Placental Transfer and Effects of Famotidine on Neonates

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The effect of famotidine on neonates was studied in 34 obstetric patients who underwent elective cesarean section.

In the famotidine group, 20 mg of famotidine was intramuscularly injected at 60 min before induction of anesthesia, and 0.5 mg of atropine was injected at 30 min before induction. In the control group, only atropine was given. Ratio of famotidine concentration in the umbilical venous blood to that in the maternal venous blood was determined as 0.64 ± 0.13 (mean ± SD). No significant differences were noted in the Apgar scores, neonatal gastric acidity, and results of liver function tests between the two groups. No side effect, such as the development of gastrointestinal infections, was observed. (Key words: famotidine, placental transfer, obstetric anesthesia)

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The risk of acid aspiration pneumonia is high for obstetric patients. H_2-receptor antagonists like cimetidine are used in obstetric anesthesia for the prophylaxis of acid aspiration. Cimetidine is the most widely studied H_2-receptor antagonist and has proven to be safe in obstetric patients[1]. Previous reports documented that the premedication with H_2-receptor antagonist could increase pH in gastric fluid in the patients[2–5]. No data, however has been reported upon changes in pH in gastric fluid of neonates who are born from the mothers medicated with famotidine or upon liver function of the neonates after the birth. However, it inhibits the mixed function oxidase enzyme system (cytochrome p-450) and decreases hepatic blood flow. These effects can reduce the metabolism of diazepam, lidocaine and propranolol[6–8].

Famotidine is a new H_2-receptor antagonist which is more potent and has a longer duration of action and less effects on hemodynamics than cimetidine[9,10]. Famotidine does not affect cytochrome p-450 or hepatic blood flow and has no known adverse drug interactions[11]. These characteristics will be preferable for obstetric patients.

This study was designed to determine placental transfer and effects of Famotidine on neonate.

Materials and Methods

Thirty four obstetrical patients who underwent spinal anaesthesia for elective cesarean section were subjected for the study. These patients were allocated randomly to either the famotidine group or the control group.

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Table 1. Patient data [mean (SD)]

	Age (yr)	Weight (kg)	Gestrastion (weeks)
Famotidine (n=17)	33.3 (5.4)	58.1 (9.0)	38.7 (1.4)
Control (n=17)	30.9 (4.6)	59.0 (5.5)	38.5 (1.1)

Seventeen patients in the famotidine group received 20 mg of famotidine intramuscularly at 60 min before induction of anesthesia and 0.5 mg of atropine intramuscularly at 30 min before induction. Seventeen control group patients received only 0.5 mg of atropine at 30 min before induction of anesthesia. A dose of 2.0 ml of 0.3% dibucaine in 5% sodium chloride solution was administered intrathecally. If systolic blood pressure fell by 20% of its initial value, left uterine displacement was ensured, the intravenous infusion rate was increased and 5 to 20 mg of ephedrine was administered. The condition of the neonates was assessed by the Apgar scores both 1 and 5 min after birth, and their course was observed during the stay in hospital.

The acidity of the neonatal gastric contents at birth and at 24 hr of age were measured using the Horiba L-7LC pH meter. At delivery, 5 ml venous blood samples were taken from the mother and from the umbilical cord vein of the delivered placenta, respectively. Each sample was heparinized and centrifuged and then the supernatant serum was stored at −20°C until required for analysis. Blood famotidine was extract with ethyl acetate under an alkaline condition using K_2CO_3, allowed to react with phenanthrene quinone in the presence of sodium hydroxide to produce a fluorescent substance, and assayed by using high performance liquid chromatography – spectrophtofluorometer. Operation condition of high performance liquid chromatography and spectrophotofluorometer were as follows:

Column: Waters Radial Pack Cartridge C_{18}

Eluent: Acetonitrile: 0.01 M acetate buffer (pH 4) = 4:5

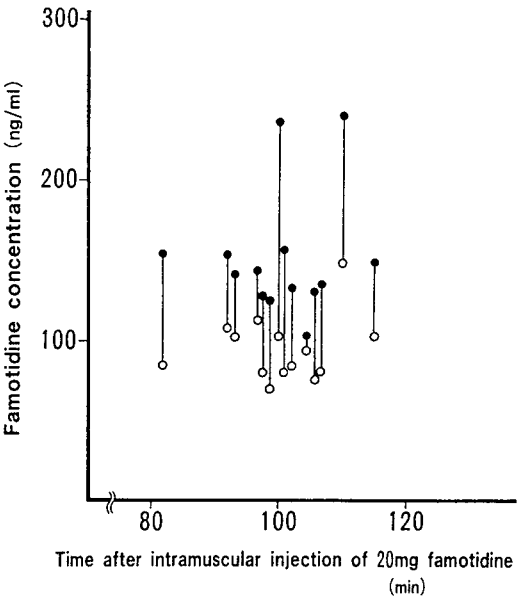

Fig. 1. Serum levels of famotidine (• = maternal blood ○ = umbilical cord blood)

Flow rate: 2 ml·min^{-1}.

Excitation wavelength: 296 nm

Fluorescence wavelength: 411 nm

Neonatal liver function tests (serum bilirubin, LDH, GOT, and GPT) were performed at 5 days of age. Comparison between the group was made by Student's t-test (for patient characteristics and hepatic function tests of neonate), the Wilcoxon rank sum test (for the pH of neonatal gastric contents), or the Chisquared test (for Apgar scores). In all cases, $P < 0.05$ was regarded as significant. Informed consent was obtained from all patients verbally, and the study was approved by the ethical Committee, Odawara Municipal Hospital. All patients were classified ASA 1 or 2. Cesarean section was carried out in those patient mostly due to cephalo-pelvic disproportion or previous operation. The clinical features of the two groups were similar (table 1).

Results

Paired maternal venous and umbilical cord venous serum levels of famotidine at delivery are shown in figure 1. The mean interval from injection of famotidine to delivery was 100 min, and ratio of famoti-

Table 2. Apgar Scores

	1 minute			5 minutes		
	10	9	8	10	9	8
Famotidine (n=17)	1	9	7	13	4	0
Control (n=17)	2	7	8	14	3	0

Table 3. Acidity of neonatal gastric contents [mean (SD)]

	at birth	1 days old
Famotidine (n=13)	7.20 (0.3)	2.97 (1.2)
Control (n=13)	6.93 (0.5)	1.96 (0.5)

dine concentration in the umbilical venous blood to that in the maternal venous blood (UV:MV ratio) was determined 0.64 ± 0.13 (mean ± SD). Apgar scores for neonates in both groups are shown in table 2, and were not significantly different. Neonatal gastric acidity level are shown in table 3. Mean pH of the gastric contents in the famotidine group of neonates at first day of age was slightly higher than that of the control group but no significant difference was revealed. None of the neonates developed febrile reaction, diarrhea, vomiting, or other symptoms suggesting gastrointestinal infection during their stay in hospital. Hepatic function tests of the neonates are shown in table 4. No significant difference was seen in between the two groups, none of the neonates showed abnormal value in the hepatic function tests, and none of them needed phototherapy.

Discussion

Preoperative oral administration of cimetidine at 1 or 2 hr before anesthesia or its intravenous or intramuscular administration at 45 to 60 min before anesthesia, is suggested as prophylaxis for acid aspiration pneumonia[2,3]. Cimetidine has a short duration of action, and anesthesia should be started within 150 min after its administration[4]. Longer acting H_2-receptor antagonists thus have a definite advantage. Famotidine has more potent and longer action than cimetidine.

The mean UV:MV ratio of famotidine was 0.64 at 100 min following intramuscular administration. Howe[12] found that the mean UV:MV ratio of cimetidine at delivery was 0.84 at 90–120 min after intravenous administration. The degree and rate of placental transfer of the drug is influenced by its extent of ionization, molecular weight, and lipid solubility. The molecular weight of cimetidine is 252.4 and that of famotidine is 337.4. Both drugs have low lipid solubility, and the pka value of cimetidine is 6.8 while that of famotidine is 7.06. The degree and rate of placental transfer of famotidine is lower than that of cimetidine, because of its greater ionization.

Most elective cesarean sections are performed under spinal anesthesia in Japan. Use of spinal anesthesia minimizes the problem of maternal aspiration, but in the case of high spinal anesthesia or total spinal block, aspiration pneumonia becomes a serious risk. A case of aspiration pneumonia in high spinal anesthesia after cesarean section was reported[13]. Thus, prophylaxis agent for aspiration pneumonia should be used in cesarean sections performed, even under spinal anesthesia.

Gastric alkalization is a common source of infection in other other sites[14]. If maternal treatment with H_2 antagonists affects neonatal gastric acidity, it would be undesirable because of disturbance of host resistance to

Table 4. Hepatic function test [mean (SD)]

	T.Bil ($mg \cdot dl^{-1}$)	GOT (IU)	GPT (IU)	LDH (IU)
Famotidine (n=7)	7.1 (3.3)	24.3 (6.8)	4.7 (1.6)	705 (90.4)
Control (n=9)	8.0 (2.8)	21.8 (5.7)	3.8 (1.3)	731 (101.0)

microorganisms system. In this study the pH of the gastric contents at birth or at 1 day old was not found to be significantly different between the two groups and the values of pH observed in this study were similar to that obtained by Miclart (range: 6.0–7.4 mean value: 6.97)[15]. Hodgkinson found that the gastric acidity of neonates whose mothers received H_2 receptor antagonists was mostly same as that of neonates whose mothers received antacids[1]. It was suggested that the reason for the lack of difference between the two groups was the low gastric acidity in neonate delivered by cesarean section. No neonate in this study developed any clinical symptoms suggesting gastrointestinal infection. McCauley studied the effects of ranitidine in cesarean section on neonatal gastric acidity and gastrointestinal infections[5]. He found no difference in gastric acidity between the ranitidine-treated group and the magnesium trisilicate-treated group, and no positive culture of the gastric contents of neonates whose mothers received ranitidine.

High incidence of cholestastic jaundice in a child who was treated with cimetidine for peptic ulcer has been reported[16]. In our study, no significant difference in the serum levels of total bilirubin, LDH, GOT, or GPT was shown between the two groups. The mean serum total bilirubin level was high in both groups, but not high for age.

In this study, the small sample size prevents them from concluding that famotidine has no adverse effect in the neonate and the larger toxicity trials are necessary to determine whether famotidine will adversely affect neonatal outcome.

In conclusion, the extent of placental transfer of famotidine indicated by the UV:MV ratio was 0.64. There were no adverse effects on the Apgar scores, gastric acidity, or liver function tests in neonates whose mothers received famotidine.

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