LAMOTRIGINE DOSES AND SERUM CONCENTRATIONS IN INFANTS LESS THAN 24 MONTHS OLD

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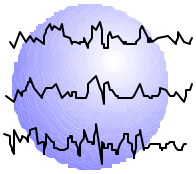

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ABSTRACT

Rationale: Lamotrigine (LTG) has been used to treat infants with epilepsy; only sparse information regarding dosing, levels and kinetics is available. Enzyme induction and metabolism have greater impacts during infancy and contributes to the difficulty of effective treatment in this age group. We reviewed our experience with infants less than 24 months old to determine the relationships between doses and serum concentrations.

Methods: Randomly selected clinic and hospital records were reviewed to find 20 infants less than 24 months of age who had been treated with lamotrigine and who met inclusion criteria for complete records for: age, weight, dose of LTG, serum concentration levels, concomitant medications, seizure type/s, and patient response to treatment.

Results: Ages ranged from 4-23 months (mean 13.7). Seven infants were treated with LTG monotherapy, 7 with concomitant enzyme inducing AEDs (EIAED), 4 with non-EIAED, 1 with VPA + EIAED, and 1 with VPA + non-EIAED. All infants except those treated with VPA were on QID schedules. The mean dose and serum concentration in the LTG monotherapy group were 13.0 mg/kg/day and 14.52 mg/L respectively. The LTG + non-EIAED group mean dose and concentration were 10.68 mg/kg/day and 7.15 mg/L. The LTG + EIAED group had a mean dose of 20.5 mg/kg/day and mean serum concentration of 5.5 mg/L. There were no significant demographic differences between groups. The dose-serum concentration ratios were consistent in all groups throughout the dose range.

Conclusions: Our results suggest that serum concentrations have a linear relationship to dose. The mg/kg dose in monotherapy is nearly equal (0.9 times) to the mg/L serum concentration; e.g., a dose of 10 mg/kg/day should give a serum concentration of 9 mg/L. However, when LTG is given with concomitant EIAED the mg/kg/day dose is 3.74 times the mg/L serum concentration, e.g., a dose of 10 mg/kg/day should yield a serum concentration of 2.7 mg/L. Our results suggest that LTG adjunctive therapy with EIAED in infants less than 24 months may require doses of 20-30 mg/kg/day or higher to attain serum concentrations of 5-10 mg/liter. Peak and trough serum concentrations in this group may vary by 3-4 times or more depending on dose schedules.

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INTRODUCTION

Lamotrigine is used to treat epilepsy in young children. Little information exists about the relationship of the dose of lamotrigine to serum concentration in this age group. Knowing about this relationship may help guide treatment. We present a retrospective review of dose and serum concentrations of lamotrigine in 20 young children. ($\pm$ 2 y.o.).

METHODS

Randomly selected clinic and hospital records were reviewed to find 20 infants less than 24 months of age who had been treated with lamotrigine and who met inclusion criteria for complete records for: age, weight, dose of lamotrigine, serum concentrations, concomitant medications, seizure type/s, and patient response to treatment.

RESULTS

- 12 males and 8 females
- Age 4-23 months with mean age at 13.7 months
- 1 infant was initial monotherapy
- 19 had failed multiple medications and began as adjunctive therapy. Six of this group were reduced to monotherapy with lamotrigine. See Figure 1 for distribution of concomitant treatments.

CONCLUSIONS

This was not a formal pharmacokinetic study. However, the results suggest that young children follow the same kinetic patterns as do older children and adults, but to a greater extreme. The dose concentration relationship appears to be linear. Enzyme induction appears to be vigorous and therefore half-life may be as short as 3-4 hours. To avoid peak level toxicity with trough levels too low to provide seizure control, doses in this young group may need to be given 3 or 4 times per day.

The addition of VPA significantly inhibits metabolism of LTG. The addition of VPA may not only be helpful with the problems of rapid metabolism, but may also benefit seizure control. (see Poster 3.194 – Gates, et al). Although the risk of hypersensitivity reactions may be increased by adding LTG to VPA, the inverse, i.e., adding VPA to LTG, appears to be safer. In this group of young children with very difficult to control epilepsy, the improvement was quite good.

Table 1. Dose Concentration Relationship		
Group (N)	Mean Dose (mg/kg)	Mean Concentration (mg/kg)
Monotherapy (7)	13.0	14.5
Non-EIAED (4)	10.7	7.2
EIAED (7)	20.5	5.5
VPA+EIAED (1)	5.8	3.2
VPA+Non-EIAED (1)	12.9	13.9

Table 2. Seizure Outcome	
Responders (10)	Non-Responders (10)
3 – Seizure Free	3 - >50% Increase
4 – 75-99% ↓ Seizures	7 - $\pm$ 25%
3 – 50-74% ↓ Seizures	
Mean Concentration: 9.9 (3.8-19.5)	Mean Concentration: 8.0 (2.6-18.6)

Case Study: #10
12-Month-Old - LTG+EIAED

LTG Dose	LTG Concentration
5 mg/kg (25 B.I.D.)	0.99
15 mg/kg (37.5 Q.I.D.)	3.6
30 mg/kg (75 mg Q.I.D.)	8.7

Case Study # 14
20-Month-Old – Monotherapy

LTG Dose	LTG Concentration
7 mg/kg	5.2
12.5 mg/kg	10.1

Case Study #5
22 Month-Old – Addition of VPA

LTG Dose	VPA Dose	LTG Concentration
100 mg/d (7.7 mg/kg)	0	5 mg/L
50 mg/d (3.8 mg/kg)	45 mg/kg	9.3 mg/L
25 mg/d (2.2 mg/kg)	45 mg/kg	4.3 mg/L

Case Study #12
14-Month-Old on EIAED – LTG B.I.D. Peak/Trough

LTG Dose	LTG Concentration
33.9 mg/kg	Peak 14 mg/L
	Trough 2.2 mg/L