Indian Academy of Pediatrics (IAP)

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Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

Lead Author
Sen Sarma M

Co-Author
Yachha S K

UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

Upendra Kinjawadekar
IAP President 2023

GV Basavaraja
IAP President 2024

Remesh Kumar R
IAP President 2022

Vineet Saxena
IAP HSG 2022-23

Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

Upendra Kinjawadekar
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IAP nRICH team

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Vaman Khadilkar

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Srinivas Murki

Nitin K Shah

Tanu Singhal

Rhishikesh Thakre

Prakash Vaidya

SK Yachha

Ceftriaxone and unconjugated hyperbilirubinemia: Friend or foe?

Sen Sarma M[1], Yachha S K[2]

Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India[1], Department of Pediatric Gastroenterology, Hepatology and Liver Transplant, Sakra World Hospital, Bengaluru, India[2]

BASED ON ARTICLE

Amin SB. Bilirubin-Displacing Effect of Ceftriaxone in Infants With Unconjugated Hyperbilirubinemia Born at Term. J Pediatr. 2023 Mar;254:91-95. doi:10.1016/j.jpeds.2022.10.030.

SUMMARY

Ceftriaxone is usually contraindicated in unconjugated hyperbilirubinemia for the fear that it will displace bilirubin from albumin and predispose to kernicterus. The author aimed to evaluate the effect of intravenous (IV) ceftriaxone on free-bilirubin concentrations in infants with unconjugated hyperbilirubinemia born at term. A prospective study was performed with the inclusion criteria: infants born at term <7 days old with sepsis and receiving IV antibiotics for >3 days and resolving hyperbilirubinemia with total serum bilirubin levels between 6 and 12 mg/dL by day 4 of life. Free-bilirubin concentrations were measured by two types of peroxidase methods: conventional unbound bilirubin (UB) analyser and the new Zone Fluidics device that minimizes dilution. Free-bilirubin was assessed before (baseline) and 15 minutes after (follow-up) IV ceftriaxone administration on postnatal days 4 to 6. The Ka (L/mmol) was measured as: total serum bilirubin - free bilirubin/ free-bilirubin(albumin - total serum bilirubin + free bilirubin). In total, 27 infants were studied. An auditory brainstem-evoked response was measured at follow-up. The mean gestational age and birth weight of the 27 infants were 39.2 weeks and 3533 g, respectively. All infants were appropriate for gestational age at birth. Ten subjects (37%) were delivered via cesarean delivery. All infants had an Apgar score >7 at 5 minutes. All infants had culture-negative sepsis. Ceftriaxone was administered on mean postnatal day 5 (range 4-6). All infants had serum albumin >2.5 g/dL. The mean TSB at baseline was 9 (range 6-11.6) mg/dL. The calculated bilirubin albumin molar ratio was <0.5 for each individual infant. When measured by a UB analyzer, the mean serum free-bilirubin concentration (mg/dL) at follow-up was not significantly different from baseline. However, the mean serum free-bilirubin concentration (mg/dL) was significantly lower at follow-up compared with baseline when measured by the Zone Fluidics device. The free-bilirubin after 2 ceftriaxone administration/free-bilirubin at baseline before initiating the ceftriaxone ratio, an index of displacing effect, was 1.02 (95% CI 0.89-1.14) with the UB analyzer and 0.58 (95% CI 0.30-0.86) with the Zone Fluidics device. There were no significant differences in the bilirubin-albumin binding affinity (Ka) between follow-up and baseline when measured by the UB analyzer or Zone Fluidics device. The mean difference between follow-up Ka and baseline Ka was 2.34 ±28 L/mmol when measured with the UB analyzer and 19.7 ± 63 L/mmol when measured with the

Zone Fluidics device, suggesting no worsening of Ka after administration of ceftriaxone. All infants passed the automated auditory brainstem-evoked response test performed within 6 hours of IV ceftriaxone administration. All infants were discharged home on the same day they received IV ceftriaxone to complete the antibiotic course with IM ceftriaxone administered once daily by a home visiting nurse or in an outpatient pediatric clinic. The author concluded that cceftriaxone was not associated with a bilirubin-displacing effect in infants with mild unconjugated hyperbilirubinemia. Home therapy with once-daily intramuscular ceftriaxone may be an alternative option for management of the sepsis in asymptomatic infants with a mild unconjugated hyperbilirubinemia born at term [1].

COMMENTARY

Ceftriaxone is an excellent antibiotic for primary care in neonates for multiple reasons: 1) Ceftriaxone works principally against gram-positive and gram-negative organisms in neonatal sepsis. 2) it has excellent cerebrospinal penetration and can hence be used in neonatal meningitis, 3) has a long half-life and hence can be used as once daily parenteral administration and 4) intramuscular delivery has near similar plasma and pathogen inhibitory concentration as intravenous administration [2]. However, ceftriaxone is avoided in unconjugated hyperbilirubinemia as it is believed that bilirubin is displaced from albumin, resulting in higher free -bilirubin and potential neurotoxicity. In yesteryears, this information was mostly derived from in vitro studies of pooled umbilical cord samples [3,4]. From older studies, this knowledge was thereafter extrapolated to clinical practice. Ceftriaxone, a potentially useful drug was therefore deemed unsafe and underutilized. We are well aware that many in vitro and in vivo experiences do not match. Ceftriaxone is also unpopular in neonates with liver dysfunction. Ceftriaxone has a proclivity toward calcium precipitation, which leads to the formation of insoluble crystals in bile secretions precipitating biliary sludge and resulting in gall bladder sludge or calculi. Ceftriaxone >2 g/day may also result in impaired gall bladder contractility [5]. However, this phenomenon is self-limiting and resolves spontaneously on discontinuation of the drug. There are many ways to look at the literature on bilirubin-induced neurotoxicity. It has been shown earlier that if the baseline free-bilirubin concentration is very low, to begin with (mild unconjugated hyperbilirubinemia), the maximum displacement factor of up to 3 may not result in significant elevations of free-bilirubin concentrations. It has also been seen that in term 3 infants, free-bilirubin concentrations <2 mg/dL, as measured by the modified peroxidase method, are unlikely to be associated with acute or chronic bilirubin-induced neurotoxicity. An indirect evidence of a clinically non-significant displacing effect was provided by an in vitro study that demonstrated that a bilirubin–albumin molar ratio of <0.4 was not associated with free-bilirubin concentrations >2.0 mg/dL when using ceftriaxone concentrations of 225-250 mmol/L. There is a paucity of in-vivo studies. Martin et al studied the reserve albumin concentration as an estimation of displacement after intravenous ceftriaxone administration 50 mg/ kg. The study reported a decrease in the reserve albumin concentration by 58% at the end of infusion and by 37% at 90 minutes after infusion [6]. There are many strengths to this study. The author selected a homogenous cohort. Sepsis, a common neonatal problem was included in the study. Sepsis negatively influences the Ka. They compared two peroxidase methods, the older conventional (42-fold dilution) versus a recent specialised (2-fold dilution) method.

The specialized method is deemed to have greater accuracy and better results. Finally, to strengthen the proof of their hypothesis, they studied the auditory brainstem-evoked response. The author made a reasonable plea that intramuscular ceftriaxone can still be used in resource-poor countries without having to fear bilirubin-induced neurotoxicity. There are a few oddities that stand out as limitations. In an era where multicentre studies are in vogue, this manuscript stands out as a single-author experience. Such prospective studies need more validation. Only when similar results are reproduced from other centres, it will stand the test of time. Serum ceftriaxone levels were not measured for correlation. Neonates with liver dysfunction may have lower albumin. Does lower albumin predispose to greater bilirubin displacement? More studies are needed on the same. In this study, the auditory brainstemevoked response was performed only once after the first dose of ceftriaxone. One-time tests in neonates have limitations in interpretation. Bilirubin neurotoxicity is far a greater problem in preterms than term babies. The real dilemma of starting antibiotics arises actually in complicated patients. This study was performed in a niche group with lesser events. For the time being, it should be cautioned that the results from this study should not yet be extrapolated for preterms, term babies with moderate-severe unconjugated hyperbilirubinemia and babies with systemic illness other than sepsis.

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