Message

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Sent: 2/11/2004 11:41:53 AM
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Subject: Importance of Mg in the US AWT Formulation

David

As requested during our conference call last Friday, I have the following points on the inclusion of Magnesium Sulphate in the US (or other daughter) AWT formulations.

The original discovery that Gramoxone could be safened was based on the simple addition of MgSO4 to Gramoxone at a loading of 400g/l. We achieved a 2X safening in rat and dog back in 1988. We had in vitro evidence that Mg competes for calcium-dependent PQ uptake in the gut. We also had evidence of a purgative effect of Mg in the rat and dog. There is additional published evidence from Fitzgerald et al that survival is better in Mg-containing PQ products such as Weedol. They attribute this to a possible purgative effect caused by the solid MgSO4 used in the manufacture of the product.

As we moved towards a gelling approach in 1989, we kept the Mg cation, following testing of many gels and other salts e.g. Na, Ca, Ba etc. Mg was always the best. However, there was not enough water space in the 200g/l product to dissolve 400g/l MgSO4 and suspend a gel so we backed off to 300 and 200 MgSO4 loading. The tox became worse in the rat as a consequence of this reduced loading. Magnesium Trisilicate was a way we could keep the Mg high since more free Mg was released as the suspended insoluble trisilicate was converted to silicon dioxide gel in the stomach. I called this complex mixture "Magnoxone" since there were several Mg additives and it was becoming a mouthful to describe. The surfactants were not changed from those in standard Gramoxone at the time, just the "safeners".

When we ran the storage stability on these high Mg forms at Yalding, crystals of MgSO4 began to appear on long term hot storage - not enough water. We therefore ran an extensive series of dog studies circa. 1992-3 to see what the minimum loading of MgSO4 could be without losing purgative benefits. In sequential dog studies we lowered MgSO4 from 150 to 100 to 50g/l (with fixed emetic and trisilicate). There was a clear dose response across the target range of 20X for the high Mg ones and down to 5X for the low Mg ones.

Mg was considered a key element of the safening and the TRC at the time endorsed that the loading of MgSO4 should be a minimum that would meet storage criteria. Cost was not an issue from the purchasing folks. Low purity MgSO4 was an insignificant cost and plentiful in supply. We settled on a 100g/l load for the heptahydrate as the optimum trade off in Magnoxone. This still stands and is equivalent to our 74g/l for the monohydrated form in Gramoxone AWT.

As you will recall Mg was examined as a potential treatment in man, since it not only inhibited PQ uptake from the gut but it also reduces lung and kidney uptake when administered intravenously. This did not work in a controlled trial since the patients were all treated beyond the 4 hour window of opportunity and had high very high ingestion levels of PQ.

In the AWT programme the benefits of MgSO4 have remained dormant until now since it is only when we get to high volume ingestion that the amount of Mg becomes osmotically effective. All the dog studies at medium and high doses have shown clinical evidence of purgation with AWT. Not every dog has had visible purgation - probably becuse the Mg is also lost via emesis, but the frequency is high and this symptom does not occur following Gramoxone.

If we did decide to remove the MgSO4 from the specification we would have to tread very carefully since any PQ left in the small intestine post emesis would continue to be absorbed in the hours after dosing if the gut was not flushed.

Jon

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