Pharmacokinetics of contraceptive steroids in patients with cystic fibrosis

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ABSTRACT The pharmacokinetics of the commonly used contraceptive steroids ethinyloestradiol and levonorgestrel were investigated after oral and intravenous administration in six women with cystic fibrosis. The results were compared with data obtained from healthy women of similar age. The total body clearance of ethinyloestradiol was significantly higher in the patients with cystic fibrosis (0·61 (SD 0·19) l/h/kg) than in control women (0·32 (0·16) l/h/kg; $p < 0.02$). In addition, the oral bioavailability of ethinyloestradiol was greater in women with cystic fibrosis than in controls (76·9% (11·7%) compared with 47·3% (7·5%); $p < 0.001$). As a result of these two changes, the area under the plasma concentration—time curve after an oral dose of ethinyloestradiol was similar in patients and controls. The pharmacokinetics of levonorgestrel did not differ significantly between patients with cystic fibrosis and healthy women. The data suggest that women with cystic fibrosis will receive similar contraceptive protection from these steroids as do healthy women.

Introduction

Most patients with cystic fibrosis are now surviving into adult life in developed countries.[1] Virtually all men with the disease are infertile owing to epididymal abnormalities, absent or defective vas deferentia, and hypoplastic or absent seminal vesicles.[2] In contrast, the disease appears to have little intrinsic effect on fertility in women, although there are reports of increased cervical mucus.[3] Amenorrhoea, and presumably failure of ovulation, occur in a few patients, who usually have advanced disease; these abnormalities are probably mainly related to undernutrition. There have now been many reports of pregnancies in women with cystic fibrosis, with widely varying outcomes.[4] There is a strong tendency for the pulmonary condition to deteriorate during pregnancy, and this tendency is related to the pregravid clinical condition. One study has suggested that only patients with near normal weight for height and only mildly reduced forced vital capacity showed no deterioration during pregnancy.[5] In addition, considerations such as reduced exercise tolerance and shortened life expectancy mean that patients with cystic fibrosis are often advised against pregnancy. Hence there is a need for highly effective and safe contraception for the increasing proportion of women with cystic fibrosis who are reaching the child bearing years, many of whom are marrying. For a few patients an intrauterine device may be satisfactory and in some patients, particularly those with more severe disease in whom pregnancy would be clearly contraindicated, sterilisation may be appropriate. For most of the fitter patients requiring contraception, however, an oral combined oestrogen and progestogen preparation is the method chosen. Combined preparations have been extensively and effectively used in our adolescent and adult cystic fibrosis clinic with no apparent adverse effects, and they are currently taken by about 30 of our patients.

Alterations in the pharmacokinetics of drugs resulting in lowered blood concentrations have been found in cystic fibrosis.[6 7] There is no information on the pharmacokinetics of contraceptive steroids in these patients, and the aim of the present study was to investigate this with particular reference to absorption and clearance.

Patients and methods

We studied six women with cystic fibrosis. All had a

sweat sodium concentration greater than 70 mmol (mEq)/l, typical pulmonary disease, and exocrine pancreatic insufficiency. Their median age was 25 (range 20–30) years, weight 48 (43–54) kg, weight as percentage of predicted normal[8] 92 (86–97), FEV_1 as percentage of predicted[9] 42 (22–87), and forced vital capacity (FVC) as percentage of predicted[9] 56 (45–99). Three patients had been taking a combined oral contraceptive preparation for at least three months; two of them were using Ovran (Wyeth) and the third Eugynon 50 (Schering), both of which contain ethinyloestradiol (50 µg) and levonorgestrel (250 µg). Other drugs taken by the patients included pancreatin (6), ranitidine (1), cimetidine (1), prednisolone—10 mg/day (2), aminophylline (1), and insulin (1). None of the patients had biochemical evidence of renal or hepatic dysfunction. They were clinically

stable and none had received oral or intravenous antibiotics within 10 days of a study day.

The study was approved by the ethics committee and informed consent was obtained. The three patients relying on oral contraceptive steroids for contraceptive protection were studied in the second half of the menstrual cycle. After an overnight fast subjects were randomly allocated to receive 50 µg of ethinyloestradiol and 250 µg of levonorgestrel orally or intravenously. Patients normally taking oral contraceptives had not received a dose within the previous 36 hours. The oral dose was given as the commercially available tablet Ovran (Wyeth). The ethinyloestradiol and levonorgestrel for intravenous administration had been separately dissolved in poly-

ethylene glycol, sterilised and sealed in separate ampoules containing 50 µg/ml and 250 µg/ml respectively. This procedure was carried out in the pharmacy department at the Royal Liverpool Hospital, where testing for sterility and pyrogens was also performed. The preparations were each diluted in sterile saline (10 ml) immediately before administration and were injected into a forearm vein through a "butterfly" needle, which was then removed. Blood samples (10 ml) were taken from an indwelling cannula into lithium heparin tubes before administration of the drugs and ½, 1, 1½, 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, and 24 hours later. After the intravenous dose the samples were taken from the arm opposite to that used for drug administration. Patients were allowed to eat 1½ hours after receiving the dose. The plasma was removed from the samples after centrifugation at 3000 rev/min for 10 minutes, and then stored at −20°C until analysis. The study was repeated with the alternative route of administration after an interval of not less than four days. Data for comparison were obtained from healthy women of similar age who were not taking contraceptive steroids or other medication.

Plasma ethinyloestradiol and levonorgestrel concentrations were measured by means of previously described radioimmunoassays.[10][11] In the three patients taking contraceptive steroids the plasma concentration values obtained were corrected by subtraction of the concentrations detected before they took the study doses. The area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) was calculated by the trapezoidal rule
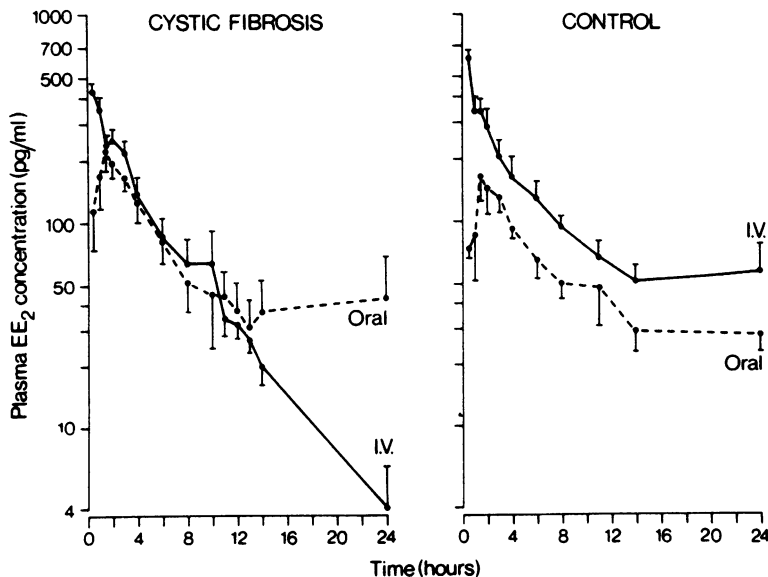

Fig 1 *Mean (SEM) plasma ethinyloestradiol (EE_2) concentrations after oral and intravenous administration of 50 µg in six patients with cystic fibrosis and six controls.*

Table 1 *Results of administration of ethinyloestradiol 50 µg*

(a) Mean (SD) area under the plasma concentration-time curve up to 24 hours (AUC$_{0-24}$) and bioavailability after oral and intravenous administration

	AUC$_{0-24}$		
	Oral (pg/ml.h)	Intravenous (pg/ml.h)	Bioavailability (%)
Cystic fibrosis (n = 6)	1275 (502)	1707 (554)	76·9 (11·7)
Control (n = 6)	1265 (463)	2707 (1057)	47·3 (7·5)
t test	NS	NS	p < 0·001

(b) Pharmacokinetic variables after intravenous administration

	Half life (h)	Clearance (l/h/kg)	Volume of distribution (l/kg)
Cystic fibrosis (n = 6)	5·2 (2·7)	0·61 (0·19)	4·84 (3·00)
Control (n = 6)	8·9 (3·6)	0·32 (0·16)	3·66 (1·13)
t test	NS	p < 0·02	NS

from the ratio of the oral to intravenous AUC$_{0-24}$ and expressed as a percentage. The elimination half life, total body clearance, and volume of distribution were also calculated for each steroid.[11]

STATISTICAL METHODS
Data from patients and controls were compared by means of Student's unpaired *t* test (two tailed).

Results

All subjects completed the study without any untoward effects.

ETHINYLOESTRADIOL
The mean ethinyloestradiol plasma concentrations after oral and intravenous administration in patients and controls are shown in figure 1. The bioavailability of ethinyloestradiol (table 1) was significantly greater in the patients with cystic fibrosis (76·9% (SD 11·7%) than in controls 47·3% (7·5%) (p < 0·001)), but the AUC after oral administration was virtually identical in patients (1275 (502) pg/ml.h) and controls (1265 (463) pg/ml.h).

There was a significantly greater total body clearance in the patients with cystic fibrosis than in the controls (0·61 (0·19) *v* 0·32 (0·16) l/h/kg; p < 0·02). The volume of distribution was not significantly
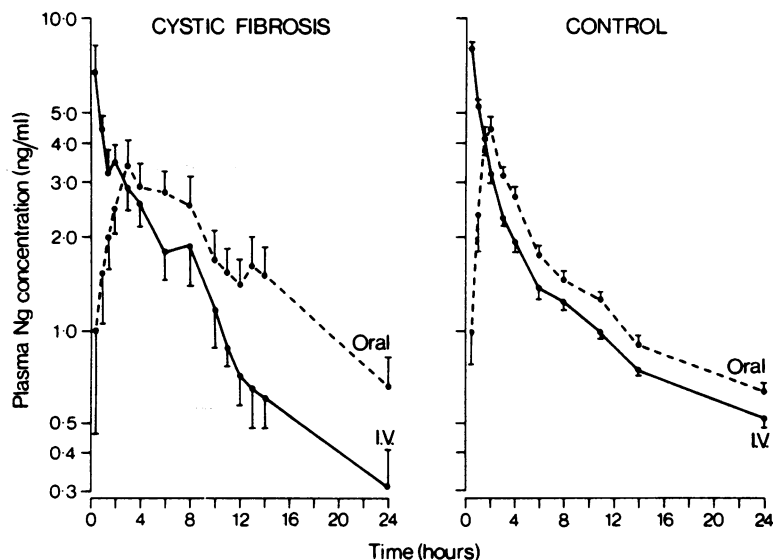

Fig 2 *Mean (SEM) plasma levonorgestrel (Ng) concentrations after oral and intravenous administration of 250 µg in six patients with cystic fibrosis and five controls.*

Table 2 *Results of administration of levonorgestrel 250 µg*

(a) Mean (SD) area under the plasma concentration-time curve up to 24 hours (AUC_{0-24}) and bioavailability after oral and intravenous administration

	AUC_{0-24}		
	Oral (ng/ml.h)	Intravenous (ng/ml.h)	Bioavailability (%)
Cystic fibrosis (n = 6)	40·0 (14·4)	36·7 (15·9)	113·6 (19·0)
Control (n = 5)	33·8 (9·0)	32·7 (6·5)	104·6 (22·3)
t test	NS	NS	NS

(b) Pharmacokinetic variables after intravenous administration

	Half life (h)	Clearance (l/h/kg)	Volume of distribution (l/kg)
Cystic fibrosis (n = 6)	6·4 (3·8)	0·16 (0·08)	1·30 (0·73)
Control (n = 5)	9·4 (1·3)	0·11 (0·02)	1·5 (0·2)
t test	NS	NS	NS

different in the patients (4·84 (3·00) l/kg) and controls (3·66 (1·13) l/kg); thus the tendency was for the elimination half life and AUC after the intravenous dose to be less in the patients, although these differences did not reach statistical significance.

LEVONORGESTREL

The mean plasma concentrations of levonorgestrel after oral and intravenous administration in patients and controls are shown in figure 2. There were no significant differences in the pharmacokinetic variables studied between the patients with cystic fibrosis and the controls (table 2), and in particular the AUCs after oral administration were very similar. Bioavailability was complete in both groups.

Discussion

Our results indicate that the clearance of ethinyloestradiol is increased in patients with cystic fibrosis. After an intravenous dose of ethinyloestradiol the clearance was significantly greater in the patients than in the controls. There was no such change with levonorgestrel. Earlier studies have shown that cloxacillin[6] and theophylline[7] have an increased clearance in this disease, and that a non-renal mechanism has apparently been responsible for the increased clearance in each case. Ethinyloestradiol is primarily metabolised in the liver after an intravenous dose and this is likely to be the site of increased clearance. Certain drugs are known to enhance the clearance of ethinyloestradiol by induction of hepatic microsomal drug metabolising enzymes (for example, rifampicin[12]) but our patients were taking no drugs known to induce liver enzymes. Chronic hypoxia appears to increase liver microsomal activity[13] and this is a possible mechanism in patients

with cystic fibrosis. It has been postulated that the lung might be a site of increased drug metabolism in cystic fibrosis[6] but this is unlikely in the case of ethinyloestradiol, which does not normally undergo pulmonary metabolism.[14]

In addition to the enhanced clearance of ethinyloestradiol, our results show an increased bioavailability of orally administered drug. The bioavailability of ethinyloestradiol was 76·9% (SD 11·7%) in patients with cystic fibrosis compared with 47·3% (7·5%) in controls (p < 0·001). The incomplete bioavailability of ethinyloestradiol in healthy control women is due to presystemic ("first pass") conjugation of the drug, mainly in the gut wall but also in the liver.[14] The increased bioavailability of ethinyloestradiol may be due to reduced conjugation of ethinyloestradiol in the gut wall of patients with cystic fibrosis but we have no direct data on this point. The overall effect of the increased clearance and increased bioavailability of ethinyloestradiol in patients with this disease is that plasma concentrations of the drug after an oral dose will be similar in women with cystic fibrosis and in healthy women.

In contrast to ethinyloestradiol, the bioavailability of levonorgestrel was normal in patients with cystic fibrosis. This might be expected since there is no appreciable "first pass" metabolism of this drug in healthy women.[15] There was also no alteration in the other pharmacokinetic variables.

Our studies were performed on patients who were not receiving systemic antibiotics. There have been reports to the Committee on Safety of Medicines of healthy women taking combined oral contraceptives becoming pregnant while also receiving oral antibiotics, of which the most commonly implicated have been ampicillin, the tetracyclines, and co-trimoxazole. This is of obvious concern in patients with cystic

fibrosis, who frequently receive broad spectrum antibiotics, both orally and intravenously, for their bronchopulmonary disease. Synthetic oestrogens are extensively excreted in the bile in man and animals as direct conjugates and conjugates of metabolites.[16 17] The direct conjugates may then be hydrolysed by intestinal bacteria, so releasing the unchanged steroid, which can then be reabsorbed, so producing an enterohepatic circulation. Ethinyloestradiol undergoes this process in the active form, whereas levonorgestrel is circulated only in the form of metabolites that have little or no biological activity. Treatment with broad spectrum antibiotics would be expected to kill the bacteria that hydrolyse these steroid conjugates and hence reduce or eliminate steroid reabsorption from the gastrointestinal tract. Enterohepatic circulation of ethinyloestradiol in rabbits and rats has been shown to be reduced by broad spectrum antibiotics and the extent of the reduction correlates well with changes in gut flora.[18 19] It is probable, however, that the enterohepatic circulation of ethinyloestradiol contributes little to plasma concentrations and hence to therapeutic effect in most women. Studies with ampicillin have suggested that there is no significant systematic interaction with ethinyloestradiol.[20] In a small proportion of women reductions in plasma concentrations of ethinyloestradiol were noted, but were not associated with evidence of contraceptive failure as judged by plasma concentrations of progesterone or follicle stimulating hormone. A further study, with ampicillin and metronidazole,[21] showed no consistent effect on ethinyloestradiol plasma concentrations; and another, concerned with cotrimoxazole,[22] showed an increase in ethinyloestradiol concentrations and evidence of increased pharmacodynamic effect. Thus most women are not at risk of contraceptive failure when given a broad spectrum antibiotic. We have not noted any evidence of subtherapeutic ethinyloestradiol concentrations such as breakthrough bleeding or contraceptive failure associated with the use of antibiotics in patients with cystic fibrosis, and they seem unlikely to be at risk of contraceptive failure due to antibiotic treatment. Further studies will be needed, however, to resolve this question completely.

It has been suggested that patients with cystic fibrosis using combined preparations may show more rapid deterioration in pulmonary function or develop polypoid cervicitis,[23] although neither of these findings was confirmed in a more recent detailed study.[24] Oral contraceptive steroids are relatively contraindicated in patients with liver disease. Abnormalities in the results of biochemical liver function tests, particularly increase in serum alkaline phosphatase activity, are common in cystic fibrosis.[25] At least 5% of adult patients progress to focal biliary cirrhosis,[26] and this figure is likely to increase as the populations of patients grows older. We have found no evidence, however, for any increase in cholestasis in patients with cystic fibrosis taking synthetic oestrogens in this way. Similarly, we have not noted an increased incidence of glucose intolerance, a common complication of cystic fibrosis in adults,[26] in patients taking these preparations.

Our results suggest that the absorption of ethinyloestradiol and levonorgestrel is not impaired by cystic fibrosis. Patients with this disease will achieve plasma concentrations of ethinyloestradiol and levonorgestrel after an oral dose of a combined oral contraceptive preparation similar to those found in healthy women, and our findings support the view that a standard combined preparation is suitable for these patients. Nevertheless, we recommend that patients are monitored closely while taking "the pill" to ensure that vaginal blood loss is regular with no evidence of breakthrough bleeding.

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