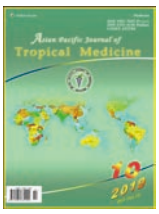

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Should pyridoxine be given to breastfed infants whose mothers are on isoniazid?

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A mother was recently started on isoniazid and rifampicin for latent tuberculosis infection. She was breastfeeding her 1-month-old infant. There was no indication to treat the child with anti-tuberculous therapy. As isoniazid can be present in breast milk, question was raised whether the baby should receive pyridoxine supplementation to prevent peripheral neuropathy or seizures. There were variable views in the management approach due to uncertainties of evidence in this topic. The authors discovered vast differences in clinical practice even among the paediatric infectious diseases experts.

Tuberculosis continues to be a threat to the global health, being one of the most important cause of mortality and morbidity among adults[1]. About 10 million people are newly diagnosed to have tuberculosis on a yearly basis[1]. The mainstay of tuberculosis treatment is with isoniazid, rifampicin, pyrazinamide and ethambutol. Isoniazid and rifampicin form the backbone of anti-tuberculous therapy and they are usually continued for minimum 6 months depending on the site and severity of infection.

One of the recognised adverse effects of isoniazid is peripheral neuropathy because it induces pyridoxine deficiency or by competitive inhibition of pyridoxal action[2,3]. Pyridoxine or vitamin B6 plays an important role in neuronal cell survival because of its coenzyme activity in neurotransmitter biosynthesis[4]. Deficiency of pyridoxine has long been attributed as a cause of peripheral neuropathy although the evidence is scant[2]. Supplementation of pyridoxine is therefore perceived to be crucial in the prevention of peripheral neuropathy especially among high risk groups *i.e.* pregnant/breastfeeding mothers, people living with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease or renal failure[5].

The occurrence of peripheral neuropathy due to pyridoxine deficiency in association with isoniazid in children is rare, up to 0.7%[6-8]. It is related to the dose of isoniazid, *i.e.* the higher the dose of isoniazid, the higher is the incidence of peripheral neuropathy[2]. There were 2 case reports indicating that isoniazid, when given to a young infant, can induce pyridoxine responsive seizures[9,10]. Multiple case series have also implicated isoniazid overdose as a cause of neurotoxicity[11].

If a mother is prescribed with isoniazid (*e.g.* for the treatment of latent tuberculosis infection) and breastfeeding her child simultaneously, whether or not the infant (who is not treated with isoniazid) should be supplemented with pyridoxine remains a controversial question[12]. In this review article we asked a structured clinical question: does giving pyridoxine [intervention] prevent peripheral neuropathy or seizures [outcome] in a breastfed infant (who is not started on isoniazid) [patient] whose mother is on isoniazid?

A literature search was performed using Medline, Pubmed, Cochrane Library, Embase, Google Scholar and Toxnet. The search period employed was between January 1950 and August 2019. These databases were searched for synonyms of "isoniazid", "pyridoxine", "lactation", "breastfeeding", "breast milk", "neuropathy", "seizure" and "tuberculosis". Boolean operators AND, OR and NOT were used within the search fields. Truncation (*) was used in order to find out variants with one or more letters *e.g.* breast*. Only articles in English and publications on human were included. We also manually scanned reference lists of pertinent studies, reviews, editorials and websites to retrieve any other relevant articles.

A total of 25 articles were identified initially and they were independently analysed by two authors (KFN and SB). Nine out of the 25 journal articles were excluded as there were no systematic review, experimental studies (randomised and non-randomised controlled trial), cohort, case-control, cross-sectional studies, case series or case reports pertinent the outcome

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(peripheral neuropathy and/or seizure) and population group of interest (breastfed infants who were not treated with isoniazid but their mothers were on isoniazid). The remaining 16 articles were 7 literature review papers and 9 national and international guidelines. They only discussed the topic of interest briefly and did not address our clinical question directly.

Various guidelines were identified and their recommendations were scrutinised. American Thoracic Society guideline recommends supplementation of pyridoxine in breastfeeding infants whose mothers are taking isoniazid but there is no recommendation from World Health Organization (WHO), National Institute for Health and Clinical Excellence (NICE), British National Formulary (BNF) and Specialist Pharmacy Service[5,13-18]. BNF states that breastfed infants of mothers on isoniazid should be monitored for toxicity[17]. Electronic Medicines Compendium (eMC) meanwhile suggests that administration of pyridoxine may be considered in breastfed infants when isoniazid is given to nursing mothers[19]. The Italian Pediatric Tuberculosis Study Group mentioned in their guidance on neonatal tuberculosis management that newborns who were breastfed by mothers on isoniazid do not require pyridoxine supplementation[20]. Inconsistencies among national and international guidelines recommendations imply that there is paucity of evidence in this area.

Isoniazid present in breast milk is estimated to be 6.4%-25.0% of an infant dose[21]. Peak isoniazid level in the breast milk occurs within 3 hours from maternal oral intake of isoniazid[22-25]. The half-life of isoniazid in breast milk was between 4 hours and 6 hours[24,25]. Only 1.2% of isoniazid is transferred to the exclusively breastfed infant, estimated to be 89.9 mg/kg/day in comparison with recommended treatment dose of isoniazid which is 10 mg/kg/day[25-27].

The rate of isoniazid acetylation is determined by genetic expression of hepatic N-acetyltransferase 2 (NAT2), rendering the population into fast and slow metabolisers[28]. A physiologic-based pharmacokinetic study calculated that oral exposure of isoniazid due to breastfeeding was 0.15 mg/kg/day among infants of fast metabolising mother (relative infant dose 0.2%) and 0.37 mg/kg/day in infants of slow metabolising mothers (relative infant dose 0.5%) when maternal isoniazid dose was 300 mg daily[28]. If the mothers were on 900 mg of isoniazid every 3 days, the oral exposure dose in infants of fast metabolising mothers was 0.44 mg/kg/day (relative infant dose 0.6%) and 1.12 mg/kg/day in infants of slow metabolising mothers (relative infant dose 0.5%)[28]. Relative infant dose in this study was defined as the ratio of total oral dose of the child to the oral dose of the mother[28].

According to most guidelines, mothers who are breastfeeding their children whilst on isoniazid should be taking pyridoxine[5,13-15,17]. Instead, eMC stated that pyridoxine supplementation for breastfeeding mothers was optional[19]. The newborn usually has higher concentration of pyridoxine (22-87 ng/mL) than his or her mother (13-51 ng/mL) at a ratio of 2:1 and the pyridoxine store in the infant at birth is dependent on maternal intake[29]. Pyridoxine is readily excreted into breast milk and the amount found in the breast milk is directly proportional to maternal intake[30-37]. Pyridoxine concentration in the breast milk peaks at 3-8 hours post-ingestion[31-33]. Breastfed infants aged below 3 months are expected to achieve current recommended dietary allowance of 0.2 mg/day if the mothers were given 20 mg/day of pyridoxine[34,38].

There is no evidence to support pyridoxine supplementation in breastfed infant (who is not treated with isoniazid) whose mother is on isoniazid therapy. The amount of isoniazid transferred to an infant *via* breast milk from mother is minimal, well below infant treatment dose and unlikely to cause clinically significant adverse effects. Breastfeeding mothers treated with isoniazid should receive pyridoxine but their infants who are not on isoniazid therapy do not require pyridoxine supplementation. However, there should be regular monitoring of these infants for short- and long-term side effects when breastfeeding mothers are treated with isoniazid.

Conflict of interest statement

No potential conflicts of interests with respect to authorship and/or publication of this article.

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Authors' contribution

KFN and SB contributed to design, analysis and interpretation, drafted, critically revised, gave final approval and agrees to be accountable for all aspects of work ensuring integrity and accuracy. SB conceptualised the work.

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