THE PHARMACOKINETICS OF METHIMAZOLE IN PREGNANT PATIENTS AFTER ORAL ADMINISTRATION OF CARBIMAZOLE

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1 A high performance liquid chromatographic (HPLC) method was used to study the pharmacokinetics of methimazole after oral administration of carbimazole to women in various stages of pregnancy.

2 In one patient it was possible to conduct the study in the first and third trimesters: there was an appreciable increase in the apparent clearance of methimazole.

3 Based on the assumption of complete absorption and hydrolysis of carbimazole to methimazole the mean apparent clearance was found to be significantly higher in pregnant patients receiving 10 mg carbimazole than in non-pregnant patients receiving the same dose.

Introduction

Antithyroid drug treatment is usually the method of choice for treating hyperthyroid pregnant patients and several review articles are available (Bokat, 1968; Goluboff, Sisson & Hamburger, 1974; Burrow, 1976).

Thiocarbamide antithyroid drugs administered during pregnancy do occasionally cause adverse effects in the neonate (Goluboff *et al.*, 1974; Burrow, 1976). Marchant, Brownlie, McKay Hart, Horton & Alexander (1976), when examining the placental transfer of ³⁵S-carbimazole, ³⁵S-methimazole and ³⁵S-propylthiouracil (PTU) in pregnant rats, and in humans, found that the rat and human placentas are freely permeable to ³⁵S-methimazole and slightly less so to ³⁵S-PTU. There was a small accumulation of radioactivity in the human foetal thyroid gland 2 h after oral administration of the drug.

The pharmacokinetics of the antithyroid drugs carbimazole and methimazole have been reported in previously untreated hyperthyroid patients (Skellern, Knight, Low, Alexander, McLarty & Kalk, 1980); this paper presents the pharmacokinetics of methimazole, the active metabolite of carbimazole, in a group of pregnant hyperthyroid patients.

Methods

Patients

A single oral dose of carbimazole (10 mg or 20 mg) was given to a group of pregnant hyperthyroid patients at various stages of pregnancy. These patients were being maintained on the drug in doses varying between 5 and 20 mg daily. The patients were instructed to eat a light breakfast on the morning of the study. An initial blood sample was taken as a control and further samples were taken at time intervals up to 12 h after the oral dose. All samples were immediately centrifuged to obtain plasma,

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Table 1 The pharmacokinetic parameters of metimazole in pregnant hyperthyroid patients following oral administration of carbimazole

Subject number	1	2	2a	3	4	5	6	7	Mean $\pm$ s.e. mean
Body weight (kg)	55.3	69.2	80.5	50.9	59.2	62.1	47.2	57.7	60.3
Age (years)	26	35	35	26	25	29	23	23	28
Trimester	3	1	3	1	1	3	2-3	3	
Dose of carbimazole (mg)	10	10	10	10	10	10	20	20	
β (h^{-1}) $\pm$ s.e. mean	0.229 $\pm .056$	0.617 $\pm .186$	0.265 $\pm .081$	0.266 $\pm .084$	0.270 $\pm .029$	0.405 $\pm .082$	0.337 $\pm .064$	0.592 $\pm .069$	0.373 ± 0.054
T_1 (h)	2.32	1.12	2.62	2.61	2.57	1.71	2.06	1.17	2.02 ± 0.22
Apparent $V_d \beta$ (l)	26.9	14.5	48.5	38.1	26.5	30.1	12.2	19.8	27.1 ± 4.3
Apparent clearance (ml min^{-1})	134	149	214	169	119	203	68	196	157 ± 17
T_3 resin uptake ratio	0.97	0.89	0.68	1.25	1.1	1.04	1.38	0.70	
FTI ^a (nmol l^{-1})	146	140	73	457	145	321	402	92	

a Normal free thyroxine index range 55 to 144 nmol l^{-1} .

which was then stored at $-20^\circ C$. Patients 2, 6 and 7 received T_3 and thyroid biochemistry was examined in all patients on the day of the study (Table 1). Patients 3, 5 and 7 were hyperthyroid at the time of the study. All patients had normal renal and liver function.

High performance liquid chromatography

The HPLC method used to determine the pharmacokinetics of methimazole after oral administration of either carbimazole or methimazole was adopted (Skellern *et al.*, 1980).

Pharmacokinetics

The method by which the pharmacokinetic parameters were calculated is described elsewhere (Skellern *et al.*, 1980).

Results

The methimazole plasma concentration *v* time curves after oral administration of carbimazole are shown in Figure 1, and the pharmacokinetic parameters are given in Table 1.

Figure 1 The methimazole plasma concentration *v* time curves from pregnant patients receiving carbimazole (10 mg).

The mean half-life of methimazole was 2.02 ± 0.22 h.

Discussion

Radiolabelled drug has been the basis of quantitation for some pharmacokinetic studies with antithyroid drugs in non-pregnant patients. However, this would be contraindicated in hyperthyroid pregnant patients. A benefit of the HPLC method is that radiolabelled drug is not the basis of quantitation, and it has therefore been possible to conduct a limited study on the pharmacokinetics of methimazole in a group of pregnant hyperthyroid patients receiving maintenance doses of carbimazole.

During the various stages of pregnancy, physiological changes occur which can alter the absorption, distribution, metabolism and excretion of drugs (Krauer & Krauer, 1977). Also in the pregnant hyperthyroid patient, abnormal thyroid function may affect the metabolism and excretion of drugs (Eichelbaum, 1976).

Serum thyroid hormone levels do not give a true indication of thyroid status during pregnancy because protein binding of the hormones is affected. However, the free thyroxine index (FTI), which is the product of the serum thyroxine concentration and the T_3 resin uptake is a more reliable measure of thyroid status (Burrow, 1976).

If the assumption is made that carbimazole is completely absorbed in the gut, and totally hydrolysed to methimazole the apparent clearances and apparent volumes of distribution can be calculated (Skellern *et al.*, 1980).

A comparison of the mean apparent clearance in the pregnant patients receiving 10 mg carbimazole

(patients 1 to 5), 164 ± 16 ml min⁻¹ (mean $\pm$ s.e. mean; $n=6$) with the mean apparent clearance in a comparable group of non-pregnant patients receiving the same dose of carbimazole, 110 ± 21 ml min⁻¹ (mean $\pm$ s.e. mean; $n=5$) (unpublished results) showed a difference ($P=0.062$) which just failed to reach significance at the 0.05 level. This latter group were also in steady state and were clinically euthyroid. A definitive explanation of the higher apparent clearance of methimazole in the pregnant group cannot be made, since the pregnant patients were at different stages in their pregnancy, and were not all considered to be euthyroid at the time of the study. Increased renal blood flow is known to increase creatinine clearances by about 50% during pregnancy (Krauer & Krauer, 1977). It was suggested that an increased clearance of the antiepileptic drug, carbamazepine, in pregnant women was due to an increased rate of hepatic metabolism of the drug (Dam, Christiansen, Munck & Mygind, 1979). However, elevated levels of thyroid hormone are known to affect drug metabolism in animal and man, although the results of the few studies in man are sometimes conflicting (Eichelbaum, 1976).

It is noteworthy that with patient 2, where it was possible to conduct the study in the first and third trimesters of pregnancy (Table 1), the apparent clearance and volume of distribution has markedly increased. This may be due either to changes in the drug's distribution or its rate of elimination during pregnancy, or to differences in the extent of absorption of the drug.

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