FINAL REPORT

Study EPP001: Investigation into the use of colestyramine as a therapy for patients with erythropoietic protoporphyria

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Abstract:
This study looked at the effect of oral colestyramine in 3 patients with EPP, to see if it decreased blood protoporphyrin concentrations. We conclude from the data fom the study that oral colestyramine does not decrease blood protoporphyrin concentrations in Erythropoietic protoporphyria and is therefore not of value as a treatment in EPP.

Introduction:
Erythropoietic protoporphyria is an inherited disease in which protoporphyrin accumulates in erythrocytes causing lifelong painful photosensitivity. There is currently no effective treatment.

One therapy that has been used in these patients is colestyramine, the anion exchange resin. The rationale is that there is limited and contradictory evidence that there is an enterohepatic recirculation of protoporphyrin in EPP. Since colestyramine is known to bind to porphyrins and that cholestyramine interrupts the enterohepatic circulation of bile acids it has been proposed that colestyramine might interrupt the enterohepatic circulation and thus increase the excretion of porphyrins into the faeces. Two case reports did show increased faecal excretion of protoporphyrin in two patients with EPP and unexpectedly it was found to increase urine protoporphyrin excretion in 3 EPP patients . Activated charcoal has been used as an alternative therapy to attempt to interrupt the enterohepatic circulation of porphyrins in various porphyrias. In variegate porphyria , one patient treated with colestyramine had improvement (your reference 13), but activated charcoal in a trial of eight patients with variegate porphyria unexpectedly led to significant clinical and biochemical worsening of the disease .

The lack of effective therapy in EPP makes it important to establish whether a treatment such as colestyramine is effective or not, and, in view of the results of charcoal in variegate porphyria, to also check that it does not actually cause deterioration of the disease.

We therefore treated 3 EPP patients with oral colestyramine for 90 days, measuring the blood protoporphyrin concentrations rather than symptoms because symptom measurement in EPP is subject to problems including biases and high short-term placebo rates.

Methods:
Three adult subjects took part, who had a diagnosis of EPP without evidence of liver disease. Red cell and plasma protoporphyrin were measured once a month for a 7 month period, with colestyramine 4g tds being taken orally for a 3 month period (months 3,4 and 5). There were no problems with adverse effects other than some bloating, flatulence and the unpleasant taste of the drug, all adverse events were mild and known to affect the majority of patients who take this drug. The patients had been warned about these adverse effects before starting the drug. No patient withdrew from the study as a result of these effects.

Results:
Please see the statistical analysis of results document accompanying this report. The first graph shows the plasma and red cell protoporphyrin concentrations for the three patients. The visual impression that there is no significant difference between the

values on and off the therapy is confirmed both by using the parametric paired t-test on the mean values before, during and after the therapy period, and using the non-parametric Skillings mack test on the individual values. There is no significant difference between the values of either plasma or red cell protoporphyrin using either test.

Conclusions:
Despite the evidence from case reports that colestyramine may be helpful in EPP, it is clear that colestyramine has no effect on blood concentrations of protoporphyrin in patients with uncomplicated EPP. Colestyramine appears unlikely to be an effective therapy in EPP.

Quality Assurance:
This trial has been conducted in compliance with Good Clinical Practice and scientific integrity has been managed and oversight retained; by the Joint Clinical Trials Office Quality Team.