Acta Medica Okayama

Volume 46, *Issue* 6 1992 *Article* 6

DECEMBER 1992

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Abstract

The ability of the human fetus and neonate to conjugate and excrete ritodrine, a beta 2-sympathomimetic drug, was investigated. Free and conjugated ritodrine concentrations in the plasma, amniotic fluid and urine were measured in 11 mother-infant pairs, to whom intravenous ritodrine had been administered before elective cesarean section at term. Ritodrine was determined by HPLC with electrochemical detection. At delivery, conjugated ritodrine values were significantly higher than those for the free form in maternal and fetal plasma. There were significant positive correlations between the concentrations in the maternal and umbilical vein plasma for both free and conjugated ritodrine. In the amniotic fluid, the total ritodrine concentrations were much higher than those in the fetal plasma, the conjugated form accounting for 90.2% of the total. Furthermore, the percentages of conjugated ritodrine in the amniotic fluid and neonatal urine were significantly higher than the percentage in the maternal urine on the day of birth. In the neonatal urine, the concentrations of free and conjugated ritodrine decreased rapidly after birth as did those in the maternal urine, on day 3 postpartum being less than 2% of the values on the day of parturition. These results indicate that the fetus at term is capable of forming conjugated metabolites of ritodrine and of excreting free and conjugated ritodrine in its urine.

KEYWORDS: ritodrine, fetus, neonate, conjugation, urinary excretion

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*PMID: 1485538 [PubMed - indexed for MEDLINE]

Acta Med Okayama 46 (6) 443-448 (1992)

Fetal and Neonatal Excretion of Free and Conjugated Ritodrine

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The ability of the human fetus and neonate to conjugate and excrete ritodrine, a β_2-sympathomimetic drug, was investigated. Free and conjugated ritodrine concentrations in the plasma, amniotic fluid and urine were measured in 11 mother-infant pairs, to whom intravenous ritodrine had been administered before elective cesarean section at term. Ritodrine was determined by HPLC with electrochemical detection. At delivery, conjugated ritodrine values were significantly higher than those for the free form in maternal and fetal plasma. There were significant positive correlations between the concentrations in the maternal and umbilical vein plasma for both free and conjugated ritodrine. In the amniotic fluid, the total ritodrine concentrations were much higher than those in the fetal plasma, the conjugated form accounting for 90.2% of the total. Furthermore, the percentages of conjugated ritodrine in the amniotic fluid and neonatal urine were significantly higher than the percentage in the maternal urine on the day of birth. In the neonatal urine, the concentrations of free and conjugated ritodrine decreased rapidly after birth as did those in the maternal urine, on day 3 postpartum being less than 2% of the values on the day of parturition. These results indicate that the fetus at term is capable of forming conjugated metabolites of ritodrine and of excreting free and conjugated ritodrine in its urine.

Key words : **ritodrine, fetus, neonate, conjugation, urinary excretion**

Ritodrine is a β_2-sympathomimetic drug commonly used as a tocolytic agent in preterm labor. Its usefulness in managing intrapartum fetal distress at term has been reported (1, 2). Ritodrine crosses the placental barrier and enters fetal circulation (3-5). Its widespread use has brought to light such fetal and neonatal side effects as hypoglycemia, hypokalemia and cardiac septal hypertrophy (6-8) which may be caused by the direct effect of the drug being transferred to the fetus. To assess the fetal and neonatal side effects of ritodrine, its pharmacokinetics in the fetus and neonate must be studied. Ritodrine is inactivated in humans by sulfate and glucuronide conjugation and excreted in the urine. The neonate also excretes conjugated ritodrine in its urine (9). Little information, however, is available about the ability of the fetus to metabolize and excrete ritodrine. We, therefore, investigated the placental transfer and excretion of free and conjugated ritodrine in the fetus and neonate.

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Materials and Methods

Subjects. Eleven healthy pregnant women who underwent elective cesarean section at 37–39 weeks of gestation were studied. None were in labor, and none had experienced placental dysfunction or rupture of the fetal membranes. The indications for cesarean section were previous cesarean section (n = 6), breech presentation (n = 3), primiparous cephalopelvic disproportion (n = 1) and placenta previa (n = 1). All the women delivered infants with normal Apgar scores above 8 and appropriate weights for the gestational age. None of the neonates had congenital anomalies. Ritodrine (Kissei Pharmaceutical Co., Ltd., Matsumoto, Japan) was administered by intravenous infusion at 31–91 μg/min for 10.5–72 h. The mean amount administered was 79.1 ± 59.3 (mean ± SD) mg and the mean time from its discontinuation to delivery was 306 ± 36 (mean ± SD) min. The informed consent of each patient was obtained before giving the ritodrine infusion.

Sample collection. Maternal blood samples were collected at the discontinuation of the ritodrine infusion and at delivery. Amniotic fluid was collected when the uterus was incised, and umbilical arterial and venous blood was collected immediately after delivery. Maternal urine was collected from the time of delivery up to 7 a. m. of the following day, after which it was collected over each 24-h period for 5 days. Neonatal urine also was collected from the day of birth through the 5th day after birth, collection being made at various times of day with a standard neonatal urine collection bag.

Blood samples were centrifuged at 1,000 × *g* for 15 min at 4℃ to separate the plasma. The urine and amniotic fluid samples were filtered through a membrane cone (Amicon CENTRIFLO® type CF 25, Beverly, Mass, USA) at 4℃. The plasma, filtered urine and amniotic fluid samples obtained were frozen at −30℃ until assay.

Sample analysis. A high performance liquid chromatograph coupled with an electrochemical detector and a data recorder was used to determine the ritodrine concentrations according to the method of Kuhnert *et al.* (10). The chromatographic system was composed of a Σ 871 pump, Σ-80 sample injector, reverse phase RP-18 T column (250 mm × 4 mm i. d.), Σ 875 electrochemical detector, and data processor CD-12 (IRICA, Kyoto, Japan). The mobile phase was methanol-phosphate buffer (40:60, v/v) with a flow rate of 0.8 ml/min. The phosphate buffer was composed of 6 mM KH_2PO_4, 0.2 mM octanesulfonic acid and 0.06 mM disodium ethylenediaminetetraacetate. The column was maintained at 45℃, and its eluate was monitored with an electrochemical detector with an applied potential + 0.8 V *vs.* Ag/AgCl reference electrode. The reference ritodrine hydrochloride was donated by Kissei Pharmaceutical Co., Ltd.. Nalbuphine hydrochloride used as the internal standard was obtained from Research Biochemicals Inc. (Natick, Mass, USA).

β-glucuronidase from *Helix pomatia* (Sigma Chemical Co., St. Louis, Mo, USA [G-0876]) with both glucuronidase and sulfatase activities was used for the enzymatic hydrolysis of the conjugated ritodrine, which gave the total amount of conjugated ritodrine, the sum of the glucuronide and sulfate conjugates (9, 11). The assay sensitivity of ritodrine was 60 pg, and the recovery rate 43.0 ± 2.7 % (mean ± SD, n = 10). The intra- and interassay coefficients of variation were 5.0 % (n = 6) and 4.2 % (n = 10).

Values are given as the mean ± standard error. Student's *t*-test and linear regression analysis were used for the statistical analyses.

Results

Maternal and fetal plasma levels. The maternal plasma cencentrations of free and conjugated ritodrine at the cessation of intravenous ritodrine administration were 42.2 ± 7.4 and 91.8 ± 10.0 ng/ml (n = 11). At delivery, these concentrations were 5.9 ± 0.6 and 27.6 ± 4.6 ng/ml, the umbilical vein concentrations 7.7 ± 0.8 and 50.7 ± 8.0 ng/ml, and the umbilical artery concentrations 6.5 ± 0.5 and 50.9 ± 8.5 ng/ml (n = 10) (Fig. 1). The concentrations of conjugated ritodrine in both the mothers and neonates were significantly higher than those of free ritodrine.

Significant positive correlations were found between the concentrations in the maternal and the umbilical vein plasma for free and conjugated ritodrine (Fig. 2). The regression line for free ritodrine was $Y = 1.19X + 0.73$ ($r = 0.801$, $n = 10$, $p < 0.01$) and for the conjugated form $Y = 1.53X + 8.52$ ($r = 0.880$, $n = 10$, $p < 0.01$).

Total ritodrine concenrations in fetal plasma

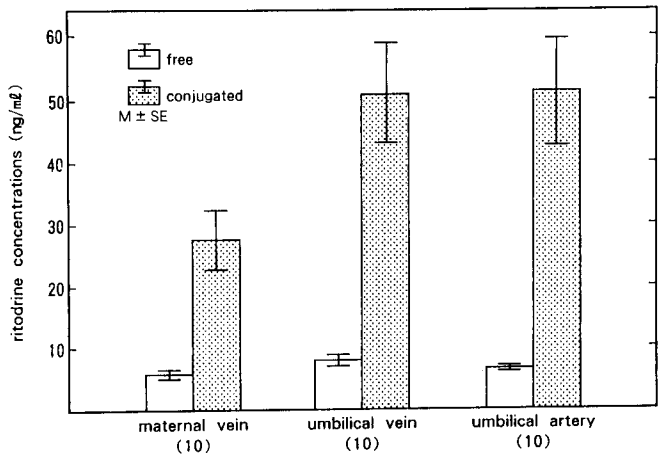

Fig. 1 Concentrations of free and conjugated ritodrine in maternal and fetal plasma at delivery. The number of subjects is shown in parentheses.

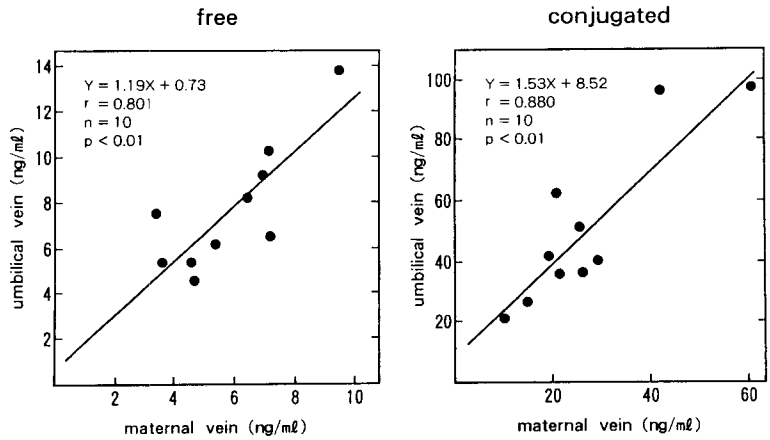

Fig. 2 Correlations between ritodrine concentrations in maternal and umbilical veins. Significant positive correlations were found for both free and conjugated ritodrine.

and amniotic fluid. The total ritodrine concentrations were 58.4 ± 8.0 ng/ml for umbilical vein (n = 10), 57.3 ± 8.3 ng/ml for umbilical artery (n = 10), and 187.9 ± 21.0 ng/ml for amniotic fluid (n = 10) (Fig. 3). The concentration in the amniotic fluid was much higher than in the fetal plasma.

Percentages of conjugated ritodrine in maternal and neonatal urine and in amniotic fluid. We compared the percentages of conjugated ritodrine in maternal and neonatal urine and in the amniotic fluid on the day of delivery. The per-

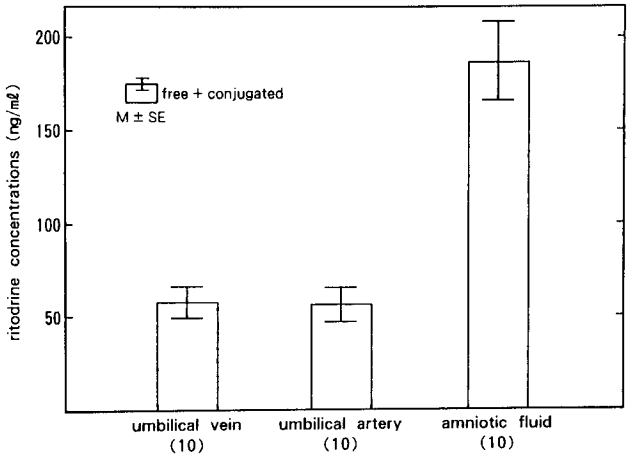

Fig. 3 Total ritodrine concentrations in fetal plasma and amniotic fluid. The number of subject is shown in parentheses.

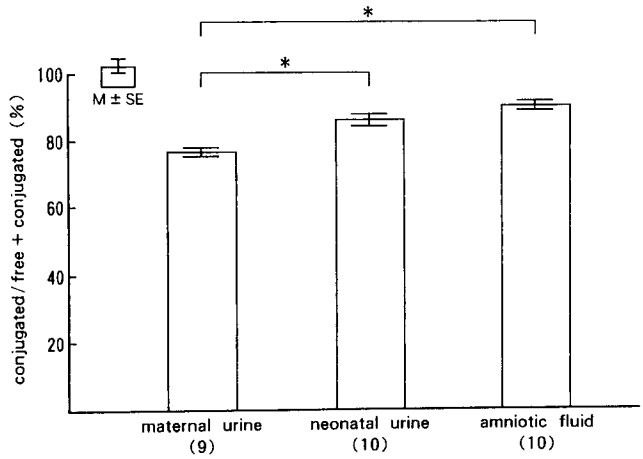

Fig. 4 Percentages of ritodrine in the conjugated form in maternal and neonatal urine and in the amniotic fluid on the day of delivery. The numbers of subjects are shown in parentheses. * $p < 0.01$

centages for both the neonatal urine (86.4 ± 1.9 %, $n = 10$) and amniotic fluid (90.2 ± 1.3 %, $n = 10$) were significantly ($p < 0.01$) higher than that for maternal urine (76.6 ± 1.2 %, $n = 9$) (Fig. 4).

Maternal and neonatal urinary excretion of ritodrine. Most of the ritodrine excreted by the mothers and neonates was in the conjugated form. The percentage of this form in neonatal urine remained unchanged for six days after birth, the range being 85.7 % to 90.3 %. The concentration of total ritodrine in both the maternal and neonatal

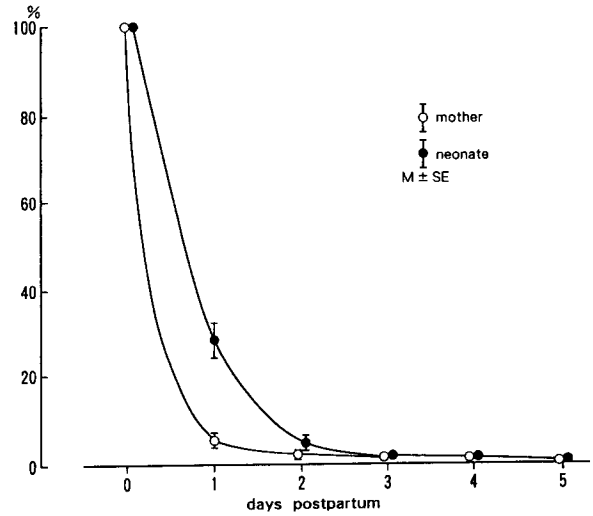

Fig. 5 Maternal and neonatal urinary excretion curves for total ritodrine during the first 6 days postpartum. Each point was expressed as percentage of the concentrations measured on the day of parturition (means of 6–11 determinations).

urine decreased rapidly after delivery (Fig. 5). On day 3 postpartum, the concentrations were less than 2 % of the values on the day of parturition.

Discussion

Caritis *et al.* (12) reported that for a constant infusion of 50 μg/min the plasma concentrations of free ritodrine in 13 pregnant women ranged from 15 to 45 ng/ml. In the study of Fujimoto *et al.* (13), in which ritodrine was infused intravenously at 72–149 μg/min for 161–355 min, the concentration of free ritodrine in maternal serum was 18.2–73.6 ng/ml at 4 h after the start of the infusion. Our value of 42.2 $\pm$ 7.4 ng/ml at the cessation of intravenous infusion agrees well with the above values.

The free ritodrine concentrations in maternal and umbilical cord blood at delivery have been reported previously (4, 5, 9, 13). Conjugated ritodrine concentrations, however, have been reported only for maternal and neonatal urine (9, 11). We measured the concentrations of free and conjugated ritodrine in maternal and umbilical cord plasma at delivery and found that the concentrations of conjugated ritodrine were much higher than those of free ritodrine in both the mothers and fetuses.

Previous studies have reported various ratios for cord blood concentrations of ritodrine to maternal blood concentrations after intravenous infusions of the drug (3, 4). Sodha *et al.* (14) studied the transfer of ritodrine across perfused human placenta *in vitro* and found that the drug diffused across the placenta. Moreover, Gross *et al.* (5) showed a significant correlation between maternal and fetal free ritodrine concentrations and the transplacental transfer of free ritodrine *in vivo*. In the present study, we found significant positive correlations between both the free and conjugated ritodrine concentrations in the maternal and umbilical vein, indicative of the transplacental passage of conjugated as well as free ritodrine.

We also found much higher total ritodrine

concentrations in the amniotic fluid than in fetal plasma, the conjugated form accounting for 90.2 %. These results indicate that term fetuses are capable of excreting both free and conjugated ritodrine in their urine because the amniotic fluid is primarily composed of fetal urine. The fetus swallows the amniotic fluid containing free and conjugated ritodrine, and excretes them. This fetus-amniotic fluid cycling of the drug may contribute to maintain the higher drug concentration in fetal blood plasma compared with the value in maternal blood plasma.

Kuhnert *et al.* (9) measured the free and conjugated ritodrine in maternal and neonatal urine and reported that the neonate excretes significantly more of the drug as a conjugate than the mother does. Brashear *et al.* (11) reported that both the mother and neonate excrete glucuronide and sulfate conjugates of ritodrine, and showed differences in their excretion profiles with respect to the relative percentages of free ritodrine and these conjugates. These results indicate that the neonate is capable of forming both glucuronide and sulfate conjugates of ritodrine. We showed that the percentages of conjugated ritodrine in amniotic fluid and neonatal urine on the day of birth were significantly higher than in maternal urine on the same day, indicating that the fetus, as well as the neonate, conjugates ritodrine.

The percentage of ritodrine excreted as conjugates by the neonate remained unchanged after birth. This finding suggests that fetus at term has enough ability to conjugate ritodrine. As for the neonate's ability to eliminate ritodrine, the concentrations of both free and conjugated ritodrine in neonatal urine decreased rapidly and were negligible on day 3 postpartum, as in maternal urine. This suggests that the neonate and mother have nearly the same ability to eliminate ritodrine.

We conclude that the fetus can conjugate ritodrine and excrete both the free and conjugated forms in urine and that the drug does not remain for a long time in the neonate.

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Received May 7, 1992, accepted June 23, 1992.