REVIEWS

Hyperbilirubinemia in the Setting of Antiviral Therapy

KEVIN M. KORENBLAT* and PAUL D. BERK*,†
*Division of Liver Disease, Department of Medicine, and †Department of Molecular, Cell, and Developmental Biology, Mount Sinai School of Medicine, New York, New York

Hyperbilirubinemia is a common side effect of antiviral medications. The mechanisms underlying its development are multiple and unique to each therapy. During administration of antiviral medications, the hyperbilirubinemia observed in the absence of liver injury is most frequently manifested by isolated increases in the indirect-reacting fraction. Relevant mechanisms leading to indirect hyperbilirubinemia in this setting include hemolysis, decreased hepatic bilirubin clearance as a result of impairment of bilirubin conjugation, or circumstances in which both processes occur simultaneously. Underlying genetic susceptibilities may potentiate these side effects of antiviral therapy. Conjugated (direct-reacting) hyperbilirubinemia can be a consequence of generalized hepatocellular injury, selective cholestatic defects, biliary obstruction, or, rarely, genetic disorders of bilirubin transport. In the specific setting of antiviral therapy, preexisting liver disease or antiviral hepatotoxicity, such as is encountered with the use of the nucleoside and non-nucleoside human immunodeficiency virus reverse transcriptase inhibitors, are the most frequent causes of direct-reacting or mixed direct- and indirect-reacting hyperbilirubinemia. Modification in antiviral drug choice or dose may be required in cases of liver injury or of brisk hemolysis leading to significant anemia. The mild indirect hyperbilirubinemia associated with impairment in conjugation tends to be well tolerated and of little consequence. The decision to continue or discontinue antiviral therapy in the face of hyperbilirubinemia should be made after an assessment of the cause of the elevated bilirubin level and a thorough assessment of the risks and benefits of antiviral therapy.

The expanding numbers of available antiviral therapies have dramatically altered the management of viral diseases. The potential benefits of these medications seem mitigated only by issues of viral resistance and side effects. The development of hyperbilirubinemia, with or without concomitant liver injury, is an increasingly recognized side effect of antiviral medications, particularly those associated with the treatment of infections caused by herpes virus, cytomegalovirus (CMV), hepatitis C, and human immunodeficiency virus (HIV). This review focuses on the mechanisms of bilirubin production and excretion and how alterations in these processes result in hyperbilirubinemia. An approach to the evaluation of hyperbilirubinemia in the patient with viral infection is provided. Emphasis is placed on distinguishing between causes of hyperbilirubinemia that may require modification in therapy and those that are of negligible clinical significance.

Mechanisms and Physiology of Bilirubin Production and Excretion

Bilirubin Production

Bilirubin is the end product of the catabolism of heme, the prosthetic moiety of hemoglobin, myoglobin, and other hemoproteins.[1] The major sites of bilirubin production are the spleen and other reticuloendothelial compartments. In normal humans, bilirubin production averages ~4 mg · kg body weight^{-1} · day^{-1} (6 μM · kg body weight^{-1} · day^{-1}),[2] and hemoglobin from erythrocyte turnover is the source of 80%–85% of the heme that is eventually catabolized to bilirubin.

Bilirubin in Plasma

Internal hydrogen bonding between polar moieties within bilirubin constrains the molecule in a rigid, non-polar, and therefore highly insoluble conformation.[1,3] As an otherwise insoluble molecule, bilirubin formed in the periphery is transported to the liver tightly bound to high affinity binding sites on albumin, at concentrations that far exceed its solubility in protein-free aqueous solutions. If the molar ratio of bilirubin to

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; HIV, human immunodeficiency virus; MRP2, multidrug resistance-associated protein 2; NIAID, National Institute of Allergy and Infectious Diseases; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(05)00083-2

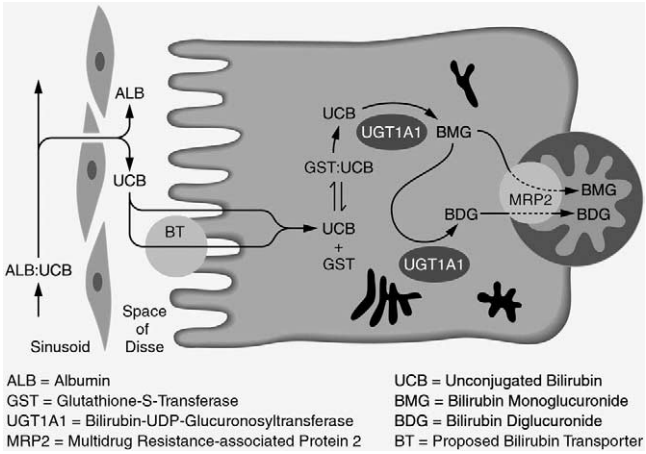

Figure 1. Efficient transfer of bilirubin from blood to bile is dependent on normal sinusoidal architecture, plasma membrane transport processes, and intracellular binding and conjugation. Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes. Within the cell it is bound to glutathionione-S-transferases and conjugated by UGT1A1 to monoglucuronides and diglucuronides, which are actively transported across the canalicular membrane into the bile. Modified and reprinted with permission from Berk et al.[3]

albumin exceeds 1:1 (a bilirubin concentration of approximately 35 mg/dL), the additional bilirubin binds to lower affinity sites, and the unbound bilirubin concentration increases rapidly with further increases in total bilirubin.

Hepatic Disposition of Bilirubin

Because bilirubin is a potentially toxic waste product, its hepatic disposition is designed to eliminate it from the body via the biliary tract. Transfer of bilirubin from blood to bile involves 4 distinct but interrelated steps (Figure 1).

Bilirubin uptake. Bilirubin bound to albumin comes in contact with the microvilli lining the sinusoidal surface of the hepatocytes by passage through the fenestrated endothelium of the hepatic sinusoids into the extrasinusoidal space of Disse. Bilirubin dissociates from albumin and is widely believed to be transported across the hepatocyte plasma membrane into the cell by a protein-mediated, facilitated uptake process, although the exact identity of the bilirubin transporter remains obscure. Recent studies have identified a purely passive, nonsaturable bilirubin uptake component, but its magnitude relative to the saturable process remains to be determined.[4]

Intracellular binding. Within the cell, bilirubin partitions between the cytosol and the lipid bilayer of various intracellular membranes. As with bilirubin binding to albumin in plasma, its cytosolic fraction is kept in solution at concentrations that far exceed its aqueous solubility by binding as a non-substrate ligand to a number of proteins, of which the most abundant and best characterized are members of the glutathione-S-transferase superfamily designated *ligandins*.[1,3]

Bilirubin glucuronidation. Making bilirubin soluble, which is essential for biliary excretion, requires disruption of its internal hydrogen bonds. This is achieved by conjugation with glucuronic acid. The resulting monoglucuronide and diglucuronide conjugates are highly soluble in aqueous solutions. The enzyme responsible for bilirubin glucuronidation is the UDP-glucuronosyltransferase isoform UGT1A1, which is encoded by the *UGT1* gene on chromosome 2.[5] This complex gene consists of 13 alternative first exons (designated A1–A13), each of which encodes a distinct N-terminal region, with a substrate-specific binding site, for one of the multiple protein isoforms produced by this single gene locus. Initiation of RNA transcription at each of these 13 exons is controlled by a separate promoter element immediately upstream of its unique exon. Alternative splicing fuses 1 of these upstream exons with the 4 exons (exons 2–5) common to all UGT1 protein isoforms (Figure 2). Exon A1 and the 4 common exons encode the UGT1A1 protein responsible for bilirubin glucuronidation.[6]

Canalicular excretion of bilirubin. The ATP-dependent transport of bilirubin glucuronides across the apical plasma membrane into the canaliculus is mediated by a membrane protein, multidrug resistance-associated protein 2 (MRP2).[7] In mouse models, effective MRP2 function requires the presence of at least one additional protein, radixin, which localizes to the canalicular membrane and directly binds the carboxy-terminal cytoplas-

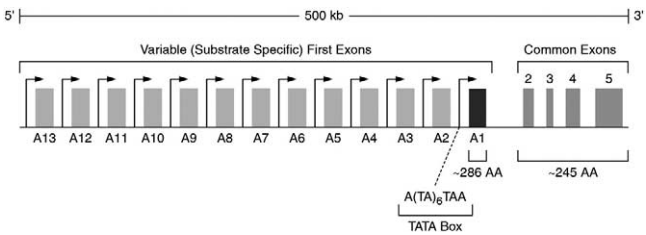

Figure 2. Structural organization of the human *UGT1* gene complex. This large complex on chromosome 2 contains at least 13 substrate-specific first exons (A1, A2, . . .), each with its own promoter, that encode the N-terminal substrate-specific 286 amino acids of the various UGT1-encoded isoforms and common exons 2–5 that encode the 245 carboxyl-terminal amino acids common to all of the isoforms. mRNAs for specific isoforms are assembled by splicing a particular first exon such as the bilirubin-specific exon A1 to exons 2–5. The resulting message encodes a complete enzyme, in this particular case UGT1A1. Mutations in a first exon affect only a single isoform. Those in exons 2–4 affect all enzymes encoded by the *UGT1* gene complex. Modified and reprinted with permission from Berk et al.[3]