Message		
From:	Ashford Emma EJ [/O=ZENECA/OU=AGUK/CN=RECIPIENTS/CN=EMMA.ASHFORD]	
Sent:	9/29/2000 9:33:03 AM	
То:	Heylings Jon GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802690]; Farnworth Mike GBAP	
	[/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802676]	
Subject:	RE: Paraquat emetic info	

Dear Jon/Mike,

Thank you both very much for putting all that information together for me. It is very much appreciated.

Kind regards,	
Emma	
Original Messag	Je
From:	Heylings Jon JR
Sent:	28 September 2000 16:04
To:	Ashford Emma EJ
Cc:	Shaunak Richa R; Farnworth Mike MJ
Subject:	RE: Paraquat emetic info

Emma

I have a few comments for you on the emetic PP796. Mike has also dug out some old studies we did back in the early 1990s.

PP796

Originally known as ICI63197. Molecular formula C9H13N5O with a MW of 207.2. I do not have its octanol:water partition coefficient (log P) but it is soluble in 500parts of water in 12 parts of chloroform and in 170 parts of alcohol.

Effective dose

Effective dose rate i.e. vomiting within 30min (ED50) in dog, monkey, marmoset and pig is 0.5mg/kg. Shown to be safe in dogs at 20mg/kg. Effective dose rate in man is also circa. 0.5mg/kg (ICI Pharms report PH20992B) when it was tested as a drug in human volunteers. The shape of the dose response curves in all species are remarkably similar and particularly steep over the 0.5-1.5mg/kg range.

Assuming a 70kg man an effective dose is 70X0.5=35mg PP796 in a lethal dose of Gramoxone which is widely agreed to be 15ml. This indicates that a concentration of 2.3mg/ml PP796 would cause vomiting within 30min in a minimally lethal dose of Gramoxone. We currently put 0.5mg/ml in the product. The 2.3mg/ml emetic version of Gramoxone provided a 5-fold safety factor in the dog (CTL/R/1250). Based on the similarities in dose response curves of the 5 vomiting species studied I would expect this to give a 5X safening in man.

Physical state and uptake

Physical state in the stomach really depends on its thermodynamic interaction with the gastric juice (pH2-3) and electrolyte composition both of which can shift solubility. The normal rule is if the PP796 is unionized at the prevailing pH it is more likely to diffuse into the lipid rich mucosal membrane and be absorbed. If it remains ionized (like paraquat itself) it will be poorly absorbed. Blood kinetics for PP796 and the vomiting response suggest it is rapidly absorbed and therefore may be difficult to boost. It would be geat, however, if we could, by formulation.

Gastric emptying

PP796 is a phosphodiesterase inhibitor and as such can affect GI motility. High doses have been shown to inhibit gastric emptying (which is good for T-gels). From our research it was concluded that over 2 hours gastric emptying itself does not seem to effect plasma emetic (PP796) concentrations in the rat, using an anaesthetised starved rat model in which the pylorus was ligated. However, at 4 hours the plasma concentrations were significantly increased when the stomach was unligated compared to ligated (138 compared to 54 ng/ml) indicating further absorption in the small intestine. In the ligated rat increasing the emetic three fold from 0.5 to 1.5 g/l in a Gramoxone formulation resulted in a similar increase in plasma concentrations to unligated animals, however the higher dose was not cleared as rapidly. On balance it would suggest that PP796 can be absorbed by the gastric mucosa.

Intestinal transit

PP796 only really effects intestinal transit at a dose of paraquat that is equivalent to 10 lethal doses at a concentration of

1.5 g/l PP796 in a 200 g/l paraquat formulation. This was concluded from a study in which an oral dose of emetic (12mg/kg) was given 1 hour prior to a charcoal bolus in the mouse, significantly (P<0.001) reduced the distance travelled by the bolus in 1 hour compared to control.

Absorption and excretion in vivo

In the rabbit when orally dosed at 40 mg/kg PQ with a similar paraquat concentration (Gramoxone formulation) containing 0.5 and 1.5 g/l resulted in a similar 3 fold increment in the peak plasma concentration and in the rate of absorption over the first 15 minutes. The emetic was rapidly cleared from the system by 24 hours post dosing irrespective of the dose of emetic.

In the dog the emetic is cleared rapidly from the plasma following a 32 mg/kg (twice lethal) dose of Gramoxone containing 1.5mg/kg emetic with emesis occurring before 10 minutes in animals with plasma concentration above 100 ng/ml at 15 minutes. The emetic plasma concentration profiles were similar to those observed with an oral dose 40 mg/kg PQ ion of Gramoxone containing the 0.5g/l emetic.

As far as I am aware there is no data generated in-house that investigated the effect of food on emetic absorption although there is no effect of removing food for a 24 hour period prior to dosing on the toxicity of paraquat in both rat and dog. Food can slow absorption of drugs particularly if it binds the drug or interferes with its delivery into the absorptive small intestine.

I hope this is of some use.