CLINICAL RESEARCH

Sulpiride improves inadequate lactation

O YLIKORKALA, A KAUPPILA, S KIVINEN, L VIINIKKA

Abstract

Twenty-eight newly delivered mothers with inadequate lactation volunteered for a placebo-controlled double-blind trial of sulpiride 50 mg thrice daily for four weeks. Treatment was allocated at random, and serum prolactin concentrations and breast-milk yields were measured before and serially during the trial. Of the 26 women who completed the trial, 14 had taken sulpiride and 12 the placebo.

In the sulpiride-treatment group the mean maternal serum prolactin concentration rose from 49·0±SE 3·6 μg/l to a maximum of 402·1±43·2 μg/l at two weeks; in the placebo-treated group, however, the concentration fell during the trial (from 84·7±24·0 μg/l to 47·8±8·6 μg/l). Mean breast-milk yields also increased in the sulpiride-treatment group (by an average of 212-265 ml) and fell in the women given placebo.

Of the 14 infants in the sulpiride-treatment group, four did not need supplementary feeds during the trial; in the control group, however, all infants continued to require such feeds. Infants in the sulpiride-treatment group gained significantly more weight than did the controls ($p < 0·05$). Three women taking sulpiride complained of mild side effects, but none occurred in the infants.

These findings suggest that sulpiride is an effective treatment for inadequate lactation in the puerperium.

Introduction

The superiority of breast feeding to artificial feeding of infants[1-3] has led to an increased prevalence of breast feeding.[3-5] Nevertheless, some 20-40% of mothers willing to breast feed suffer from inadequate lactation.[3] These mothers may benefit from treatment with the prolactin-stimulating agent metoclopramide.[6] Sulpiride is also a potent prolactin-releasing drug,[7 8] and we have therefore evaluated the effect of sulpiride on insufficient lactation.

University of Helsinki, Haartmaninkatu 2, SF-00290 Helsinki 29
O YLIKORKALA, MD, associate professor of obstetrics and gynaecology

University of Oulu, SF-90220 Oulu 22, Finland
A KAUPPILA, MD, associate professor of obstetrics and gynaecology
S KIVINEN, MD, senior lecturer in obstetrics and gynaecology
L VIINIKKA, MD, senior lecturer in clinical chemistry

Subjects and methods

All mothers being delivered in our hospital were told about the study and asked to contact us if during the first four months after delivery they thought that their milk yields were insufficient. Of those who contacted us, mothers with breast or other diseases possibly responsible for poor lactation were excluded. The remainder were asked to breast feed without medication for one day and to measure the milk yields and supplementary feeds required, as described below. After this baseline period mothers returned to the centre, and only those whose yield of breast milk was at least 30% below the estimated normal breast-milk intake (165 ml/kg/day[9]) were included in the study.

Twenty-eight women satisfied our criteria (see table), of whom three had no milk yield at all. Ten had given birth to their first child, and 18 were multiparous and had breast fed their other infants for 1-10 months (mean 3·5±SE 0·6 months). All of the mothers gave informed consent and the study was approved by the local ethical committee.

The mothers were given consecutively numbered packages containing, in random order, either 50 mg sulpiride tablets or an identical-looking placebo. The tablets were taken three times a day for four weeks. Maternal blood samples for serum prolactin measurements (prolactin radioimmunoassay kit, Diagnostic Products Corporation, Los Angeles, California) were collected at the beginning of the trial and at the end of each treatment week one to three hours after the last tablet. We also measured the height of the nipples (nipple tip to nipple base) with a special ruler calibrated in millimetres.

Milk yield was estimated by weighing the infant immediately before and after breast feeding on the baseline day and on days 3, 5, 7, 14, 21, and 28 of treatment. The mothers breast fed as often as they judged appropriate, and the sum of these milk yields was taken as the total daily yield (see table). The mothers also measured all the supplementary feeds needed on the test days. The table shows the comparability of the two treatment groups.

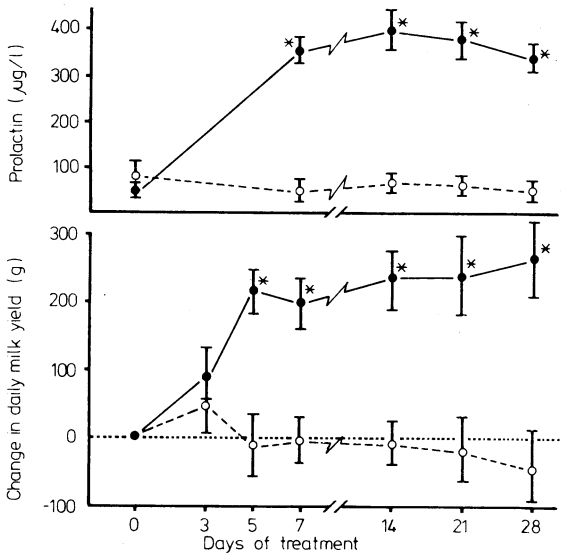
After completion of the trial a code identifying the drugs was broken. Student's t test, binomial t tests, and regression analysis were used for statistical evaluations.

Results

Two women in the placebo group discontinued the trial because of lack of effect of the treatment and were excluded from the final analysis.

Clinical details of study populations at start of trial. Figures are means±SE (ranges in parentheses)

	Group allocated to sulpiride	Group allocated to placebo
No of women	14	14
Age (years)	29·7±1·3	29·1±1·5
Parity	1·4 (1-5)	1·4 (1-4)
Height of nipples (mm)	8·9±0·6	8·6±0·7
Infants' weight (g)	5097±505	4909±266
Milk yield (ml/kg/day)	76·4±47 (0-110)	72·3±56 (0-105)
Days from delivery to entry to study	62·1±12·1 (14-100)	55·6±9·5 (18-120)
Duration of use of supplementary feeds (days)	22·3±6·7 (3-49)	33·1±9·1 (2-45)
Supplementary feeds (ml)	498±88	434±68
No of breast feeds/day	5·3±0·3 (4-7)	5·3±0·3 (4-7)



Mean (±SE) serum prolactin concentrations and changes in daily milk yields in 14 mothers receiving sulpiride (●) and 12 receiving placebo (○). *p<0·001.

Maternal serum prolactin concentrations—Before the trial serum prolactin concentrations showed no difference between the two treatment groups (fig). Basal concentrations were not related to basal daily milk yields. Sulpiride treatment was accompanied by persistent rises in serum prolactin concentrations (fig).

Breast-milk yields—In 13 of the 14 women given sulpiride the daily milk yields increased by 90-730 ml. In the other patient the daily milk yield decreased by 30-40 ml despite a rise in serum prolactin concentration to 628 μg/l. Increased breast-milk yields showed no relation to serum prolactin concentrations, time intervals between delivery and start of the trial, or size of the nipples. In three of 12 women treated with placebo the milk secretion increased (100-230 ml), but in the others secretion fell. From the fifth treatment day onwards the changes in daily milk yields differed significantly between the two treatment groups (fig). Of the women who completed the trial with sulpiride and placebo, 11 and three, respectively, regarded the treatment as effective ($p < 0.01$).

Supplementary feeds—All infants needed supplementary feeds before the trial (table). During the trial, however, four infants in the sulpiride-treatment group (one after five days, two after seven days, and one after 14 days) no longer needed artificial feeds; in contrast all infants of mothers receiving placebo continued to require supplementary feeds during the trial.

Weight gain of infants—Infants of mothers given sulpiride showed a greater increase in weight (mean 1081±SE 111 g) ($p < 0.05$) than the infants of mothers receiving placebo (mean 795±35 g).

Side effects—During sulpiride treatment one woman complained of headache and two of tiredness. There were no side effects of placebo. No neonatal side effects were reported with either agent.

Discussion

As a result of much study and discussion[1 3] mothers are much more interested in breast feeding than they were a few years ago.[3-5] Nevertheless, despite a positive attitude to breast feeding there are always some mothers in whom lactation does not become established or stops too early.[3] Such mothers soon become frustrated and may regard themselves as inadequate, which may seriously disturb the developing mother-infant relationship.

Evidence suggests that an important reason for insufficient lactation is deficient secretion of prolactin.[10-14] In this regard nipple size may be a factor, since stimulation of the nipple triggers the neural pathways resulting in prolactin release during suckling.[13] Attempts to improve lactation with oral thyrotrophin-releasing hormone were initially encouraging,[15] but the treatment did not increase the measured breast-milk yields; possibly this was due to failure of thyrotrophin-releasing hormone to maintain raised serum prolactin concentrations.[16] More promising results were obtained by stimulating prolactin secretion with the antidopaminergic drug metoclopramide.[6] Also oxytocin nasal spray enhances lactation in mothers using a breast pump.[17]

Our study is the first to show that sulpiride improves established lactational deficiency, apparently by increasing prolactin secretion. Though increased prolactin secretion was observed within a few hours,[7 8] the lactational response did not occur before the fifth day of treatment. This accords with our findings using metoclopramide[6] and suggests that the lactogenic effect of prolactin is a long process requiring possibly profound biochemical changes in the breasts. This delayed response may also explain why no relation was seen between the actual prolactin concentrations and milk yields. Sulpiride may, however, increase milk secretion sooner in normally lactating mothers during the first postpartum week.[18]

The effect of sulpiride on breast milk resulted in four infants no longer needing supplementary feeds. Furthermore, probably even in the remainder the increased yield had important nutritional, biochemical, anti-infective, and psychological value. This is supported by the faster weight gain in the infants in the sulpiride-treatment group.

Sulpiride caused no serious maternal or neonatal side effects. The drug is excreted in breast milk, and a concentration of about 1 μg/l was reported during maternal treatment with 100 mg daily; the milk was otherwise normal.[18] Hence with an average daily intake of 700 ml of milk an infant would receive less than 1 mg sulpiride daily. Such a small amount would be very unlikely to stimulate prolactin release or have other central and peripheral actions[8] in the infant; nevertheless, before sulpiride is adopted for more widespread use in inadequate lactation, possible endocrinological and other effects on the infant should be studied.

This study was supported by the Finnish Academy of Science. Sulpiride and placebo tablets were donated by Leiras Ltd, Turku, Finland.

References

1 Jelliffe DB, Jelliffe EFP. Current concepts in nutrition. "Breast is best": modern meaning. *N Engl J Med* 1977;**297**:912-5.
2 Fleischman AR, Finberg L. Breast milk for term and premature infants, optimal nutrition. *Semin Perinatol* 1979;**3**:397-405.
3 Winikoff B, Baer EC. The obstetrician's opportunity: translating "breast is best" from theory to practice. *Am J Obstet Gynecol* 1980;**138**:105-17.
4 Sloper KS, Elsden E, Baum JD. Increasing breast feeding in a community. *Arch Dis Child* 1977;**52**:700-2.
5 Coles EJ, Cotter S, Valman HB. Increasing prevalence of breast feeding. *Br Med J* 1978;ii:1122.
6 Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. *Lancet* 1981;i:1175-7.
7 Mancini AM, Guitelman A, Vargas CA, Debeljuk L, Aparicio NJ. Effect of sulpiride on serum prolactin in humans. *J Clin Endocrinol Metab* 1976;**42**:1881-4.
8 Jenner P, Marsden CD. The substituted benzamides—a novel class of dopamine antagonists. *Life Sci* 1979;**23**:479-86.
9 Anderson PO. Drugs and breast feeding. *Semin Perinatol* 1979;**3**:271-8.
10 Tyson JE, Friesen HG, Anderson MS. Human lactational and ovarian response to endogenous prolactin release. *Science* 1972;**177**:897-900.

[11] Noel GL, Suh HK, Franz AG. Prolactin release during nursing and breast stimulation in postpartum and non-postpartum subjects. *J Clin Endocrinol Metab* 1974;**38**:413-23.
[12] Tyson JE, Khojandi M, Huth J, Andreassen B. Influence of prolactin secretion on human lactation. *J Clin Endocrinol Metab* 1975;**40**:764-73.
[13] Tucker HA. Endocrinology of lactation. *Semin Perinatol* 1979;**3**:199-223.
[14] Lunn PG, Prentice MA, Austin S, Whitehead RG. Influence of maternal diet on plasma-prolactin during lactation. *Lancet* 1980;i:623-5.
[15] Tyson JE, Perez A, Zanarty J. Human lactational response to oral thyrotropin releasing hormone. *J Clin Endocrinol Metab* 1976;**43**:760-8.
[16] Ylikorkala O, Kivinen S, Kauppila A. Oral administration of TRH in puerperal women: effect on insufficient lactation, thyroid hormones and the responses of TSH and prolactin to intravenous TRH. *Acta Encrinol (Copenh)* 1980;**93**:413-8.
[17] Ruis H, Holland R, Doesburg W, Broeders G, Corbey R. Oxytocin enhances onset of lactation among mothers delivering prematurely. *Br Med J* 1981;**283**:340-2.
[18] Aono T, Shioji T, Aki T, Hirota K, Nomura A, Kurachi K. Augmentation of puerperal lactation by oral administration of sulpiride. *J Clin Endocrinol Metab* 1979;**48**:478-82.

(*Accepted 5 May 1982*)

Response of patients to upper gastrointestinal endoscopy: effect of inherent personality traits and premedication with diazepam

M J WEBBERLEY, A CUSCHIERI

Abstract

The influence of personality traits on the reaction of patients to upper gastrointestinal endoscopy was studied prospectively in 86 patients. High N (neuroticism) scores on the Eysenck personality inventory were associated with poor tolerance to and future compliance with the procedure. Although premedication with diazepam did not affect the degree of discomfort and distress during the procedure, it guaranteed acceptance of repeat endoscopy by virtue of its strong amnesic effect. By contrast, not giving premedication to patients who were anxious and had high N scores jeopardised future compliance.

These findings suggest that a version of the Eysenck personality inventory should be used to assess patients' neurotic phenotype and their need for premedication before endoscopy. Alternatively, all patients might be given premedication.

Introduction

Considerable controversy exists regarding the benefit of premedication with diazepam in patients undergoing fibreoptic upper gastrointestinal endoscopy,[1-3] but most studies have neglected the influence of personality traits on the patients' reaction to endoscopy despite the prevalent clinical impression that neurotic individuals exhibit poor compliance to this investigative procedure. The use of diazepam seems justified by its powerful anxiolytic and amnesic effects. On the other hand, there are well-documented disadvantages to its use, including its long half life in the circulation, inducement of violence in young alcoholics, respiratory depression, and thrombophlebitis due to a local irritant effect at the site of injection, although this last has been reduced considerably by use of a combination of diazepam and intralipid (Diazemuls). These adverse effects have precluded its use by some endoscopists particularly when the procedure is performed on outpatients. The aim of this study was to evaluate any influence of inherent personality traits on patient reaction to endoscopy with and without diazepam with a view to improving overall patient compliance.

Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY
M J WEBBERLEY, final-year medical student
A CUSCHIERI, MD, CHM, professor

Patients and methods

The study was undertaken prospectively on 86 patients (38 women, 48 men) selected at random and about to undergo upper gastrointestinal endoscopy in a clinical measurement unit served by several endoscopists (physicians and surgeons). The patients were aged 16-85 years; 77 were outpatients and nine inpatients.

The nature of the forthcoming procedure was explained to each patient by a nurse. Thereafter each patient was asked to complete the Eysenck personality inventory[4] and to indicate his degree of anxiety on a linear anxiety scale. The Eysenck personality inventory is used to assess the phenotype of patients' personality traits and is well validated. It contains three scales: N measures degrees of neuroticism, E measures extraversion or introversion, and L denotes the lie scale, which indicates whether an individual is faking his responses. A high L score should lead the examiner to regard the N and E scores with scepticism.

After completing the inventory each patient was conducted to the endoscopy room. Patients received intravenous diazepam (10 to 20 mg) and atropine or no sedation or premedication in accordance with the practice of the endoscopist, some of whom administered diazepam routinely to all their patients and others not. We did not actively interfere in the procedure. Fifty-nine of the 86 patients were given diazepam. All patients were examined in the left lateral position in an illuminated room with an Olympus paediatric fibreoptic endoscope.

Observer assessment during endoscopy was aimed at noting the patients' tolerance to the procedure, co-operation, anxiety, and reaction to insertion of the endoscope and air insufflation. All patients were interviewed briefly on recovery and asked to complete a questionnaire about their impressions of and feelings on the procedure and more specifically their memory of the procedure, their attitude towards it, and their willingness to undergo further endoscopy if necessary. A further questionnaire was sent to each patient one to two weeks after endoscopy; this covered the same points, albeit in more detail, and was intended to assess whether patients' delayed impressions differed from their reactions immediately after endoscopy. Statistical analyses were carried out using Student's t test for unpaired data and the χ^2 test as appropriate.

Results

Anxiety—The patients were subgrouped according to whether they were very anxious, moderately anxious, or not anxious before the procedure (table I). The very anxious subgroup had a marginally higher mean N score than the rest, but this difference was not significant ($0{\cdot}5 > p > 0{\cdot}01$). Anxiety before the procedure did not significantly alter tolerance to it ($p > 0{\cdot}5$).