SULPIRIDE ISOMERS AND MILK SECRETION IN PUERPERIUM

F. POLATTI

Obstetric and Gynecologic Clinic
University of Pavia (Italy)

SUMMARY

The effect of oral administration of sulpiride isomers on PRL secretion and breast engorgement was studied in 60 multiparous nursing mothers, according to a double blind schedule: 45 women were orally given 50 mg sulpiride (L, D, L-D form) twice daily during the first 5 days of puerperium, 15 were given a placebo in the same way.

Basal, the 3rd and 5th day serum PRL levels were determined and every day milk secretion was evaluated. On milk samples obtained on the 5th day, sulpiride concentration was measured.

40 women with insufficient lactation and 20 with total lack of milk, 25-40 days after delivery, were treated in the same way, in double blind.

Milk secretion was evaluated at the beginning and at the 5th, 10th and 15th day.

The mean total milk yield (± S.D.) during the first 5 postpartum days in sulpiride groups were significantly greater than that in the control group. Plasma PRL levels resulted significantly higher in sulpiride treated groups than in placebo group.

All women with insufficient or absent milk secretion could avoid supplemental bottle-feeding after 10 days of treatment.

It has been well documented that PRL plays a very important role in the stimulation of puerperal lactation and induces the synthesis of beta-caseine ([1]) and alpha-lactalbumine ([2]) in the alveolar cells.

Attempts have been made to increase puerperal lactation by hyperprolactinemic drugs, like metoclopramide ([3, 4]) and sulpiride ([5]).

The effect of TRH treatment on milk secretion is contradictory ([6, 7]) thought it raises serum PRL levels ([8]).

It has been reported that sulpiride ([5]) and metoclopramide ([4, 9]) increase milk secretion in puerperium, and breast growth and milk production in male ermaphrodites ([10]); furthermore, sulpiride is often used in early childhood ([11, 12]) with inconsistent side effects and does not interfere with thyroid hormones ([9]).

Detailed analysis of the lactational effects of puerperal sulpiride therapy has not yet been performed: this prompted us to study the effect of oral sulpiride isomers on the initiation of lactation and to evaluate which of the three forms (L-sulpiride, D-L-sulpiride, D-sulpiride) is the most active.

Further we have evaluated the effectiveness of sulpiride in inducing milk secretion in women with poor or absent lactation, 25-40 days after delivery.

MATERIAL AND METHODS

60 multiparous women, aged 24-32 years, who had normally delivered and referred insufficient lactation in previous puerperia partecipated in this investigation after receiving detailed information about the trial. These patients were divided into 4 groups (A, B, C, D) and treated in double blind conditions with sulpiride (L-sulpiride, D-L sulpiride and D-sulpiride) or placebo, orally given in 50 mg doses twice daily at 6.30 a.m. and 6.30 p.m. for the first 5 days after delivery.

Serum PRL levels were determined on basal conditions, on the 3rd and 5th treatment day. Measurements of PRL were performed in duplicate by a RIA kit supplied by Biodata Serono ([16]).

Milk yield was estimated by test weighing infants before and after nursing. After nursing

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Table 1. — *Mean serum PRL levels in ng/ml (± S.D.) in nursing mothers.*

Group	Treatment	No. cases	Basal	3rd day	5th day
A	Control	15	109±13.4	100± 7.1	64± 8.2
B	D-sulpiride	15	107±14	198±18 [a]	170±13 [a]
C	D-L-sulpiride	15	111±13.6	191±29 [b]	162±19.8 [b]
D	L-sulpiride	15	111±13.8	239±22.9 [a b]	192±17.5 [a b]

[a] $p<0.001$
[b] $p<0.001$

the breasts were emptied by breast-pump until flow almost ceased. Milk volume obtained by pump-extraction was also recorded.

A single milk sample of more than 50 ml was obtained from each woman on the 5th post-partum day, 4 hours after the drug administration; analysis of sulpiride concentrations was performed after the pH of the milk had been adjusted to 10 by addition of 1 M glycine buffer. Sulpiride was extracted with chloroform containing isoamilalcohol ([5]) and measured by spectrophotofluorimetric method ([13]).

Sixty volunteer puerperal women entered the trial 25-40 days after delivery: 40 patients with poor lactation (i.e.: less than 350 ml/day of milk) were divided into 4 randomized groups (EFGH) and 20 patients without lactation were also randomized into 4 groups (ILMN).

Sulpiride (L-sulpiride, D-L sulpiride or D-sulpiride) at 50 mg doses or placebo were orally administered in double blind conditions, twice daily for 15 days.

Milk yield was evaluated on the 5th, 10th, 15th day according to the same procedure as reported for patients of groups A, B, C, D.

RESULTS

Serum PRL levels and milk volumes obtained in groups A, B, C and D are reported in table 1 and 2. Milk volumes obtained in patients with poor lactation and in those without lactation are reported in table 3 and 4 respectively.

Mean sulpiride concentrations in milk samples obtained on the 5th day of treatment from patients of A, B, C and D groups, were: A = undeterminable; B = 0.84±0.10 ug/ml; C=0.85±0.15 ug/ml; D=0.81±0.11 ug/ml.

Minimal value, among the three treated groups, was 0.32 ug/ml and the maximum 1.46 ug/ml.

Statistical analysis of results was performed according to paired and unpaired Student's t test.

The mean percent increase of milk volume of B, C and D group (being 100%

Table 2. — *Mean milk yielding (± S.D.) in nursing mothers.*

Group	Treatment	No. cases	1 st day	2nd day	3rd day	4th day	5th day	Total milk (%)
A	Control	15	0	57±23	143±42	241±52	334±38	775±48 (100%)
B	D-sulpiride	15	0	65±28	270±19 [a]	415±35 [a]	540±21 [a c]	1290±66 (166.4%)
C	D-L-sulpiride	15	15.4±10	116±22	285±21 [b]	430±30	565±17 [b c]	1410±79 (182%)
D	L-sulpiride	15	18 ±22	154±39	334±26 [a b]	485±46	596±24 [a b]	1587±53 (204%)

[a] $p<0.001$
[b] $p<0.001$
[c] $p<0.001$

Table 3. — *Mean milk yielding (± S.D.) in women with insufficient lactation.*

Group	Treatment	No. cases	Basal	5th day	10th day	15th day
E	Control	10	301±24	310±40	270±32	—
F	D-sulpiride	10	280±30	372±21 [a b]	450±18 [a]	530±26 [a]
G	D-L-sulpiride	10	301±14	410±25 [a b]	461±25 [a]	544±38 [a]
H	L-sulpiride	10	288±19	460±15	515±22	605±21

[a] $p<0.001$
[b] $p<0.001$

A group) resulted: 166.4% (B group), 182% (C group) and 204% (D group) (on the 5th day of treatment).

In women with insufficient lactation the increase, being the basal value of control group = 100%, was 176% (F group), 181% (G group) and 201% (H group).

All women with insufficient lactation could avoid supplemental alimentation for their infants after 6 days of treatment.

Women without lactation treated with L-sulpiride interrupted supplemental bottle-feeding after the 10th day, those treated with D-sulpiride or D-L-sulpiride did it after the 15th day.

No side effects were reported during treatment. Withdrawal of treatment with D, D-L, L-sulpiride in patients with insufficient or absent lactation induced a progressive reduction of milk secretion.

DISCUSSION

Sulpiride administration induced in all treated women a remarkable increase of serum PRL levels (tab. 1).

The different PRL values obtained with sulpiride isomers may depend on their relative potency and specificity for dopaminergic receptors ([14]).

The increase of serum PRL levels, together with PRL activity on the synthesis of alpha-lactoalbumine ([2]) and beta-caseine ([1]) may well explain the increased milk production.

Results obtained with D-L-sulpiride confirm those of Aono *et al.* ([5]); D-sulpiride and D-L-sulpiride had a similar activity both in insufficient lactation and in absence of milk: this is likely due to similar serum PRL levels induced by long lasting isomer treatment ([15]). L-sulpiride induced the greatest milk production and the quickest increase of secretion, this is probably related to the higher PRL levels induced by L-isomer ([15]).

Sulpiride administration in women with insufficient lactation induced an increase of milk secretion higher than reported by Kauppila *et al.* ([9]) with metoclopramide for 21 days (144%).

It is worthy to note that in mothers with total absence of milk (tab. 4) L-sulpiride allowed the suspension of supplemental feeding after 6-7 days of administration.

Table 4. — *Mean milk yielding (± S.D.) in women with absent lactation.*

Group	Treatment	No. cases	Basal	5th day	10th day	15th day
I	Control	5	0	15±10	20±12	0
L	D-sulpiride	5	0	75±11	235±14	456±19
M	D-L-sulpiride	5	0	90±15	250±26	464±32
N	L-sulpiride	5	0	140±22	440±31	585±26

As far as milk composition is concerned no significant difference between the mean concentration of fat, protein and lactose in milk from control and sulpiride treated mothers has been reported ([5]).

The increase of milk production observed in patients with insufficient lactation and total absence of milk is due to the increase in plasma PRL levels induced by sulpiride, and baby's suckling.

The lack of serious side effects both in mothers and in infants, indicates sulpiride as a new and effective drug to increase milk production both in absent and in insufficient lactation.

L-sulpiride resulted the most effective isomer in all groups studied, inducing the greatest amount of milk and the fastest increase of secretion. Nevertheless we must underline that the hyperprolactinemia induced by sulpiride without baby's suckling, produces only a modest galactorrhea.

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