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Rectal Acetaminophen Pharmacokinetics

To the Editor:—We read with interest the recent study by Birmingham *et al.*[1] concerning the pharmacokinetics of rectal acetaminophen in children. The estimate for clearance (CL/F) of 5.46 $ml \cdot kg^{-1} \cdot min^{-1}$ is similar to that previously reported in children after rectal administration.[2] However, the volume of distribution (Vd/F) estimate of 385 ml/kg seems to be low. The relative bioavailability (F) of rectal compared with oral acetaminophen formulations has been reported as 0.52 (range, 0.24–0.98)[5] and even as low as 0.3.[6] Estimates[3,4] of acetaminophen's Vd/F in children are within the range of 700–1,000 ml/kg after oral administration. We would therefore expect Birmingham *et al.*[1] to have found a Vd/F of at least 1,400–2,000 ml/kg, which is similar to the value of 1,903 ml/kg previously reported after rectal administration.[2] Figure 1 shows the "average" profile observed by Birmingham *et al.*[1] (20 mg/kg), and predictions made using their dissolution time model with a Vd/F of 385 ml/kg compared with a Vd/F of 1,400 or 2,000 ml/kg assuming rapid dissolution. The "average" concentrations illustrated[1] after 20 mg/kg peak around 5–6 μg/ml, not 8–10 μg/ml predicted by Birmingham *et al.*'s[1] model. However, when Vd/F in the range of 1,400–2,000 ml/kg is used, the model approximates more closely the reported "average" concentrations. It is clear that Birmingham *et al.*'s[1] model does not match their own observed values.

Finally, we agree that suppository size may affect absorption characteristics. However, there is no consistent pattern in the dissolution times reported by Birmingham *et al.*[1] The rate at which suppositories dissolve does not seem to be a simple function of suppository dose size. Dissolution times decrease within the smaller suppository size group and within the larger size group, yet dissolution times increase from the small to the large suppository size group. The authors admit they have less confidence in this component of their model, and although it may improve the goodness of fit, it is not revealing about any mechanism of suppository dissolution and may have distorted their estimate of Vd/F.

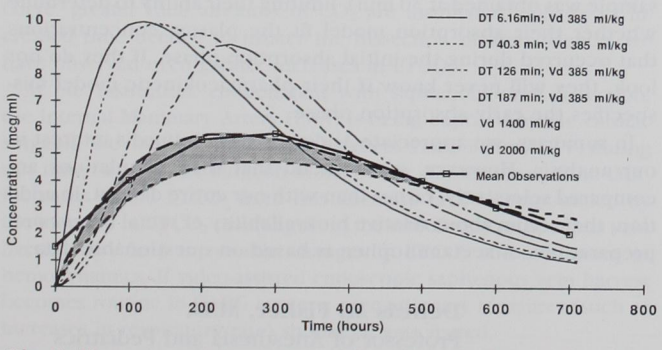

Fig. 1. Time–concentration profiles after administration of 20 mg/kg rectal acetaminophen. Parameters[1] used were CL/F, 5.46 $ml \cdot kg^{-1} \cdot min^{-1}$; Ka, 0.00468 min^{-1}; Vd/F and zero order dissolution times (DT) as shown. The simulations using Vd/F of 1,400 or 2,000 ml/kg assumed rapid dissolution.

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