG Pharmacokinetics**

Age plays an important role in LTG pharmacokinetics and dosage adjustment, because LTG concentration/dose ratio increases significantly from infancy to adult age\(^77\). The mean t\(_{1/2}\) was \(\leq 10\) hours in children administered LTG combined with enzyme-inducing AEDs\(^35\). This value was increased to 15 to 26.6 hours in children also receiving VA plus enzyme-inducers, and further increased to 44 to 94 hours in epileptic children taking LTG with VA alone\(^35\).

Vauzelle-Kervroëdan et al.\(^78\) studied the single-dose kinetics of LTG in children aged 6 months to 5 years, who were treated with three types of co-medication: The LTG t\(_{1/2}\) was 7.7±1.8 hours in children treated with enzyme inducers (receiving CBZ, PHT), 21.9±6.8 hours in patients on others (receiving co-medication not known to modify drug metabolism or no co-medication) and 44.7±10.2 hours in patients on inhibitors (receiving VA). These data suggest that t\(_{1/2}\) in children taking enzyme-inducing agents is shorter than t\(_{1/2}\) in adults treated with inducers (~15 hours). The t\(_{1/2}\) of the drug in children in the “other” and “inhibitor” groups was comparable to adults (29 hours and 59 hours, respectively). This suggests that children may be more prone to enzyme induction than adults (Fig. 8). This hypothesis was confirmed by Bartoli et al.\(^79\). The fact that the age dependency of plasma LTG levels was most evident in patients co-medicated with enzyme inducers may indicate a greater susceptibility to induction in children\(^79\).

The findings confirm that in children and young adults, plasma LTG concentrations at steady-state are linearly related to dosage, at least up to a daily dose of 21 mg/kg\(^79\).

Eriksson et al.\(^80\) demonstrated that there was a linear relationship between the dose administered and C\(_{\text{max}}\) in 31 children and young adults (aged 2.5 to 22 years)\(^80\). This suggests that there is no saturation of absorption or elimination in this population at the doses studied.

Battino et al.\(^81\) evaluated the influence of pediatric age and antiepileptic co-medication on the single-dose pharmacokinetics of LTG. Nineteen patients with epilepsy (10 co-medicated with enzyme inducers and 9 co-medicated with VA) aged 8 months to 30 years received a single oral dose of LTG (0.6 to 2.2 mg/kg) after an overnight fast. t\(_{1/2}\) and Cl/F values were significantly lower and higher, respectively, in patients co-medicated with enzyme inducers than in those receiving VA (t\(_{1/2}\)= 8.1 vs 41.7 hours; Cl/F= 0.11 vs 0.04 L/h per kg), whereas C\(_{\text{max}}\) and t\(_{\text{max}}\) values were comparable in the two groups. The differences in pharmacokinetic parameters persisted when comparisons were made within subgroups stratified according to age. Within groups of patients homogeneous for type of co-medication, C\(_{\text{max}}\) and AUC values tended to be lower in children aged less than 12 years than in older patients. However, there was no significant relationship between t\(_{1/2}\) values and age. It was concluded that both age and type of co-medication influence LTG pharmacokinetics. The reduction in
concentrations caused by enzyme inducers and the elevation caused by VA can be explained by stimulation and inhibition, respectively, of LTG glucuronidation. These interactions occur similarly in younger and older children, in agreement with findings reported before in pediatric patients given single and multiple doses of LTG.

The pharmacokinetic properties of a single oral 150 mg dose of LTG in healthy elderly volunteers (aged 65 to 76 years) have been compared with those of a younger group (aged 26 to 38 years). $C_{\text{max}}$ values were increased by 27% and AUC values by 55% in elderly vs younger subjects, and CI of LTG was 35% lower in the elderly group. $t_{1/2}$ was 31 hours in the elderly and 25 hours in the younger volunteers.

Cl of the drug is slightly lower in patients with Gilbert’s syndrome, who have decreased activity of UDP-glucuronosyl transferase. Cl is significantly reduced in patients with hepatic or renal impairment. Gender and smoking status do not appear to significantly affect LTG pharmacokinetics. However, Cl was 25% lower in non-whites compared with whites. A single oral dose of LTG was administered to seven volunteers with Gilbert’s syndrome (unconjugated hyperbilirubinemia). In the subjects with Gilbert’s syndrome, mean Cl/F was 32% lower and $t_{1/2}$ was 37% longer than in the normal controls (30.2±7.7 vs. 44.2±7.5 ml/min and 31.2±7.4 vs. 22.8±4.4 hours, respectively). The amount of unchanged LTG excreted in the urine was 30% higher in the subjects with Gilbert’s syndrome. These subjects have some impairment of elimination, but this is unlikely to be clinically important because of the high therapeutic index of LTG.

However, as in patients with Gilbert’s syndrome, although $t_{1/2}$ was lengthened from 24.9 hours in young adults to 31.2 hours in the elderly, this latter value is similar to that generally reported for healthy young volunteers. Urinary recovery of the LTG dose was similar in elderly vs young subjects (65.4 vs. 68.6%).

The pharmacokinetics of a single 100 mg oral dose were investigated in 24 subjects with various degrees of liver cirrhosis and in 12 healthy controls. The pharmacokinetics of LTG were comparable between the patients with moderate cirrhosis and the healthy subjects. Cl/F mean ratios (90% confidence interval) in patients with severe cirrhosis without or with ascites to healthy subjects were 60% (44%; 83%) and 36% (25%; 52%), respectively. Plasma $t_{1/2}$ mean ratios (90% confidence interval) in these two patient groups to healthy subjects were 204% (149%; 278%) and 287% (202%; 408%), respectively. It was concluded that initial, escalation and maintenance doses should generally be reduced by approximately 50 or 75% in patients with severe cirrhosis with or without ascites.

LTG Cl is significantly reduced in patients with hepatic or renal impairment. The pharmacokinetics of a single 100 mg oral dose of LTG were studied in six healthy volunteers and in 20 patients with various degrees of renal impairment. $C_{\text{max}}$, $t_{\text{max}}$, $V_d$ and Cl were not significantly modified by the degree of renal impairment. $t_{\text{max}}$ was approximately 25 h in subjects with normal renal function and 50 h in uremic patients. Renal clearance (Cl$_R$) of LTG was significantly reduced. Urinary elimination of unchanged and conjugated LTG was reduced in uremic patients. Thus, it seems necessary to treat patients with a very severe renal insufficiency carefully, since very large variations in pharmacokinetics were found.

Hemodialysis shortened $t_{1/2}$ from 59.6±28.1 h during the interdialysis period to 12.2±6.4 h during the dialysis period; 17% of the dose was extracted in this way.

**Drug Interactions**

Because the primary route of LTG elimination is through glucuronidation, the pharmacokinetics of LTG are complicated by interactions with co-medication. While CBZ, PHT, PB, primidone (PRM) and oxcarbamazepine (OXC) reduce the levels of LTG, VA enhances it. In one study, pharmacokinetics and tolerability of the combination of LTG and OXC were investigated in healthy volunteers. It was found that AUC and $C_{\text{max}}$ of LTG, OXC and its active metabolite 10-monohydroxy were not significantly affected by
Understanding the pharmacokinetic relationship to daily doses of approximately 125 mg of VA.

µ50% inhibition below 5.5 g/ml, which corresponds VA then begins to decrease rapidly, with less than approximately 250 mg. The inhibition of LTG Cl by This concentration corresponds to a VA daily dose of µconcentration exceeding approximately 20 g/mL.

The magnitude of inhibition effect does not vary with that following low, multiple doses of VA (steady-state effects of VA on the Cl of LTG clearly demonstrate

in LTG Cl (~70%) as compared with monotherapy.

with VA has been determined as a marked reduction to that in unmedicated individuals. When VA is withdrawn, therefore, L TG concentrations can be expected to fall substantially. Similarly, removal of an enzyme-inducing anticonvulsant such as CBZ or PHT will produce a rise in circulating LTG. Mean LTG plasma concentrations will approximately double following the withdrawal PHT; however, increases of only 60% may occur following the withdrawal of CBZ. The pharmacokinetic impact of co-medication with VA has been determined as a marked reduction in LTG Cl (~70%) as compared with monotherapy. The mechanism of the interaction with valproate is through VA competing with LTG for glucuronidation, rather than an effect on ClR or absorption. Co-medication with valproate in combination with enzyme inducers gives a t1/2 similar to that in unmedicated individuals. When VA is withdrawn, therefore, L TG concentrations can be expected to fall substantially. Similarly, removal of an enzyme-inducing anticonvulsant such as CBZ or PHT will produce a rise in circulating LTG. Mean LTG plasma concentrations will approximately double following the withdrawal PHT; however, increases of only 60% may occur following the withdrawal of CBZ. The pharmacokinetic impact of co-medication with VA has been determined as a marked reduction in LTG Cl (~70%) as compared with monotherapy. The mechanism of the interaction with valproate is through VA competing with LTG for glucuronidation, rather than an effect on ClR or absorption. Co-medication with valproate in combination with enzyme inducers gives a t1/2 similar to that in unmedicated individuals. When VA is withdrawn, therefore, L TG concentrations can be expected to fall substantially.

An interaction between LTG and CBZ, resulting in increased serum levels of carbamazepine 10, 11 epoxide (CBZ-E) and developed neurotoxicity, has been reported by some authors but not confirmed by others. An interaction between LTG and CBZ may give rise to CBZ toxicity, which resolves with a reduction in the dose of CBZ. This may be due to increases in CBZ-E, the primary metabolite of CBZ or a pharmacodynamic interaction. The precise mechanism of this interaction remains controversial with varying reports of the effect of LTG on CBZ and CBZ-E pharmacokinetics.

The Cl of LTG is increased by paracetamol (acetaminophen) but not to such a degree as to be clinically significant. In a double-blind, randomized, crossover, placebo-controlled study, the effect of multiple oral doses of acetaminophen on LTG disposition was examined in healthy volunteers. Eight volunteers received two single 300 mg oral doses of LTG, administered 20 days apart. Acetaminophen (900 mg tid) or placebo was taken for 24 hours before and continued for 10 days after each LTG dose. AUC for LTG and LTG t1/2 were statistically decreased by 20%
(229.0±62.5 µg/h/ml vs. 191.2±42.1 µg/h/ml) and 15% (35.7±9.3 hrs vs. 30.2±7.3 hrs), respectively, when concurrently administered with acetaminophen. The percentage of dose of LTG recovered in the urine (total) was significantly higher during the acetaminophen treatment (65.9±12.3% vs. 72.5±5.7%). Acetaminophen seems to facilitate LTG removal through an as yet to be determined mechanism\textsuperscript{98}. Sertraline has potent interactions with LTG metabolism. Inhibition of glucuronidation is responsible. Preliminary observations suggest that a significant increase in serum LTG may be caused by sertraline\textsuperscript{99}. The modest increase in LTG levels caused by felbamate is probably of little significance\textsuperscript{59}. Rifampicin-altered pharmacokinetics of LTG in healthy subjects are due to induction of the hepatic enzymes responsible for glucuronidation. Rifampicin increased both the Cl/F of LTG and the amount of LTG in urine excreted as glucuronide. Additionally, co-administration of rifampicin was associated with a 30% shortening of the LTG t\textsubscript{1/2}, whereas co-administration of cimetidine to ongoing LTG therapy had negligible effects on LTG pharmacokinetics\textsuperscript{100}. The pharmacokinetics of lithium were not significantly changed by co-administered LTG\textsuperscript{101}. Also, LTG pharmacokinetics were not altered by co-administered bupropion in healthy volunteers. However, absorption of LTG was significantly decreased in rats given concomitant imipramine. In vitro metabolism of LTG was not significantly affected by clozapine, fluoxetine, phenelzine, risperidone or trazodone, and was minimally affected by amitriptyline, clonazepam, haloperidol or lorazepam\textsuperscript{41}. Potentiation of the anticonvulsant effect of LTG with aspirin, which is the prototype prostaglandin synthesis inhibitor, was shown in the pentylenetetrazole model in mice, indicating that prostaglandins could play an important role in this seizure model\textsuperscript{102}. A synergistic pharmacodynamic interaction between the AEDs tiagabine and LTG has been shown in the rat\textsuperscript{103}. Levetiracetam did not affect the steady-state serum concentrations of LTG. Co-administration of escalating doses of topiramate in a group of 25 patients resulted in only slight decreases in average LTG levels compared with baseline. LTG levels were decreased 20 to 30% in three of the patients, consistent with the notion that topiramate is a weak enzyme inducer. Co-administration of ritonavir and LTG may result in decreased serum concentrations of LTG. The postulated mechanism is enhanced UDP-glucuronosyl transferase activity by ritonavir\textsuperscript{86}. The potential interaction between retigabine and LTG was evaluated in 29 healthy subjects. Retigabine and LTG exhibited a modest pharmacokinetic interaction with each other. Under co-administration of LTG, mean retigabine t\textsubscript{1/2} and AUC were increased by 7.5% and 15%, while Cl/F was decreased by 13%. Under co-administration of retigabine, mean LTG t\textsubscript{1/2} and AUC were decreased by 15% and 18%, respectively, while Cl/F increased by 22%\textsuperscript{104}. 

**CONCLUSION**

In summary, LTG as add-on therapy improves seizure control in some patients with intractable partial seizures, and appears to have particular efficacy in secondarily generalized tonic-clonic seizures. Further elucidation of its longer tolerability and its use in patients with other seizure types, including Lennox-Gastaut syndrome, in children and as monotherapy is important in establishing its precise position among the new generation of AEDs. At present, LTG offers a worthwhile alternative to current approaches to the management of patients with refractory partial seizures, with or without secondary generalization, and displays potential for application in other types of epilepsy. LTG shows several pharmacokinetic properties desirable in an AED. The linear kinetics, reliable absorption and long half-life simplify administration and permit once daily administration as monotherapy. Unlike the problematic enzyme induction of the older AEDs, LTG is free of enzyme-inducing properties, making combination therapy, as well as treatment with oral contraceptives, much easier than in the past. However, interindividual kinetic variability is prominent, and further amplified by the influence of age, pregnancy, disease states and co-medication with other AEDs. Pharmacokinetic variability plays a major role in the dosage requirements. LTG has a broad spectrum, is well tolerated and its kinetics are compatible with once- or twice-daily dosing. However,
its use is complicated by the need of slow dose escalation and prominent interaction with concomitant anticonvulsants, which may require adjustment of LTG dose when co-medication is changed.

REFERENCES
22- Böttiger Y, Svensson JO, Stähle L. Lamotrigine


45- Battino D, Buti D, Croci D, Estienne M, Fazio A,


89- Gidal BE, Sheth R, Parnell J, Maloney K, Sale M. Evaluation of VPA dose and concentration effects on lamotrigine pharmacokinetics: implications for conversion to lamotrigine monotherapy, Ep-