Letter to the Editors

Evaluation of a morphine maturation model for the prediction of morphine clearance in children

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The primary objective in the Mahmood paper [1] is to evaluate the predictions of a model for morphine clearance reported by Anand *et al.* [2]. It should be noted that the Anand paper did not claim to predict morphine clearance in individual subjects. A model was developed to describe the pattern of size and maturation changes of morphine clearance and its variability. These patterns are clearly confirmed from external data sources including those proposed by Mahmood [1]. The primary descriptive features of the model are clearly evident over three orders of magnitude of clearance i.e. very low clearance in premature infants, size adjusted maturation being reached around 50 weeks post-menstrual age (PMA) and a mature clearance value close to adult values.

Acceptable prediction bias is proposed to be 10% but this is an unrealistic figure in clinical practice. The typical bioequivalence criteria of 80–125% show that a bias of up to 25% in the delivered dose from an equivalent formulation is widely acceptable while up to two-fold differences in clearance may also be acceptable for regulatory purposes [3].

Acceptable precision of the prediction is proposed to be 15%. However, as shown in Sheiner & Beal [4] (reference 20 in Mahmood's paper) the mean square error is the sum of the squared bias and mean square deviation from the mean. In this context the mean squared deviation from the mean is the between subject random variance around the typical clearance value. The square root of this variance was estimated to be 48% by Anand *et al.* [2]. Thus even if the bias was zero, the root mean square error would be 48% and so a precision target of 15% is unattainable even if the prediction model is perfect.

The percentage mean prediction error (%MPE), used to estimate bias, is calculated by Mahmood [1] relative to the average observed clearance. This is not an appropriate way to calculate MPE when there is a wide range of values being compared. It minimizes the MPE at low clearance values and exaggerates it at higher values. The prediction error in clearance is important relative to the observed

value not relative to a value that may be an order of magnitude or more different.

The text and figures include coefficients of determination to support the assertion that the model makes poor predictions. Yet Mahmood acknowledges 'Correlation coefficient (r^2) (sic) is however, not a good measure for the assessment of the predictive power of a model'. The coefficients of determination add nothing to the evaluation of the data and should be ignored. The use of a regression line rather than a line of identity and unequal axis sizes distort the comparison of predictions with observations (e.g. Figure 2). These figures are more informative about the predictions when they show the line of identity (e.g. Figure 1).

Mahmood challenges the definition of the age at which the clearance in a child is 50% of an adult value (page 11). He proposes a definition which uses an adult size standardized value (70 kg) but then fails to apply a similar size standard before comparing clearances in children and adults. We believe a major strength of our approach using size standardized values is that it allows a meaningful description of maturation independent of size. He goes on to say that our prediction that morphine clearance approaches adult size standardized values around 1 year is incorrect because physiological development continues past this age. However he offers no evidence to show that morphine metabolism continues to mature independently of size after 1 year.

We retrieved the individual clearance estimates from the 10 original publications used by Mahmood. A comparison of the plots of clearance values shows that some data points appear to be missing (Figures 1 and 2). He reports more observations (147 vs. 144) but appears to have omitted two of the subjects with 'divergent kinetics' (Figure 3) reported by Dahlstrom *et al.* [5]. Clearance estimates above 400 ml min⁻¹ appear to be missing from Figure 1 of Mahmood's manuscript (Figure 4). We believe there may be errors in the data used by Mahmood and these discrepancies should be resolved.

Figure 1

Predicted and observed clearance in 75 neonates (GA < 37 weeks) based on literature cited by Mahmood [1]

Figure 2

Mahmood [1] Figure 1 showing predicted and observed clearances in 75 neonates. There seem to be points missing at observed clearances around 8–11 ml min⁻¹

Individual predictions of morphine clearance (and thus dose) may be guided initially by the model predictions but of course should be refined by direct observation of clinical response. Clearance, and thus the appropriate dose rate, changes rapidly in the first few weeks of life and is determined by both age and weight. We would assert that initial dosing, based on typical subject clearances of morphine, is of practical value. This is directly opposed by Mahmood who states '...the prediction of morphine clearance ... and the magnitude of prediction error was too high to be acceptable for any practical use.' We also cannot agree with the conclusion that the maturation model in the abstract 'may not be of any practical value for the prediction of morphine clearance in this age group.' This assertion is presented without any justification or evidence that it would not be of practical value.

The 'secondary objective' of Mahmood is to evaluate the allometric exponent of 0.75. Mahmood provides no justification for claiming that the allometric model with an exponent of 0.75 is erroneous. Predictions from Method II (using just this allometric model) are applied to all subjects

Figure 3

Predicted and observed clearance in 144 neonates and children (age ≤ 5 PNA years) found in the literature cited by Mahmood [1]. Circled symbols refer to clearance estimates in the original publication that the original authors identified as being 'divergent'. Comparison of the figures suggests Mahmood did not include these values

Figure 4

Mahmood [1] Figure 2 showing predicted and observed clearances in 147 neonates and children. There seem to be points missing at observed clearances greater than 400 ml min⁻¹

and ignore age. Necessarily the predictions are bad for the neonates when neither maturation nor prematurity are included. He acknowledges that including maturation makes the predictions much better but still wants to claim that 0.75 'introduces substantial error' (bottom of page 12).

This claim about 'introducing substantial error' is perhaps the most unacceptable part of the paper because it is not supported by what is presented. There is nothing in this paper to show that the use of the allometric exponent of 0.75 introduces error in the predictions. Indeed, Mahmood demonstrates that in children who are predicted to be mature, the clearance is adequately predicted from weight using the allometric model with an exponent of 0.75. The only 'substantial error' is when he uses allometric scaling alone but that is exactly why we have proposed additional biologically based models for describing why size alone is not adequate.

Competing Interests

There are no competing interests to declare.

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