Paraquat Improvement Project

Proposal 2

Emetic Booster Formulation - Gramoxone EB

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Summary

This proposal describes a technical approach to produce a new formulation of Gramoxone which contains the current concentration of ICIA0796 at 0.5g/l but the dispersion of the emetic agent in this system has been optimised in an attempt to deliver the agent faster to the bloodstream, thereby shortening the time to emesis and improved removal of the product from the stomach. Gramoxone containing an emetic booster (Gramoxone EB) would provide a potentially novel method of improving the acute toxicity of the product without increasing the concentration, and hence cost of additional emetic. This could result in a reduction in acute oral toxicity by a **factor of up to 5X** if the current absorption rate of the emetic could be significantly improved. This approach could be evaluated quickly with little resource required. The chances of success here are **rated at moderately high**.

Background

The only effective method to markedly reduce the oral toxicity of paraquat once a lethal dose has been ingested is to rapidly remove the material from the gastrointestinal tract. Once paraquat has moved from the stomach into the small intestine it rapidly enters the bloodstream via a facilitated uptake process. Gels, emulsions, and chelators can delay absorption for a short time but have little overall effect on reducing the toxicity. The digestive system has a very effective way of breaking up particles by acid hydrolysis and dispersing insolubles with bile salts and enzymes until any trapped material is eventually available for absorption. By understanding the process of digestion you can delay and reduce the exposure of paraquat to the absorptive small intestine by switching off the acid hydrolysis (antacids), slowing gastric emptying (in situ gelling) and increasing water secretion (purgation). This buys more time for the bulk removal of the formulation by emesis. This concept has been proven in animal studies and was significantly imroved when the formaulation contained a 3 fold increase in the emetic agent, PP796 which maximised the effectiveness of this approach. An overall 10-20X reduction in acute toxicity could be achieved by combining gels, purgatives and binders with a high emetic concentration.

Emetic Booster (EB) Formulation

The new challenge is to achieve a significant safening e.g. up to5X **without** increasing the ICIA0796 level and **without** additional additives. The latter approach of finding non-trisilicate gel-forming systems which remove gastric acid is the subject of a separate proposal. However, we may be able to improve the effectiveness of the emetic agent by **reducing** the time it takes to reach an effective blood concentration following oral ingestion. This so-called “emetic booster” effect is based on the fact that this lipophilic phosphodiesterase inhibitor may not be fully dispersed in the aqueous formulation concentrate at 0.5g/l and hence may not be optimally delivering an effective emetic dose. The time-to-emesis is the critical component of safening and this applies to both Gramoxone and other formulations. The facts that have lead us to think along these lines include the loss of some safening when we reduced the pyridine bases, since they help to disperse the PP796 and also the use of new adjuvants in the pharmaceutical industry which aid drug delivery e.g. cyclodextrins and drug systems such as fast acting pain killers.

Logistics of the Proposal

The nature of this proposal is straightforward and does not involve complex formulation technology. The main resource requirements would be for toxicology (CTL) and formulation (Yalding). Efficacy testing would only be confirmatory late in the programme since a range of emetic concentrations have been tested already. A testing strategy in the sequence of 1) Formulation 2) Toxicology would be required. The technology and scientific personnel who have the necessary knowledge and experience are already in place i.e. no specific recruitment would be needed nor development of new technology.

Plan of Work

1. Select candidate chemicals which will aid the dispersion of PP796 in an aqueous concentrate. Yalding (Richa Shaunak) has already suggested N-methyl pyrollidone and even castor oil. CTL (Jon Heylings/Mike Farnworth/Pharms) will also compile a list of drug adjuvants used with the PP796 type of chemistry in aqueous and suspension medicinal systems. Compatability with Gramoxone's components and practicalities/cost will help to keep this a manageable number. Pyridine bases should be included as one data point.

2. Determine the effect of these chemicals in blank non-paraquat aqueous solutions on the gastrointestinal absorption of PP796 using the in vitro isolated small intestine. This model is used routinely by my group at CTL as a pre-screen for pesticide and drug absorption. Essentially it is a membrane system which allows compounds or mixtures to be applied to the absorptive surface and the appearance of the chemical on the blood side is measured over a time course. Several PP796 mixtures could be tested per week by one person. We have a validated fluorometric method for PP786 and plently of neat chemical in our stocks.

3. Select the most promising "emetic boosters" and determine optimum concentration in the in vitro model. Success criteria would be a reproducible and significant increase in the percentage, rate and extent of PP796 absorption as well as no adverse effects on the tissue.

4. Determine the feasibility of incorporating these agents into Gramoxone would follow. We would then examine the PP796 bioavailability from a paraquat formulation in vivo in a pharmacokinetic study using a non vomiting species e.g. the rabbit. Success criteria here would be enhanced absorption of PP796 into blood and tolerance (safety) of the new component. This could be done over a short time course (several hours) using Gramoxone i.e. ahead of any adverse effects and would therefore be an ethically acceptable experiment.

5. Ultimate proof of effect would be in man and human volunteer studies with PP796 have been done, so it is not out of the question to examine PP796 bioavailability in man with and without the new "dispersant" (without the paraquat, of course!). However, we would probably recourse to the dog, a vomiting species, to determine the effectiveness of a new emetic "booster", if the previous stages and decision points above warranted this.

In terms of chances of success? If we can increase bioavailability of PP796 by a significant margin then this has got to be moderate to high. If we cannot improve the bioavailability of PP796 then this would be a minimal investment and the project would stop at stage 2.

Resource and Timing

The likely resource needs would be 3mm CTL plus 3mm Yalding in 1999, rising to 12mm CTL plus 12mm Yalding in 2000. The evaluation and optimisation phases of small scale preps would be achievable in this time frame.

Likelihood of Success

The success of this project can only be judged in man. However, the effects of the emetic agent have been thoroughly evaluated in animals and human volunteer studies. Also, from the large number of human cases involving ingestion of the current product, the impact that even a 5X reduction in toxicity would have is a significant reduction in fatalities and possible elimination of accidental deaths. Taken together, the chances of success here should be rated at moderately high.

Intellectual Property

Zeneca has a patent covering a wide range of ICIA0796 concentrations in paraquat. The manufacture and use of this agent is a competitive advantage for the business.

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