Message

From: Heylings Jon GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802690]
Sent: 6/16/2005 5:34:16 PM
To: Kelly Christine AUSY [/O=NOVARTIS-AG/OU=AUSYCP01P/cn=Recipients/cn=611898]
CC: Shaunak Richa CHBS [/O=NOVARTIS-AG/OU=CHBSPP01P/cn=Recipients/cn=804471]; Winten Rowley AUSY [/O=NOVARTIS-AG/OU=AUSYCP01P/cn=Recipients/cn=574132]; Elliott Barry GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802673]; Clapp Mike GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802648]; Smith Lewis GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802825]
Subject: Raw data supporting INTEON
Attachments: PQ JRH.pdf

Chris

PQ JRH.pdf

As requested when we spoke this morning, I am sending you the relevant raw data I have managed to locate in my old research files. These are intended to support the conclusions in the summary slides that you have. We have done many studies on Gramoxone and new formulations in the dog. I have located the relevant raw data that supports the position we have that A3879BU is likely to be less toxic than Gramoxone containing high emetic.

By way of orientation for yourselves and the Reviewer I have the following notes.

Method

The methodology used back in the 1990s when most of the Gramoxone research was conducted is essentially the same as we run now. This includes the Beagle strain and the sampling times and calculations etc. The details of the protocol, methodology etc can be found in study report CTL/XD7201 which has been submitted as part of the A3879BU package. I was personally involved in the studies conduced 15 years ago and the current studies, that are now, of course to GLP and have standardised reporting procedures. However, I can vouch for the historic data being an accurate reflection of the research conduced within my group. I have authenticated the data by signing the raw data in the attached file.

Controls

Gramoxone controls were run periodically in the 1980s and 1990s and less frequently since (due to ethical constraints). Page 1 in the attached file has the raw data for Gramoxone controls compiled from several separate studies over 4 years. The data are presented as plasma paraquat concentrations from 15min to 24h for 6 groups of dogs from June 1987 to Jan 1991. The plasma profile for a sub lethal dose of paraquat (8mg ion/kg , equivalent to 44mg/kg formulation/kg) are very consistent. We have used both capsule and gavage and in some presentations we have combined the 2 approaches, since essentially they give very similar plasma profiles. We used capsules for A3879BU, since removal of the gavage dosing tube can deposit some formulation on the oesophagus and we want to avoid this. The data across all these studies show that peak plasma is around 4ug/ml at 1h following Gramoxone at this sub-lethal dose.

A3879BU

The report on A3879BU (CTL/XD7201) submitted for review contains all the detail of this study. Page 2 and Page 3 are extracts showing the plasma values from 15min to 24h for doses from 8mg/kg ion/kg (46mg formulation/kg) up to 128mg ion/kg (736mg formulation/kg). It is clear that the performance of A3879BU is much better than Gramoxone and the lack of dose response demonstrates that the safening components more than compensate for the increased dose of the new formulation. Across the dose range for A3879BU peak values seen in controls (above) of around 4ug/ml are not seen until 8 times the dose level was given.

High Emetic Gramoxone

Back in 1990 we explored the ability of the emetic agent already present in Gramoxone to further safen the product. At this time we were studying 100g/l emulsion formulations containing 1.2g/l emetic. The Gramoxone controls were given at the same 100g/l concentration for comparison. Since twice the volume was given to dogs to dose the same mg/kg body

weight of paraquat ion, this is equivalent to a 200g/l Gramoxone containing 2.4g/l emetic. Page 4 of the attachment shows the raw data from the 3 high emetic Gramoxone studies in February and March 1990. The doses were 16, 32 and 48mg paraquat ion/kg (equivalent to 80, 160 and 240mg formulation in the A3879BU currency). Data shown are ug/ml PQ in plasma, the ug/ml.h 24h AUC, and the time to emesis. The data are presented for 3 dogs at each of the 3 doses with the plasma paraquat concentrations and mean values shown above the AUC values for the same animals (coded 413 etc). The dosings occurred on Feb 13th 1990, Feb 21st 1990 and March 20th 1990. in study XD1328, E32, E33 and E34, respectively

Increasing the dose of the emetic reduced the time to emesis but as the dose of paraquat was increased the plasma levels began to break away at 48mg ion. In fact, one dog was humanely terminated at this dose due to excessive systemic exposure and symptoms of paraquat toxicity. Therefore the inclusion of a very high emetic dose has limited ability to provide additional safening. In contrast, A3879BU, which contains a lower level of emetic at 1.5g/l, progressed well beyond this dose level and did not show any high plasma PQ levels until 128mg ion/kg (736mg formulation/kg).

Therefore, we can conclude that A3879BU is a much safer formulation of paraquat in the dog than Gramoxone containing high emetic and no alginate gel. This is consistent with our hypothesis that productive emesis decontaminates the stomach more effectively than emesis per se, since liquid formulations like Gramoxone pass through the stomach very quickly. Alginate makes emesis an effective built-in method to reduce the gastrointestinal absorption of paraquat.

Submitted slides

In the limited amount of time available I have sourced sufficient raw data to support the conclusions drawn in the slides already submitted. However, these are not the full data underlying the slides. I can corroborate all but one of the bars for the high emetic Gramoxone. However, the raw data clearly demonstrate that all doses of high emetic at each time point have much higher plasma paraquat concentrations than the A3879BU formulation.

Conclusion

We can conclude from these investigations in the dog that the alginate-containing formulation of paraquat A3879BU offers significant benefit over, not only standard Gramoxone, but also when compared with Gramoxone fortified with very high emetic. This indicates that emesis is much more effective when the ingested product is held in the stomach by the bulking effect of alginate.

Please contact me if further clarification is required.

Jon

Jon R. Heylings Ph.D.
Head. Absorption & In Vitro Toxicology
Research and Investigative Toxicology
Syngenta CTL, UK Tel:44(0)1625 514550