ENHANCED INTESTINAL ABSORPTION OF CARCINOGENS OF DIETARY ORIGIN IN PATIENTS WITH GASTROINTESTINAL DISEASE AND IN PATIENTS RECEIVING CALCIUM CHANNEL BLOCKERS

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SUMMARY

The discussion paper argument is here summarized in compressed form. There is an increased incidence of cancer in patients with gastrointestinal disease and in those patients taking calcium channel blocker. Increased carcinogen uptake is proposed to be the common factor. Dietary carcinogens exist as heterocyclic amines or can be converted into such forms by intestinal bacteria. There is increased uptake of aminoquuinolines during intestinal secretion in experimental animals, also increases weak base absorption in gut disease and reduced base secretion after verapamil exposure in animal. Hence there is likely to be increased absorption of carcinogens in the form of highly potent amnioquinolines both because of changes in intestinal mucosal surface pH and because of mdr protein inhibition. In patients on calcium channel blockers, inhibition of mdr protein is likely to inhibit efflux of dietary carcinogenic amines back into the lumen in the same way that verapamil inhibits resistance to amnioquinoline uptake in the malaria parasite. This hypothesis may additionally explain the link of incidence of cancer with dietary fat and also with the site and type of carcinoma in these diseases.

It has been known for some time[1] that there is an increased incidence of tumours in celiac disease and in other intestinal disease. The latest reported findings form

the long running Birmingham series of patients confirms[2] the earlier observations of an increased incidence of lymphoma in celiac disease. More recent collections of data[3] have similarly confirmed the association of adenocarcinoma with inflammatory bowel disease.[4] These studies and isolated reports of increased tumour incidence in middle eastern gut disease[5] reinforce the obvious and plausible conclusion that gastrointestinal disease itself some how predisposes to cancer. However, a recent unrelated paper demonstrating increased cancer incidence in patients taking calcium channel blockes[6] allows the emphasis to be placed more on diet and carcinogen uptake rather than gut disease in the first instance. The theme of this present discussion paper is the hypothesis that the common factor in the increased incidence of carcinoma in g.i. and in heart disease may be deranged absorption rather than the gastrointestinal disease process. We propose that enhanced carcinogen uptake in gut disease and in verapamil treated patient is the factor causing increased cancer incidence.

It is evident that carcinogens are present in the diet and absorbed to a variable extent. We hypothesize that many of the carcinogens in the diet are basic heterocyclic amines or are neutral compounds capable of conversion to these forms by intestinal bacteria. Some of the most potent mutagens are weakly basic compounds such as the methylimidazole quinolines found in brolied foods after cooking.[7] In addition, bacterial can produce mutagenic indoles[8] or convert food dyes to aromatic amines.[9] Mutagenic and presumable carcinogenic amines are present in the diet and are able to able absorbed. It is know that there are significant changes in mucosal surface PH in the gut in disease states and we propose that this on balance leads to a greater carcinogen uptake since although many are neutral or even weak acids, in aggregate the heterocyclic amines will predominate. We hypothesis that there is increased dietary uptake of these carcinogens in most forms of gut disease and that thee will be less uptake of heterocylic amine carcinogens in normal subjects than in the patient groups that have a higher incidence of carcinoma. We propose that patients taking calcium channel blockers fail to excrete absorbed carcinogen into the gut lumen and that patients with the indicated gut diseases absorb more carcinogen or have combination of both reduce efflux and enhanced absorption of carcinogen. The enhancement of absorption comes about by localized pH changes at the gut surface and the failure to secrete because of interference with the proper working of the multidrug resistant (mdr) protein.

In the first case, increased carcinogen uptake occurs in intestinal diseases where the normally slightly acidic (pH 6.1) mucosal surface pH is shifted to neutral or to slightly alkaline values. A change in pH from 6.1 to 6.9 is small change in pH but can mean an eightfold increase in the concentration of undissociated absorbable form of a compound. In the normal human small intestine, the mucosal surface pH is about 6.0 in vivo[10] and is altered to closer to neutrality in celiac and Crohn's disease.[11] This shift in mucosal surface pH favours the absorption of weak bases and ins associated with increased intestinal absorption of lipophilic weak bases in celiac disease, the only gut disease in which this phenomenon has been studied. In reviewing the available literature (12-16), it is important to consider the dissociation and the lipophilicity of weak bases and not just to compare the amounts of dissociation. For example, increased propranolol absorption has been found in celiac disease but no practolol. Both drugs have similar pKa values but differ consid-

erably in their lipophilicity and hence the lack of enhanced absorption of practolol should be attributed to the fact that its lower lipophilicity means that it does not partition into the enterocyte.

An experimental model of the shift in mucosal surface pH seen in celiac disease is provided by the secretion induced by E.coli heat stable (STa) enterotoxin. STa will both induce secretion but also cause alkalinisation of the intestinal lumen and more importantly the mucosal surface.[17] This results in an increase in absorption of several weak bases, among them the 4-amnio-quinoline anitmalarial chloroquine. This enhancement of absorption by physicochemical means, despite fluid secretion, explains why weak base absorption is unaffected or increased in dysentery and in malabsorption syndrome.[18,19] The neutralization of the mucosal surface after STa definitely enhances amnioquinoline uptake and this is particularly interesting as the food carcinogens referred to above are also amino-quinolines. It seems extremely likely that neutralization of the mucosal surface either because of immaturity of the enterocyte, interference with sodium: hydrogen ion exchange or inflammatory processes would cause enhanced uptake of the dietary heterocyclic amine carcinogens.

A second mechanism cold be interference with intestinal drug efflux pumps. It has been known for some time that the intestinal mucosa can pump xenobiotic compounds back into the intestinal lumen. The basis for this is likely to be the multiple drugs resistance (mdr) protein present in the enterocyte brush border. Rhodamine 123 secretion into the lumen can be inhibited by verapamil and diltiazem.[20] Verapamil is known to inhibit mdr protein and is the basis for overcoming chloroquine resistance in the malaria parasite.[21] Verapamil my well also prevent chloroquine efflux form the enterocyte as it does this is Plasmodium and it is highly likely that it would prevent the exit of food based carcinogenic aminoquinolines. Hence, interference with the intestinal secretion of absorbed carcinogen amines may be the reason for the increased frequency of tumours in the unrelated patient group taking calcium channel blockers.[6] In this group, verapamil was most associated with increased tumour frequency and those that did arise were on quarter associated with the gastrointestinal tract and one third associated with the gastrointestinal tract and the lymphatic system. Little is known of the functioning of mdr protein in gastrointestinal disease but we can propose that there will be reduced drugs efflux in celiac disease given that mdr is a brush border protein. Hence in intestinal disease, enhanced carcinogen uptake could become about both by enhanced absorption and by reduced exit of these weak bases.

The hypothesis underling this discussion paper is one of enhanced carcinogen uptake in some forms of gastrointestinal disease and in patients taking calcium channel blockers. What is the essence of the hypothesis and what else will it explain? In essence, the hypothesis rests on the premise that dietary carcinogens are primarily lipid soluble heterocyclic bases. Normal subjects and patients reside in the same environment but the patient group take up more of the carcinogens for the above reasons. The lipophilic nature of the carcinogens may explain the dietary association of lipid intake with cancer,[22] since the greater the amount of fat in the diet the greater the availability of lipid solvent in which the lipid soluble carcinogenic amines can dissolve and be absorbed. Similarly, the lipid nature of the carcinogen may mean enhanced uptake by the lymphatic system and explain the greater number of lymphomas in the celiac and calcium channel blocker groups.

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