Original Article

# Excretion of Acebutolol and its Major Metabolite Diacetolol into Infant Blood Circulation and the Breast Milk

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#### Abstract

Acebutolol (AC) is a chiral  $\beta$ -adrenergic blocking drug, which is useful clinically as the racemate in treating hypertension and is metabolized to an equipotent chiral metabolite, diacetolol (DC). In this paper we report a case of a 32 year old woman who was receiving AC during her pregnancy and lactating time for management of hypertension. The maternal plasma level and breast milk as well as cord blood collected to see whether the drug is transferred to the fetus through the mother stereoselectively. A stereospecific high-performance liquid chromatographic (HPLC) assay was used to measure the enantiomeric concentrations of AC and DC. AC and DC enantiomers are stereoselectively excreted into the milk, although the concentrations of DC enantiomers were higher than those of AC. AC concentrations were very low in both cord artery and vein samples four hours after taking the drug however, the stereoselective concentrations of metabolite, DC, was found in these samples. In conclusion, AC and DC enantiomers are excreted in human breast milk in concentrations much higher than that in maternal plasma. Furthermore, DC was found in the infant's plasma indicating that accumulation of metabolite did occur in this infant.

Key Words: Acebutolol; Diacetolol; Enantiomers; Milk; Infant.

# Introduction

Acebutolol (AC) is a chiral  $\beta$ -Adrenergic receptor blocking agent possessing ISA, and membrane stabilizing effects cardioselectivity (1, 2). It is clinically effective in the treatment of hypertension, suppression of premature ventricular contractions and other cardiac arrhythmias (3, 4). Like most  $\beta$ blockers, the pharmacological activity of the racemate resides predominantly with the Senantiomer in man (5). AC is extensively metabolized upon first pass through the liver (6, 7) and the disposition of both AC and its active metabolite diacetolol (DC) are stereoselective (7). Moreover, the concentration of DC enantiomers in human plasma is 2-3 times more

than that of parent drug (8).

In the present study the stereoselective excretion of AC and DC in breast milk as well as fetus were investigated during prenatal period.

# Case history

A 32 year old woman with essential hypertension since 1985 has been with AC since 1991. She has had a number of other health problems including thyroiditis, irritable bowel syndrome, and iron deficiency anemia of unexplained cause. Agents other than beta blockers and other beta blockers have not been effective in treating her blood pressure.

Her first pregnancy occurred in 1994. During this pregnancy, she was treated with AC and aspirin. She was induced at 38 weeks gestation for pregnancy-induced hypertension after two short hospitalizations for management

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of hypertension. The baby was delivered, weighing 4400 g. His physical examination was within normal limits although his mother felt he had decreased tone. His blood pressure was not measured in the immediate neonatal period. He was discharged home with his mother on the MABLE (Mother and Babies Leave Early) program after two days. She showed a video to her physician that had made of the baby at 9 days of age. In this, he appears to have the muscle tone of a preterm infant at approximately 34-36 weeks gestation. He had an episode of fever and hypotonia at 10 days of age for which he was admitted to the IWK hospital in Halifax. Although the working diagnosis was acute viral infection, this was never proven. The baby recovered but continued to be somewhat hypotonic. The problem was felt by the mother and pediatrician to be due to the AC which baby would have received across the placenta as well as from the breast milk. Breast milk levels of AC were unable to be tested because there was no method available at the time. The mother subsequently discontinued AC in order to breast feed for several months. The infant continued to have strider and possible sleep apnea. He appears to be developing normally, is bright and curious. However his parents feel he still does not have the muscle strength of his peers; in particular, he has difficulty climbing stairs. In the past he has shown an excessive startle reaction, particularly to loud noise.

In the present pregnancy the mother was followed by her family doctor and obstetrician for chronic hypertension. She began taking low dose aspirin early in the pregnancy. She continued on the AC, preferring not to switch to alternatives and monitored her blood pressure at home. She was admitted to hospital because of elevated blood pressure (167/111) with palpitation and headaches. Reflexes were 3+ but there were no clues. The ultrasound showed the baby to be in transverse lie and planning score was good (8/8). Liver enzymes were not elevated and her coagulation profile was normal. The following day, her blood pressure had stabilized and the baby was felt to be a cephalic presentation. Her planning score was 8/8 and her blood pressure was 110/78. She was discharged home to be followed up in clinic. She was readmitted next day with 3-week

history of increasing blood pressure. On admission, she had a blood pressure of 152/106; a trace of proteinuria and a planning score 10/10. As her baby was in breech position, it was planned to attempt an external version. This was carried out a week later. After 3 attempts at unsuccessful version, it was decided to proceed with cesarean section. A male delivered by cesarean section under spinal anesthesia. The baby weighed 3350 g, and had APGAR scores of 9 at 1 minute and 9 at 5 minutes. It had been planned to monitor the baby in the intensive care unit initially, and the baby was transferred to the NICU for monitoring. The baby did well in NICU; there was no hypoglycemia, or respiratory distress. Blood pressure measurements were within the normal range. The heart rate measured in the low range at 100/minutes, at times dipping down to 80-90 per minute with no associated change in color. There was no respiratory distress. On physical examination, there were no abnormalities other than decreased tone including lying with extremities extended and incomplete Moro response. There was marked head lag. The baby appeared to be quite 1/2 h post feeding, but roused to wakefulness readily and was easily soothed.

After 24 h of monitoring, the infant was transferred to the full term nursery to be with his mother. Intermittent monitoring continued with respiratory and heart rate q4h, blood pressure and temperature q12h. Vital signs continued to be stable. Because of concerns of ongoing decreased tone (when improvement might have been expected with decreasing AC levels), metabolic and hematological screens were carried out. Blood gases, electrolytes, glucose, CBC, white cell differential and urine analysis were all within normal limits. The baby was seen by a physician who agreed that the tone was globally decreased, there was very poor head control and marked ventral suspension. He felt that the infant moved well and that muscle strength was within normal limits. Deep tendon reflexes were brisk and sensation was intact. Etiology was not clear but possibility of AC effect remained as it has been suggested that acebutolol is one of the most toxic beta blockers (9).

The infant was fed on similac 20 or carnation good stay during his hospital course.

His weight decreased to 3281 g by 2 days of age, and then increased by discharge to 3460 g. The etiology of central hypotonia was unknown. The role of AC was also unknown; the blood and breast milk levels of AC were collected to be measured.

## **Experimental**

One hundred mg of AC (Moniton, Wyeth-Ayerst) was taken in the morning at 8:00 AM. The maternal plasma sample was collected after delivery at 12:26 PM. At this time two plasma samples were also taken from baby (Cord blood). Further, the maternal plasma samples were taken the day after delivery at 16:00 and at the third day at 13:10. The breast milk was taken at 16:10 and at 12:30 at the second and third days of post delivery, respectively.

Concentrations of R- and S-AC and R- and S-DC in plasma and breast milk were determined utilizing a previously reported stereospecific HPLC method (10, 11). Briefly, samples were extracted with diethyl ether after addition of racemic pindolol as the IS and subsequent alkalization with 1 M sodium hydroxide. After the extract was evaporated, the resulting residues were derivatized with the homochiral reagent, S-(+)-1-(1-naphthyl) ethyl isocvanate. The resulting diastereomers corresponding to the enantiomers of AC and DC were chromatographed via normal phase HPLC using fluorescence detection.

#### **Results and discussions**

The current report supports previous observation (12) that AC and its major metabolite DC are excreted in breast milk (Table 1). In that report a non stereoselective



**Figure 1.** The enantiomeric concentrations of acebutolol and diacetolol in breast milk 4.5 and 8 h after the acebutolol administration.

method has been used for AC measurement, consequently they did not report any stereoselectivity for this drug in milk. Our results are indicated that the clearance of AC in milk was stereoselective in favor of R-AC. Consequently, the concentration of R-DC was higher than that of its antipode.

The concentrations of AC in milk 4 hours after drug administration was 127 and 148 ng/ml which were decreased to 41 and 48 ng/kg after 8 hours for R- and S-AC respectively. This value for R- and S-DC was 112 and 57 ng/ml however; it was increased to 141 and 88 ng/ml after 8 hours for R- and S-enantiomers, respectively (Table. 1). This indicated that DC enantiomers are more concentrated than that of AC in breast milk. This is a plausible finding as DC is less protein bound and more hydrophilic than the parent drug. Further, the DC half-life is reportedly longer than that of AC in plasma (8).

In the infant described in this report, we did not find AC in cord blood samples four hours after drug administration, the concentrations of DC enantiomers however, were 90 and 66 ng/ml in cord vein and 70 and 50 ng/ml in cord artery for R-and S-DC, respectively. This could be explained by the longer elimination half life and the higher concentration of DC enantiomers in maternal plasma which results in higher concentrations of DC enantiomers in fetus and breast milk.

The pharmacological effects of AC results from both unchanged drug and its metabolite DC which is equipotent to AC. In animal experiments, DC has greater  $\beta_1$  selectivity (13). It has also weak intrinsic sympathomimetic activity but does not have substantial membrane stabilizing activity. Thus, the observed effects of AC in this infant may be contributed to DC, since plasma and milk concentrations of the metabolite are consistently higher than those of the parent drug during AC therapy.

| Table 1. The concentrations of AC and DC enantiomers in |
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| maternal plasma and milk and in infant plasma.          |

| Sample type | Date     | Time     | Concentrations, ng/ml |     |            |     |
|-------------|----------|----------|-----------------------|-----|------------|-----|
|             |          |          | Acebutolol            |     | Diacetolol |     |
|             |          |          | R                     | S   | R          | S   |
| Plasma      | March 29 | 12:30 PM | 69                    | 81  | 125        | 104 |
| Baby vein   | March 29 | 12:30 PM | ND                    | ND  | 90         | 66  |
| Baby artery | March 29 | 12:30 PM | ND                    | ND  | 70         | 50  |
| Breast milk | March 30 | 400 PM   | 41                    | 48  | 141        | 88  |
| Plasma      | March 30 | 00 PM    | ND                    | ND  | 62         | 45  |
| Plasma      | April 1  | 100 PM   | 39                    | 65  | 202        | 154 |
| Breast milk | April 1  | 12:30 PM | 127                   | 148 | 112        | 57  |

ND, Not detectable due to low concentration

In Conclusion, this case demonstrates that DC is stereoselectively distributed to the fetus through the cord. Further, our results support previous report that AC and DC are excreted in milk however we found that this is stereoselective. Moreover, the concentrations of DC enantiomers are always higher than that of AC in milk and fetus as it has been reported for human plasma.

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