The effect of tri-potassium di-citrato bismuthate on the duodenal mucosa during ulceration

An ultrastructural study

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Summary

The manner in which tri-potassium di-citrato bismuthate (TDB) promotes duodenal ulcer healing is not known. Endoscopic biopsy specimens were taken from the edges of duodenal ulcers from 5 patients before and after treatment with TDB. Using the bismuth contained within this drug as an electron-dense marker, the mode of action of TDB was determined by transmission electron microscopy. TDB was found to promote ulcer healing by adhering to the ulcerative mucosa, thereby providing an effective barrier to the substances which cause and maintain ulceration.

Microscopic examination

Sections of the resin-embedded tissue (1 μm) were cut with either a Cambridge Huxley or Sorval MTI ultramicrotome, mounted on glass slides and stained with 1% aqueous alkaline toluidine blue. The sections were examined and areas of interest photographed using a Zeiss photomicroscope. Ultrathin sections of approximately 70 nm (silver/gold interference colours) were cut with glass knives, floated onto distilled water and mounted on copper grids. Sections were double-stained with 1% ethanolic uranyl acetate and Reynold's lead citrate. Electron micrographs of the material were obtained with either a Zeiss EM10B or a Zeiss EM9S2 electron microscope.

Results

Pretreatment

The 1 μm sections showed flattened and eroded villi, often with large areas of desquamating cells. The epithelium was largely composed of mucin-secreting cells (mucous neck cells;
MNCs) with no normal goblet or absorptive cells in evidence. No brush border could be discerned (Fig. 1).

Ultrastructurally the cells were of columnar type with a basal longitudinally opposed nucleus (Fig. 2). In the immediate supranuclear cytoplasm was a well-developed Golgi complex surrounded by many secretory vesicles. Between the Golgi complex and the luminally situated store of secretory granules were many mitochondria, often encircled by whorls of rough endoplasmic reticulum. The secretory granules were of differing electron densities and of a variety of sizes and shapes. Microvilli were sparse, being on average 0.3 μm in length and 0.1 μm in diameter. The glycocalyx was largely confined to the surface of the microvilli from where filamentous threads stretched 0.05 μm into the lumen (Fig. 3). The extensive plasmalemmal spaces between the microvilli often had no glycocalyx.

1 hour after TDB

Histologically and ultrastructurally the epithelium in most respects was similar to that described above. However, there was electron-dense material in the lumen, which presumably represented the bismuth contained in the drug (Fig. 4). There was a subtle change in the appearance of the glycocalyx, which appeared more electron-dense and adherent to the microvilli. Strands of material often connected adjacent microvilli, giving the surface a 'sticky' appearance (Fig. 5).
1 week after TDB

The epithelium was similar in many respects to untreated specimens. Most cells were of the mucin-secreting type described above, although the cell content of secretory granules was markedly reduced. The microvilli were, on average, a little longer (± 0.5 μm) and more closely packed than in untreated specimens, with a filamentous glycocalyx of ± 0.07 μm radiating from the entire plasmalemmal surface. A few mature goblet cells, but no normal absorptive cells or brush border was seen. There were a few discrete electron-dense particles associated with the glycocalyx in one specimen, which again presumably represented the deposition of bismuth.

6 weeks after TDB

In 3 of the 5 cases the epithelium appeared normal (Fig. 6). Absorptive cells with densely packed microvilli ranging in length from 0.6 to 0.92 μm and a glycocalyx 0.3 μm thick were interspersed with actively secreting goblet cells (Fig. 7). In the remaining 2 cases, the epithelium contained characteristic goblet and absorptive cells together with some MNCs in similar stages of development as those after 1 week of treatment. These specimens probably represent a transitional stage of healing. No bismuth was seen adhering to the surfaces of the specimens, nor was any observed within the cytoplasm of epithelial cells at any stage in the study.

Discussion

Duodenal ulceration has been associated with increased acid and pepsin secretion in the stomach. The resultant excess of acidic fluids passing into the duodenum is thought to be a major contributing factor in the aetiology of duodenal ulceration.9 In the antrum, MNCs have evolved to protect the gastric mucosa against the acidic fluids in the stomach by secreting a special mucoprotein (neutral G-mucosubstance).12 By secreting this mucosubstance in the duodenum, MNCs are thought to limit the spread of a developing ulcer by isolating the zone of erosion from the healthy mucosa, and, by continuously secreting gastric mucin, they protect the ulcer crater from luminal acids, thus promoting healing.13 As healing progresses, the MNCs which exclusively populate the ulcerative epithelium are replaced by absorptive and goblet cells. This metaplastic transformation occurs gradually. The MNCs lose their secretory capabilities and develop absorptive cell features.14 It is probable that many duodenal ulcers develop and heal at a subclinical level. In more severe cases where ulcers manifest themselves clinically, appropriate drug therapy may be used to remove or alleviate the factors which cause ulceration, thereby aiding the process of natural healing. Drug therapy must therefore be aimed at reducing acid and pepsin secretion in the stomach, neutralizing the acidic fluids passing into the duodenum or, as is thought to be the case with TDB, protecting the duodenum from luminal acidic fluids, especially after an ulcer has formed.

Protection could be achieved in two ways: by formation of a barrier between the damaged mucosa and the acidic material in the duodenal lumen or by absorption of the drug into the duodenal epithelium, thus initiating a metabolic protective response by the cells. Since no bismuth could be discerned within the cells at any stage of therapy during this study it does not appear to be absorbed by the epithelial cells.

However, an electron-dense material thought to be bismuth was seen both in the duodenal lumen and adhering to the plasmalemma and glycocalyx 1 hour after the introduction of TDB (Figs 4 and 5). In later specimens, little trace of this material was found. As healing progresses there is a reduction of secretory activity by MNCs as they undergo metaplastic change. The decrease in both bismuth and secreted G-mucoprotein in specimens from healing ulcers suggest a relationship between these two substances. It is possible, therefore, that the protein-bismuth complexes referred to by Wilson4 are in fact complexes...
formed between the bismuth in TDB and the mucoprotein secreted by active MNCs bordering an ulcer.

As TDB has been shown to promote duodenal ulcer healing, it is probable that the G-mucoprotein-bismuth complex formed in the ulcer crater and adhering to the surrounding mucosa after treatment with this drug is a more effective barrier to the acids which cause and maintain ulceration than G-mucoprotein alone.

Conclusions

The role of TDB in duodenal ulcer healing is protective. By forming complexes with G-mucoprotein secreted by metaplastic MNCs bordering an ulcer, TDB provides an effective barrier between the ulcerated epithelium and the acidic material in the duodenal lumen, thus promoting the natural process of healing.

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REFERENCES


Nuus en Kommentaar/News and Comment

Alkohol en borskanker

Onvermoeide poginge om borskanker met ’n soort voedings- of omgewingsfaktor te associeer, ’n baie verwarrende prentjie. Dit is baie moeilik om ’n bevolking te wys wanneer daar so baie ander moontlikhede is.

Om hierdie rede sal ‘n onlangs verslag wat alkoholverbruik met borskanker verbind (Rosenberg et al., Lancet 1982; l: 267), met die nodige skeptisme beskou word. Die outeurs erken self dat hierdie verwantskap wat in hulle studie bespreek word, moontlik verklaar kan word deurdat daar nie genoeg kontrole oor die korrelasie tussen voeding en alkoholverbruik bestaan nie.

Alcohol consumption in epilepsy

An international epilepsy congress was held in Holland late last year and is briefly commented on in Medisch Contact (1982; 37: 43). One of the most interesting comments is about alcohol consumption and epilepsy. Sufferers from epilepsy have usually been told that they must avoid alcohol, since this is liable to increase the number of their attacks and also to interfere with their medication. However, a double-blind study described at the congress showed quite clearly that social use of alcohol had no effect whatsoever on epilepsy or on the EEG, while blood levels of anti-epileptic drugs were unchanged when alcohol was consumed. Arising out of this study, a survey had been undertaken to determine what proportion of neurologists told their epileptic patients not to drink. The results showed quite an astonishing diversity of thought. Whereas all the neurologists in Hungary, Austria, Poland, Spain, Czecho-Slovakia and Belgium prohibited their patients from drinking, 80% of Danish neurologists and 60% of English and Irish neurologists permitted social drinking. In South Africa apparently 52% of neurologists allowed drinking, which is in line with the figures given for France, Canada, orway, and the USA. Clearly, with this diversity of opinion, it cannot matter very much.

Another interesting point is the fact that many epileptic employees conceal their disorder from their employers. In a British study only 44 out of 177 epileptic patients discovered out of a work force of 150 000 had told their employers of their disability. The remaining 133 had claimed that the attack they eventually had during their employment was the first one.