Propofol-Induced Green Breast Milk: A Case Report

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INTRODUCTION

Propofol is indicated for the induction and maintenance of general anesthesia, for sedation during intensive care, and for conscious sedation during surgical and diagnostic procedures.[1] Propofol undergoes extensive metabolism in the liver to form water-soluble metabolites that are renally excreted.[1] Some of the metabolites have been associated, in a multitude of case reports, with green discoloration of the patient's urine.[2-9] Propofol is also highly lipophilic.[1] It has been reported that propofol passes minimally into maternal breast milk.[10] One previous publication reported the occurrence of green breast milk after propofol administration, although the authors were unable to confirm the presence of propofol in the breast milk by laboratory analysis.[11] Here, we present another case report of green breast milk following propofol administration and discuss the pharmacokinetic characteristics of this drug that could explain its possible excretion into breast milk. We also suggest a diligent approach to analysis and care for future cases.

CASE REPORT

A 27-year-old woman presented to the emergency department with a 4-day history of increasing right lower quadrant, periumbilical pain, and decreased appetite.* She reported no oral intake since 2 days before presentation. The patient's obstetric history consisted of 5 pregnancies and 5 full-term births, her last child having been born 8 months before the presentation. She was actively breastfeeding at a frequency of 6 to 8 times daily without any reported complications.

The patient's prior medical history included bicornuate uterus, insertion of an intrauterine device 2 months after the most recent birth, and abdominal hernia repair 2 years before the current presentation. She reported daily use of a multivitamin and an omega-3 supplement, as well as occasional intake of acetaminophen, but no use of prescribed medications. She had no allergies and denied using recreational drugs, smoking tobacco, or consuming alcohol.

The results of hematological and biochemical laboratory tests showed no abnormalities. All microbiological tests yielded negative results, including blood and urine culture. The attending staff diagnosed acute appendicitis, and the patient underwent appendectomy under general anesthesia. Intraoperative findings included an extremely fibrotic appendix and meso-appendix, both of which were removed.

During the procedure, the patient received cefazolin, granisetron, ketorolac, propofol, rocuronium, succinylcholine, and sufentanil. The patient also received 2 induction boluses of propofol (IV), with the first dose of 150 mg being followed shortly after by the second dose of 50 mg. The surgery was successful, with no complications and minimal blood loss.

Twenty-two hours after the procedure, the patient extracted her breast milk for the first time since surgery. The collected breast milk had a light green colour. However, no discoloration of the urine was noted. Her active medications at that time were regular acetaminophen, cefazolin, ibuprofen, and pantoprazole, as well as as-needed doses of oxycodone and dimenhydrinate. A sample of the extracted green breast milk was analyzed by gas chromatography–mass spectrometry for the presence of propofol.[12] However, this technique yielded negative results. The patient refrained from breastfeeding but continued extracting her milk. She experienced no postoperative complications and was discharged home from the hospital in stable condition on postoperative day 2. The patient reported that her breast milk spontaneously and progressively returned to its usual colour and was completely free from any green discoloration by postoperative day 4, at which point breastfeeding was resumed with no issues.

*The patient provided verbal consent for publication of this case report. Approval was also granted by the local institutional research ethics board.

DISCUSSION

Few studies have demonstrated the passage of propofol into breast milk.[10,11] However, many of propofol's pharmacokinetic properties favour this transfer. After its administration, propofol rapidly distributes from the blood to surrounding tissues in a 3-compartment model.[1] Propofol is highly lipophilic and non–water soluble, with a volume of distribution of 2.85 to 6.07 L/kg.[1] Therefore, even after a single bolus dose, propofol is widely distributed and has a terminal half-life of up to 480 min.[1] This significant lipophilicity favours its diffusion through the mammary alveoli and its solubility and accumulation in the lipid fraction of breast milk.[13] Furthermore, any medication with a molecular mass less than 500 daltons may easily diffuse into breast milk.[13] Propofol's low molecular mass of 178.3 daltons[1] therefore favours its passage into breast milk. Conversely, propofol is highly protein-bound (up to 99%), and molecules that are more than 95% protein-bound are less likely to diffuse into the breast milk.[13]

Propofol undergoes extensive metabolism in the liver to form water-soluble inactive metabolites that are renally excreted.[4,6,14,15] Less than 1% of propofol is excreted unchanged in the urine.[16] The main metabolic pathway of propofol includes oxidation by the cytochrome P450 2B6 isozyme, and to a lesser extent cytochrome P450 2C9 isozyme, as well as phase II metabolism to form the drug's main metabolites: propofol glucuronide, quinol-1-glucuronide, quinol-4-glucuronide, and quinol-4-sulphate conjugates.[4,6,12,16] Other minor metabolites have also been identified.[12,14]

The pharmacokinetic properties of propofol metabolites have not been thoroughly investigated. However, Bleeker and others[17] found that propofol and its glucuronide metabolites were detectable in the plasma up to 15 h after surgery, with the glucuronide metabolites being excreted in the urine for more than 60 h after surgery, following continuous infusion of propofol in 9 patients who underwent lung surgery. Therefore, in the case reported here, it is possible that propofol metabolites were present in the patient's breast milk when it was extracted 22 h after surgery.

Many case reports have described the effect of propofol on the colour of urine. Most of the published cases have reported the occurrence of green discoloration after continuous infusion of propofol. There have also been a few cases in which green urine was observed shortly after a single bolus induction dose of propofol.

In 3 cases, propofol induction doses (100 to 200 mg), administered for endotracheal intubation or preoperative sedation, were associated with green discoloration of the urine within just a few hours after administration or as little as 1 h after surgery.[9,18,19] In the first case, the green colour resolved by the end of the 2.5-h surgery.[9] In the 2 other cases, urine colour returned to normal 24 h after administration[18] and 48 h after surgery.[19]

Lee and others[3] reported 3 cases of green discoloration of the urine after continuous infusion of propofol. Sedation was maintained with propofol infusion rates of 3 to 4 mg/kg per hour.[3] In 2 of these cases, the green urine appeared after 6 h of infusion, whereas in the third case the discoloration was observed after 64 h. In all cases, urine colour returned to normal 3 to 6 h after propofol discontinuation.[3] No concomitant use of medication known to cause green urine discoloration was reported.

The green colour of urine following propofol administration is believed to be caused by the inactive phenolic metabolites of this drug (1-glucuronide, 4-glucuronide, and 4-sulphate conjugates).[1,4] In the current case, the gas chromatography–mass spectrometry analysis did not detect propofol or its metabolites in the green breast milk. However, the sensitivity of the technique to detect these molecules in breast milk had not been determined in the laboratory at that time. Therefore, it is possible that propofol and its metabolites were present in the breast milk sample, but were below the limits of detection. We suggest validating the sensitivity of a gas chromatography–mass spectrometry analysis for the detection of propofol and its metabolites in future cases.[12]

Only 2 previous reports of green breast milk have been published, with inconclusive results as to the cause of the green colour. In the first report, Birkholz and others[11] hypothesized that the green breast milk was due to propofol administration. However, these authors also reported that they were unable to identify propofol and its conjugated metabolites in the expressed breast milk.[11] The breast milk discoloration was first seen 8 h after surgery and had resolved by 48 h after surgery.[11] In the current case, the discoloration resolved on postoperative day 4, much later than in the previous case. Nevertheless, divergent timing of green urine discoloration secondary to propofol has also been reported, and this variation may be due to interpatient pharmacokinetic differences. In the second prior report of green breast milk, Yazgan and others[20] hypothesized that the green discoloration was due to the iron content of the reddish-brown multivitamin that the mother had been taking daily since delivery. In the current case, the patient also had postpartum exposure to a multivitamin, which might have contained iron. However, the timing of the appearance and disappearance of the green discoloration of the breast milk, combined with the fact that the mother had been taking the multivitamin for months before this observation, led us to believe that the propofol used for anesthesia was a more likely cause than the multivitamin. Furthermore, given the common use of iron-containing multivitamins by women who are breast-feeding, green breast milk would be observed more frequently if iron supplementation was the cause. We calculated a Naranjo score of 4, indicating propofol as a possible cause of the adverse drug reaction of green breast milk in this case.[21]

CONCLUSION

Propofol metabolites may discolour biological fluids other than urine. We have described a second case of green breast milk following administration of propofol. Health care professionals and patients should remain vigilant for this possible, though rare, adverse event. Given the uncertainty about trace amounts of propofol in the green breast milk, breastfeeding in this situation might expose the infant to uncertain effects; therefore, we recommend caution in the continuation of breastfeeding until the colour returns to normal. If breastfeeding is pursued, we recommend that the infant be closely monitored.

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