

## **Population pharmacokinetics of clobazam and its active metabolite in pediatric patients with epilepsy: Effect of weight, genotype and co-therapy.**

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**Objectives:** The aim of this analysis was to characterize a population model of clobazam (CLB) and its active major metabolite, N-desmethyclobazam (N-CLB) in a target population of pediatric patients with Lennox-Gastaut syndrome following oral administration of CLB.

**Patients and Methods:** Data were from a dose-ranging Phase-II, randomized, double-blind, efficacy and safety trial in pediatric patients and young adults with Lennox-Gastaut Syndrome (LGS). This 11-week study included a 4-week baseline period, 3 weeks of dose titration, and 4 weeks of maintenance dosing. Randomization was done within 6 weight groups to either low dose (0.25 mg/kg/day) or high dose (1.0 mg/kg/day); CLB was administered twice daily. Patients were allowed up to 3 concomitant antiepileptic drug (AED) medications. Plasma drug and metabolite concentrations were available from week 5 and week 7 of study. One plasma sample at steady-state was collected per visit at a time that was convenient to patients. Data were fitted using NONMEM (version V, level 1.1, ADVAN 5), with FOCE INTERACTION method used for estimation. Due to sparse data early post-dose, covariate screening was performed only for apparent clearance (CL/F). An allometric model in which weight was standardized to a 70-kg adult <sup>(1)</sup> was used for clearance of CLB and N-CLB. This was followed by exploration of other covariates including age, concomitant therapy with felbamate, lamotrigine, or valproic acid; CYP2C19 genotype (normal/poor metabolizers), and gender.

**Results:** 204 total plasma concentrations of CLB and NCLB were available from 56 patients. A 1-compartment model in which the absorption rate constant was fixed to 2.5 /hr and a first-order conversion of CLB to N-CLB was assumed. A proportional error model for residual variability and exponential model for inter-subject variability were deemed appropriate. For CLB, population standardized CL/F was 5.94 L/hr/70kg (RSE 6.97%); volume of distribution estimate was 95.8L (34.4%). The apparent volume of distribution of N-CLB was fixed to that of CLB while population standardized clearance was estimated to be 1.15L/hr/70kg (10.4%). After accounting for weight, clearance of CLB and N-CLB did not appear to be further influenced by age in pediatric patients and young adults. No other covariates were found to be significant for CL/F of CLB. Concomitant therapy with felbamate and poor CYP2C19 metabolic status were associated with reduced apparent clearance of N-CLB by 45% (55%) and 48 % (29.5%) respectively.

**Conclusions:** Pediatric estimates of CLB CL/F after standardizing to a 70 kg adult were almost twice higher than adults <sup>(2)</sup>. This interesting finding suggests CLB is more extensively metabolized in children. A similar finding in children has been reported previously <sup>(4)</sup>. Estimates of standardized N-CLB clearance were comparable to adults. The lower clearance of N-CLB relative to CLB supports its elimination-rate limited disposition and higher accumulation ratio as reported previously <sup>(2)</sup>. High inter-patient variability in CLB and N-CLB clearance (48% and 72% respectively) is in agreement with results in adult healthy volunteers <sup>(2)</sup>. However, inclusion of genotype and concomitant AED therapy reduced variability in N-CLB clearance from 88% to 72% <sup>(3)</sup>.

### **References:**

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