Dose-related changes in vaginal cytology after topical conjugated equine oestrogens

Symptoms of ovarian failure confined to the lower genital tract are probably most sensibly treated with topical oestrogens. The optimal dosage should relieve local discomfort without causing systemic side effects. Topical oestrogens, however, are rapidly absorbed into the peripheral circulation[1] and may depress gonadotrophin concentrations.[2] The recommended dosage of Premarin Vaginal Cream (conjugated equine oestrogens), 1·25 mg daily, yields plasma oestrogen concentrations almost identical with those after oral administration of that dose.[1] Excessive endometrial stimulation and hyperplasia may develop.[1 3] To determine whether a lower dose would reduce the local beneficial effects we have investigated the vaginal response to four different dosages of oestrogen cream.

Patients, methods, and results

We studied 24 patients aged 43-63 years. All had symptoms of lower genital tract atrophy and either had not menstruated spontaneously for 12 months or had menstruated but with at least three months between menses.[4] None had received any medication for three months.

After assessment patients were assigned at random to one of four groups (six women in each) allocated to receive 2 g cream nightly for one month containing either 0·1, 0·4, 0·8, or 1·25 mg conjugated equine oestrogens. The cream was inserted with an applicator, and neither the patients nor their attendants knew which dosage they were receiving. During treatment and for four weeks afterwards patients attended at weekly intervals. Symptoms were recorded and smears prepared from cells aspirated from the posterior fornix. Smears were fixed in shorr and haematoxylin and the oestrogen index[4] measured to assess epithelial cell proliferation and maturation.

Distribution of values in each group at each time was examined by calculating the arithmetic and geometric means, standard deviation (before and after log transformation), median, and degrees of skewness and kurtosis. Data were best described by a log-normal model. Oestrogen indices were compared using Student's t test on logged data.

The four groups were similar in age, menopausal state, and pretreatment oestrogen indices. With each regimen the mean oestrogen index was significantly increased after one week and the maximal response achieved after two weeks; values then declined (table).

Oestrogen indices in menopausal women before, during, and after treatment with four dosages of vaginal oestrogen cream. Figures are percentages (geometric means and ranges)

Weeks of study	Dose of oestrogen cream (mg/day)			
	0·1	0·4	0·8	1·25
		Before treatment		
0	4·7 (2–38)	3·1 (1–18)	2·7 (1–19)	10·4 (2–56)
		During treatment		
1	27·0 (5–80)*	72·0 (52–95)***	68·0 (50–90)***	64·7 (50–80)*
2	29·4 (10–74)**	72·5 (46–88)***	67·5 (54–92)**	81·5 (62–94)*
3	22·3 (3–80)*	52·3 (36–68)***	56·6 (38–84)***	59·6 (56–72)*
4	23·8 (2–78)*	50·2 (28–66)**	33·3 (6–80)**	47·0 (16–90)
		After treatment		
5	9·0 (6–12)*	24·5 (8–42)*	28·2 (20–64)**	33·9 (6–72)
6	13·5 (9–28)*	7·0 (2–14)	6·8 (2–30)	29·6 (22–52)
7	13·4 (5–22)*	5·3 (1–21)	2·5 (1–4)	7·5 (1–23)
8	13·1 (1–15)*	1·2 (1–2)	1·6 (1–3)	5·0 (1–30)

Compared with values before treatment: *$p<0.05$; **$p<0.005$; ***$p<0.0005$.

Oestrogen indices observed in our department during the menstrual cycle are between 15% and 30%, and the lowest dosage of oestrogen produced values within this range. Dosages of 0·4, 0·8, and 1·25 mg produced higher values than normal for women of reproductive age, and there were no significant differences in values among the three higher dosages.

Oestrogen indices remained significantly above baseline throughout the four weeks of follow-up after 0·1 mg, for one week only after 0·4 and 0·8 mg, and not at all after 1·25 mg.

Comment

Despite the wide range of oestrogen indices with all four dosages of oestrogen cream, indicating interpatient variation, the minimum daily dosage to induce premenopausal values for vaginal cytology was 0·1 mg. Though the three higher dosages are necessary for the relief of hot flushes, they are unlikely to be essential for relief of vaginal symptoms since equally beneficial local effects (paper in preparation) were observed with all dosages. Thus the manufacturer's recommended dosage can be greatly reduced.

The decrease in oestrogen index during the third and fourth weeks of treatment with all regimens confirms the loss of local effect with prolonged treatment.[1] There was no evidence of decreasing patient compliance. More likely was a loss of sensitivity to oestrogen within the vaginal epithelium: responsive tissues may become refractory when oestrogen stimulation lasts beyond 14 days.[5] Vaginal sensitivity may be lost because of changes such as tissue cornification or because of intracellular modifications, such as down-regulation of the receptor mechanism. Whatever the explanation, the oestrogen index decreased most in the last two weeks with dosages exceeding 0·4 mg and least with 0·1 mg.

The duration of the beneficial "carry-over" effects apparently depended on the initial dosage. The oestrogen index returned to the pretreatment range within seven days of stopping 1·25 mg and within 14 days of stopping 0·8 and 0·4 mg. With 0·1 mg, however, the mean values remained significantly above baseline during the four weeks of follow-up. Cellular responsiveness to oestrogen disappeared most rapidly with higher dosages, which also caused the quickest return to baseline after treatment. Failure to obtain symptomatic relief with high dosages of creams may be better managed not by further increasing the dosage but by stopping treatment for a short interval and then restarting at lower dose.

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Requests for reprints should be sent to Dr M I Whitehead.

1 Whitehead MI, Minardi J, Kitchin Y, Sharples MJ. Systemic absorption of estrogen from Premarin Vaginal Cream. In: Cooke ID, ed. *The role of estrogen/progestogen in the management of the menopause*. Lancaster: MTP Press Ltd, 1978:63-71.

2 Schiff I, Tulchinsky D, Ryan KJ. Vaginal absorption of estrone and 17β-estradiol. *Fertil Steril* 1977;**28**:1063.

3 Widholm O, Vartianen E. The absorption of conjugated oestrogen and sodium oestrone sulphate from the vagina. *Ann Chir Gynaecol* 1974;**63**: 186.

4 Campbell S, Whitehead MI. Estrogen therapy and the menopausal syndrome. In: Greenblatt RB, Studd JWW, eds. *Clinics in obstetrics and gynaecology*. Vol 4. No 1. London and Philadelphia: W B Saunders, 1977:31-47.

5 King RJB, Whitehead MI, Campbell S, Minardi J. Effects of estrogen and progestin treatments on endometria from postmenopausal women. *Cancer Res* 1979;**39**:1094-101.

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Paranoid psychosis after abuse of Actifed

Paranoid psychotic symptoms after the administration of ephedrine have been described.[1-3] The symptoms and their course are similar to those of psychosis induced by amphetamine-like drugs.[4 5] Ephedrine is found in many proprietary decongestant medications. I describe a case of paranoid psychosis after abuse of Actifed, a proprietary decongestant and antihistamine (5 ml Actifed contains 30 mg pseudoephedrine hydrochloride and 1·25 mg triprolidine hydrochloride).

Case report

A 27-year-old single male clerical worker presented at the psychiatric outpatient department in May 1981 complaining of acute psychotic symptoms. He had a six-year history of a bipolar affective disorder and from October

1980 had been treated with lithium (Liskonum 225 mg in the morning and 450 mg at night), since when his mood had been stable. He attended regularly for follow-up.

He described a 10-day history of paranoid symptoms, with ideas of influence (vibrations in his body) and auditory hallucinations (third-person commentary). He believed that his neighbours were trying to influence him and spying on him. These psychotic symptoms occurred in the absence of mood change and in the presence of clear consciousness. He had never experienced similar symptoms in the past. At this stage diagnosis was in doubt. Lithium treatment was continued as before and trifluoperazine 5 mg nightly added.

Two days later he was admitted to the psychiatric unit after the onset of muscle spasm and opisthotonos thought to be a dystonic reaction to the neuroleptic. This settled on admission after administration of procyclidine. Paranoid symptoms also settled quickly on the day after admission. He was discharged four days later taking the same medication. At follow-up 10 days later he appeared well, with no relapse of paranoid symptoms. Here the aetiology became clear. He admitted to having abused Actifed for many years, taking one to two bottles at weekends to help him relax, and he also found that it caused pleasant perceptual changes (sounds seemed louder and colours more vivid). Two weeks before presentation he had increased his intake to two bottles a day. He denied abuse of LSD or amphetamines. The hallucinations disappeared the day after he stopped Actifed.

Comment

There have been no previous reports of paranoid psychosis due to pseudoephedrine, which is a stereo isomer of ephedrine. Pseudoephedrine hydrochloride and ephedrine are structurally closely similar in formula to methylamphetamine hydrochloride, which has been specifically noted to induce psychosis. Actifed is a proprietary medicine, freely available over the counter. Pharmacists report that it sells well and is widely used. The possibility that Actifed abuse is common must be considered.

Routine questioning on abuse of Actifed may be appropriate in new cases of paranoid illness and also for known psychiatric patients, in whom the condition is likely to be misdiagnosed.

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[1] Roxanas MG, Spalding J. Ephedrine abuse psychosis. *Med J Aust* 1977; **2**:639-40.
[2] Otto KR, Nause R. Paranoid hallucinatory psychosis following chronic Asthmolytan. *Psychiatr Neurol Med Psychol (Leipz)* 1980;**32**:492-5.
[3] Herridge CF, A'Brook MF. Ephedrine psychosis. *Br Med J* 1968:ii:160.
[4] Snyder SH. Amphetamine psychosis: a "model" schizophrenia mediated by catecholamines. *Am J Psychiatry* 1973;**130**:61-7.
[5] Bell DS. Comparison of amphetamine psychosis and schizophrenia. *Br J Psychiatry* 1965;iii:701-7.

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Low doses of factor VIII for selected ankle bleeds in severe haemophilia A

Episodes of bleeding into the ankle joints in patients with severe haemophilia respond to 7 units of factor VIII/kg as well as to 14 units/kg.[1] We treated ankle bleeding with this reduced dose except when the joint had lost all movement or when less than one month had elapsed since the last bleed into that joint, when we used 14 units/kg. We treated 201 episodes with this regimen and report our results.

Patients, methods, and results

Forty-two pupils at this college with severe haemophilia A and without inhibitors of factor VIII bled into 66 ankle joints on 201 occasions during an academic year. Factor VIII at a dose of 14 units/kg was transfused during 106 bleeding episodes, and at a dose of 7 units/kg in 95 episodes.

The affected limb was always raised until signs and symptoms began to regress, and weight bearing was eliminated in the acute stages. The presence or absence of restriction of baseline movement, stiffness or pain as a presenting symptom, history of trauma, warmth, visible swelling, and the degree of movement restriction was noted on presentation. The loss of less than 50% of baseline movement was designated grade 1 and of more than 50% grade 2. The time taken from the onset of symptoms until the start of treatment was also noted. The joints were assessed at eight and 24 hours and every 12 hours thereafter until complete resolution. Further transfusions were given at eight hours for progression of signs or symptoms and thereafter for poor prognosis.

Twenty-four of the bleeds treated with 14 units/kg (23%) required a further transfusion compared with only 10 (11%) of the bleeds treated with 7 units/kg. This difference was significant ($\chi^2 = 4{\cdot}4$, $p = <0{\cdot}05$). The table shows factors associated with successful or unsuccessful treatment of bleeding episodes at the two dosage values, using retransfusion as a criterion. Differences between the proportions of bleeding episodes associated with success or failure, using a fourfold table, were not significant for any factor at the lower dose value. When the higher dose was used a significant increase in the proportion of bleeds presenting with pain ($\chi^2 = 6{\cdot}78$, $p = <0{\cdot}01$) and with loss of more than 50% of baseline movement ($\chi^2 = 7{\cdot}67$, $p = <0{\cdot}005$) was noted in the group of bleeding episodes treated unsuccessfully.

Number (%) of ankle haemarthroses in which various factors were present related to dose of factor VIII and success of treatment

Factors at presentation	Mean dose of factor VIII			
	7 units/kg		14 units/kg	
	Success (n = 85)	Failure (n = 10)	Success (n = 82)	Failure (n = 24)
Restriction of baseline movement	14 (16)	3 (30)	5 (6)	4 (17)
Stiffness	23 (27)	3 (30)	18 (22)	7 (29)
Pain	39 (46)	4 (40)	38 (46)	19 (79)
Trauma	23 (27)	1 (10)	14 (17)	8 (33)
Tenderness	68 (80)	8 (80)	73 (89)	24 (100)
Warmth	25 (29)	2 (20)	36 (44)	13 (54)
Swelling	61 (72)	7 (70)	72 (88)	24 (100)
Delay in treatment:				
<1 hour	49 (58)	5 (50)	37 (45)	15 (62)
1-2 hours	28 (33)	5 (50)	32 (39)	7 (29)
2-3 hours	5 (6)		5 (6)	1 (4)
>3 hours	4 (5)		7 (9)	1 (4)
Movement loss:				
Grade 1	60 (71)	5 (50)	40 (49)	20 (83)
Grade 2	25 (29)	5 (50)	52 (51)	4 (17)

Comment

When the ankle is not a target joint and retains some movement at presentation, bleeding may be treated with 7 units factor VIII/kg. There are no apparent predictive factors for the 10% of these bleeds needing retransfusion. Twenty-two per cent of recurrent bleeds or those causing complete loss of movement needed retransfusion despite a double initial dose of factor VIII. Pain and loss of more than 50% of baseline movement were the only two predictive factors for failure. Similar findings have been found with bleeding into the knees and elbows,[2 3] but in addition tenderness was an indicator of poor prognosis in those joints. This sign is so common in ankle joints, presumably because of the limited joint space, that it could not be discriminatory.

Before this approach was adopted our standard dose of factor VIII for treating all ankle bleeds was 14 units/kg. The reduction of 7 units/kg for 95 bleeds occurring in one academic year saved 30 000 units of factor VIII. This is not a large amount but if repeated nationally and internationally would result in substantial conservation of a scarce and expensive resource.

[1] Aronstam A, Wassef M, Choudhury DP, Turk PM, McLellan DS. Double-blind controlled trial of three dosage regimens in treatment of haemarthroses in haemophilia A. *Lancet* 1980;i:169.
[2] Aronstam A, Wassef M, Hamad Z, Aston DL. The identification of high-risk haemorrhage in adolescents with severe haemophilia A. *J Pediatr* 1981;**98**:776.
[3] Aronstam A, Wassef M, Hamad Z, Aston DL. The identification of high-risk knee bleeds in adolescents with severe haemophilia A. *Clin Lab Haematol* (in press).

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