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The role of the gut flora in the reduction of sulphoxide containing drugs

Sulphinpyrazone and sulindac each contain a sulphoxide moiety which can undergo both oxidation and reduction to the sulphone and sulphide (thioether) analogues. The sulphide metabolites are more potent in their activities (anti-platelet-aggregatory and anti-inflammatory respectively) than the parent drugs. Due to the longer half-lives the sulphides are probably responsible for much of the therapeutic effect seen during chronic administration [1, 2].

Both the liver and gut microflora are possible sites for formation of these sulphide metabolites. Studies on the fate of sulphinpyrazone in rats [3] and rabbits [4] showed that the gut flora was the principal and possibly the sole site of reduction *in vivo*. The peak plasma concentration of the sulphide occurred about 8 hr after a single oral dose of sulphinpyrazone. In contrast the liver of rabbits shows extensive reduction of sulindac *in vitro* [4], whilst *in vivo* peak plasma concentration of the sulphide occurred soon after that of the parent compound [5].

The role of the gut flora in the reduction of these drugs in man has been determined by comparison of the plasma concentration–time curves after a single oral dose in normal volunteers and in ileostomy patients (who have undergone surgical removal of the lower bowel). The remaining intestine of such patients is not sterile but contains greatly reduced numbers of strict anaerobes. The absorption of sulphinpyrazone assessed by peak concentration and the area under the plasma concentration–time curve (AUC) was normal in ileostomy patients. However, the sulphide metabolite, which in normal subjects reached a peak concentration (1.6 μg/ml) about 15 hr after dosing was almost undetectable (0.08 μg/ml) [6]. The 25-fold difference in AUC for the sulphide *in vivo* showed a strong correlation ($P < 0.001$) to the extent of reduction by samples of faeces and ileostomy effluent. These data indicate that the gut flora is the sole site of sulphinpyrazone reduction in man. In contrast the sulphide metabolite of sulindac showed a similar initial peak plasma concentration and time to peak (about 3 hr) in both subject groups. This suggests that sulindac is reduced rapidly by the liver to the sulphide metabolite. In normal subjects the sulphide showed a long half-life, and the AUC from 12 hr after dosing to infinity represented about 55% of the total AUC. In ileostomy patients the levels of sulphide in plasma decreased rapidly so that none was detectable at 24 hr and the AUC 12-α was tenfold less than that in normal volunteers. Ileostomy effluent showed a limited ability to reduce sulindac compared with normal faeces [7]. These data suggest that the gut flora contribute significantly to the formation of sulindac sulphide in man, probably by the reduction of sulindac which is excreted in the bile [8].

Thus the reduction of sulphoxides may be due to the liver and/or the gut flora. The relative importance of these two sites is dependent on the substrate and the delivery of the substrate to the hind gut flora.

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