Br. J. Pharmac. (1977), **59**, 433–434

THE RELEASE OF PROLACTIN BY MEDROXY-PROGESTERONE ACETATE IN HUMAN SUBJECTS

R.R. CHAUDHURY, S. CHOMPOOTAWEEP, N. DUSITSIN, H. FRIESEN[1] & M. TANKEYOON

WHO Research Team for Clinical Evaluation of Fertility Regulating Agents, Chulalongkorn Hospital Medical School, Bangkok, Thailand

Medroxyprogesterone acetate an injectable contraceptive when administered to four lactating women at a dose of 150 mg every three months significantly raised prolactin levels over those observed in four control women. Prolactin levels were higher at all times during 4–17 weeks in the drug-treated women, irrespective of whether the samples were collected before or after suckling. It was also observed that while suckling clearly released prolactin in both groups the difference was greater in the women receiving the injection, indicating that the drug enhanced the release of prolactin in response to the suckling stimulus.

Introduction A contraceptive agent which also caused an increase in the secretion of milk would be of great benefit, particularly in developing countries where mothers nurse their infants for long periods. It has been suggested that the injectable contraceptive, medroxyprogestone acetate (MPA) increases milk secretion in nursing mothers (Karim, Ammar, El Mahgoub, El Ganzoury, Fikri & Abdou, 1971; Koetswang, Chiemprasert & Kochananda, 1972), but there has been no detailed study of this attribute. The effect of MPA on the serum prolactin levels of lactating women has, therefore, been assessed in this investigation.

Methods The eight subjects aged 20–39 years were of similar socio-economic status and all had a previous history of successful lactation. The women nursed their infants at least five times a day for a minimum of 17 weeks. The 4 control women used non-hormonal means of contraception while the other 4 women were given an intramuscular injection of 150 mg MPA (Upjohn Ltd) at 2 and 14 weeks after parturition. The mothers were instructed not to nurse the babies for at least 3 h before coming to the clinic. At the clinic, a blood sample was taken and the infant was then immediately allowed to suck at one breast while milk was collected from the other by means of an Egnell breast pump. A second sample of blood was collected after 30 min of suckling. Similar pairs of blood samples were obtained at the end of weeks 1, 2, 4, 6, 8, 12, 15 and 17 of lactation.

The serum was immediately separated from the blood samples collected and stored at –40°C until assayed for prolactin by the radioimmunoassay procedure described by Hwang, Guyda & Friesen (1971). There is no cross-reactivity in this assay with thyrotrophin, growth hormone or human placental lactogen. The sensitivity was 1–5 ng/ml prolactin. The inter- and intra-assay variations were 15% and 10% respectively.

The prolactin levels at weeks 1 and 2 after birth were compared with the Wilcoxon Sum Test (Hollander & Wolfe, 1973). A regression analysis was used to determine the change in prolactin levels as lactation continued (Snedecor & Cochran, 1967). A paired t test or a sign test were used to evaluate the differences in the prolactin levels (Snedecor & Cochran, 1967).

Results The results are shown in Table 1. The basal levels of circulating prolactin were those at weeks 1 and 2, before the MPA treatment had started. The apparent differences between the median prolactin levels of the control and MPA-treated women before and after suckling at weeks 1 and 2 were not significant ($P > 0.10$ for all four comparisons), indicating that the two groups of women were therefore comparable.

There were significant declines in prolactin levels as lactation proceeded except for the blood samples taken after suckling in the women treated with MPA. In the control women the decline was 8.56 ± 0.67 (s.e. mean) ng prolactin ml^{-1} $week^{-1}$ before suckling and 16.01 ± 6.40 ng ml^{-1} $week^{-1}$ after suckling.

Prolactin levels were higher at all times during weeks 4–17 in the MPA-treated women than in the controls, irrespective of whether the samples were collected before or after suckling.

Discussion The results obtained in this investigation suggest that the significantly raised levels of prolactin in the blood in the MPA-treated group at all times was a result of the MPA administration. Since it appears unlikely that the drug would interfere with the metabolism of normally released prolactin during lactation it appears that MPA acts either by directly releasing prolactin from the anterior pituitary or by inhibiting the normally occurring secretion of the prolactin inhibitory factor from the hypothalamus. Suckling clearly released prolactin in both groups, but

[1] Department of Physiology, University of Manitoba, Medical School, Winnipeg, Canada.

Table 1 Median (and range) prolactin levels (ng/ml serum) before and after suckling during lactation of women treated with medroxyprogesterone acetate (MPA)

Weeks after birth	*Before suckling*		*After suckling*	
	*Control**	*MPA**	*Control**	*MPA**
1	112 (27–250)	128 (28–285)	125 (55–250)	205 (160–285)
2†	80 (18–205)	64 (29–170)	188 (25–275)	133 (85–165)
4	54 (13–145)	56 (30–90)	130 (13–180)	133 (60–195)
6	44 (12–80)	48 (33–95)	72 (27–155)	113 (47–165)
8	26 (21–75)	35 (11–75)	46 (32–115)	80 (31–100)
12	20 (9–75)	32 (11–40)	37 (21–145)	116 (21–255)
15	19 (8–145)	25 (15–45)	28 (20–150)	72 (45–140)
17	20 (14–105)	23 (16–50)	44 (16–105)	49 (40–140)
Value of regression	<0.05	<0.02	<0.05	NS
Value of difference between groups	<0.02		<0.01	

* 4 women/group; † MPA treatment started after this sampling period.

the difference was greater in the women receiving MPA, suggesting that the drug not only induces release of prolactin but also enhances the release of prolactin in response to the suckling stimulus. These findings have two clinical implications. If the amenorrhoea and delayed return of ovulation associated with the use of MPA is the result of the release of prolactin then treatment with bromocryptine, a drug which suppresses the formation of prolactin may prevent the occurrence of these side effects. It is also possible that this pharmacological release of prolactin could be used to increase milk secretion where it is inadequate.

We thank Dr J.J. Schlesselman of the NICHHD, Bethesda U.S.A. and Mrs Yupha Onthuam of the WHO Research Team for the statistical analyses.

References

HWANG, P., GUYDA, H. & FRIESEN, H. (1971). A radioimmunoassay for human prolactin. *Proc. Natn. Acad. Sci. U.S.A.*, 1902–1906.

HOLLANDER, M. & WOLFE, D.A. (1973). *Non-parametric Statistical Methods*. New York: Wiley.

KARIM, K., AMMAR, R., EL MAHGOUB, S., EL GANZOURY, B., FIKRI, F. & ABDOU, I. (1971). Effect of injectable contraceptive progestogen on lactation and breast fed infant. *Br. med. J.*, **1**, 200–203.

KOETSWANG, S., CHIEMPRASERT, T. & KOCHANANDA, P. (1972). The effects of injectable contraceptives on lactation. *Clin. Proc. I.P.P.F. S.E. Asia and Oceania Regional Medical and Scientific Congress* pp. 84–90. Sydney. Published by I.P.P.F.

SNEDECOR, G.W. & COCHRAN, W.G. (1967). *Statistical Methods*. Ames: Iowa State University Press.

(Received November 27, 1976.)