

## COMMENTS FROM GATES FOUNDATION

- How predictive is this model if you perform *in silico* modeling for adults and compared with real clinical PK data (e.g. Cmax; AUC, %time>desirable conc.)?
- What would the data look like if you modeled twice a day dosing. Would the advantages outweigh the inconvenience?
- Page 2: Figure 1: may want to put units on Y axis (mcg/mL)
- Figure 4. Are calculated values for infants or children?
- Might be nice to put in a (adult) toxicity line for the Cmax plots for each drug (where known), so can put exposure predictions in context with safety.
- What is known about the safety in infants/children for the doses used in these calculations? Should cut-off values be added?
- Questions around some of the assumptions:
  1. The pharmacokinetic parameters used in these simulations (derived from primary and secondary medical literature) offer a reasonable approximation of those that would be observed in the infants and children receiving the fixed-dosing combination under evaluation. **Assumptions 1 & 2: Do these assumptions take into account differential hepatic function of infants/children compared to adults? Have these assumptions proven to be true in any real life examples?**
  2. The pharmacokinetic parameters employed herein represent values that approximate those that would be observed after repeated drug administration.
  3. The pharmacokinetic parameters used for the simulation of any given drug represent values that approximate those that would be observed with concomitant administration of the other two drugs (i.e. no accounting for drug-drug interactions). **What about Rif induction of CYP2D6 and CYP3A4? I see on bottom of page 15 some reference to CYP induction, but seems like one should be able to use whatever is know from adult Rif induction and, for a first approximation, build that into the model. May not be perfect, but will be a little closer to reality.**
  5. No dose-dependent (i.e. zero-order, mixed zero-order/first-order) absorption is observed within the range of doses evaluated. **Is this true in adults?**
  6. There are no appreciable age-dependent differences in the rate and extent of absorption between the age groups evaluated. **Any evidence for this assumption?**
  7. There are no appreciable age-dependent differences in the extent of drug distribution within the age groups simulated. **Any evidence for this assumption?**
  8. Systemic drug exposure resulting from dose escalation within any given individual is linear and does not vary with age. **Any evidence for this assumption?**
  9. There are no formulation specific (i.e. physicochemical) effects that would independently alter the disposition of the component drugs under evaluation.
- How well do these simulations predict what is known in the literature? Are there other variables (e.g. GI volumes, liver function, GI tract permeability differences) that could be incorporated into the model for improved predictivity?

Some examples of children/infant TB drug studies from literature are below.

- 1) V. Roy et. Al.; , The International Journal of Tuberculosis and Lung Disease, Volume 3, Number 2, February 1999 , pp. 133-137(5)] Children aged 6 to 12 years suffering from pulmonary tuberculosis: The serum concentrations of pyrazinamide were above the minimum inhibitory concentration of 20 µg/ml of pyrazinamide for *Mycobacterium tuberculosis* up to 6 hours after drug administration in all the patients, and up to 12 hours in six patients. The mean peak serum concentration of pyrazinamide was  $41.2 \pm 11.8$  µg/ml, and this was attained in (Tmax)  $2.9 \pm 1.7$  hours. The elimination half life was  $10.9 \pm 4.5$  hours, the volume of

distribution  $16.1 \pm 10.9$  litres and clearance  $20.2 \pm 16.3$  ml/minute. The corresponding mean residence time was  $19.9 \pm 14.6$  hours. The serum pyrazinamide concentrations achieved with a dose of 35 mg/kg were above the minimum inhibitory concentration of pyrazinamide for *M. tuberculosis* for over 6 hours after drug administration. It appears that the absorption and the clearance of pyrazinamide is slower, the elimination half life longer and the volume of distribution higher in children compared with the reported values in the adult population.

2) George H. McCracken et al; PEDIATRICS Vol. 66 No. 1 July 1980, pp. 17-21

Pharmacokinetic studies of rifampin were performed in 38 infants and children after administration of three different oral formulations. Mean peak serum concentrations of from 9 to 11.5 µg/ml were observed one hour after a 10-mg/kg dose and the average half-life was 2.9 hours. Patients who received rifampin suspension in applesauce had smaller serum concentrations and area-under-the-curve values than did those who were given suspension alone. The mixture of rifampin powder and applesauce resulted in more variable serum levels. The concentrations of drug in tears from 18 subjects were similar to those in serum. All but one of 118 saliva specimens obtained from two to eight hours after the 10-mg/kg dose had antimicrobial activity. Of samples taken at two hours, 95% contained rifampin levels that exceeded the minimal bacterial concentration for 15 *Haemophilus influenzae* type b strains. Bactericidal activity against *Haemophilus* correlated with salivary rifampin concentrations and was detectable in virtually all specimens containing [Unknown]0.8 µg/ml. These data provide the pharmacokinetic basis for rifampin prophylaxis of close contacts of *H influenzae* type b disease, but are insufficient alone to recommend routine usage of rifampin for this purpose until results of additional epidemiologic studies are available

3) <http://www.blackwellpublishing.com/medicine/bmj/nnf5/pdfs/commentary/isoniazid.pdf>

Little is known about how the body handles isoniazid in early infancy, but such evidence as there is suggests that clearance is much reduced in babies only a few days old (Holdiness, 1987) and for that reason this text continues to recommend that children should not receive more than 5 mg/kg in the first month of life. Indeed several studies have shown that most older children also do very well when given 5 mg/kg once a day (Roy *et al.*, 1996). However, recent research (Schaaf, *et al.*, 2005) has shown that drug elimination in young children is more rapid than is generally appreciated, and that it also varies widely, depending on whether the child has inherited a fast-acetylator genotype or not. There is, as a result, real concern that some children will be sub-optimally treated if they are only given 5 mg/kg a day once they are more than a few weeks old. Since it is not generally realistic to try and assess a child's acetylator status, 10 mg/kg a day is probably the most pragmatic dose regimen to choose. Further research is clearly needed to optimise treatment while minimising the risk of toxicity in young children.