From: Heylings Jon GBAP
Sent: 22 August 2006 15:30
To: Pastoor Tim USGR; Elliott Barry GBAP; Botham Phil GBAP; Akins Jonathan USGR; Swain Cindy GBAP
Subject: AUC as a Prognostic Tool

Colleagues

Apologies for adding to the proliferation of E mails on this subject, but I guess the deeper we evaluate the available data, the more likely we are to get the best experimental design. In response to Tim's request, I have the following on the prognostic value of AUC to predict mortality following oral dosing of PQ formulations.

1. Historical CTL data (1989-92)

AUC mortality relationship.pdf...

Attached is the chart we compiled in the early 1990s of all the CTL XD studies (207 individual dosings). The legend hopefully explains the plot. There were 190 survivors (92%) and 17 mortalities (8%).The data are an assembly of various "safer" formulation options and existing products from round the world form a large number of independent research projects. All the formulations studied contained emetic. This was not published since it not only covered a range of confidential formulation options but the concern at the extent of testing going on in this species. The low mortality (8%) would not have been achieved without the use of kinetics to predict the likely outcome at the next dose.

The plot is obviously weighted at the survival end, but I don't think an intervention below an AUC of 20 ever happened during these studies. Likewise, a survivor above 40 was a very low probability. I have never favoured the peak plasma value, since many of these mortalities only had modest peaks but had persistent systemic exposure over 24h, indicative of renal failure and poor clearance into urine. This loads the AUC well beyond the peak and alters the shape of the curve.

INTEON CTL data 2003-2006

PQ AUC Prognosis.xls

I have pulled out all 84 individual dosings that have been undertaken more recently. This includes all the INTEON formulations we have tested (these are all reported). It excludes the recent 12 dosings with the Japanese INTEON which is in progress. (these are all survivors). In the 84 dosings we have 78 survivors (93%) and 6 mortalities (7%). This is a very similar picture to the historic CTL data. Perhaps not surprising since it uses the same kinetic support criteria and operates under the same Home Office authority and Project Licence Holder (myself).

For this analysis, I have examined the individual animal AUC values not the group mean. My rationale for this is the older studies often failed at 32mg/kg and technologies that were less reliant on emesis like microcapsules and multiple emulsions reached a more consistent failure point (less variable) and had broader plasma profiles. The technologies that are dependent on gastric emptying, by virtue of the gelling and the effectiveness of emesis e.g. INTEON, MAGNOXONE etc are much less toxic. For example, the INTEONs break away at much higher doses where there is more likelihood of individual animals having high exposures if the PQ dose was too high for the technology to protect the animal. When the group variance is high, the group mean is of less use to the AUC prognostic argument than the individual animal AUC. Please challenge this. It is difficult to explain in an E Mail.

The attached spreadsheets should be self explanatory. The first one shows the 84 animal dosings (survivors and mortalities) across all the INTEON studies. The second sheet shows all 78 survivors.This gives a mean AUC of 7.5

+/- 0.5ug/ml.h. The third sheet examines the 6 mortalities. The mean AUC is five times higher at 35.4 +/- 9.3. (Note the overall mean would have been even higher had we not intervened with the 2 worst cases at 6h).

The modern data fit reasonable well with the old plot of AUC and mortality probability. There is one rather low AUC intervention at 11.2. This animal was taken out at Day 6, but it is afterall a probability relationship prone to biological variability/animal sensitivity etc. Apart for this one individual, my old "guideline" of no mortalities below AUC of 20 fits for the modern day studies where we have undertaken n=84 dosings.

I have put this together rather rapidly so we have it for our next call tomorrow (if needed). It needs a thorough audit if we were to utilise this outside our team.

I fully realise that the objective is to determine the toxicity of the INTEON and non-INTEON products. However, this prognostic approach should provide a platform that we can use in the post-dosing period together with the clinical observations. On an animal use point, the 84 dosings only involved 33 animals over 4 years, due to our study design and re-use criteria.

Please get back to me if you wish me to clarify any of this.

Regards

Jon

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