

Summary of literature search on toxicity of cotrimoxazole in the neonates

Prepared by

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B. Pharm. 1954 L. M. College of Pharmacy, Gujarat University, Ahmedabad

M.S. (Pharmacology) 1957 College of Pharmacy, University of Southern California, Los Angeles, CA., U.S.A.

Ph.D. (Pharmacology) 1965 College of Pharmacy, University of Florida, Gainesville, FL., U.S.A.

Positions held from years 1965 to 2011-

1965-1966 (January) Assistant Prof. of Pharmacology Goa College of Pharmacy, Panaji, Goa.

1966-1974 (September) Senior Research Officer, Pharmacology V.P.Chest Institute, Delhi University, Delhi.

1974-1988 (November) Research Associate Professor, Department of Pharmacology, School of Medicine, University of Maryland, Baltimore, MD., U.S.A.

1988-1998 (July) Principal Investigator, Pharmacology, Department of Neurobehavioral Toxicology, United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD., U.S.A. Retired from full time employment

1998-2011 (December) Part time contractor (through Battelle Scientific Services, Chapel Hill NC, U.S.A.) at the Department of Neurobehavioral Toxicology, United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD., U.S.A.

Current: Total retirement

Background

Co-trimoxazole is a candidate antimicrobial agent for treating in the community settings the infections in neonates. However, it is not recommended in neonates (USA) or recommended with caution (WHO) due to an apprehension that the sulfamethoxazole component in cotrimoxazole may displace bilirubin from albumin and thus may increase the risk of kernicterus in neonates. How valid/evidence-based is this apprehension? The theoretical possibility arose because sulfisoxazole use in 1950s in the neonates was associated with kernicterus when used in 1950s. Is there any evidence that this may actually happen with sulfamethoxazole component of co-trimoxazole as well?

Specific Question: Does cotrimoxazole (trimethoprim and sulfamethoxazole combination abbreviated as CTX in the rest of this report) if administered in neonates cause displacement of bilirubin and increased risk of kernicterus?

If it does- are there any case studies, case series or historic data? What is the estimated risk?

Literature Search Strategy: Literature search strategy included the use of keywords and their combination. Search included Medline, Pub Med, Toxnet and information from WHO Bulletins. Also checked cross references from published papers that gave even a slightest hint about CTX-induced toxicity in neonates.

Key words and search terms: cotrimoxazole, trimethoprim, sulfamethoxazole , cotrimoxazole and neonates and jaundice, sulfamethoxazole and neonates and jaundice, trimethoprim and neonates and jaundice, cotrimoxazole-induced jaundice and neonates, trimethoprim and newborn babies, sulfamethoxazole and newborn babies, Trimethoprim and neonate kernicterus, sulphamethoxazole and neonate kernicterus

Pub Med- cotrimoxazole[All Fields] AND induced[All Fields] AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields]) AND ("jaundice"[MeSH Terms] OR "jaundice"[All Fields])

using newborn : cotrimoxazole[All Fields] AND induced[All Fields] AND ("jaundice, neonatal"[MeSH Terms] OR ("jaundice"[All Fields] AND "neonatal"[All Fields]) OR "neonatal jaundice"[All Fields] OR ("newborn"[All Fields] AND "jaundice"[All Fields]) OR "newborn jaundice"[All Fields])

In addition, phrases using key-words (such as development of kernicterus in neonates by cotrimoxazole or sulfamethoxazole) were put on Google search engine to gather relevant information.

We also inquired to the child health division in the WHO headquarters in Geneva which referred us to Dr. K. Hoppu who had investigated this topic for the WHO in 1990s. An inquiry was sent to him as well.

Summary of Search Results

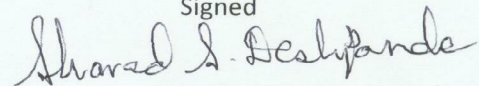
1. An extensive literature search covering a period of 40 years prior to March 2012 failed to find any reference/s that showed evidence of occurrence of any case of kernicterus associated with the clinical use of cotrimoxazole (CTX) in neonates .
2. In fact a report published in 2005 (Daveluy A. et al., Review of data related to side effects of drugs used in congenital toxoplasmosis. *Urotoxo* 2005; p.21) clearly states that the possibility that sulfamethoxazole in foetus and newborn could displace bilirubin from plasma binding sites and cause kernicterus to develop is currently theoretical.
3. Dr. Hoppu wrote to us that question of CTX interaction with bilirubin was important. However, during his inquiry in 1990s he was not able then to find any report of kernicterus caused by CTX. When approached, the manufacturers of CTX (Wellcome and Roche), informed him that they also did not have any published or unpublished reports. His very recent Medline search did not reveal any information either.
4. My extensive search of literature produced only one relevant in vivo study conducted in neonates (C. Springer, F. Eyal and J. Michel, Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. *J. Pediatrics*, 100, 647-650, 1982). The pharmacokinetic parameters of CTX were measured in 12 newborn infants of less than 3 days postnatal age following intravenous administration of daily therapeutic dose of CTX (trimethoprim 5 mg/kg, sulfamethoxazole 25 mg/kg) for 3 days to treat infection. The mean birth weight of neonates was 1800 g (range 840 to 3100 g) and mean gestational age of 33 weeks (range 28 to 40 weeks). The measurements included serum half life of active trimethoprim, unmetabolized sulfamethoxazole and creatinine clearance. The results showed that the serum average sulfamethoxazole concentration measured at 24 hours was 20 µg/ml., whereas with repeated doses for 3 days, average drug level in serum measured 24 hours after the last dose was 42 µg/ml. No untoward side effects or kernicterus were seen in these neonates after repeated intravenous administration of the drug combination.
5. The same authors studied the effect of sulfamethoxazole on the bilirubin binding capacity (an assay done in vitro where various doses of CTX are added to the serum isolated from neonatal blood and the quantity of bilirubin displaced from its albumin binding site is measured). It was observed that sulfamethoxazole concentration of 400 µg/ml (nearly 10 to 20 times the therapeutic concentration reached in neonates) was required to displace bilirubin and reduce the serum bilirubin binding capacity. It is extremely unlikely that dangerous concentrations of sulfamethoxazole in serum approaching 400µg/ml would ever be reached in the clinical use of CTX for neonatal sepsis or pneumonia. These findings provide a safe basis for continued use of CTX without any overt toxicity.
6. In an extensive global review (Gutman L. T., The use of trimethoprim-sulfamethoxazole in

children: A review of adverse reactions and indications. Ped. Inf. Dis. **84**, 349-357,1984), the author reviewed several published reports on children less than 2 years of age receiving CTX for 7 to 10 days. A review of 9 separate reports that included a total of 2061 cases revealed no major side effects of any kind. It was further stated that "sulfamethoxazole is particularly inefficient compared with other sulfonamides in displacing bilirubin from albumin".

This reviewer of the literature did not find substantiating experimental or clinical evidence that warrants discontinuation of CTX use in neonates.

It is, therefore, opinion of this reviewer that an evidence linking CTX to toxicity in neonates is lacking, On the contrary, the only in vivo study reports no occurrence of bilirubin displacement or kernicterus.

Signed

A handwritten signature in cursive script that reads "Sharad S. Deshpande". The signature is written in dark ink and is positioned below the word "Signed".

(Dr. Sharad S. Deshpande Ph.D.)