Epilepsy & Behavior Case Reports 2 (2014) 22–23

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Probable topiramate-induced diarrhea in a 2-month-old breast-fed child — A case report ☆

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ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 20 December 2013
Accepted 23 December 2013
Available online 20 January 2014

Keywords:
Topiramate
Breast-feeding
Pharmacokinetics
Adverse drug reaction
Diarrhea

ABSTRACT

An infant developed a severe condition of recurrent and persistent watery diarrhea at 40 days of age. The child had been partially breast-fed, and the mother used topiramate for epilepsy. Hospital examination excluded a viral or bacterial infection and failed to identify any other potential cause. After two weeks, topiramate exposure was suspected to be the cause, and breast-feeding was suspended. The diarrhea ceased within 2 days. Analysis of the breast milk showed a topiramate concentration of 15.7 μmol/L (5.3 μg/mL). There is little information on the use of topiramate in breast-feeding women. The potential effects on the children are not known. Topiramate passes into breast milk, and the concentration may equal the therapeutic plasma concentration. In this case, the infant may have ingested up to 40% of the mother's weight-adjusted dose. Diarrhea is a well-known adverse reaction to topiramate and has the potential to cause serious electrolyte disturbances in neonates and infants. The condition improved rapidly after suspension of breast-feeding. Topiramate in breast milk may reach levels that cause adverse effects in infants. Based on the adverse reaction profile of topiramate and the milk concentration, the diarrhea was assessed as a probable adverse drug reaction in the infant.

1. Introduction

Topiramate is one of the newer antiepileptic drugs and is also approved for migraine prophylaxis [1]. There is little information concerning topiramate use in breast-feeding women, but case reports indicate that it is transferred into human milk and that milk concentrations may equal those in maternal plasma [2–5]. We report a case of long-lasting diarrhea in a breast-fed infant exposed to topiramate.

2. Case report

A patient with epilepsy, aged 31, had been treated with topiramate 100 mg/day for several years. The treatment was continued unchanged throughout her pregnancy with good therapeutic effect. A healthy girl with a birth weight of 2735 g was born after an induced birth 2 days after term. The topiramate treatment was continued while breast-feeding. In order to reduce infant exposure to topiramate, two daily breast milk meals were replaced with formula meals a week after birth. The baby initially thrived and had a normal development. At 40 days of age and body weight of 4735 g, she became ill, with 8–10 watery, foamy stools a day. No other family member had diarrhea or gastrointestinal upset. Her weight gain rate eventually declined, and she was referred to the hospital outpatient clinic. Relevant differential diagnoses such as infection or somatic cause of the diarrhea were excluded, but she still suffered from diarrhea. After 18 days of frequent, watery stools, the general practitioner suspected a causal relationship with topiramate, and breast-feeding was suspended. Within 2 days, the frequency was reduced to 2–3 stools a day, and the mother observed more solid feces, with smell and color returning to normal.

While breast-feeding was suspended, the mother used a breast pump and stored the milk in a freezer (−20 °C). She gave her consent to have the milk analyzed for topiramate, and the milk was sent for analysis after a storage time of 4.5 months. A sample was analyzed for topiramate by fluorescence polarization immunoassay based on the competitive binding principle (Innofluor Topiramate Assay System, Seradyn, Indianapolis, IN, U.S.A.). The assay system was used on a TDx

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2213-3232/$ – see front matter
http://dx.doi.org/10.1016/j.ebcr.2013.12.006

analyzer (Abbott, Abbott Park, IL, U.S.A.). The lower limit of detection was 0.3 μg/mL (0.89 μmol/L). Precision studies have shown a coefficient of variation (CV) of <5%. The analysis showed a topiramate concentration of 15.7 μmol/L in the mother's milk, corresponding to 5.3 μg/mL. The plasma concentration in the child was not measured.

3. Discussion

Breast-feeding is generally recommended, even if the mother is using antiepileptic drugs, but adverse effects in the child may necessitate reduction or withdrawal of breast-feeding. Little is known regarding the use of topiramate in breast-feeding women and the risk of adverse effects in their children. Animal studies have demonstrated the excretion of topiramate in milk [6]. While there are no systematic studies of topiramate excretion in human milk, some study results indicate a considerable transfer. The product information does not state explicitly that topiramate is contraindicated during breast-feeding but advises that a risk/benefit assessment should be made before deciding whether to stop breast-feeding or to withdraw topiramate [6].

A literature search in Medline Ovid, EMBASE, handbooks, and databases on drugs and lactation provided little additional information. Published case reports of topiramate use while breast-feeding [2–5] include a total of only eight patients. A general finding is transfer into breast milk and milk/plasma ratios of 0.6–1.1. Concentrations of topiramate in the breast milk of three patients were 1.6–3.6, 6.9, and 13.7 μmol/L (0.5, 2.3, and 4.7 μg/mL), respectively, after daily doses of 150 or 200 mg, measured 14–97 days after delivery. The weight-adjusted relative dose to the infant was estimated at 3–23% of the maternal dose. Two of the mothers were using carbamazepine, a substance known to induce the metabolism of topiramate [3]. Another case report found a topiramate concentration of 3.1 μg/mL (9.1 μmol/L) after a daily dose of 150 mg in one patient 12 days after delivery [5]. We have not found any studies investigating stability of topiramate in breast milk, but topiramate in human plasma stored for a period of 1 month at −80 °C has shown that the drug is stable [7]. Topiramate is not metabolized to any great extent unless the patient is using concomitant CYP enzyme inducers [6].

The child's plasma concentration will depend on the amount of drug in the milk, the amount absorbed from the intestine of the child, and the child's ability to eliminate the compound. In five of six mother/infant pairs, plasma levels of topiramate in the infants were 10–20% of the maternal plasma levels and in one case could not be detected [2,3]. In the case reported here, a milk concentration of 5.3 μg/mL (15.7 μmol/L) and an estimated daily intake of 450 mL of mother's milk in an infant weighing 4735 g would result in a daily dose of 0.5-mg/kg topiramate. Other case reports have described theoretical infant dosages of 0.1–0.7 mg/kg/day [3] and 0.6 mg/kg/day [5]. The mother's body weight was 70 kg, and the relative infant dose was estimated at 0.35. The infant described here may have ingested a topiramate dose of 35% of the mother's weight-adjusted dose.

Withdrawal of breast milk was associated with rapid clinical improvement of the child's condition, supporting the theory of an adverse drug reaction. Diarrhea is a well-known and very common adverse reaction to topiramate [6], and the infant's condition improved upon withdrawal of topiramate. The diarrhea was assessed as a probable adverse reaction to topiramate in the breast milk. Other case reports describing topiramate use in breast-feeding women do not describe side effects in the children. To our knowledge, this is the first report of probable topiramate-induced diarrhea in a breast-fed infant. Infant diarrhea increases the risk of electrolyte disturbances, and topiramate in the breast milk may be a hitherto unknown risk factor.

The case has been reported to the National Health Authorities in Norway, registered as number NO-NOMAADVRE-RELISS-2008-5232.

Conflict of interest

The authors have received no funding to write the manuscript and have no conflicts of interest.

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