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Secretion of Dantrolene into Breast Milk after Acute Therapy of a Suspected Malignant Hyperthermia Crisis during Cesarean Section

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IMMEDIATE intravenous administration of dantrolene is the pharmacologic first line treatment of malignant hyperthermia (MH) crisis.[1] There exist extensive data about its pharmacology and its placental transfer when administered during pregnancy and delivery.[2,3,4] However, it was unclear whether and for what duration dantrolene is detectable in human breast milk after intravenous administration of therapeutic doses.[5]

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Case Report

Tachycardia, respiratory acidosis, and hyperthermia (39.8°C) developed in a 37-yr-old pregnant woman (62 kg body weight) shortly after the induction of general anesthesia for urgent cesarean section because of oblique fetal position. Succinylcholine and thiopental were used for the induction of anesthesia, which was maintained with oxygen/nitric oxide and isoflurane, 0.4%. Despite immediate discontinuation of isoflurane administration and hyperventilation with oxygen, 100%, the symptoms did not vanish, and an MH crisis was suspected.

Intravenous dantrolene (160 mg) was administered after the umbilical cord was clamped and after the delivery of a healthy and obviously unaffected newborn (birth weight, 3.1 kg; gestational age, 36 weeks; Apgar score, 8 at 1 min of age, 10 at 5 min of age) was accomplished. Postoperatively, the patient was transferred to the intensive care unit, where intravenous dantrolene was continued in decreasing doses for 3 days until full recovery (560 mg on day 1, 320 mg on day 2, and 80 mg on day 3). Because of potential exposure of the newborn to dantrolene, on day 1 after delivery the question arose of whether breast feeding could be allowed. Because reliable data were not found in the literature, written informed consent was obtained from the mother to determine dantrolene concentrations in her breast milk. Dantrolene concentrations were measured using an HPLC-technique according to

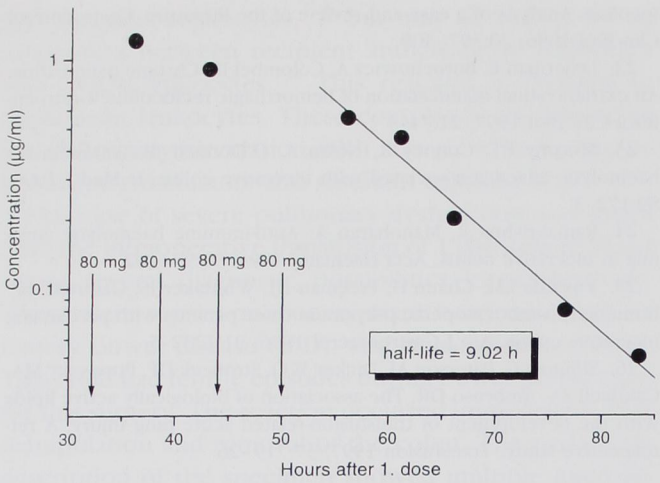

Fig. 1. Estimation of half-life of dantrolene in breast milk by log-linear fitting of the terminal elimination phase (dantrolene measured in breast milk by HPLC, reverse-phase high-pressure liquid chromatographic column, by in-line ultraviolet absorption spectrometer; detection limit, 0.02 μg/ml).

Katogi *et al.*[6] in a registered laboratory of clinical chemistry with special expertise in dantrolene determinations (Dr. H. Sirowej, Dortmund, Germany).

As expected, dantrolene was found in the breast milk and concentrations were measured, ranging from 1.2 μg/ml on day 2 to 0.05 μg/ml on day 4. Based on the concentrations observed after the last bolus administration of dantrolene, the half-life of dantrolene in breast milk was calculated to be 9.02 h using a log-linear fitting of the terminal elimination phase (fig. 1).

Six months after the event, *in vitro* contracture testing using halothane and caffeine according to the protocol of the European MH Group[7,8] did not confirm the suspected MH of the mother, who was clearly classified as MH nonsusceptible.

Discussion

Until now, no data were available about the secretion of dantrolene into human breast milk after intravenous administration of therapeutic doses to women during labor. Therefore, a potential influence of dantrolene on breast-fed neonates in such a case was unclear. Nausea, vomiting, fatigue, and muscle weakness are known side effects of therapeutic doses in adults and might also potentially occur in breast-fed newborns.

In our patient, the highest concentration of dantrolene in breast milk (1.2 μg/ml) was detected 36 h after the first intravenous bolus of 160 mg dantrolene (day 2 after delivery, when breast-feeding normally would have been started). At that time, the total dose administered was 720 mg. Even if 70% of orally administered dantrolene is expected to enter the circulating blood (80 ml/kg) by gastrointestinal absorption,[11] the resulting dantrolene peak levels (<0.5 μg/ml) after breast-feeding are assessed to be far less than those described as uneventful after the transfer of dantrolene across the placental barrier.[5,9,10] Morison[9] found dantrolene in venous cord blood (1.39 μg/ml) without obvious side effects in neonates, and also Shime *et al.*[5] described neonatal dantrolene serum concentrations of 0.72 ± 0.36 μg/ml (half-life, 20 h) without adverse effects in newborns. In a maternal-fetal sheep model, no relevant adverse effects of intravenously administered dantrolene (1.2 mg/kg and 2.4 mg/kg respectively) could be shown.[10] Moreover, based on the determined half-life of 9.02 h for dantrolene in breast milk, breast-feeding can be expected to be safe for the newborn 2 days after discontinuation of intravenous dantrolene administration in the mother.

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The Use of Inhaled Sevoflurane for Endotracheal Intubation in Epiglottitis

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ACUTE epiglottitis is a serious infection of the supraglottic structures, which carries the potential for lethal, total airway obstruction necessitating urgent airway management. In epiglottitis, a protocol that involves tracheal intubation after administration of general anesthesia induced by inhalation anesthetic has been recommended.[1] However, the airway obstruction may worsen or become complete as the patient becomes anesthetized or when the airways are manipulated. Sevoflurane has been reported to have a minimal effect on respiratory mechanics, with little airway irritation when used for anesthesia induction.[2] We describe three cases of epiglottitis necessitating urgent airway management in which tracheal intubation was performed successfully during administration of sevoflurane inhalation anesthesia.

Case Report

Case 1

A previously healthy, 15-yr-old boy was first admitted to a local hospital for hoarseness and difficulty in swallowing with no respiratory symptoms. With rapidly progressing symptoms, he was transferred to our institution. At admission he was distressed, unable to speak, had difficulty swallowing, and had moderate difficulty breathing while in the sitting position and while leaning forward. His temperature was elevated (38°C), but his erythrocyte count was normal. Indirect laryngoscopy revealed a large, swollen epiglottis. Glycopyrrolate (0.2 mg) was administered intravenously, and the patient was transferred to the operating room. He was placed in a semisitting position. Anesthesia was induced by mask inhalation of high concentrations of sevoflurane (up to 5%) in 100% oxygen through a Bain circuit. Spontaneous breathing was sustained. When relaxation for intubation was adequate, a size-6 endotracheal tube was passed through an extremely swollen arytenoid region and edematous epiglottis orotracheally. After taking blood and throat culture samples, intravenous cefuroxime (1.5 g × 3) was administered. Subsequent to intubation, he was transferred to the intensive care unit.

Case 2

A 40-yr-old, otherwise healthy man was admitted to the emergency room. He had a sore throat, a fever, and progressive difficulty breathing for 3 days. At admission his temperature was elevated (39°C), he was unable to swallow, and he used his accessory muscles for breathing. During indirect laryngoscopy, his epiglottis was extensively swollen. After glycopyrrolate (0.2 mg) was administered intravenously, anesthesia was induced while the patient was in the sitting position using a high concentration of sevoflurane (up to 7%) and 100% oxygen. The patient was slowly assisted to a supine position and a size-6.5 endotracheal tube was introduced through the swollen and edematous arytenoids and epiglottis orotracheally. The patient was transferred to the intensive care unit.

Case 3

An obese, 54-yr-old woman with a history of hypothyroidism was admitted with a sore throat, a high fever, and progressive difficulty breathing. She was sitting, leaning forward, using all her accessory respiratory muscles, was drooling, was unable to swallow, had inspiratory stridor, and her speech was hoarse. After a sevoflurane induction performed in a fashion similar to the previous cases, a size-7 endotracheal tube was inserted uneventfully using direct vision through the swollen arytenoids and epiglottis. The patient was transferred subsequently to the intensive care unit.

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