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Effect of Crohn's Disease on Villous Length and CYP3A4 Expression in the Pediatric Small Intestine

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Effect of Crohn's Disease on Villous Length and CYP3A4 Expression in the Pediatric Small Intestine

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Describe role of Submitting/Presenting Trainee in this project (limit 150 words):

Assisted in experimental design, data analysis and interpretation of results.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background:

Villi play a critical role in making the small intestine the major site of absorption for orally administered drugs. Active small intestinal inflammation in Crohn's disease (CD) is associated with histopathological changes to the absorptive epithelium such as villous blunting. The structural pathologies frequently observed in active CD have the potential to alter oral drug bioavailability. Cytochrome P450 3A4 (CYP3A4) is the most abundant cytochrome P450 isoform in the small intestine and is capable of extensively metabolizing many orally absorbed drugs during first-pass. While much is known about the regulation of CYP3A4 expression in the healthy adult intestine, there is a paucity of literature regarding alterations in CYP3A4 expression in CD, with a critical information gap for pediatric patients.

Objectives/Goal:

We sought to investigate whether alterations in CYP3A4 expression occur in the duodena and ilea of children with CD, both during active inflammation and remission. Gene expression of ABCB1, an efflux transporter believed to modulate CYP3A4 activity, and PXR, a nuclear receptor known to regulate intestinal CYP3A4 expression were also evaluated.

Methods/Design:

Fresh flash frozen duodenal and terminal ileal mucosal biopsies from children with CD and children without inflammatory bowel disease were assessed for extent of inflammation and villous length by two independent pediatric pathologists. RNA was extracted from the biopsies and the expression of *PXR*, *CYP3A4* and *ABCB1* was determined via real-time PCR. Differences in villous length and gene expression in the duodenum and ileum, and the relationships to disease state and inflammation extent explored via Spearman's correlation; statistical significance considered at $\alpha < 0.05$ after Bonferroni correction for each family of statistical tests. On the basis of tissue availability, a set biopsies was also subjected to immunohistochemical staining to evaluate changes in CYP3A4 protein expression in CD. The relationship between villous length and CYP3A4 protein expression pattern was also evaluated by ANOVA.

Results:

A significant reduction in villous length in the inflamed duodena and ilia of children with CD was observed. Individuals in remission displayed villi of comparable length to controls for the respective small intestinal region in remission. No association was observed between age and villous length. Expression of CYP3A4 mRNA was significantly reduced in ilia, but not the duodena, of children with CD during active regional inflammation. Duodenal and ileal PXR and ABCB1 mRNA expression were not significantly altered in CD, regardless of the presence of active regional inflammation. Expression of CYP3A4 protein was significantly different in the duodena of children with CD, adopting a patchier or weaker immunohistochemical staining intensity during duodenitis. Duodenal CYP3A4 staining was comparable between children with and without CD in the absence of duodenal inflammation. Interestingly, in controls where duodenal villi were at a reduced basal length, the pattern of CYP3A4 protein expression resembled that of children with CD-associated duodenitis.

Conclusions:

Our results suggest that orally administered drugs that are substrates of CYP3A4 may have altered bioavailability in children with CD-associated gut inflammation and provides a basis for further research that more quantitatively evaluates CD-dependent changes in intestinal surface area and CYP3A4 expression.