Atypical Bile Acids and Their Possible Role in Neonatal Diarrhea

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Bile acids are both acted on by the gut and act on the gut. Bile acids undergo an enterohepatic circulation and are absorbed by specific mechanisms for bile acid transport in the ileum (1). At the same time, bile acids influence salt and water transport in the intestine (2). This is probably of greatest clinical importance in patients with defects that permit excessive quantities of bile acids to enter the colon. Bile acids stimulate colonic salt and water secretion, and such patients experience watery diarrhea. Moreover, bile acids can exert indirect effects on colonic function: since bile acids partially govern lipid absorption, bile acid deficiencies can lead to excess entry of fatty acids into the colon and steatorrhea.

The relationships between bile acids and the gut in low-birth-weight infants are, as Dr. Balistreri has indicated (W. F. Balistreri, this volume), different from those in adults. First, bile acid pool sizes, synthesis rates, and duodenal intraluminal concentrations are all low in comparison with those of adults (3). Bile acid deficiency contributes to the steatorrhea commonly observed in low-birth-weight infants. Second, the ileal mechanism for active bile acid transport is unmeasurable at birth (4–6). The timing of the maturation of this mechanism in the newborn infant has not been defined. In rats, maturation occurs between 15 and 25 days of life, whereas in dogs maturation occurs between 2 and 5 weeks. Deficiency of the ileal bile acid transport mechanism might have three divergent effects. If less bile acid is absorbed, more may enter the colon, thereby tending to increase colonic secretion. Alternatively, if less bile acid is absorbed, the body pool may be diminished, ultimately decreasing the amount of intraluminal bile acid available to enter the ileum or colon. Finally, decreased bile acid concentrations in the small bowel might lead to fat malabsorption and steatorrhea. The extent and interaction of these factors in the newborn is ill-defined at present, and careful documentation is badly needed if rational therapy is to be developed. The net result, however, of immaturity of mechanisms for conserving bile acid in the low-birth-weight infant is an increased tendency to develop diarrhea.

An additional factor, discussed by G. D. Potter and R. Lester (this volume), has to do with bile acid interaction with the developing colon. As they note,
the perinatal colon in rats is anatomically and functionally distinct from the adult colon. The limited information available suggests that the human colon matures anatomically earlier in gestation, but the extent of functional colonic maturation during the perinatal period is largely unknown. It is entirely possible that colonic absorptive function is immature in low-birth-weight infants. The response of an immature colon to stimulation with bile acid is unknown. The effects of increased entry of bile acid and/or fatty acid into the neonatal colon on colonic salt and water transport need definition.

Additional factors add to the complexity of analyzing the role of bile acids as agents influencing diarrhea in the newborn. The traditional view is that there are four human bile acids: the primary bile acids, cholic and chenodeoxycholic acid; and the secondary bile acids, deoxycholic and lithocholic acid. Studies of bile-acid-induced gut secretion have suggested that the two dihydroxy bile acids, chenodeoxycholic and deoxycholic acid, are more potent stimulators of colonic secretion than the trihydroxy cholic acid (2). Studies with lithocholic acid have been technically difficult to perform because of solubility problems and because toxicity for epithelial tissue might introduce a contaminating variable in the examination of epithelial secretion per se.

The simple picture that there are four human bile acids, however, is no longer valid. Specimens of infant plasma and bile contain the four traditional bile acids and an additional atypical unsaturated, monohydroxylated bile acid, 3β-hydroxychol-5-enoic acid (7). The bile acid content of meconium, however, is much more complex and is only now being analyzed systematically (8–12). As an interim report, meconium contains the following classes of bile acid: (a) typical bile acids; (b) atypical isomers of typical bile acids; (c) unsaturated bile acids; (d) “long-chain” bile acids; and (e) “short-chain” bile acids. The bile acids in meconium in the first category are the traditional four mentioned above. Those in the second category include hyocholic acid, ursodeoxycholic acid, and each stereoisomer of lithocholic acid at the 3 and 5 positions of the molecule. 3β-hydroxychol-5-enoic acid is the best-defined member of the third category found in meconium, but preliminary evidence indicates that others are present.

The fourth and fifth categories are conceptually different from typical bile acids and deserve a special word. Typical bile acids contain 24 carbon atoms with a five-carbon acidic side chain at position 17. Long-chain bile acids have more than 24 carbon atoms and more than five carbon atoms in their side chains. Although other sources may contribute, the major fraction of long-chain bile acids are incompletely oxidized intermediates of the typical bile acid synthetic pathway from cholesterol (Fig. 1).

The existence of short-chain bile acids has only recently gained wide recognition (9,10). They contain 20 to 23 carbon atoms with side chains of one to four carbon atoms (Fig. 2). Their origin probably is diverse: some may be secondary bile acids, some may be maternal colonic bacterial oxidation products of cholesterol, and some may be steroid hormone degradation products (11,12). It is, thus, unclear if they originate in fetus, placenta, or mother. Certain of them
are present in meconium in high concentrations. For example, although it had been thought previously that the principal monohydroxylated bile acid in meconium was either lithocholic or 3β-hydroxychol-5-enolic acid, it is now known to be 3α-hydroxy-5α-androstan-17β-carboxylic acid, a 20-carbon short-chain bile acid (11). Similarly, there is approximately as much of certain of the dihydroxylated 21-carbon, short-chain bile acids in meconium as there is of the typical dihydroxylated chenodeoxycholic acid (13).

Virtually nothing is known about the function of these atypical bile acids, and, more specifically, nothing is known about their interaction with mature
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FIG. 2. Examples of "short-chain" bile acids found in meconium: 20-, 21-, and 22-carbon bile acids are shown.

and immature colon. Moreover, little is known about the bile acid content of the normal neonatal colon during the days after it is emptied of meconium or of the colonic content of bile acids of low-birth-weight infants during their first weeks of development. Similarly, the effects of changes in colonic bacterial flora on bile acid metabolism have not been fully explored. These unknowns must be evaluated if the role of bile acids in neonatal diarrhea is to be approached successfully.

A final consideration relates to the form of bile acid conjugation rather than variations of the steroid moiety. Previous studies have examined the effects of taurine and glycine conjugates and of unconjugated bile acids on salt and water absorption and secretion by the gut (2). A significant fraction of the bile acid content in meconium is in the form of sulfate and glucuronide conjugates (11,12). This is especially true of the bioactive monohydroxylated bile acids and of certain short-chain bile acids. The metabolism, transport, and bioactivity of sulfate and glucuronide bile acid conjugates have not been well defined, nor has the persistence of these compounds in the gut during the neonatal period.
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and infancy. Further definition of this area will be necessary in order to evaluate
the possible role of bile acids in neonatal and infant diarrheal syndromes.

In a word, the relationship between bile acids and diarrheal syndromes
of the newborn is an area with many questions and few answers. The subject badly
needs investigative exploration.

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