

Brockner Ryan, Beth

From: Barry H. Rumack [barry@rumack.com]
Sent: Thursday, July 01, 1999 10:24 AM
To: Ball, Robert
Subject: RE: 2 compartment PK model

I will ponder this and ask Dan Spyker his thoughts as well. I spent time yesterday trying to relate our method and that of Clarkson to see if we could have one unified method. The thought was that Clarkson does not have any elimination and if we could take our burden numbers and translate them then we'd have both. The problem is the Clarkson inherently uses a V_d of 1.4 (5% of the mercury load into 7% of the body - he also used 8.5% for smaller kids which makes it perhaps 1.6. I don't think that is correct. We took the data from Pfab and got 1800L/kg (83000 mcg/kg divided by 46 mcg/L = 1800).

Now, lets debate the burden vs. blood level information. I realize that most of the work being reported relates to blood levels but that does not mean it is correct. The blood levels simply reflect some of the body burden and we do not really know the distribution. The actual toxicity of Hg is not from the amount in blood but rather the amount in tissue. In my work with Hg and other heavy metals I have been impressed with the need to understand that burden. Thus we have used a chelation challenge test. If you collect urine for 24 hours and measure the metal and then give a chelator for 24 hours and measure it you will either get a rise or not. If you do not get a rise over the non-chelated amount we have presumed that there must be little additional body burden. If it goes up (and I have seen it go up 20 or 30 times over baseline) then you presume that you are changing the equilibration and have a body burden. We have taken patients such as this and chelated them for 10 days or so, then waited and re-challenged. After doing a few cycles you may eventually get it so there is a small if any rise in the challenge and presumably you have diminished the body burden. Thus, I believe that it is knowledge of the body burden that is important and not necessarily the blood level. I think that those using the blood level are doing work with cognitive evaluation, etc. to try and relate something to the blood levels that they see. After looking at all of those articles you can see that sometimes they relate and sometimes they do not. Perhaps this is because of different body burdens and hence different toxicity.

The body burden model we gave you adjusts the EPA and FDA levels in a way which is relative to the changes in half life, etc. and directly relate to the immunization burden. We also do not have to make a presumption of volume of distribution. The key point we were trying to make was that if you take the EPA or FDA levels you can draw the steady state for total burden and then compare that to the burden you would get with intermittent dosage. We could do the same with the EPA or FDA levels and calculate blood levels. I just do not know what volume of distribution to accept. Clarksons use of 1.4 or so is empirical and seems too low. We could calculate an elimination rate constant and utilize various half lives to bound it. Our suggestion is to not use the blood level data but use burden data comparisons. I think it would not be hard to take the data from Faroe or Seychelles and do a burden analysis since the assumptions are in the articles. Then you could compare apples and apples (or fish and fish!).

Looking at the Pfab data and some of the other data it really looks like the rapid phase is primarily a distribution phase. While you might consider an immunization to be 100% absorbed it will still distribute into the tissues. The method you have proposed appears to accommodate this but would require an assumption of both distribution and elimination. The model we built does not require a volume of distribution and I think we need to look at total body load. All this points to the basic questions that can probably only be answered in the laboratory. We are all operating under the difficulty of lack of data.

Barry