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Proposed Use of Deoxycholic Acid (DCA) and Ursodeoxycholic Acid (UDCA) in a Treatment Regimen for Barrett's Esophagus

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INTRODUCTION

Huo et al [1] first placed 250 uM of the hydrophobic bile acid (DCA) into the esophagus of patients with Barrett's esophagus (BE) and left it there for 5 min. The DCA was dissolved in alcohol. Subsequent examination of the biopsies taken from the esophagus showed that the DNA was damaged and the nuclear factor NF-kB was activated. Additionally, many other pre-cancerous lesions were activated. Similar treatment with the hydrophilic bile acid (UDCA) was ineffective, suggesting that UDCA could be an anti-carcinogen.

In a subsequent study, Sue Peng et al [2], showed that equal amounts of DCA and UDCA would cancel out each other and that UDCA had a protective effect on esophageal cancers.

Banerjee et al [3] fed Barrett's esophagus (BE) patients with UDCA (13-15 mg/Kg body weight) daily for six months. Biopsies taken during this time showed no effects on carcinogenesis as detected by oxidative DNA damage, cell proliferation, or apoptosis. There was however a dramatic increase in the metabolic products of UDCA. This suggested that UDCA was not getting into the BE tissues despite six months of daily UDCA intake. To overcome this discrepancy, it was suggested that liposome technology could be used to coerce UDCA to enter into the BE cells [4].

Liposomes are phospholipid vesicles measuring 10-90 nm in diameter. They are composed of phospholipids and cholesterol generally in the ratio of 10 to 1. They are able to entrap hydrophilic compounds like UDCA in their aqueous interior. In their outer membrane sections, hydrophobic compounds like DCA would be entrapped. Both compounds (UDCA and DCA) could not exist in the same vesicle since they would cancel each other.

In the proposed study, liposomes containing UDCA in their aqueous interior would be used. The liposomes would make direct contact with the BE tissues thus bypassing the RES (reticuloendothelial system), a network of phagocytic cells all over the body that is designed, among other functions, to remove foreign substances (like liposomes) from the systemic circulation.

METHOD

Using the model system of Huo et al [1]. BE patients would first receive an alcoholic solution of the hydrophobic DCA (250 µM) in their esophagus for five minutes. This would perfuse the cell membranes of the esophagus of these patients. The pre- cancer features, first described, would still occur [1]. Liposomes bearing UDCA in their aqueous compartment would then be added to the esophagus in a similar way, after the DCA treatments. On contact with the BE epithelia, the liposomes would fuse with the BE cell membranes and deliver their contents of UDCA inside the cells. There they would prevent DNA damage, reactive oxygen species (ROS) generation and NF-kB activation and remain inside the cells to neutralize any later DCA incursions. The results of this study could be followed by taking biopsies at regular intervals.

MECHANISM OF CELL: LIPOSOME FUSION

Jean-Louis et al [4] using the colonic cells as a membrane model, examined the action of DCA on the cell membrane. They found that DCA could perturb the cell membrane structure and cause a marked rearrangement of its cholesterol. As well, they found that DCA caused a decrease in membrane fluidity and cholesterol levels. There was no such effect when UDCA was similarly used. Using liposomes as another membrane model, they found a similar effect when DCA was

added. In both cases cholesterol levels as well as membrane fluidity were affected. Thus, the total effect was to pull the liposome closer to the BE membrane and cause liposome: cell fusion. Once fusion is achieved between the liposomes and the BE cells, UDCA from the liposome well enter the cell and start a reaction that will neutralize the DCA and hopefully stop carcinogenesis.

More details of the earlier work that led to this liposome study can be found in reference where a similar treatment was suggested for polyps in early colon cancer studies [5].

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