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Review

Disorders of bilirubin binding to albumin and bilirubin-induced neurologic dysfunction

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SUMMARY

Bilirubin-induced neurologic dysfunction (BIND) is a syndrome of subtle bilirubin neurotoxic disorders. The risk for developing BIND in newborns usually increases with elevated serum/plasma concentrations of unconjugated bilirubin. This risk is further increased by disorders of bilirubin binding to albumin, which includes a reduction in serum albumin concentrations or in the bilirubin-binding capacity and affinity of albumin, and the presence of displacing substances or infection. Serum unbound bilirubin (UB) concentration may be an ideal marker that reflects changes in bilirubin binding to albumin. Kernicterus, the chronic and with the most severe manifestations beyond BIND, is diagnosed by the presence of motor impairments with athetosis, abnormal magnetic resonance imaging, and/or brainstem auditory-evoked potential findings during infancy and childhood. Preterm infants sometimes have acute bilirubin encephalopathy without marked hyperbilirubinemia, such that bilirubin neurotoxicity occurs at bilirubin thresholds lower than usually associated with kernicterus. Disorders of bilirubin binding to albumin may be associated with the clinical signs of neurological injury associated with the lower bilirubin levels observed in preterm infants.

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1. Introduction

Bilirubin-induced neurologic dysfunction (BIND) is a syndrome of subtle bilirubin neurotoxic disorders that are associated with bilirubin thresholds lower than associated with acute and chronic bilirubin encephalopathies. Acute bilirubin encephalopathy (ABE) is the acute phase of bilirubin neurotoxicity manifested as lethargy, hypotonia, motor abnormalities, irritability, and impairment of sucking [1]. The term “kernicterus” has often been used to describe the chronic form of bilirubin encephalopathy and presents with athetoid cerebral palsy (CP), auditory dysfunction, dental enamel dysplasia, and upward gaze paralysis and a variety of movement disorders. Kernicterus was originally a pathological term referring to the yellow staining of the basal ganglia, specifically of the globus pallidus and subthalamic nuclei found at autopsy [2]. Recent advances in diagnostic technologies, such as brain magnetic resonance imaging (MRI) and brainstem auditory-evoked potential (BAEP) tests, have enabled kernicterus to be clinically diagnosed in the infantile period (called “clinical kernicterus”) in the last decade [3,4].

The risk for developing BIND is dependent not only on the serum/plasma concentration of unconjugated bilirubin, but also on the ability of serum albumin to bind bilirubin, including bilirubin-binding capacity (BBC), and the total amount of albumin. The presence of displacing substances also affects bilirubin binding to albumin. As a result, unbound or free bilirubin (UB) will rise, increasing an infant's risk for developing BIND. In this review, we focus on disorders of bilirubin binding to albumin and risk of BIND in preterm infants.

2. Basic mechanism of developing disorders of bilirubin binding to albumin

Albumin contains a primary high-affinity site for bilirubin and a secondary low-affinity site [5]. When unconjugated bilirubin increases, the primary high-affinity site becomes oversaturated by bilirubin, and bilirubin is transported to the secondary low-affinity site. When the BBC or the total amount of albumin is reduced, the oversaturation may easily occur. Alternatively, some displacing substances, such as free fatty acids (FFAs) and certain drugs (such as benzyl alcohol, sulfisoxazole), preferentially bind to albumin at its

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high-affinity site. They can thus displace bilirubin from its high-affinity site, resulting in its transport to the secondary low-affinity site. In both situations, aromatic anions, in turn, can displace bilirubin from this secondary site, thereby increasing serum UB concentrations [6]. When circulating UB increases, UB can enter the brain across the blood–brain barrier (BBB) and cause neurotoxicity [7,8].

3. Clinical factors affecting bilirubin binding to albumin

A reduction in serum albumin concentrations or BBC and affinity of albumin, and the presence of displacing substances or infection, are major factors affecting bilirubin binding to albumin in the clinical setting (Box 1). Because these processes can result in higher UB concentrations than those at a comparable total serum/plasma bilirubin (TB), caution should be taken when interpreting the risk of BIND using TB concentrations, which have been traditionally used to identify newborns at risk for developing BIND.

3.1. Serum albumin concentrations

The mass action relationship between serum UB, TB and albumin (Alb) concentrations, and the binding constant (K) is shown in the following equation:

$$[UB] = [TB] / K^*([Alb] - [TB])$$ [8].

At any given TB concentration, UB concentrations usually correspond to those at comparable TB concentrations, when albumin concentrations are constant. A reduction in albumin concentrations leads to high UB concentrations. Albumin concentrations are decreased as gestational age (GA) decreases [9]. Preterm infants are at high risk for developing hypoalbuminemia, resulting in high UB concentrations. Ebbesen et al. reported that the effect of albumin infusion is mainly due to an increase in the non-binding fraction of albumin while the bilirubin–albumin concentrations are unchanged [10]. However, Caldera et al. and Hosono et al. showed that albumin infusion therapy combined with phototherapy leads to a rapid and early reduction in UB concentrations [11,12].

For risk assessment of BIND, the bilirubin:albumin molar ratio (BAMR) has often been used clinically because TB and albumin concentrations are measured using routine laboratory techniques, and their ratio can easily be calculated [1,13]. In the current consensus, the BAMR can be used together with, but in not in lieu of, TB concentrations for evaluating newborns with hyperbilirubinemia [1,13]. We have also shown that the BAMR may be a useful clinical tool for predicting critically high UB concentrations in late-preterm and term infants, although the BAMR in preterm infants is a less sensitive predictor than that in late-preterm and term infants (I. Morioka et al., unpublished data).

Box 1
Major clinical factors affecting bilirubin binding to albumin.

Reduction in:
serum albumin concentrations
bilirubin-binding capacity and affinity of albumin
Presence of:
displacing substances.
Free fatty acids by intravenous lipid emulsion.
Antibiotics, such as sulfonamides, cephalosporin, and penicillin.
Ibuprofen
infection/sepsis
other poor health conditions.

3.2. BBC and affinity of albumin

Cashore et al. measured BBC by using the Sephadex G-25 gel filtration technique in newborns aged >26 weeks of GA [9]. Bender et al. estimated BBC and affinity by using the Scatchard plot [14]. Both studies demonstrated that the BBC shows a positive correlation with GA [9,14]. BBC, which is equal to K, is more likely to be variable in newborns, regardless of GA and health status [14,15]. Because preterm infants have a reduced BBC, UB concentrations should easily be able to increase at a given TB concentration.

3.3. Displacing substances

3.3.1. FFAs

When the FFA:albumin molar ratio is >4, FFA concentrations are known to displace bilirubin from a primary albumin-binding site. This leads to a decrease in bilirubin-binding affinity and an increase in UB concentrations only in extremely preterm infants [6,16,17]. Serum FFAs can be increased by exogenous lipid emulsions as well as by stress. However, we recently assessed postnatal FFA concentrations and the FFA:albumin molar ratio in a large number of sick newborns who were admitted to our neonatal intensive care unit (NICU), and found that all of the patients had an FFA:albumin molar ratio <4 [18]. Because endogenous serum FFA concentrations do not affect UB concentrations, pediatricians should be aware of the potential displacing effects of FFAs in extremely preterm infants receiving >1.5 g/kg/day of exogenous, intravenous lipid supplementation [17].

3.3.2. Antibiotics

Some antibiotics have been shown to displace bilirubin from binding sites with different levels of activity [19,20]. The most potent displacers are sulfonamides, cephalosporins, and penicillins [19,20]. Not using these antibiotics in preterm infants with hyperbilirubinemia to prevent BIND may be reasonable. New antibiotics have been introduced for the treatment of neonatal infections in the last decade, such as carbapenems, anti-methicillin-resistant *Staphylococcus aureus* drugs, and anti-virus drugs (e.g., influenza and cytomegalovirus). Studies are urgently required to determine whether these antibiotics possess bilirubin-displacing effects.

3.3.3. Ibuprofen

Ibuprofen, one of the drugs used for treating patent ductus arteriosus in preterm infants, is a potent bilirubin displacer and has been shown to increase UB concentrations in vitro [21,22]. However, recent in-vivo studies have shown that ibuprofen does not displace bilirubin and increase UB concentrations in preterms with mild to moderate hyperbilirubinemia [23,24]. Therefore, bilirubin-displacing effects of ibuprofen may be weak in the clinical situation.

3.4. Infection/sepsis

Newborns with bacterial infections or sepsis are at high risk for developing kernicterus [25]. They often have higher UB concentrations than those at comparable TB concentrations at any given TB concentration. This indicates that bacterial infections can affect bilirubin binding to albumin. Infection may also be associated with decreased BBC by endotoxin and increased BBB permeability [26]. However, the mechanism by which bacterial infections affect bilirubin binding to albumin is still unclear.

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