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Intravenous midazolam passage into breast milk

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Introduction

It is desirable to allow breast-feeding as soon as possible after anesthesia. It is common for anesthesiologists to encounter nursing mothers who invariably question whether breast feeding after anesthesia can harm their infants [1]. Only limited reviews concerned with diffusion into breast milk could be found, and in particular there were no studies on breast-feeding after intravenous administration of midazolam to the mother. The present study reports the degree to which intravenously administered midazolam passed from plasma to breast milk in one patient.

Patient Background

A 20-year-old 51-kg woman, diagnosed with cholelithiasis was admitted to our hospital for laparoscopic cholecystectomy. She had delivered a healthy baby 4 months before and was currently nursing the infant. Informed consent for this study was obtained from her and her mother.

Roxatidine 75 mg was given orally 120 min before surgery followed by 0.5 mg atropine, 15 mg pentazocine, and 25 mg hydroxyzine intramuscularly 60 min before surgery. An infusion of acetated Ringer's solution was given intravenously before induction of anesthesia and was maintained at 10 ml·kg^{-1}·h^{-1} during operation. The electrocardiogram, pulse oximetry (SpO_2), and arterial blood pressure were monitored. Temperature was monitored by a rectal thermistor and maintained at 36.5° ± 0.5°C.

After induction of anesthesia with 6 mg midazolam and 8 mg vecuronium, the trachea was intubated. Anesthesia was maintained with nitrous oxide (N_2O) in 67% O_2 and isoflurane; and muscle relaxation was achieved with vecuronium. Arterial blood and milk samples (7 ml) were obtained at 30 min and 1, 2, 4, 6 and 24 h after administration of midazolam. Milk was expressed manually by nurses, and the first 1 ml was discarded. Blood was centrifuged at 4°C, and serum and milk samples were frozen immediately at −20°C prior to assay. Serum and milk midazolam concentrations were determined by gas chromatography using an HP-5 column (Hewlett Packard, USA). The limit of the assay was 5 ng·ml^{-1}. After operation, acetated Ringer's solution 2000 ml per day was given intravenously. Urinary output was measured perioperatively. Postoperative pain was managed by intramuscular injection of 15 mg pentazocine when the patient complained of pain.

Urinary output was about 50 ml·h^{-1} during and after the operation. The serum and milk midazolam concentrations are shown in Table 1. The milk/plasma (M/P) ratios in the first three samples were 0.38, 0.34, 0.28, respectively.

Discussion

Excretion of drugs in breast milk depends on factors such as dose, route, and frequency of administration, plasma protein binding, volume of distribution, metabolism, and clearance [1]. Owing to the difference in the pH of plasma (7.4) and milk (6.6–7.1) [2,3], weak acids are secreted in lower concentrations in milk than plasma, whereas weak bases undergo "ione trapping" in the milk, leading to higher concentrations in milk than

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Table 1. Midazolam concentrations in plasma and milk after midazolam administration

	Values at 0.5 to 24 h					
Parameter	0.5	1	2	4	6	24
Plasma ($ng \cdot ml^{-1}$)	65	35	25	12	11	<5
Milk ($ng \cdot ml^{-1}$)	25	12	7	<5	<5	<5
M/P ratio	0.38	0.34	0.28			

Midazolam was given as a 6-mg dose.
The detection limit was $5 ng \cdot ml^{-1}$; <5 indicates a value under the detectable limit.
M/P ratio, milk/plasma ratio.

plasma [4]. Because midazolam is a weak basic drug it diffuses across the lipid membranes into milk. Milk secretion is related to factors such as hydration, postoperative nausea and vomiting, and pain. In this case, the patient was well hydrated and free from nausea and vomiting. Postoperative pain was mild, and analgesics were needed only twice. Therefore the factors mentioned above did not affect milk secretion.

The breast is an area that has not been well researched, as ethical concerns prevent free experimentation on lactating breast tissue in humans. For most of the anesthetic and nonanesthetic drugs studied, the maximum amount secreted in breast milk is seldom more than 1–2% of the maternal dose [4,5]. The maximal observed concentration of midazolam in milk was $9 ng \cdot ml^{-1}$ and that of α-hydroxymidazolam was $3 ng \cdot ml^{-1}$ 1–2 h after drug intake. Moreover, no drug effects were observed in the infants fed at that time. On the basis of these observations, the maximum ingested dose of midazolam plus α-hydroxymidazolam to the suckling infant during a feeding session would be 0.1% of the weight-adjusted maternal daily dose of midazolam [6]. In our case, the concentrations in milk were 12 and $7 ng \cdot ml^{-1}$ at 1 and 2 h after administration, respectively. Although we did not measure the concentration of α-hydroxymidazolam, the midazolam concentration in milk was comparable to that after peroral midazolam administration. Therefore we suggest that the ingested dose of midazolam to the suckling infant during a feeding session is low.

The M/P ratio of drug concentration may be used to estimate the dose of a drug in breast milk as a function of the maternal plasma concentration [1]. There are no data for the M/P ratio after intravenous administration of midazolam. In cases of oral intake of 15 mg midazolam, the M/P ratio was found to be 0.15 ± 0.06, and no measurable midazolam was detected in breast milk about 7 h after intake [2]. The average M/P ratio in our patient at 30 min and 1 h and 2 h after administration was 0.33. The reason the M/P ratio after oral intake differed from the ratio after intravenous administration is unclear. The M/P ratio range for diazepam has been reported to be 0.10–0.58 [6]. Similarly, individual variation played a significant role in the M/P ratio for midazolam. It is not known if the observed M/P ratio equals the true M/P value based on area-under-the-curve (AUC) calculations [2]. Spigset [6] stated that ideally M/P ratios are based on AUC calculations, or at least on multiple pairs of samples. Moreover, for another hypnotic, zopiclone, M/P ratios based on paired samples and AUCs were closely correlated [7]. Therefore the M/P ratios reported here were considered to be nearly equal to the true M/P value.

In conclusion, it is possible that the passage of midazolam into breast milk is higher after intravenous administration than after oral intake. However, the midazolam concentration in milk was relative low and at a harmless level for the infant. The risk for the suckling infant therefore seems to be low.

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