

poor, nausea and vomiting were reduced by increasing the dose of the maintenance infusion during subsequent treatment to 5 and 6 mg/kg, respectively. This shows that the antiemetic effect of the drug can be optimised individually.

Neither regimen produced excessive side effects. Interestingly, diarrhoea was considerably reduced in the group receiving the continuous infusion, and it may be that wide fluctuations in plasma metoclopramide concentrations result in excessive intestinal hurry with resultant diarrhoea. Extrapyramidal reactions to metoclopramide are rare in this age group.

In view of an increasing tendency towards combination antiemetic treatment for emesis induced by cytotoxic drugs and the attendant concern over potential drug interactions the optimal use of individual antiemetics is considerably important. Thus we are encouraged by the considerable improvement in antiemetic effect achieved by high dose metoclopramide given as a loading dose and maintenance infusion after the application of simple pharmacokinetic principles. Future studies need to address the problems of the route and technique of administration of antiemetics and the dosage as well as identifying new compounds and combinations. Kris *et al* documented the time course of nausea and vomiting after administration of cisplatin.² They showed that nausea persisted for five days in 40% of patients and vomiting in 20%, with a peak incidence at three days after administration. In our study there was no difference in the duration of nausea and vomiting between the two arms, but the peak incidence of delayed nausea at three days agrees with the study of Kris *et al*.² This suggests that control of acute emesis after cisplatin does not necessarily reduce subsequent delayed emesis, and thus further improvements are required.

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Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women

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Abstract

The effect of the plasma oestradiol concentration on climacteric symptoms, gonadotrophin release, and bone resorption was studied in three groups of postmenopausal women given 0.025 mg, 0.05 mg, or 0.1 mg transdermal oestradiol daily. There was a dose related reduction in symptoms, plasma follicle stimulating hormone concentration, and urinary calcium and hydroxyproline excretion. The relation of the response to plasma oestradiol values was similar for each variable with an initial large reduction and little change in response to increases in the plasma oestradiol concentration above 150 pmol/l (41 pg/ml).

Hormone replacement therapy producing an effect equivalent to higher oestradiol concentrations is likely to increase the risk of side effects without conferring any additional benefit.

Introduction

Oestrogen replacement in postmenopausal women reduces both symptoms of the climacteric and excess bone resorption in a dose dependent manner.^{1,2} During the menstrual cycle, however, though the changes that occur in the plasma oestrogen concentration are of the same order of magnitude as those in women receiving postmenopausal hormone replacement therapy, they are not accompanied by any change in either oestrogen dependent symptoms or bone turnover.³ A possible explanation for this difference is that the response to oestrogen is near maximal at the plasma concentration present during menstruation and that only small changes in response occur with oestrogen concentrations within and above the premenopausal range.

If the response in bone to oestrogen has this relation it has implications for postmenopausal hormone replacement treatment, since the adverse effects of oestrogen treatment are dose related.⁴ Moreover, high doses of oestrogen have unwanted effects on bone as a result of inhibition of bone formation, which would be avoided by using the minimal dose of oestrogen to suppress resorption.

The establishment of such a dose has thus far been difficult because oestrogens are usually given by mouth. This causes hepatic "first pass" metabolism of the oestrogen, which appears in plasma as various metabolites with variable biological activity⁵ and increased concentrations of sex hormone binding globulin, which reduces the free hormone.⁶ Taken together these two phenomena make it impossible to assign any meaningful biological value

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to measured oestrogen concentrations after oral administration. Transdermal oestrogen, however, avoids both of these effects^{5,7} and the plasma oestradiol concentration is then an accurate indicator of biological activity.

Recently a means has been devised to administer drugs transdermally at a fixed rate by using a skin patch incorporating a rate limiting membrane.⁷ We have used this method of delivery to study the response of symptoms, gonadotrophin release, and bone resorption to varying concentrations of plasma oestrogen in postmenopausal women.

Patients and methods

We studied 26 normal postmenopausal women attending our clinic because of symptoms of the climacteric. All were postmenopausal as defined by at least six months' amenorrhoea together with raised plasma follicle stimulating hormone and low plasma oestradiol concentrations. No patient had received any hormone replacement therapy in the month before the study and none was receiving any drug known to affect calcium or bone metabolism. All patients received treatment with transdermal oestradiol from an adhesive patch with a controlled rate of release (TTS Estraderm; Ciba-Geigy, Horsham, Sussex). Patients were randomly allocated to receive one of three different sized patches delivering oestradiol at a rate of 0.025 mg, 0.05 mg, or 0.1 mg daily. The table gives the details of patients within each group.

All patients were studied basally and after three weeks of treatment. On each occasion a clinical assessment was made to enable a symptom score to be derived and blood and urine were obtained after an overnight fast for estimation of plasma follicle stimulating hormone and oestradiol concentrations and urinary excretion of calcium, creatinine, and hydroxyproline. Urinary calcium and creatinine were measured by standard autoanalyser techniques. Urinary hydroxyproline was measured by an automated colorimetric procedure after resin catalysed hydrolysis.⁸ Follicle stimulating hormone and oestradiol concentrations were measured by specific radioimmunoassays.

Statistical analysis within each treatment group was by paired *t* tests where the data were normally distributed and the Wilcoxon signed rank test otherwise.

Results

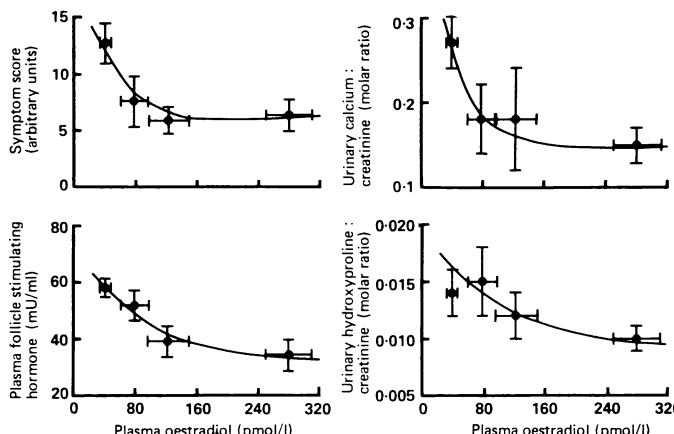
Treatment with the three doses of oestradiol resulted in a progressive rise in the mean plasma oestradiol concentration at three weeks. This rose from 36 (SE 4) pmol/l (9.7 (1.1) pg/ml) to 79 (18) pmol/l (21.3 (4.9) pg/ml) ($p < 0.05$) with 0.025 mg/day; from 46 (16) pmol/l (12.4 (4.3) pg/ml) to 122 (27) pmol/l (32.9 (7.3) pg/ml) ($p < 0.01$) with 0.05 mg/day; and from 41 (6) pmol/l (11.1 (1.6) pg/ml) to 281 (31) pmol/l (75.9 (8.4) pg/ml) ($p < 0.001$) with 0.1 mg/day (table).

All doses of oestrogen led to some relief of symptoms, but this was more pronounced with the two highest doses (table).

Plasma follicle stimulating hormone concentrations fell with all doses of oestrogen: from 62.5 (SE 3.6) mU/ml to 51.7 (4.8) mU/ml ($p < 0.01$) with 0.025 mg daily; from 53.6 (7.7) mU/ml to 38.6 (5.7) mU/ml (not significant) with 0.05 mg daily; and from 58.6 (3.7) mU/ml to 34.3 (5.2) mU/ml ($p < 0.001$) with 0.1 mg daily (table).

Treatment with 0.025 mg oestradiol daily caused a fall in urinary calcium excretion from 0.24 (SE 0.04) (molar ratio to creatinine) to 0.18 (0.04), but this failed to reach statistical significance. The higher doses produced significant changes: from 0.28 (0.07) to 0.18 (0.06) ($p < 0.01$) with 0.05 mg daily, and from 0.28 (0.05) to 0.15 (0.02) ($p < 0.05$) with 0.1 mg daily. Similar changes also occurred in urinary hydroxyproline excretion, which

rose non-significantly with 0.025 mg daily but fell from 0.014 (SE 0.003) (molar ratio to creatinine) to 0.012 (0.002) (not significant) with 0.05 mg daily and from 0.014 (0.002) to 0.010 (0.001) ($p < 0.05$) with 0.1 mg daily (table).



Relation between climacteric symptoms, plasma follicle stimulating hormone concentration, hydroxyproline:creatinine ratio, and calcium:creatinine ratio in urine collected after overnight fast and plasma oestradiol concentration in postmenopausal women treated with transdermal oestradiol. Data expressed as means and SE; untreated data combined for the three groups. In each case curved line is arbitrary line illustrating change in that variable with plasma oestrogen concentration.

Conversion: SI to traditional units—Oestradiol: 1 pmol/l \approx 0.27 pg/ml.

Since there were no significant differences in untreated values of symptom score, follicle stimulating hormone concentration, and urinary calcium and hydroxyproline excretion among the three treatment groups the untreated data were combined, allowing each of the measured variables to be related to the ambient plasma oestradiol concentration as a set of dose response curves. The figure shows the result.

Discussion

This study confirms the dose dependent action of oestrogen in reducing climacteric symptoms, gonadotrophin secretion, and bone resorption in the postmenopausal state.^{1,2} Because transdermal oestradiol does not undergo "first pass" hepatic metabolism and does not alter plasma binding proteins like oral oestradiol it is possible to relate the biological responses to the measured plasma concentrations of oestradiol achieved during treatment (figure). Despite the symptom study being uncontrolled the four responses were dose dependent, the greatest response occurring in the postmenopausal range of oestradiol but becoming asymptotic above a plasma oestradiol concentration of 150 pmol/l (41 pg/ml). This agrees with the observation that the changes in plasma oestradiol concentrations during the menstrual cycle, which are all above 150 pmol/l, have no measurable effect on bone turnover.³

Other workers have noted that the dose of oral oestrogen required to achieve each of its actions is different.¹ This does not appear to be the case with oestradiol administered transdermally; the dose

Patient details and response to treatment. Values are means (95% confidence limits in parentheses)

Oestradiol dose (mg/day)	No of patients	Age at study (years) [range]	Age at menopause (years) [range]	Plasma oestradiol (pmol/l)	Symptom score (arbitrary units)	Plasma follicle stimulating hormone (mU/ml)	Urinary calcium:creatinine (molar ratio)	Urinary hydroxyproline:creatinine (molar ratio)
Nil	26	50 [37-61]	45 [33-57]	41 (30-52)	13 (11-15)	58 (52-64)	0.27 (0.21-0.33)	0.014 (0.010-0.018)
0.025	7	49 [37-57]	45 [36-53]	79 (35-123)*	8 (3-13)	52 (40-63)**	0.18 (0.08-0.28)	0.015 (0.007-0.023)
0.05	8	50 [39-54]	46 [32-53]	122 (58-186)**	6 (3-8)**	39 (23-52)	0.18 (0.05-0.31)**	0.012 (0.007-0.015)
0.1	11	51 [37-61]	45 [28-57]	281 (212-350)***	6 (3-9)***	34 (23-46)***	0.15 (0.11-0.19)*	0.010 (0.007-0.012)*

Compared with baseline values within same treatment group: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Conversion: SI to traditional units—Oestradiol: 1 pmol/l \approx 0.27 pg/ml.

response curves for climacteric symptoms, gonadotrophin release from the pituitary, and bone resorption are all congruent. This equivalence adds weight to our previous studies which suggested that the action of oestrogen on bone is a direct receptor mediated response similar to that underlying the reduction in follicle stimulating hormone and not an indirect action via altered concentration of the calcitropic hormones, which might be expected to produce different dose response characteristics.^{9,10}

It is clear from these results that there is little to be gained from using doses of oestrogen above that which gives an effect equivalent to that produced by a plasma oestradiol concentration of 150 pmol/l (41 pg/ml). Indeed, any substantial increase in dose above this level is likely to increase adverse reactions without clinical benefit. Among these is the excessive suppression of bone remodelling,¹¹ which is probably essential for the maintenance of healthy bone.

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Hepatocellular carcinoma in urban born blacks: frequency and relation to hepatitis B virus infection

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Abstract

Chronic hepatitis B virus infection is far less common in urban born than in rural born southern African blacks, who also have a high incidence of hepatocellular carcinoma. A case-control study was carried out to determine the relative frequency of hepatocellular carcinoma and its relation to hepatitis B virus infection in urban born blacks. Three hundred and ninety two black patients with hepatocellular carcinoma and matched controls seen at two city hospitals were classified by questioning as urban born or rural born. The ratio of rural born to urban born blacks among the controls was 1.1:1.0 (207/185), whereas in the patients with cancer the ratio was 4.8:1.0 (324/68) ($p < 0.0001$). Analysis of the prevalence of hepatitis B markers in 62 urban born and matched rural born blacks with hepatocellular carcinoma showed no differences in the frequency of current or past hepatitis B virus infection.

It is concluded that urban born blacks are less likely than rural born blacks to develop hepatocellular carcinoma, but when they

do the tumour is equally likely to be related to infection with hepatitis B virus. The findings lend further support to an important role for chronic hepatitis B virus infection in the aetiology of hepatocellular carcinoma.

Introduction

Both chronic hepatitis B virus infection¹⁻³ and hepatocellular carcinoma^{4,5} are common in blacks born in rural areas of southern Africa. Rates of carriage of hepatitis B virus of up to 20% have been recorded in rural blacks.¹⁻³ The infection is almost always acquired in early childhood, predominantly as a result of horizontal transmission.^{2,3} Rural blacks develop hepatocellular carcinoma while relatively young^{6,7} and have age standardised frequency rates which may be as high as 104/100 000 yearly.^{4,5} Almost all of these patients show serological markers of current or past hepatitis B virus infection.⁸ Nothing is yet known about either the incidence of hepatocellular carcinoma or its relation to chronic hepatitis B virus infection in blacks who are born and grow up in an urban environment. We, however, have recently shown that urban black children have a carriage rate of hepatitis B virus of only 1%.⁹ If chronic infection with this virus is proved to be a main cause of hepatocellular carcinoma—and published evidence is persuasive^{10,11}—then the incidence of this tumour in blacks born in urban areas should be appreciably lower than that in blacks born and growing up in rural areas. We have therefore carried out a case-control study to determine the frequency of hepatocellular carcinoma in blacks born and living in an urban environment and to investigate the hepatitis B virus state of these patients.

Subjects and methods

Case-control study—The case-control study comprised 392 urban but otherwise unselected southern African blacks with histologically proved hepatocellular carcinoma and 392 matched controls. "Urban" blacks were

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