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Clinical Articles

Effects of Tetracycline on Fecal Bile Acid Pool Composition in a Human: A Preliminary Report†

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We studied the effect of tetracycline on bile acid pool composition in a human subject. A dosage of 250 mg (qid) of tetracycline for one week completely eliminated deoxycholic and lithocholic acid from the pool. Tetracycline may be of value for limiting the build-up of lithocholic acid in patients who are treated with chenodeoxycholic acid to dissolve gallstones.

One problem associated with the dissolution of cholesterol gallstones of patients treated for a long time with chenodeoxycholic acid is the large-scale production of lithocholic acid (1). Lithocholic acid is a secondary bile acid synthesized from chenodeoxycholic acid in the large intestine in a reaction catalyzed by reductive 7α-dehydroxylating enzymes found in certain bacteria (2). Although lithocholic acid is efficiently detoxified and is difficult for the human body to absorb, it is hepatotoxic and may increase the risk of colon cancer (1). It would therefore appear desirable to limit its production.

Recent in vitro experiments by Hirano, et al (3) demonstrate that neomycin inhibits reductive 7α-dehydroxylation during anaerobic incubation. If bacteria synthesizing the dehydroxylases could be inhibited in vivo, it might be possible to administer measured amounts of the antibiotic together with chenodeoxycholic acid in order to limit lithocholic acid formation during gallstone dissolution. This concept is supported by the work of Hamilton (4), who demonstrated that deoxycholic acid, a major secondary bile acid synthesized by reductive 7α-dehydroxylation of cholic acid, disappeared from the fecal bile acid pool when neomycin was administered for some time. In the experiment reported below, we investigated the effect of tetracycline on the formation of lithocholic acid in a patient who had persistent diarrhea and, presumably, a small pool of colonic bacteria.

Patient History

Our patient was a 63-year-old white woman with a history of stage IIIB cancer of the cervix. It had been diagnosed in 1977, and she received both external and internal radiation therapy. During radiation therapy, she developed diarrhea, which has persisted to the present time. Initial and subsequent barium studies of the small bowel and colon have been unremarkable. On several occasions mild proctitis was noted by sigmoidoscopy but was believed to be radiation-induced. Since the patient’s diarrhea started, multiple medications have been used to reduce her bowel frequency with varying success. Recently, she was given a trial of tetracycline for one week (250 mg, qid), at which time stool specimens were collected for our study.

Materials and Methods

All chemicals, solvents, enzymes, and standard bile acids were of the same purity and were obtained from previously identified sources (5,6).

Determination of fecal bile acid pool composition

Pool composition was determined by a method developed in our laboratories and previously reported (6). Briefly, fecal homogenates are prepared and extracted with ethanol. Aliquots of these extracts are applied to
Bile Acid Analysis

channeled thin-layer chromatography plates, which are developed with ethyl acetate:iso-octane:glacial acetic acid (10:10:2 v/v) to separate individual bile acids. Each channel on the developed plates is marked at one-half cm intervals. Silica gel at these intervals is transferred to centrifuge tubes, and its bile acid content is determined fluorometrically with resazurin reagent. Individual bile acids separated on the developed plates are identified by Rf values and standard comparisons. If identification is questionable, it is confirmed or established by gas-liquid chromatography.

Experimental plan

Feces samples (72 hours) were collected before tetracycline treatment started, one week after treatment began, and one month after the treatment was stopped. Each sample was assayed for fecal bile acid pool composition, and the results were compared.

Results

Before treatment with tetracycline, fecal bile acid pool composition was normal (Fig. 1, bottom), containing large amounts of deoxycholic and lithocholic acids and small amounts of cholic acid. No bile acid conjugates (which remain at the origin) were seen. The results indicate that intestinal flora contained adequate quantities of bile acid deconjugates and reductive 7α-hydroxylases to produce their specific reactions. During tetracycline treatment (Fig. 1, middle), deoxycholic and lithocholic acids were eliminated from the pool. Cholic acid, the precursor of deoxycholic acid, and chenodeoxycholic acid, the precursor of lithocholic acid, were the major pool components. Very small amounts of conjugated bile acids were present. It is apparent that 7α-hydroxylation was completely curtailed, while bile acid deconjugation was only slightly suppressed. This suggests that tetracycline selectively inhibited different types of fecal flora. An alternate possibility is that before tetracycline treatment, flora-producing reductive 7α-dehydroxylating enzymes were present in smaller quantity than those producing bile acid deconjugates, and tetracycline acted equally on both types of flora. Thirty days after tetracycline was discontinued, pool composition had returned to normal (Fig. 1, top).

Discussion

It appears that in vivo tetracycline treatment can effectively eliminate lithocholic acid from the fecal bile acid pool. One must, however, be cautious when extending the results to other individuals. This patient had rather marked diarrhea and, as a consequence, this may have resulted in a small intestine flora pool. Normal and/or constipated patients and patients receiving chenodeoxycholic acid for gallstone dissolution might require larger initial doses of tetracycline to produce the same effect. Nevertheless, the results indicate that when present in sufficient amounts, tetracycline prevents conversion of chenodeoxycholic acid to lithocholic acid. It may be useful in preventing the build-up of lithocholic acid in patients who receive chenodeoxycholic acid to dissolve gallstones.

Fig. 1

Fecal bile acid pool composition before, during, and after tetracycline treatment. A = conjugated bile acids; B = cholic acid; C = chenodeoxycholic acid; D = deoxycholic acid; E = lithocholic acid.
References