Suppression of Puerperal Lactation with an Ergot Alkaloid: A Double-blind Study

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Summary

A double-blind trial was performed in 60 women to establish the effectiveness of an ergot alkaloid, 2-Br-alpha-ergocryptine (ergocryptine; CB 154), in suppressing puerperal lactation and to compare it with stilboestrol and a placebo. At the doses selected ergocryptine and stilboestrol were equally effective.

Introduction

Recent evidence strongly suggests the existence of pituitary prolactin as a separate entity from growth hormone (Frantz and Kleinberg, 1970; Friesen *et al.*, 1970; Forsyth *et al.*, 1971). Nevertheless, the present inability to measure conveniently prolactin reliably in plasma samples makes it difficult to assess a drug which may specifically inhibit this hormone. In animals the ergot alkaloid 2-Br-alpha-ergocryptine (ergocryptine; CB 154) has been shown to inhibit lactation and other prolactin-dependent functions (Flückiger and Wagner, 1968, and unpublished data; Yanai and Nagasawa, 1970a). Recently ergocryptine has been shown to inhibit prolactin release from human pituitary tissue cultures (Pasteels *et al.*, 1971). On the basis of these and other laboratory data, ergocryptine was given to patients suffering from non-puerperal galactorrhoea. The results of these clinical observations (Lutterbeck *et al.*, 1971) are consistent with the assumption that ergocryptine specifically inhibits prolactin secretion. The ability of ergocryptine to suppress puerperal lactation would provide further evidence for a specific anti-prolactin action.

The purpose of this investigation was to use the inhibition of puerperal lactation as a model to compare the potential effectiveness of ergocryptine with that of stilboestrol and placebo under double-blind controlled conditions.

Subjects and Method

The study was conducted on 60 consecutive non-breast-feeding mothers who were randomly assigned to one of three groups. The groups were similar as regards age, height, weight, parity, number of pregnancies, and duration of pregnancy. Three identical cachets were used containing either a placebo, stilboestrol, or ergocryptine. After delivery each subject received two cachets a day—one before breakfast and one before dinner—for the first six days followed by a single cachet before breakfast for the next three days. The dosage schedule for oestrogen included 20 mg twice daily for the first three days, 10 mg twice daily for the second three days, and 10 mg a day for the last three days. This dosage schedule is similar to a regimen once used in all Cardiff hospitals (Daniel *et al.*, 1967). Those receiving ergocryptine were given 5 mg twice daily for the first six days and 5 mg a day for the last three days. Under double-blind conditions therapy was initiated within 24 hours after delivery, on average within 12 hours.

The nurse filled in a form which required observations for nine days on the state of the breasts and on the occurrence of mammary congestion and acute mammary engorgement. The same nurse observer was used throughout the course of the trial, including the follow-up period. The patients were not given supportive measures such as cathartics or breast binders. The nurse was instructed to use analgesics freely so that no patient suffered unnecessary pain. The degree of mammary congestion was graded as absent (0), mild (1), moderate (2), or severe (3). The assessments were made three times daily, at about 08·00, 12·00, and 16·00 hours. In most cases patients were sent home on the seventh postpartum day. Until the ninth day each patient returned for at least one daily assessment. Acute mammary engorgement was noted as +, its absence as −. Blood pressure and pulse measurements were performed shortly before the intake of each cachet and again one hour thereafter. Side effects were recorded and a follow-up assessment of the patients after discharge from the hospital was obtained.

Results

The results of the three groups (see Table) clearly show that ergocryptine and oestrogen suppress postpartum lactation in comparison to placebo. The difference is highly significant ($P < 0.001$). In the placebo group, 18 out of 20 women experienced acute mammary engorgement while only one in each of the two other groups did so. Follow-up questioning suggested that there was less rebound mammary engorgement with ergocryptine (5 out of 20) than with stilboestrol (9 of 20). No changes in blood pressure, pulse, or other side effects were reported. Throughout the course of the study there was no evidence of thromboembolic disease in any of the three groups.

Frequency of Mammary Congestion (M.C.) and Acute Mammary Engorgement (A.M.E.)

Placebo			Ergocryptine			Oestrogen		
Case No.	M.C.*	A.M.E.	Case No.	M.C.*	A.M.E.	Case No.	M.C.*	A.M.E.
1	23	+	2	8	+	4	2	−
5	17	+	3	5	−	6	0	−
7	15	−	8	0	−	10	13	−
9	21	+	11	0	−	12	7	+
15	16	+	16	0	−	13	0	−
18	45	+	17	0	−	14	0	−
19	19	+	20	0	−	21	0	−
23	22	+	22	0	−	24	0	−
25	15	+	28	1	−	26	0	−
27	12	+	30	0	−	29	0	−
31	16	+	33	1	−	32	0	−
34	13	+	36	0	−	35	0	−
37	9	−	39	0	−	40	0	−
38	17	+	41	0	−	42	0	−
44	27	+	47	0	−	43	0	−
46	5	+	48	0	−	45	0	−
49	16	+	50	0	−	52	0	−
51	4	+	54	0	−	53	0	−
56	16	+	59	0	−	55	0	−
57	15	+	60	0	−	58	0	−

* Numbers indicate total cumulative score after nine days following the scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

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Discussion

The results clearly show that ergocryptine suppresses postpartum lactation. Our previous experience with ergocryptine in the treatment of non-puerperal galactorrhoea (Lutterbeck *et al.*, 1971) also suggests a specific antiprolactin action. In the doses used the efficacy of ergocryptine and stilboestrol was similar. The only woman who received ergocryptine (Case 2) to experience acute mammary engorgement and exhibit definite congestion continued to suffer from galactorrhoea with amenorrhoea for five months after delivery. Shortly after readministering ergocryptine (1 mg thrice daily) to this patient galactorrhoea ceased and normal menstruation with ovulation started. This patient's response as well as that of others will be the subject of a separate report attempting to elucidate the mechanism of action of ergocryptine.

In several patients other than those in the trial ergocryptine was found to be effective not only when administered immediately post partum but also when lactation was established. In the latter situation oestrogens are much less effective, often failing or requiring much higher doses, which in turn may cause undesirable side effects. The above-mentioned dosages of ergocryptine were well tolerated and produced no side effects.

An exact dosage and duration of treatment schedule for ergocryptine is not yet available, but it seems that the schedule used in the trial will be very close to the most effective regimen. Of particular importance is the gradual lowering of the dose to avoid the rebound mammary engorgement which has been observed in several cases on discontinuing the higher doses.

The overall objective of this study was further to support the findings of various investigators in animals that ergocryptine interferes with pituitary prolactin (Flückiger and Wagner, 1968; Heuson *et al.*, 1970; Yanai and Nagasawa, 1970b, 1971; Billeter and Flückiger, 1971; Cassell *et al.*, 1971; Pasteels *et al.*, 1971; Quadri and Meites, 1971; Stahelin *et al.*, 1971; Hoekfelt and Fuxe, 1972; Schams *et al.*, 1972). We think that our results, along with those obtained from our experience in treating non-puerperal galactorrhoea, strongly indicate that ergocryptine may indeed interfere with pituitary prolactin. Studies involving prolactin blood levels in appropriate clinical conditions before and after ergocryptine administration are at present in progress.

Despite the possibility of an association between the use of oestrogen and the incidence of thromboembolism (Daniel *et al.*, 1967, 1968a, 1968b; Jeffcoate *et al.*, 1968), the evidence is by no means entirely conclusive (Gillibrand and Huntingford, 1968; Gunther and Kohorn, 1968; Llewellyn-Jones, 1968; Drill, 1972; Drill and Calhoun, 1972). A much larger series of cases must be studied before any conclusions can be drawn on whether there is an increased incidence of thromboembolism in subjects treated with oestrogens.

This preliminary study, showing the ability of ergocryptine to suppress puerperal lactation, should encourage further investigation. Detailed hormonal evaluation of the pharmacology of ergocryptine in various clinical states will be needed to establish more specifically the mechanism of action. Whether ergocryptine is preferable to oestrogen therapy in the puerperium will depend on the results of substantial additional investigations, particularly the incidence of thromboembolism.

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Clinical Screening of Epipodophyllotoxin VM26 in Malignant Lymphomas and Solid Tumours

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Summary

Epipodophyllotoxin (VM 26; 4′-demethyl-epipodophyllotoxin-β-D-thenylidene glucoside) has been proved, in clinical screening, to be able to induce apparently complete remissions and pronounced though incomplete regressions in Hodgkin's disease, reticulosarcoma, and bladder cancer, as well as incomplete regressions in lymphosarcoma. Apparently complete regressions of malignant pleural effusions have been obtained after giving this drug systemically. It has a notable toxic action on the bone marrow.

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Introduction

Epipodophyllotoxin (VM 26; 4′-demethyl-epipodophyllotoxin-β-D-thenylidene glucoside) (see Formula) is a semisynthetic