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SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF IDEBENONE IN A DOSE-ESCALATION TRIAL IN PATIENTS WITH FRIEDREICH'S ATAXIA. N. A. Di Prospero, MD, PhD, C. Sumner, MD, A. Atkinson, MD, K. Fischbeck, MD, J. P. Taylor, MD, PhD, National Institutes of Health, University of Pennsylvania, Bethesda, MD.

Friedreich's ataxia is a progressive neurodegenerative disorder caused by a GAA trinucleotide expansion within the fraxatin gene. This mutation results in a loss of the frataxin protein within mitochondria leading to reduced activity of key enzymes, excess production of free radicals, and defective oxidative phosphorylation. Recent studies suggest that the antioxidant, idebenone, may prevent disease progression and greater efficacy may be seen with higher doses. In order to explore the full dose range, 81 patients divided evenly among adults, adolescents, and children participated in an unblinded, 1 day dose-escalation trial of oral idebeonone divided TID. No dose limiting toxicity was observed, and the maximum allowed dose of 75 mg/kg was achieved in all cohorts. Analysis of serum levels of total idebenone revealed a large variation in absorption of the drug. This variation precluded complete analysis of plasma concentration obtained during repetitive dosing; however, the terminal half-life following the last dose was consistent across the dose levels, indicating dose proportionality. A follow-up study in 15 patients revealed that a dose of 60 mg/kg/day was safe and well tolerated for 1 month. These findings indicate that higher doses of this drug should be explored for efficacy in Friedreich's ataxia and other diseases associated with oxidative stress.

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NEUROTOXIC PYRIDINIUM METABOLITES OF HALOPERIDOL, HPP^+ AND $RHPP^+$, ARE TRANSPORTED BY A SUBSET OF MEMBRANE TRANSPORTERS. H. Kang, MS, J. Ryu, MD, S. Lee, PhD, K. Liu, PhD, J. Shim, MD, PhD, J. Shin, MD, PhD, Department of Pharmacology and PharmacoGenomics Research Center, Busan, Republic of Korea.

HPP+ and RHPP+, known neurotoxic haloperidol pyridinium metabolites, has been known to distribute into the brain from systemic circulation. It is expected that various membrane transports expressed in BBB may contribute on that disposition. This study is to evaluate whether HPP+ and RHPP+ are substrates of organic cation transporters (OCTs) and P-glycoprotein (Pgp). From accumulation study of Caco-2 cells, both HPP^+ and $RHPP^+$ were accumulated with the estimated *Vmax* and *Km* of 97 pmol/ug protein/min and 4.5 μM. The intracellular concentrations of both compounds were decreased two to four fold by the pretreatment of 100 μM varapamil, 50 μM prozosin, 50 μM cimetidine, 50 μM phenoxybenzamine, and 50 μM corticosterone, which are known to have an inhibitory potential on OCTs activity. In addition, the intracellular uptake of HPP^+ and $RHPP^+$ in the OCT1 cRNA injected Xenopus oocytes were 3 folds higher than that in water injected oocytes. In the accumulation study of OCT1 and OCT2 transfected MDCK cells, over three fold higher concentrations of both metabolites were accumulated when compared to those in untransfected cells. However, there was no significant difference in the accumulation of both compounds in MDR1 overexpressed cells. These results suggest that OCTs involve in the uptake of HPP+ and RHPP+, but those seems not to be substrates of Pgp. Further study is in progress to evaluate the involvement of other membrane transporters on the disposition of both metabolites.

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ABSTRACT WITHDRAWN.

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ORAL PHARMACOKINETICS OF DOXAPRAM IN PRETERM INFANTS. S. N. de Wildt, MD PhD, S. D. Sie, MD, R. C. Dullemond, MD, A. P. Vulto, PharmD, PhD, J. N. van den Anker, MD, PhD, ErasmusMC-Sophia Children's Hospital, Children's National Medical Center, Rotterdam, The Netherlands.

BACKGROUND: Doxapram is frequently administered orally to treat apnea of prematurity. However, in contrast to IV, oral pharmacokinetic data are scarce in this population.

METHODS: Preterm infants on a level 3 neonatal intensive care unit received doxapram for treatment of apnea of prematurity. Doxapram was infused orally (loading dose 2.5 mg/kg followed by 1 mg/k/h infusion). Blood samples were taken at least 24 hours after start of the continuous oral infusion, assuming steady-state. Doxapram plasma concentrations were determined using HPLC. Clearance was calculated as: Cl=Css/infusion rate, oral bioavailability as Clor/Cliv.

RESULTS: For 8 patients (GA 28 6/7 ± 1 1/7 weeks, postnatal age 29.6 ± 12.6 days), median oral doxapram clearance was 0.81 l/kg/h (range 0.49–2.02 l/kg/h). Doxapram oral bioavailability could be determined for one patient, as this patient also received an IV infusion before oral administration, its oral bioavailability was 72%.

DISCUSSION: This study presents first data on oral clearance of doxapram in preterm infants. Clearance values are in the same range as intravenous data from the literature, which suggests a higher oral bioavailability than reported in adults.