

Clinical Pharmacokinetics

COMMENT ON: Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential Implications for Dose Optimisation in Epilepsy Patients

--Manuscript Draft--

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1 **COMMENT ON: Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential**
2 **Implications for Dose Optimisation in Epilepsy Patients**

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48 Dear Editor,

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51 We read with interest the recent paper detailing the pharmacokinetics of lamotrigine by van

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54 Dijkman *et al*¹ and would like to congratulate the authors for compiling such a comprehensive

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

31 In Figure 1 we have plotted the change in predicted values of CL/F with post natal age (PNA) as
32 reported by the authors, using a continuous function to predict typical weight for age³. Here it can
33 be seen that CL/F peaks at a post-menstrual age (PMA) of approximately 110 weeks (PNA of 1.3
34 years), then declines, and does not reach the same rate again until approximately 280 weeks PMA
35 (PNA of 4.6 years). Between us we have extensive experience of modelling pharmacokinetic
36 studies over large age ranges⁴⁻⁸, analysed how clearance in general changes for thousands of
37 hypothetical drugs (e.g. see Calvier *et al*⁹ in this journal), and systematically reviewed clearance
38 maturation functions in children^{10,11}. The authors describe an extremely rare (possibly the first)
39 case of decreasing CL/F with increasing age in infants and young children. Since CL/F determines
40 steady-state concentration, and in this case maintenance dose, it is important that this change in
41 CL/F with age is further explored. There are several possible explanations:

42 Firstly, the arbitrary step function used to describe decreasing CL/F with age above 65 years may
43 be causing an under-estimation of the true young adult value, and hence the dematuration function
44 the authors report is merely a result of this under-estimate exacerbated by limited data in children
45 aged 4-12 years. A more granular breakdown of goodness-of-fit to age groups of less than 1, 1-2,
46 3-4 year olds and 12-30 year olds would show whether model fit was consistent amongst each age
47 group.

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

50 since immediate and extended release formulations have been reported to be bioequivalent¹², and
51 lamotrigine is generally well absorbed, but changes in bioavailability with age cannot be ruled out.

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

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

62 **Figure Legend**

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

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