Conjugation of phenols in human colonoctyes

**LETTERS TO THE EDITOR**

**Conjugation of phenols in human colonoctyes**

**STIR**—The role of altered colonic detoxication mechanisms in various pathophysiological conditions including ulcerative colitis and carcinogenesis cannot be overemphasized. We have thus read with great interest the recent report of Ramakrishna *et al* about sulphation as a mechanism of phenolic compound inactivation in human colonoctyes (*Gut* 1991; 32: 46-9). Though the work provides valuable new information, we feel obliged to make a few critical comments. Firstly, the title and parts of the text may be misunderstood: in fact, paracetamol (acetaminophen) and not phenol sulphation has been investigated. Secondly, the mention that 'studies, on phenolic compound inactivation, using colonoctyes from resected colon specimens have not been undertaken' is not entirely correct. Indeed, we have reported preliminary results about the conjugation of 1-naphthol, another phenolic compound, in human isolated colonic cell preparations. 1-Naphthol was extensively conjugated in human colonic crypts, mainly by sulphation (75%), but also by glucuronidation (24%). These results were in agreement with those of Cohen *et al* in cultured human colonic mucosa, where normal colonic predominantly sulphated 1-naphthol, in contrast, cancer tissue showed a glucuronidation predominating pattern. In the study of Ramakrishna *et al* paracetamol was poorly glucuronidated in normal colonoctyes. This finding is not representative of the metabolic activity of human colonoctyes for all phenolic compounds, since 1-naphthol was efficiently glucuronidated. Moreover, this discrepancy may also come from the higher substrate concentration used by Ramakrishna *et al* as it has been observed in animal species that glucuronidation is more readily saturable than sulphation.

In dialyses of patients with ulcerative colitis, known preneoplastic condition, Ramakrishna *et al* found no increase of paracetamol glucuronide concentrations and a reduction of sulphated conjugates, which they interpret as an impairment of the capacity of the mucosa to sulphate phenols. However, the reduced recovery of sulphate in dialysate may alternatively be interpreted as increased paracetamol sulphate absorption. Moreover, reduced sulphation activity in colonoctyes from ulcerative colitis patients would be at variance with other reports of enhanced bio- transformation reactions. These discrepancies between different compounds and experimen- tal models, and the strong pathophysiological relevance of colonic biotransformation activities, emphasise the need for further studies in this field.

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**Reply**

**STIR**—We are pleased to respond to the comments by Dr Dechettele and Professor Schweng. Paracetamol (N-acetyl-p-aminophenol) was used as an example of a phenol because much is known about the metabolism of paracetamol and because it is implicated in causing exacerbations of ulcerative colitis.

The evaluation of colonic metabolism by rectal dialysis does have limitations, in particular, underestimation of metabolite formation due to rectal absorption. This point was discussed in detail in a previous paper and has also been addressed by Sund and Lauterbach. The latter study indicated that the dialysis technique may underestimate detoxification mechanisms by at least 50%. Given these limitations, we found that glucuronidation was absent in a large number of healthy control subjects. We accept that colonoctyes can detoxify phenols by glucuronidation. However, using rectal dialysis in subjects with ulcerative colitis paracetamol glucuronide was undetectable in most cases and consequently we did not discuss this finding in detail.

The reduced metabolism of sulphated para- cetamol in ulcerative colitis is in part a pheno- menon of reduced sulphation by colonic epithelial cells, an observation to be published shortly. In acute and chronic ulcerative colitis absorption of some colonic metabolites, including phenol sulphate, is diminished and the low recov- ery rate of sulphated phenol in dialyse may not necessarily be due to an accelerated absorption process. To prove or disprove either point of view further experimentation would be needed.

We thank Dr Dechettele and Professor Schweng for drawing our attention to glucu- ronidation processes in colonic epithelial cells.

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3 Sund RB, Lauterbach F. Drug metabolism and metabolite transport in both small and large intestine: experiments with 1-naphthol and phenolphthalein by luminal and enteral administration in the isolated guinea pig mucosa. *Acta Pharmacol Toxicol* 1986; 58: 74-83.


**Ranitidine and non-steroidal anti- inflammatory drugs (NSAIDs) associated gastric duodenal ulcers**

**STIR**—We read with interest the recent article by Lancaster-Smith *et al* (*Gut* 1991; 32: 252-5). The authors performed in a prospective study of 81 patients that ranitidine was effective in treating gastric and duodenal ulcer related to NSAID use whether or not the NSAIDs were continued and even effective in patients in whom the NSAIDs were discontinued. Thus gastric ulcers had healed at eight weeks in 63% of those still taking NSAIDs compared with 95% of those who had stopped NSAID treatment. Duodenal ulcers healed in 100% in those who stopped NSAIDs at eight weeks compared with 84% of the group who continued NSAIDs, but the healing rates were slower.

The question remains of whether NSAID induced ulcers behave differently to those that seem to have been induced by taking NSAIDs different rates of healing or recurrence with or without H2 antagonists or by other treatments. Any future studies evaluating the efficacy of famotidine in NSAID induced duodenal and gastric ulcers as well as ulcers unrelated to the use of NSAIDs did show differences in healing rates at eight weeks in patients in whom the ulcers were temporally related to NSAID use and those in whom there was no relation to the use of NSAIDs. Thus of 160 patients with duodenal ulcers, 40 (25%) were entered into the trial with a history of recent or prolonged NSAID use who had NSAID/aspirin just before presenting with their ulcer. All (100%) healed in eight weeks with famotidine when the NSAIDs were stopped at the beginning of the trial. This contrasts with the group of patients who were non-NSAID users where only 88% were endo- scopically healed at the end of eight weeks. Furthermore, of the 110 who went onto six weeks maintenance treatment only 20 (18%) of the NSAID, all those previously related to NSAID use remained healed at six months (100%) against 74% of patients with ulcers not related to NSAID use. Among the 66 patients with gastric ulcers, 50% had taken NSAIDs just before presenting with gastric ulcer; 88% had complete healing with famotidine when NSAIDs were discontinued within eight weeks compared with the non-NSAID users who had a healing rate of 75% (unpublished data). These studies suggest that NSAID/aspirin induced duodenal and gastric ulcers not only have a different pathogenesis to de novo ulcer but may also have a different response to NSAID treatment in this group. All past reviews evaluating NSAID use with other treatments and future studies on peptic ulcer disease need to be stratified to examine the difference in the healing rates of NSAID induced ulcers com-