Message

From: Loke Peter SGSG [/O=NOVARTIS-AG/OU=SGSGCP01P/CN=RECIPIENTS/CN=847858]
Sent: 1/16/2004 5:49:05 PM
To: Heylings Jon GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802690]; Wilks Martin CHBS [/O=NOVARTIS-AG/OU=CHBSPP01P/CN=RECIPIENTS/CN=804593]
CC: Clapp Mike GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802648]; Wheals Ian CHBS [/O=NOVARTIS-AG/OU=CHBSPP01P/CN=RECIPIENTS/CN=804621]
Subject: RE: Preglox and AWT

Thanks a lot for the very useful info, Jon.

Peter

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-----Original Message-----
From: Heylings Jon GBAP
Sent: Saturday, January 17, 2004 1:34 AM
To: Loke Peter SGSG; Wilks Martin CHBS
Cc: Clapp Mike GBAP; Wheals Ian CHBS
Subject: RE: Preglox and AWT

Peter

Thanks for this. A couple of comments. When Berni Hart, Lewis and I reviewed the Ohno Japanese poisonings cases in 1988 we did observe a number of very high ingestion volumes. I guess nothing will save these patients, even AWT. However, the mean ingestion volume was actually only 67ml of product in a subset of 69 cases where we had good evidence of volume intake, out of the 300 or so cases investigated in Japan. The survival rate was 26% in these cases. I cannot see the rationale that one culture would drink a much larger volume than another if the product had the same physical constituency and stench.

On the emetic response. We are are aware that since inclusion of the emetic there have been some cases where prolonged emesis has occurred. In my view this is not unexpected with the liquid non gelling formulations, Gramoxone and Preglox. This also occurs in dogs with Gramoxone. They vomit much later and over a longer time following Gramoxone compared with AWT. The prolonged emesis is due to the irritant effects on the mucosa of the upper gastrointestinal tract and is an autonomic vagal reflex. This should not be confused with an overdose of a centrally acting emetic. With AWT dogs vomit quickly and this usually stops by 2 hours. The gut wall is probably protected by the film forming properties of the gel, as in Gaviscon. Once the formulation has emptied from the stomach with liquids like Gramoxone, it is difficult to vomit it back and it begins to damage the mucosa since there is longer contact and even a CNS vomiting reflex cannot achieve this. With AWT, the gelled formulation containing the extra emetic is expelled as soon as the drug stimulates the vomit centre in the brain and the emetic is removed along with the Paraquat as the whole stomach contents are expelled.

In terms of human safety of high emetic formulations, we already have a high level of emetic in the French formulation (2g/l) which is even higher than AWT (1.5g/l). I am not aware of prolonged emesis and the symptoms you describe from poisonings involving this French product. Furthermore, we have not seen any cardiovascular effects in animals exposed to very high doses of AWT and hence very high doses of the emetic.

Regards

Jon

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-----Original Message-----
From: Loke Peter SGSG
Sent: 16 January 2004 02:46
To: Wilks Martin CHBS
Cc: Clapp Mike GBAP; Heylings Jon GBAP; Wheals Ian CHBS
Subject: Preglox and AWT

Dear Martin,

Its been interesting finding out the situation in Japan, and the issues faced here. One thing that appears clearer to me is the likely reason as to why dilution of paraquat does not seem to have worked in terms of 'successful' suicide attempts here in Japan; the Japanese tend to ingest relatively large quantities at a time in cases of intentional ingestion (average of 200-300mls!) compared to people of the other countries I have visited.

The one 'concern' I have relating to low concentration Preglox, AWT and the Japanese 'culture' of large quantity ingestion is the impact the AWT formulation might have with regard to Preglox in Japan. Taking into account that AWT is expected to work, but perhaps not in all circumstances, is it not even more likely to work with the lower paraquat concentration strength formulation, assuming that the alginate and emetic concentrations are the same in the Preglox formulation as the Gramoxone AWT formulation? The longer term result of that could be clear data that indicates that whilst Gramoxone AWT results in significant safening, Preglox AWT could almost completely eradicate successful suicide attempts when PregloxAWT is ingested. The pressure to market the diluted product might then increase rather than decrease in the longer long term. ('Totally' safe product vs Relatively safe product)

In addition, I asked Shigeno Takeo (who has the longest experience with paraquat and its history) for his opinion, purely on an observational basis, of the effectiveness of the emetic in reducing deaths, and he had apparently got much feedback previously from doctors in Japan that the emetic increases the death rate due to its immense tachycardic effect (not sure if its an inherent effect of the emetic or purely vaso-vagal from vomiting?) and the asphyxiation that often results from the vomiting. Perhaps at least for the Preglox formulation, we might wish to explore this further and consider a less than three-fold increase in the emetic concentration?

What is your opinion? Maybe we can discuss about this next week when we talk?

Thanks; have a good weekend.

Peter

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