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Ursodeoxycholic Acid has a Chemopreventive Effect on Gastrointestinal Cancers, Liposome Encapsulation of This Drug Would Assure its Optimal Delivery into the Epithelial Cells thus Stopping Carcinogenesis

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ABSTRACT

Acid Suppression Therapy (AST) Solubilizes Bile Acids (BAS) in the stomach and on reflux into the esophagus they will start carcinogenesis. Therefore their use should be re-evaluated. Topical application of liposomes bearing Ursodeoxycholic Acid (UDCA) onto the esophagus (or colon) may be a better alternative treatment.

INTRODUCTION

A new version of the EDA (esophageal duodenal anastomosis) technique was used in which the stomach was removed surgically and the esophagus was then anastomosed directly onto the duodenum [1]. This allowed the contents of the duodenum to reflux directly into the esophagus causing cyclooxygenase -2 (COX-2) expression and an increased production of dysplastic tissues, esophagitis, BE(Barrett's esophagus) and cancer. This suggested a mechanism for BA promotion of esophageal cancer, which did not involve gastric contents nor added carcinogen. Further, it showed that esophagitis, one of the early steps in the development of BE was also not caused by acids.

Huo et al [2] placed a DCA (deoxycholic acid) solution into the esophagus of BE patients and after five minutes, biopsies were taken. Examination revealed that the DNA in the biopsies had been damaged, which could lead to carcinogenesis. As well, they showed that the nuclear factor, NF- kB had been activated. This factor would cause a decrease in the activity of apoptosis, the method used by the cell to remove damaged DNA. Failure to repair the damaged DNA would lead to carcinogenesis. As a control, the same concentration of UDCA, a hydrophilic bile acid found abundantly in bears, was used. Although this BA was similar to DCA, no carcinogenesis occurred. This suggested a chemo-preventive role for UDCA. (See later section).

The above implicated DCA in the carcinogenesis of the esophagus. A brief look at the composition and chemistry of the BAs is described below:

Bile is made in the liver and stored in the gall bladder and when secreted into the duodenum it helps in food digestion and many other functions. BAs are detergents and some are carcinogens:

(1) Glycine conjugates, about 75% of bile, are formed when the free BAs (cholic, deoxycholic, chenodeoxycholic and lithocholic acids) are conjugated with the amino acid glycine. The resulting pKa of these compounds is ~ 4. If these conjugates reflux into the stomach where the pH is acid (< pH 3), they would become ionized and thus unable to enter the epithelial cells. They would eventually leave the stomach along with the food in a few hours- a good outcome.

(2) Taurine conjugates, about 22% of bile, are sulphonic acids,

and are formed when taurine is conjugated with the free bile acids. They are strong acids, soluble at all body pH and their pKa is < 2. Their main dietary source is animal fats, hence they play a promoting role in heart and stroke diseases. Kaun-Hao Chen et al [3] showed that their concentration in bile could be controlled by eating low animal fat diets. By keeping the concentration of the taurine conjugates low, both heart attacks and stroke as well as esophageal cancers could decrease.

(3) All four free BAs are carcinogens. Bernstein et al [4] showed that 17 out of 18 mice, developed colon cancer when fed a diet containing 0.2% DCA. This was the first reported case of a free BA promoting cancer. If the stomach pH exceeds 3.8, bacterial overgrowth would occur and the bacteria could produce an abundant supply of this carcinogen by de-conjugating the glycine and taurine conjugates [5]. To avoid this reaction, an acid stomach should be maintained especially since this would keep the BAs ionized and thus prevent their entry into the epithelial cells.

Hofmann and Mysels [6] showed that" free and glycine conjugated BAs are insoluble at acid pH but as the pH is increased, their solubilities would increase exponentially until the CMC (critical mycellar concentration) is reached at ~ pH 7.2 when they would become almost completely soluble" . At this pH micelles would be formed and the BAs would be protonated allowing them to easily enter the cells. Many other researchers showed that the free and glycine conjugated BAs, are ionized at low pH, and hence are insoluble at low pH values and they may even be precipitated at very low pH [7-9]. None of these other workers studied this solubility phenomenon of the BAs at high pH values where they are increasingly soluble and thus could easily enter the esophageal cells.

This Principle explains how free and glycine conjugated BAs behave generally. At the CMC, the BAs are protonated (their charges are neutralized) and they could easily enter the epithelial cells and this would start carcinogenesis. Based on this Principle, it was hypothesized that AST medication would raise the pH of the stomach to ~ 7 and with the help of salivary bicarbonate, carcinogenesis would occur [10-12]. Boeckxstaens et al [13] showed that GERD (gastro esophageal reflux disease) patients on AST medication would have pH values of about ~ 7 in the stomach. With the help of salivary bicarbonate, which has a pH ~ 6.5-8.4, the BAs would achieve the CMC, where they would be protonated (neutralized) and thus could easily enter the cells, react with the DNA and this would result in carcinogenesis. Thus, when Huo et al [2] put an un-buffered alcoholic solution of the carcinogenic DCA into the esophagus of BE patients, it would meet the salivary bicarbonate. This would help the protonation of the BA, allowing it to reach the CMC and thus easily enter the esophageal cells. It should be noted that DCA can cause double strand breaks in the DNA and thus become an even more powerful carcinogen. This would start the carcinogenesis process described and thus support our hypothesis. If a 5 minute exposure of the esophagus to soluble DCA produces these measurable carcinogenic events, we can only wonder what many years of daily exposure to AST drugs would do! Once the neoplastic progression reaches the BE stage it may be irreversible thus putting another nail in the coffin of AST.

Esophageal cancers are the fastest growing cancers in the Western world with a growth rate of > 6 fold annually [14].This cancer development process starts out as GERDS and changes to esophagitis followed by BE and finally esophageal cancer. At the present time, the only non-invasive treatment for the disease is AST which uses predominantly 2 types of drugs:

A) Histamine receptor antagonists were developed in 1975. These drugs block the histamine receptors in the stomach and for about 6 hours, no hydrochloric acid could be made and stomach pH would reach about pH 6.

B) The other type of drug is the Proton Pump Inhibitor (PPI) developed in ~1985. This drug would block the hydrogen/potassium adenosine ATPase activity with a half-life of over 26 hours. The first proton pump inhibiting drug was called Prilosec. Other drugs in this series have half-lives measured in days. These types of drugs were very efficient in removing stomach acid, but acid was not the cause of the disease. This was made evident when Marshall and Warren [15] discovered that ulcers were caused by a simple bacterium called H. Pylori and that antibiotics would kill the bacteria and cure the ulcer problem permanently in months at very little cost. At this time both types of drugs should have been discarded, but they were re-introduced as treatment for acid reflux diseases. Thus the incidence of esophageal continued to rise.

From the above it can be concluded that AST solubilizes BAs in the stomach and on reflux into the esophagus they will start carcinogenesis. Hence AST should be re-evaluated since it facilitates entry of carcinogenic BAs into the esophagus.

Recently, researchers have been experimenting with the hydrophobic bile acid DCA and its hydrophilic counterpart, (UDCA). They were trying to find better ways to study, and perhaps treat this ever dangerous cancer that had been increasing annually (2). DCA is hydrophobic and is carcinogenic (3). It has two hydroxyl groups at position 3 and 12 on the steroid nucleus and is formed in the stomach at pH < 3.8 as de-

scribed previously. As well, it is formed in greater abundance in the colon where the bacterial population is greater and the BA concentration is much higher.

UDCA is hydrophilic with its two hydroxyl groups at position 3 and 7 on the steroid nucleus. (The positions of the two hydroxyl molecules in these compounds may be important since it was shown that an equimolar mixture of them was inactive [16]. UDCA has been used for generations in Eastern medicine to treat various maladies in the liver and has been used in Western medicine, to treat gallstones. Many other uses have been mentioned, including experimental treatment for colon cancer. Many groups of researchers are currently studying UDCA as a chemo-preventive agent in the study of both esophageal and colon cancers [16-18].

Continuing the work of Huo et al [2] and Peng et al [16], using esophageal biopsies of BE patients, confirmed that oral UDCA could prevent toxic BAs from causing DNA damage and NF-kB activation. Using BE cells, it was found that UDCA could prevent DCA-induced ROS generation, DNA damage and NF-kB activation. They also showed that UDCA could protect against BA-induced oxidative injury in BE chemotherapy. At neutral pH, DCA would be protonated and could easily enter the cells and be very reactive. The patients used in these studies were on AST medication which would allow the BA's to more easily achieve the CMC and thus enter the cells. Comparison of Peng's work with the work of others authors can be misleading, especially researches involving BA cocktails. In one such study, Goldman et al [17], used a BA cocktail buffered at pH 4 which contained five BAs. One of the BAs was taurocholic acid (TCA), a sulphonic acid which is soluble at all pH and thus could easily enter the epithelial cells. The other four BAs in the cocktail would be ionized at this acid pH (6, 7, 8) and so could not enter these cells, hence only the TCA would be active. This cast some doubt on Goldman's BA cocktails and their usefulness in these kinds of studies. (At higher pH values, the buffers used by Goldman would ensure that the CMC was never reached!)

A study by Ojima et al [18], using male Wistar rats that had received a duodeno-esophageal reflux procedure, were divided into 2 groups. One group received Chow and was the control while the other group received UDCA. The animals were sacrificed 40 weeks after surgery and analysis showed that in the UDCA group, the rats had milder esophagitis, decreased incidence of BE and EAC was not seen. Cdx2 and NF-kB were greater in the control group. These findings led to the conclusion that UDCA may be a chemo preventive agent against EAC.

If UDCA therapy supplants acid suppression therapy, then:

A) >70% of the free bile acids and their glycine conjugates would be ionized and hence would leave the stomach with the food in a matter of hours, long before they could contribute to any carcinogenic event.

B) The Theisen studies (5) would not occur at acid pH (pH < 4) further reducing the formation of the carcinogenic bile acids (like DCA) and hence their contribution to carcinogenesis would be missing.

All of this would help in lowering the incidence of esophageal cancer. Chemotherapeutic studies like the above involving UDCA are long overdue. The main problem is getting sufficient UDCA into the epithelium.

Banerjee et al [19] fed 21 BE patients with UDCA (13-15 Mg per Kg body weight daily for 6 months. At the end of this period their analysis showed that the carcinogenic events reported by Huo [2] or Sue Peng [16] did not occur. This suggested that the UDCA was not getting into the esophageal tissues of these patients. To remedy this situation, we propose the use of liposome technology to assist in getting the UDCA into the epithelial cells.

Liposomes are phospholipid vesicles that can easily be made from lipids like cholesterol and lecithin. As well one can incorporate the hydrophilic ursodeoxycholic acid into the aqueous interior of the liposomes [20]. Liposomes measure ~ 10- 90 nM in diameter and on topical application, they can evade the reticuloendothelial system (a collection of phagocytes all over the body that removes foreign substances from the circulation). They would then fuse with the cell membranes and hopefully deliver their load of UDCA directly inside the cell. There they would prevent the DCA from damaging the DNA and produce other carcinogenic events as described and remain inside the cells long enough to protect further DNA damage [16].

EXPERIMENTS TO TEST THESE HYPOTHESES ON BARRETT'S ESOPHAGUS AND COLON CANCER PATIENTS

Esophagus:

Huo (2) and Sui Peng (16) showed that UDCA could enter the BE cells and be very reactive in a short exposure. Banerjee (21), despite a 6 month of daily exposures, could not verify entry. To show that UDCA could enter the BE cells we could use autoradiography. Tritiated UDCA could be entrapped into liposomes and mixed with BE biopsies (or BE cells). Various exposure periods could be used. Entry of liposomal tritiated UDCA into the cells could be confirmed by developing the autoradiograms. As a control, free tritiated UDCA could be used,

replacing the liposomes. This type of experiment would also show that our proposal to use liposome encapsulated drugs is a viable alternative.

During an endoscopic examination of BE patients, UDCA bearing liposomes could be delivered on the surface of the esophagus, (with the help of a bronchoscope). The liposomes would then fuse with the cell membrane and deliver their UDCA load inside the epithelial cells. Once inside, the UDCA would prevent DNA damage and other damaging effects described by Huo et al [2] and Peng et al [16]. This could be repeated at regular intervals (monthly). Before each repeat operation, biopsies could be collected and measurements of the parameters used in Huo's studies could be repeated. As a control, free UDCA could be used on other similar patients. After many such measurements, the progression or regression, of the disease could be estimated by comparing the control with experimental patients. Animal studies using the Hashimoto model [1] could also be used.

Colon

During colonoscopy, precancerous lesions like polyps could be identified, mapped and photographed so that they could be easily located in the future. Apply free UDCA solution to the colons of some patients (controls) and to others, a sample of UDCA bearing liposomes. On subsequent colonoscopy examinations, these lesions could be identified and compared. This would paint a picture of the progression, or regression, of the disease and its response to UDCA liposomes.

Animal studies using rats that were injected intra-peritonially with the colon carcinogen AOM (azoxymethane) could be used. The development to cancers could be followed on a regular bases (monthly) by sacrificing some animals and recording the pre cancer lesions. These would eventually produce cancers which could be quantitated.

A preliminary version of this manuscript appeared in Medical Hypotheses 2015 [21].

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