Clinical Pharmacokinetics

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--Manuscript Draft--

Manuscript Number:	CPKA-D-18-00106
Full Title:	COMMENT ON: Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential Implications for Dose Optimisation in Epilepsy Patients
Article Type:	Letter to the Editor
Funding Information:	
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COMMENT ON: Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential Implications for Dose Optimisation in Epilepsy Patients

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Number of tables: 0 Number of figures: 1

Keywords: lamotrigine; pharmacokinetics; NONMEM; paediatrics

Dear Editor,

We read with interest the recent paper detailing the pharmacokinetics of lamotrigine by van Dijkman *et al*[1] and would like to congratulate the authors for compiling such a comprehensive

dataset, which they have used to evaluate apparent clearance (CL/F) changes from young infants to elderly adults. In particular these results are important in patients aged younger than 2 years for whom the drug is currently unlicensed. We note that an extensive *erratum*[2] has attempted to correct the interpretation of the proposed dosing guidelines, although recommendations for patients with different co-medications would have been useful. Before considering dose guidelines derived from the model however, we feel there is a more fundamental question on the underlying assumptions in model that warrants further discussion; namely the proposed function to describe changes in CL/F with age.

In Figure 1 we have plotted the change in predicted values of CL/F with post natal age (PNA) as reported by the authors, using a continuous function to predict typical weight for age[3]. Here it can be seen that CL/F peaks at a post-menstrual age (PMA) of approximately 110 weeks (PNA of 1.3 years), then declines, and does not reach the same rate again until approximately 280 weeks PMA (PNA of 4.6 years). Between us we have extensive experience of modelling pharmacokinetic studies over large age ranges[4–8], analysed how clearance in general changes for thousands of hypothetical drugs (e.g. see Calvier *et al*[9] in this journal), and systematically reviewed clearance maturation functions in children[10,11]. The authors describe an extremely rare (possibly the first) case of decreasing CL/F with increasing age in infants and young children. Since CL/F determines steady-state concentration, and in this case maintenance dose, it is important that this change in CL/F with age is further explored. There are several possible explanations:

Firstly, the arbitrary step function used to describe decreasing CL/F with age above 65 years may be causing an under-estimation of the true young adult value, and hence the dematuration function the authors report is merely a result of this under-estimate exacerbated by limited data in children aged 4-12 years. A more granular breakdown of goodness-of-fit to age groups of less than 1, 1-2, 3-4 year olds and 12-30 year olds would show whether model fit was consistent amongst each age group.

A second possibility is that bioavailability (F) is for some reason lower in infants taking the immediate release formulation, consequently making CL/F seem high. This does seem unlikely

since immediate and extended release formulations have been reported to be bioequivalent[12], and lamotrigine is generally well absorbed, but changes in bioavailability with age cannot be ruled out.

A third possibility, and one we think most likely, is that drug-drug interactions are causing confounding given that different age groups had different co-medication frequencies. Re-fitting the model to data only in patients not taking carbamazepine, phenytoin or valproic acid and re-evaluating maturation parameters would determine this. Such an analysis would give confidence that the relative contribution of maturation and drug-drug interactions are correctly captured by the model. Further insight may also be achieved through PBPK analysis which may predict how CL/F could change with both age and in the presence of drug-drug interactions.

This finding of decreasing CL/F with increasing age in infants and young children is a novel unexpected result, and further exploration to confirm whether it is a real phenomenon, and if so why it happens with lamotrigine, is required.

Figure Legend

Figure 1: Plot of lamotrigine CL/F versus age estimated by van Dijkman *et al*[1]

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Figure

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