J Anesth (2010) 24:935–937
DOI 10.1007/s00540-010-1004-4

CLINICAL REPORT

Severe methemoglobinemia after dental anesthesia: a warning about propitocaine-induced methemoglobinemia in neonates

Yukari Doko · Hiroshi Iranami · Keisuke Fujii · Akinori Yamazaki · Manabu Shimogai · Yoshio Hatano

Received: 25 January 2009 / Accepted: 16 July 2010 / Published online: 13 August 2010

Abstract Methemoglobinemia is a fatal complication of local anesthesia. We describe a case report of female neonate who developed severe methemoglobinemia after extraction of neonatal teeth conducted with general anesthesia plus local injection of Citanest-Octapressin® (propitocaine of approximately 10 mg/kg). Central cyanosis appeared within an hour after surgery. The percentage of methemoglobin reached up to 43.9%. Not only pediatric dentists but also anesthesiologists generally agree with the idea that local anesthesia provides various benefits in painful procedures in neonates. However, this case may serve as a warning when using Citanest-Octapressin®, which is still commercially available for neonatal patients.

Keywords Dental anesthesia · Local anesthetics · Methemoglobinemia · Neonate

Introduction

Regional anesthesia and peripheral nerve blocks have become routine procedures in general anesthesia for infants, but potential toxicities of local anesthetics is a concern [1]. This consideration might be well known by anesthesiologists and pediatric dentists. Among the several considerations in pediatric dental surgery, each specialist has priorities with regard to potential toxicities related to local anesthetics: anesthesiologists may consider that local anesthesia for the gingiva provides important preemptive analgesic effects, and pediatric dentists may consider that it provides minimal surgical bleeding. We describe a female neonate who developed an acquired methemoglobinemia following the local injection of Citanest-Octapressin® for the extraction of neonatal teeth. This case may serve as a warning regarding local-anesthetic-induced methemoglobinemia in neonates who undergo extraction of neonatal teeth.

Y. Doko (✉) · H. Iranami · K. Fujii · A. Yamazaki · M. Shimogai
Department of Anesthesiology, Japanese Red Cross Society Wakayama Medical Center, 4-20 Komatsubara-dori, Wakayama, Wakayama 640-8558, Japan
e-mail: yukari_d@khaki.plala.or.jp

H. Iranami · Y. Hatano
Department of Anesthesiology, Wakayama Medical University, 811-1 Kimiidera, Wakayama, Wakayama 641-8509, Japan

Case presentation

An 18-day-old girl was referred to the pediatric dental department by her attending pediatrician for evaluation of erupted neonatal teeth on maxillary and mandibular incisors. She was born full term at 40 weeks and 2 days and had a birth weight of 3,136 g (Apgar score 9/10), but she gradually developed congestive heart failure. At day 8, reconstruction of the aorta with ductal division was performed for the coarctation of the aorta with patent ductus arteriosus. General anesthesia was administered with a balanced anesthesia using fentanyl, midazolam, and isoflurane.

During the perioperative period, no hemoglobinopathy was detected. The postoperative course was uneventful but for difficult breast feeding due to her neonatal teeth. Examination by the pediatric dentist revealed that the position of the erupted teeth was at the maxillary and mandibular incisors, and the gingiva surrounding both teeth was infected. Difficult breast feeding and possible occurrence of endocarditis of gingival origins led to the decision to extract the neonatal teeth at day 26. The anesthesiology consultation revealed no contributory findings except for

the neonatal teeth with infected gingiva. The patient's blood count and blood chemistry showed no abnormalities. Her body weight was 3,138 g. Electrocardiogram, indirect systemic blood pressure, pulse oximetry (SpO_2, Nellcor N-550, Tyco International. Ltd. USA), and rectal temperature were monitored. Anesthesia was induced with thiopental 20 mg IV, and tracheal intubation was facilitated with vecuronium 0.2 mg IV. Anesthesia was maintained with isoflurane 0.5% and nitrous oxide ($FiO_2 = 0.3$). Prior to teeth extraction, approximately 0.5 ml of Citanest-Octapressin® (Dentply-Sankin K.K. Tokyo, Japan) was injected in the gingiva around each neonatal tooth (total 1 ml containing propitocaine 30 mg and felypressin 0.03 U). Teeth were extracted with rongeur forceps. No curettage of the extracted sites was performed. The tracheal tube was removed uneventfully after administration of neostigmine 0.33 mg and atropine 0.17 mg. The surgical and anesthesia durations were 10 and 48 min, respectively. SpO_2 values ranged from 98 to 100% throughout the anesthesia, and no cyanotic appearance was observed. The patient gradually developed central cyanosis immediately after transfer to the neonatal intensive care unit (NICU), but SpO_2 remained at 100% for the first 30 min, followed by an abrupt decrease to 93%. Cyanosis was unresponsive to oxygen therapy of 3 l/min via face mask. Arterial blood sampled 2 h after the end of anesthesia revealed pH 7.417, partial pressure of oxygen in arterial blood (PaO_2) 298 mmHg, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) 30.6 mmHg, base excess (BE) −1.2 mmol/l, hemoglobin 91.4%, and methemoglobin 43.9% (ABL 700, Radiometer Medical ApS., Denmark). From these data, acquired methemoglobinemia was diagnosed as the cause of the postoperative cyanotic episode. NICU physicians determined the patient should receive methylene blue 0.8 mg/kg IV twice, with interval of 1 h. A 1% solution of methylene blue (Wako Pure Chemical Industries, Ltd. Japan) was made in the pharmacy department using distilled water. The percentages of methemoglobin after the first and the second methylene blue therapies were 9.1 and 3.5%, respectively. After the second treatment, SpO_2 increased to 98% from 93% under the same condition of oxygen therapy, and the central cyanosis disappeared. The NICU physicians performed the methylene blue therapy immediately after acquisition of informed consent from the patient's parents without waiting approval from the ethics committee of our institution. After treatment, the patient's postoperative outcome was uneventful.

Discussion

This patient developed an acquired methemoglobinemia after extraction of neonatal teeth conducted with general anesthesia plus the local injection of Citanest-Octapressin®. The central cyanosis appeared within an hour after the local injection, but the decrease in SpO_2 was delayed for another 30 min. A conventional pulse oximeter (but not Co-oximeter) displays estimated values of oxyhemoglobin percentages but cannot detect other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin [2]. Therefore, the limited function of the conventional pulse oxymeter was the reason for the time lag between the appearance of central cyanosis and the decrease in SpO_2. The patient's methemoglobinemia was unresponsive to oxygen therapy, but she was successfully treated with methylene blue IV administration.

Numerous agents have the potential to oxidize hemoglobin directly and indirectly, but Citanest-Octapressin®, used for local anesthesia, was considered the most probable cause of methemoglobinemia in this patient. Citanest-Octapressin® contains propitocaine (relates to prilocaine) as an anesthetic and felypressin as a vasopressor. Case reports indicate that local injection of prilocaine as well as application of lidocaine–prilocaine cream (EMLA) has the possibility of causing methemoglobinemia in infants, especially in neonates [3–7]. According to the literature review regarding prilocaine-induced methemoglobinemia in dental surgeries, cyanosis appeared a couple of hours after local injection of prilocaine (approximately 8–10 mg/kg), and the percentages of methemoglobin ranged between 10% and 38% [3]. In this patient, the pediatric dentist performed local injection of Citanest-Octapressin® 0.5 ml in each gingiva along the neonatal tooth. The injected volume of 0.5 ml in the gingival did not seem to be large, but administered propitocaine resulted in the overdosage (10 mg/kg; recommendation dosage <8 mg/kg) [3]. Cyanosis appeared within an hour, and the percentage of methemoglobin was as high as 43.9%. In addition, fetal hemoglobin is more vulnerable to oxidation than is adult hemoglobin [8]. Therefore, the Citanest-Octapressin®-induced methemoglobinemia in this patient was considered severe.

Indications for extraction of neonatal teeth include hypermobility, difficulties during breast feeding, traumatic ulcerations on tongue, frenulum, and lips, and inflammation [9]. An important consideration when deciding to extract neonatal teeth is the potential risk for hemorrhage, because neonates tend to develop hypoprothrombinemia by vitamin K deficiency [10]. Guidelines for pediatric dental surgeries recommend either adequate injections of local anesthetics containing vasopressors or gauze compression as preferable maneuvers for hemostasis whether patients received general anesthesia or not [11, 12]. Although several case reports regarding local-anesthetic-induced methemoglobinemia in dental practices have been explored, this complication is likely to be underrecognized and rare among pediatric dentists [3]. However, pediatric dentists should have no

reason to use Citanest-Octapressin® instead of other, safer, local anesthetics, such as lidocaine containing epinephrine. In some sense, the occurrence of methemoglobinemia was an inevitable result of an overdose of Citanest-Octapressin®. However, it is also true that the patient's background may have led to the decision to use preoperative local injection with Citanest-Octapressin® in this case. Further, it is generally accepted that peripheral nerve blocks and local anesthesia in pediatric patients, including neonates undergoing general anesthesia, is a safer procedure than in adults [13]. EMLA has been suggested to ameliorate procedural pain, such as central venous catheterization, circumcision, and heel lance [14, 15]. On the other hand, an overdose with EMLA has been reported to cause methemoglobinemia in neonates [4, 5, 7].

Effective treatment for methemoglobinemia includes methylene blue infusion, exchange transfusion, ascorbic acid administration, and conservative strategies [16]. In our case, the NICU physicians initiated methylene blue infusion after acquiring informed consent from the patient's parents without waiting the approval of the institutional ethics committee. However, methylene blue infusion requires approval of the ethics committee, which has a great possibility of delaying treatment. Guay recommends that benzocaine should no longer be used, and that prilocaine should not be used in children younger than 6 months old [16]. Citanest-Octapressin® is still commercially available in Japan. This case suggests that both anesthesiologists and pediatric dentists should always be aware of the common risk that using Citanest-Octapressin® in neonatal dental surgeries has a great possibility of causing methemoglobinemia.

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