Concentration Changes of Medroxyprogesterone Acetate in Serum and Milk in Lactating Woman Who Used Depo Geston®

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Objective  To determine the concentration changes of medroxyprogesterone acetate (MPA) in serum and milk in the Chinese lactating women who used Depo Geston®

Methods  Ten postpartum and breastfeeding women received an injectable contraceptive of Depo Geston® (depo medroxyprogesterone acetate, DMPA, 150 mg/ampoule). Serum and milk samples were collected in the 1st, 2nd, 4th, 6th, 8th, 10th and 12th week after contraceptive injection. The concentrations of medroxyprogesterone acetate (MPA) in serum and milk were determined by radioimmunoassay.

Results  The highest MPA concentration in serum was observed at the 1st week and then the level of serum MPA decreased obviously at the 2nd and 4th week. After the 4th week, the decline of serum MPA level slowed down. The concentration of milk MPA reached the highest level at 1st week. But at the 2nd week the average level of MPA in milk dropped by half. The MPA concentration in the milk was changed in the range of 5.2–8.3 ng/mL in the following 10 weeks. During observation, the average ratios of concentration and area under curve (AUC) in milk/serum were both 0.55. There was a wide variation in MPA concentrations and ratios of milk/serum between subjects.

Conclusion  MPA concentrations maintained a certain level at the 12th week after DMPA injection. However, whether mother’s intake of DMPA during feeding period has effect on children’s growth, especially pubertal growth, deserves further studies.

Key words: depot medroxyprogesterone acetate (DMPA); injectable contraceptive; duration of lactation; MPA concentration and ratio in serum/milk

As single progesterone contraceptive injectable, DMPA has been used for over three
decades. This injectable contraceptive was introduced to China in 1986, and registered again in 1994. From 1995 to 1997, Institute of Family Planning Research, Zhejiang Academy of Medical Sciences, conducted two multicenter clinical trials on two preparations of DMPA, Depo Provera and Depo Geston. Depo Provera contains 150 mg MPA in 1 mL sterile aqueous suspension and Depo Geston contains 150 mg MPA in 3 mL sterile aqueous suspension in each vial respectively. The results showed that MPA injectable contraceptive has the same high efficacy for Chinese women as in other countries. As a convenient and reversible contraceptive, DMPA has no side effect especially on breast-feeding and provides a better contraceptive choice for lactating women. But, in China, there were few research reports on the concentrations of MPA in serum and milk and their effects on the growth and development of next generation whose mother used DMPA during lactation.

Subjects & Methods

Depo Geston® (P.T. Triyasa Nagamas Farma, Indonesia, batch number 8507003), an MPA long-acting injectable contraceptive, contains 150 mg DMPA in 3 mL aqueous microcrystalline suspension. Radioimmunoassay reagent kits were provided by the Immunometrics Ltd., UK. Totally 10 subjects were enrolled in this study.

Criteria of admittance

Healthy, postpartum and lactating women who ages between 20–35 were selected. All subjects were volunteered to participate in this study and had signed their consents. They agree to use only Depo Geston® as contraceptive method and do not use any other drugs that has influence on the metabolism of MPA, e.g. aminoglycosides preparations. They were able to pay follow-up visits to the clinic on-schedule for collection of serum and milk samples.

Criteria of exclusion

Subjects with any of the following conditions were excluded: no lactation after parturition, diabetes, grade III or above Papanicolaou smear, confirmed hypertension, history of thromboembolism, vaginal bleeding of unknown etiology, history of severe liver disease, or abnormal liver function, diagnosed or suspected malignancy, and abnormal discharge from nipples.

Methods

Follow-up visits

The subjects received the injection in the first five days of their menstrual cycle, or at any convenient time after 6 weeks post-delivery if their menstrual cycle did not initiate by then. In the morning of the 1st, 2nd, 4th, 6th, 8th, 10th and 12th week after injection, the subjects visited the clinic to collect intravenous blood (5 mL) and milk from their bilateral breasts (10 mL). Serum was obtained after centrifugalizing and separating of the blood samples. All samples of serum and milk were stored at −20°C for determination.

Determination of MPA

Radioimmunoassay was used to detect MPA concentrations in serum and milk. The serum MPA concentrations were measured after ether extraction. The
Breast milk samples were precipitated by methanol to remove most of the interfering proteins before ether extraction. The between-batches CVs were <12% and the values of ether blank all were within the 95% confidence limit of B0 value. The final results were obtained with the method, i.e., the values read off standard curve were multiplied by a factor that corrects for the volume of serum and milk extracted and allows for procedural losses.

Results

Subjects’ characteristics

The subjects were postpartum (1.5 to over 7 months) and breast-feeding women who had 1–2 deliveries and sufficient milk-secretion in the study duration. Their average age was 28 years (21–34 years old) and BMI was 19.81–27.89.

MPA concentrations in serum

From the first week to the 12th week after Depo Geston® injection, the average MPA concentrations in serum dropped gradually from 23.25 ± 6.90 ng/mL to 10.84 ± 3.73 ng/mL. A sharp decrease in the serum MPA concentrations was observed during week 1–4. Among the subjects, there were variant changes in the MPA concentrations of serum. For example, the highest MPA concentration at the first week and an obvious decline afterward (33.90–9.00 ng/mL) were found on subject No. 7; while a lower MPA concentration and slight fluctuation were observed on subject No. 6 (14.71–9.88 ng/mL) (Figure 1).

MPA concentration in milk

From the first week to the 12th week after Depo Geston® injection, the average MPA concentrations in milk dropped gradually from 16.83 ± 9.61 ng/mL to 6.61 ± 3.43 ng/mL. By the 2nd week, the average concentration almost halved, and then the MPA concentrations varied only in a small range (5.20–8.30 ng/mL) for the following ten weeks. Significant individual differences were found in the MPA concentrations in milk. For example, subject No. 8 exhibited a lower MPA concentration in milk; yet for subject No. 6, higher MPA concentrations in milk were detected at the first and second week after injection and afterward dropped rapidly and were maintained at less than 9 ng/mL (Figure 1).

Ratios of MPA concentration and AUC in milk/serum

The average ratios of MPA concentration in milk/serum were between 0.43–0.75 during the study period. The highest ratio value was found at the first week after injection and the total average ratio was 0.55. There were evident individual differences both between subjects and in the same subject at different times. The milk/serum ratios were of wide variance at each visit between subjects. The lowest ratio was 0.09 and the highest one reached 1.70. This phenomenon could be found in the same subject too. For example, the ratios of MPA in milk/serum were...
fluctuating between 0.25–1.12 at follow-up visits in subject No. 3 (Figure 2).

The data indicated again there were individual differences between subjects. The ranges of AUC ratios were 0.17–1.35, being the average of 0.55. We can observe that the levels of MPA in milk were higher than those in serum and the ratio values were larger than 1 at 10 visit times in 4 subjects. The inverse ratios of AUC were found in subjects No. 1 and No. 4.

**Discussion**

WHO and some countries have conducted some studies of MPA concentrations in serum or plasma and the amount of MPA transferred to milk. Saxena et al.\(^1\) has found that the ratio of concentration of MPA in milk: plasma was almost 1:1 in 7 lactating women after
using injectable contraceptive DMPA. WHO[4] has reported that some MPA in maternal plasma transfers into milk and their ratios range is 100:60 to 1:1. In Thailand, a study showed the changes of MPA concentrations in milk and serum in 6 women using DMPA. At the 1st week after injection, the range of MPA concentrations in serum were 9.4-38.5 ng/mL and on average decreased to less than 5 ng/mL at the 8th week. The MPA concentrations in milk were 5.6–16.5 ng/mL at the 1st first week and on average dropped down to less than 2 ng/mL at the 4th week[5]. Another control study of the same author has reported the results from 10 subjects who were followed-up 12 weeks after injecting contraceptive DMPA. The results have showed that the ratios of MPA in milk and serum were 0.12–2.60, with the average of 0.88. At the 8th week, the MPA concentrations in serum were higher than 400 pg/mL. At the 12th week, only 2 subjects had less than 100 pg/mL levels of MPA concentrations in serum. The MPA concentrations in milk were usually lower than those in serum. But at 26% of the follow-up timepoints it appeared that MPA milk levels were higher than those in serum and there was a wide individual variation between subjects[6]. We found in our study that the average MPA concentrations in serum are 23.25 ± 6.09 ng/mL at the 1st week after injection in 10 subjects. The average levels of MPA concentration in milk are 5.20–16.83 ng/mL. There are also significant individual differences between subjects and in the same subject at different times. These findings are consistent with the foreign research results mentioned above. The serum MPA is only loosely bound to albumin in serum and theoretically available for transfer into milk in full dose. But much of the reported information, including our laboratory results, showed the ratio of serum/milk was not 1:1[4-6]. So a large number of samples and more detailed researches would be needed to find out the causes of the differences. However, at the 12th week, the MPA concentrations in serum and milk are 10.84 ± 3.73 ng/mL and 6.29 ± 3.48 ng/mL, respectively, which are higher than those of the foreign research results; while the average AUC ratio in milk/serum (0.55) in our study is slightly lower than that of similar researches in other countries.

Injectable contraceptive DMPA has been applied clinically for over three decades. Many countries, including some Asia countries, have conducted researches into effects on secreting milk and development in next generations. These studies indicate that MPA does not have significant effects on secreting and components of milk[7-9]. A laboratory research shows that serum MPA levels in the infants whose mothers were exposed to DMPA during breast-feeding are at or below trace levels due to very low protein binding coefficient of MPA in serum and milk. The study conducted by Emery[8] also indicates that an infant can ingest 0.08–0.25 μg/(kg·d) DMPA and it receive 1.5–6.0 μg/(kg·d) progesterone when it ingests cow’s milk. The prospective surveys on growth and development in infants and children do not find any adverse evidences[4,10,11]. In China, two injectable contraceptive DMPA have been introduced successfully and they obtained the same contraceptive efficacy in fertile women, especially for lactating women. However, few reports were found in this aspect. Zhao et al.[12] conducted a tracking study on growth and
development in children (4–6 years old) whose mother used injectable contraceptive DMPA during lactation and they found no negative proof.

Our study provided some laboratory evidences for MPA ingestion of baby by breast feeding. However, some studies indicate that the ratio of progesterone component transferring from blood to milk in DMPA is larger than that in other steroid contraceptives (e.g. norethisterone, D-norgestrel)\[^{3,4,6}\]. We found that the MPA concentrations in milk still maintained at a certain level at the 12th week after DMPA injection. Judging from our laboratory data, suppose an infant consumes 800 mL of milk/d, then his/her daily intake of MPA will be obviously higher than the amounts of MPA ingested by an infant per day per kilogram, which has been reported by other literature. So further studies need to be conducted to determine whether mother’s intake of DMPA during breast-feeding period has effect on children’s growth, especially pubertal growth.

**References**


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