CASE REPORT

Possible Ibuprofen-Induced Kernicterus in a Near-Term Infant with Moderate Hyperbilirubinemia.

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A 36-week gestation newborn was admitted to the neonatal intensive care unit for treatment of primary pulmonary hypertension and possible sepsis. The infant developed hyperbilirubinemia on day 4 of life and peaked on day 5 at a total serum bilirubin of 19 mg/dL. Phototherapy was started on day 4 and continued for 5 days. On day 8 of life, ibuprofen was started for fever; a concurrent total serum bilirubin was 15.7 mg/dL. The subsequent hospital course was uneventful, and discharge occurred on day 22 of life. Because the patient failed a hearing screen at discharge, he was referred for a diagnostic audiology workup. He subsequently failed formal audiometric testing on two occasions one week apart, and was given a diagnosis of auditory dys-synchrony and/or auditory neuropathy, consistent with kernicterus. At 5½ months of age, he was reported to be hypotonic and to have frequent arching movements. Since the total serum bilirubin did not exceed 19 mg/dL, concern was raised that ibuprofen may have caused displacement of bilirubin from its albumin binding site, resulting in kernicterus due to excessive unbound bilirubin concentrations. Ibuprofen should be administered with caution in preterm infants at risk for kernicterus.

KEYWORDS adverse effect, bilirubin, ibuprofen, kernicterus, neonate, non-steroidal anti-inflammatory drugs

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INTRODUCTION

Ibuprofen is commonly used for fever in infants older than 6 months and has comparable efficacy and safety to acetaminophen.[1] It also has been studied in numerous clinical trials and has been recently approved by the Food and Drug Administration as therapy for closure of the patent ductus arteriosus (PDA) in preterm infants.[2,3] However, concerns over the ability of ibuprofen to displace bilirubin from protein binding sites, and to thereby predispose to kernicterus, may limit the safety of ibuprofen in jaundiced neonates.[4-6] If confirmed, such a risk in selected neonates with sufficient baseline risk for kernicterus, would potentially expose those neonates to a drug which may cause excessive concentrations of unbound bilirubin. In a recent authoritative review of ibuprofen use for PDA closure in premature infants, Aranda argued that ibuprofen, at con-

ABBREVIATIONS BAER, Brainstem Auditory Evoked Response; DPOAE, Distortion Product Otoacoutic Emission; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension; TSB, total serum bilirubin

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centrations achieved with recommended doses, did not significantly displace bilirubin from albumin, and thus the risk of kernicterus was not increased.[7] Since the neurodevelopmental and hearing studies from different ibuprofen clinical trials are unknown, and since unbound bilirubin concentrations are not routinely measured in clinical practice, it remains to be determined if standard doses of ibuprofen increases the risk of kernicterus in neonates. Considering the recent approval of ibuprofen for PDA closure, it is important to be vigilant for development of kernicterus in newborn infants receiving ibuprofen, irrespective of total serum bilirubin (TSB) concentrations. We describe a case where displacement of bilirubin by ibuprofen may have contributed to bilirubin-associated auditory dys-synchrony/auditory neuropathy.

CASE REPORT

A 36-week gestational age male infant was referred to the audiologist at 2 months of age, due to an initial abnormal hearing screen using the Natus Algo 2 Automated Auditory Brainstem Response screener. Brainstem Auditory Evoked Response (BAER) testing was performed using the Biologic Traveler. The BAER is used to estimate hearing levels by identifying neural responses of the VIII nerve and lower brainstem. Testing was completed with the infant in a natural sleep, using 92 dB nHL rarefaction and condensation clicks presented to each ear separately through inserted earphones at a rate of 37.7 clicks/sec. The BAER single-channel recordings montage consisted of high forehead to ipsi-lateral mastoid with contra-lateral mastoid as ground. Recordings were performed using a 15 milliseconds time window with physiological amplifiers set to a bandpass of 30 to 1500 Hz. Testing was performed during two sessions, one week apart, because the patient was not sound asleep during the first test. On both occasions, BAER testing showed no identifiable waves; however, a cochlear microphonic, which clearly reversed with the change in click polarity, was present in each ear. During the second test, when the patient was in a deep sleep, the amplitude of the cochlear microphonic was visibly larger. Distortion Product Otoacoutic Emission (DPOAE) assesses cochlear outer hair cell function. DPOAE results showed the presence of cochlear outer hair cell function in each ear in the 3,000-10,000 Hz frequency range. Tympanograms using a 1000 Hz probe tone showed restricted eardrum mobility in each ear. Acoustic reflexes were absent to broadband noise in the left ear and could not be completed in the right ear due to patient movement. Because of the complete absence of waves I through V, the patient was diagnosed with bilateral auditory dyssynchrony/auditory neuropathy. These findings resulted in a careful review of the patient's chart to consider the possible etiology for the particular pattern of auditory abnormalities documented in this infant.

The patient was born via normal vaginal delivery, to a 26-year-old mother with late prenatal care and a history of marijuana, cocaine, and tobacco use. Apgar scores were 8 and 9 at 1 minute and 5 minutes, respectively. He was originally admitted to the normal newborn nursery, but transferred to the neonatal intensive care unit at 5 hours of life because of developing respiratory distress. He progressed clinically to persistent pulmonary hypertension (PPHN), which was managed with ventilator support, including 3 days of high-frequency oscillator ventilation; associated systemic hypotension was treated with dopamine and dobutamine for 2 days. He also received 2 doses of furosemide 2 mg/kg over the first 10 days of life. PPHN resolved over approximately 5 days. He remained on a conventional ventilator until day 7 of life, when he was extubated to a nasal canula. His admission chest x-ray was consistent with congenital pneumonia, and he received parenteral ampicillin and gentamicin for 7 days. Gentamicin peak and trough concentrations were maintained below 10 mg/L and 2 mg/L, respectively, throughout therapy. The patient had hyperbilirubinemia, with a TSB of 13.8 mg/dL on day 4, peaking at 19 mg/dL on day 5. Serum albumin at this time was 2.9 g/dL. Phototherapy was started on day 4 and continued until day 9 of life when the TSB was 14.4 mg/dL. Off phototherapy, the TSB continued to decline the next day to 12.6 mg/dL. While on phototherapy, the direct bilirubin increased from 1.0 to 1.9 mg/dL and continued to rise after discontinuing phototherapy to a maximum of 2.1 mg/dL. An abdominal ultrasound was

normal. Liver enzymes were also normal, and tests for a viral etiology including urine CMV, TORCH titers, hepatitis B, and hepatitis C were all negative.

On day 8 of life, the patient developed a fever to 37.5°C and was treated with vancomycin 10 mg/kg every 6 hours (documented peak and trough concentrations were 27.1 and 16.0 mg/L, respectively) and piperacillin/tazobactam for 7 days. Because of worsening cholestasis, the practitioner was reluctant to use acetaminophen, and consequently started ibuprofen, assuming it was shown to be safe in neonates treated with this drug for PDA. Ibuprofen was dosed as 10 mg/kg every 8 hours as needed for fever, and at least 2 doses were documented as having been administered within the first 24 hours, with at least one additional dose on the subsequent day. Thus a total of 30 mg/kg over 2 days was documented. On day 8, the TSB was 15.7 mg/dL. No etiology was found for the fever. Cranial ultrasound on day 16 of life was normal, and medical problems had resolved. The patient was discharged on day 22 of life.

The patient was next seen in our multidisciplinary developmental clinic at 5½ months postnatal age or a corrected age of 4¼ months. At this visit, he was noted to have moderate to severe central hypotonia with frequent arching movements. He was referred to physical therapy and additional audiologic follow-up and evaluation.

Since the maximum TSB of 19 mg/dL on day 6 of life did not adequately explain the suspicion of kernicterus in this near-term infant,[8,9] other predisposing factors were considered. Based on the classification of kernicterus suggested by Shapiro,[10] and given the audiologic findings of a neural type hearing loss (auditory dys-synchrony/auditory neuropathy) with the presence of cochlear function, the diagnosis of bilirubin toxicity was considered a possible etiology. The presence of central hypotonia and arching movements further raised our concerns for kernicterus. Other potential risks for hearing loss in this patient include PPHN and cochlear toxicity of gentamicin; however, none of these other risk factors are associated with normal cochlear outer hair cell function and abnormal neural function as found in this case. Rather, these risks are typically associated with a peripheral type hearing loss involving the cochlear outer hair cells.[11] The potential displacement of bilirubin from albumin by ibuprofen could play a role, and clinicians should use this drug cautiously in patients at risk for kernicterus.

DISCUSSION

To properly document kernicterus, changes in the brain are confirmed at autopsy or by magnetic resonance imaging (MRI).[10] However, MRI may normalize over time.[10] In our case, we did not feel clinically justified to create the expense of an MRI for the family, so clinical criteria were applied. However, auditory brainstem responses have been used in previous reports as the primary method to document bilirubin-associated toxicity in newborns.[12,13] Kernicterus in its classic form is made up of auditory system dysfunction; athetotic or dystonic movement disorders; oculomotor disturbances, especially paresis of upgaze; and dental enamel hypoplasia of primary teeth.[14] The neurologic findings reflect damage to the most vulnerable areas of the brain, i.e. globus pallidus and subthalamic nucleus of the basal ganglia, and the Perkinje cells of the cerebellum.[14,15] However, auditory toxicity from bilirubin may occur as an isolated lesion at bilirubin levels previously considered safe.[14,15]

The complication of sensorineural hearing loss was examined in the 81 survivors from the Canadian arm of the Neonatal Inhaled Nitric Oxide Study. These patients had experienced severe respiratory failure due to PPHN, and they had been exposed to various other risk factors for ototoxicity, including aminoglycosides, vancomycin, furosemide, and high frequency ventilation.[16] None of these risk factors were important at the exposure level seen in this patient. Sensorineural hearing loss is a broad term, which includes different types of hearing loss. Sensory refers to a cochlear hearing loss, which is typically associated with abnormal DPOAEs. Neural refers to disorders of the VIII nerve; in these cases DPOAE results are typically normal but BAER waves are severely abnormal or absent. Although PPHN, ototoxicity, and auditory dyssynchrony/auditory neuropathy are all classified as sensorineural hearing losses in the broadest sense, the damaged areas of the auditory system are very different.

For PPHN, vancomycin, and aminoglycoside ototoxicity, DPOAE responses are abnormal, indicating damage in the cochlea. Auditory dys-synchrony/auditory neuropathy is a term presently used to describe a condition, found in patients who display auditory characteristics consistent with normal cochlear outer hair cell function and abnormal neural function at the level of the spiral ganglion cells/VIIIth (vestibulo-cochlear) nerve.[17]

Measures of free unconjugated bilirubin predict isolated hearing loss and cognitive dysfunction better than total serum bilirubin or total unconjugated bilirubin.[11-15,18-21] In preterm newborns, unbound bilirubin levels above 0.5 mg/mL are associated with auditory brainstem response changes, and kernicterus becomes likely above 1 mg/dL.[21] Many factors affect unbound bilirubin concentrations, including concurrent illness, central nervous system damage, serum albumin, and concurrent drugs or excessive lipids which may displace bilirubin from albumin binding. In our patient, a concurrent acute infectious process appeared to be occurring, but the albumin concentration of 2.9 g/dL was not particularly low as a risk for a high unbound bilirubin concentration. Intralipid infusions in our patient remained at 1 g/kg/day or less and serum triglycerides remained below 100 mg/dL. Concurrent drugs such as sulfisoxazole also displace bilirubin from binding sites, and have resulted in catastrophic several-fold increase in the incidence of kernicterus in clinical trials.[22] Bilirubin binding can be assessed by several different assays, but results from different assays do not always concur. Two assays that showed good agreement were Sephadex gel filtration and the peroxidase method.[19] This is important because studies correlating unbound bilirubin and kernicterus or comparing unbound- to total bilirubin as predictors of kernicterus generally involved one of these two assays.[19,20] The peroxidase method seems to be the most used and accepted in clinical trials. The procedure has historically used a serum dilution ratio of 1:41, but this dilution underestimates unbound bilirubin in the presence of competing ligands such as free fatty acids or drugs (e.g., sulfonamides), and the added serum may actually increase the binding of bilirubin to albumin.[19] This was discussed by Ahlfors in his study of ibuprofen-induced displacement of bilirubin from albumin.[4] In this study, he used a 1.6-fold sample dilution and 2 different peroxidase concentrations to maximize accuracy. The unbound fraction of bilirubin is 5- to 10-fold greater when the smaller sample dilution approach is taken.[19] Aranda, when challenging the significance of the bilirubin displacement by ibuprofen, noted absence of a displacement interaction using different assays.[7] However, the risk of false positive or negative tests for displacement of bilirubin from albumin is a concern, given the disparity between several assays for unbound bilirubin. In this regard, the results from the Ahlfors[4] study and the peroxidase assay method appear superior to the results of other studies. The peroxidase method in Ahlfors's study can be confirmed by using a known bilirubin binding displacing drug (e.g., sulfisoxazole) as a control to document bilirubin displacement and comparing the ability of ibuprofen to displace bilirubin to the known control, in this case sulfisoxazole.

Some studies cannot be considered equally as credible as the Ahlfors study for the following reasons: either they did not use the peroxidase assay to examine the ibuprofen displacement of bilirubin, or they did not use a known bilirubin displacer as a control. Also, human clinical trials and animal study data support the validity of the approach in that some have correlated unbound bilirubin with audiologic changes, using the peroxidase assay to determine unbound bilirubin concentrations.[14,15,18]

The use of ibuprofen in preterm infants for the purposes of closure of a PDA is particularly concerning, since the risk of kernicterus at lower TSB levels is greater in sick preterm infants, and unbound bilirubin appears to be the best predictor of auditory dys-synchrony/auditory neuropathy.[13] The risk of bilirubin displacement from albumin binding seems to be greatest when ibuprofen serum concentrations exceed 50 mg/L. Using recommended doses, peak ibuprofen concentrations were shown to exceed this threshold in several patients, whereas trough concentrations usually remained below 50 mg/L.[23] Depending on whether bilirubin displacement occurs rapidly when ibuprofen is present in serum, ibuprofen use may pose an unnecessary risk of kernicterus. This is especially unnecessary since

an alternative drug, indomethacin, has been shown not to cause displacement of bilirubin from albumin.[18] The advantage of ibuprofen over indomethacin for closure of a PDA is a reduced renal toxicity presenting as a temporary decrease in urine output and increase in serum creatinine.[7]

CONCLUSIONS

It is the authors' view that displacement of bilirubin by ibuprofen is a potentially serious problem. For near-term infants and jaundiced term infants, ibuprofen should be used only as a second-line agent for PDA, until the risk for kernicterus can be resolved. Ibuprofen for treatment of neonatal fever should be avoided unless further research for this indication demonstrates it is safe.

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