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THE PHARMACOKINETICS OF METHIMAZOLE AFTER ORAL ADMINISTRATION OF CARBIMAZOLE AND METHIMAZOLE, IN HYPERTHYROID PATIENTS

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1 Methimazole plasma concentrations were measured in two groups of hyperthyroid subjects after the oral administration of either carbimazole or methimazole.

2 With the HPLC method it was also possible to measure the concentration of a methimazole metabolite, 3-methyl-2-thiohydantoin in one patient.

3 Large interindividual differences were observed, especially within the carbimazole group.

4 Incomplete absorption of carbimazole could explain particular high apparent volumes of distribution and apparent clearances.

Introduction

Carbimazole (1-carbethoxy-3-methyl-2-thioimidazole) and methimazole (1-methyl-2-thioimidazole) (Figure 1) are drugs widely used in the U.K. and U.S.A., respectively, for the treatment of hyperthyroidism. In practice, if a patient is found to be hyperthyroid the recommended starting dose of these drugs is 30 to 60 mg daily as a divided dose (Solomon, 1978). When the patient becomes euthyroid as indicated by the circulating thyroid hormone levels, the daily dose is reduced to 5 to 20 mg. This course of treatment has been established by observing that a particular dose of drug is clinically effective. Interindividual pharmacokinetic differences have not been considered in arriving at this course of treatment (Koch-Weser, 1975).

In the majority of pharmacokinetic studies of these drugs in humans, ^{35}S-labelled methimazole and carbimazole have been used (Alexander, Evans, MacAulay, Gallagher & Londono, 1969; Crooks, Hedley, McNee & Stevenson, 1973). A colorimetric method (Ratliff, Gilliland & Hall, 1972) based on the derivatization of methimazole with 2,6-dichlorobenzoquinonechlorimine has also been used in pharmacokinetic studies with methimazole (Pittman, Beschi & Smitherman, 1971; Vesell, Shapiro, Passananti, Jorgensen & Shively, 1975). Both of these methods would include sulphur-containing metabolite concentrations in the observed drug concentration.

Carbimazole is rapidly hydrolysed to methimazole, either in the presence of plasma or at an alkaline pH (Stenlake, Williams & Skellern, 1970). A metabolite, 3-methyl-2-thiohydantoin, has been identified in plasma, thyroid tissue and urine of patients receiving either methimazole or carbimazole (Skellern, Knight, Luman, Stenlake, McLarty & Hooper, 1977).

More specific assays depend upon a prior chromatographic separation to resolve the metabolites from the drug to be measured. Thin layer chromatography (Marchant, Alexander, Lazarus, Lees & Clark, 1972), gas-liquid chromatography (Stenlake *et al.*, 1970; Bending & Stevenson, 1978) and high-pressure liquid chromatography (Skellern, Stenlake, Williams & McLarty, 1974; Skellern, Knight & Stenlake, 1976; Melander, Rosendal-Helgeson, Sjöberg & Wåhlin, 1978) have all been used to determine methimazole concentrations in biological fluids and tissue.

This paper describes the pharmacokinetics of methimazole in previously untreated hyperthyroid patients receiving either 60 mg carbimazole or 60 mg methimazole orally.

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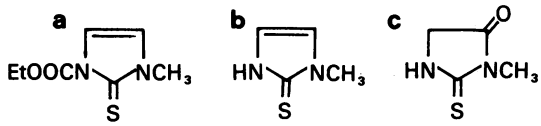

Figure 1 Structural formulae of a) carbimazole, b) methimazole and c) 3-methyl-2-thiohydantoin.

Methods

Chemicals

Methimazole (Aldrich) was recrystallized from toluene and *p*-toluamide (BDH) was analytical grade. 3-Methyl-2-thiohydantoin was prepared according to the method of Scott & Henderson (1968). All solvents were AnalaR grade or had been redistilled before use. Standard solutions of methimazole, 3-methyl-2-thiohydantoin and *p*-toluamide were prepared in methanol.

Patients

Fifteen previously untreated hyperthyroid patients attending two thyroid out-patient clinics took part in this study. All the patients were clinically hyperthyroid and this was confirmed by thyroid function tests (Tables 1 and 2). Although patient 6 had a normal T_4 level this patient had a high T_3 level and an elevated 20 min thyroid ^{132}I-iodide uptake. The patients were not receiving any other medication at the time of the study. Ten of the patients received a single oral dose of carbimazole (12 × 5 mg tablets with water) 1 h after a light breakfast. The other five patients received a single oral dose of methimazole (6 × 10 mg tablets with water) under similar conditions. An initial blood sample was taken as a control, and then eight to ten blood samples were taken at varying time intervals between 30 min and 24 h. All blood samples were immediately centrifuged to obtain plasma, which was then stored at −20°C.

High-pressure liquid chromatography (HPLC)

All HPLC analyses were performed on a Spectra-Physics Model 3500B Liquid Chromatograph with UV detection at 254 nm. A modified version of a published method was adopted (Skellern *et al.*, 1976). The modification entailed the use of *p*-toluamide as internal standard, in place of benzamide.

Quantitation of methimazole and 3-methyl-2-thiohydantoin was achieved by adding a methanolic solution (1 ml) containing known amounts of methimazole, 3-methyl-2-thiohydantoin and *p*-toluamide to patient control plasma (1 ml), in triplicate.

Table 1 The pharmacokinetic parameters of methimazole in hyperthyroid patients following oral administration of 60 mg carbimazole

	Patient number										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean ± s.e. mean*
Body weight (kg)	53	65.8	63	63.2	62.3	64.7	51.5	54.1	48.3	44.5	57.0
Age (years)	26	40	18	52	27	47	57	35	54	45	40
Sex	F	F	F	M	F	F	F	F	F	F	
β (h^{-1})	0.277	0.264	0.160	0.213	0.208	0.31	0.248	0.198	0.307	0.139	0.232 ± 0.018
± s.e. mean	±0.058	±0.048	±0.082	±0.046	±0.041	±0.067	±0.072	±0.076	±0.036	±0.012	
$T_{\frac{1}{2}}$ (h)	2.50	2.62	4.33	3.25	3.33	2.24	2.79	3.50	2.26	4.99	3.18 ± 0.29
Apparent $V_d\beta$ (l)	31.7	31.0	56.9	97.5	69.5	153	23.3	21.7	17.6	27.7	53.0 ± 16.8
Apparent clearance (ml min^{-1})	147	137	152	345	241	793	96	72	90	64	204 ± 69
T_4(nmol l^{-1})*	163	172	202	192	210	142	249	232	192	243	200
Serum creatinine (mg/100 ml)		0.96	0.49	1.2	0.98			0.68	1.3	1.2	0.97

Liver function normal. *Normal T_4 range: 55 to 144 nmol l^{-1}.

Pharmacokinetics

Examination of the data graphically indicated that the distribution and elimination of methimazole could be described in terms of a one-compartment model. Terminal log-linear points were used to calculate the elimination rate constant, β, by an adaptation of Metzler's (1969) NONLIN program developed by Dr W.J. Jusko of the State University of New York at Buffalo.

Results

The HPLC method permitted the analysis of methimazole and its metabolite, 3-methyl-2-thiohydantoin, simultaneously (Figure 2). The methimazole plasma concentration *v* time curves for patients 1 to 10, who received 60 mg carbimazole orally (Figure 3), show that maximum plasma concentrations occurred between 30 min and 1 h, with an inflexion on the curve at around 4 h after drug administration with some patients. After oral administration of methimazole to patients 11 to 15, similar plasma concentration—time curves (Figure 4) were obtained with less pronounced inflexions at 4 h. In patient 13 it was possible to measure the plasma concentration of the metabolite, 3-methyl-2-thiohydantoin, over a 24 h period (Figure 5). The biological half-life of 3-methyl-2-thiohydantoin in this patient, calculated from plasma concentrations at 12 and 24 h, was 13.5 h. In the majority of the other patients 3-methyl-2-thiohydantoin was only partially resolved from endogenous plasma material and was not accurately determinable.

All the patients had normal renal and liver function except patient 14, who had abnormal liver function as shown by raised serum transaminase activity, which may be reflected in this patient's $T_{\frac{1}{2}}$ for methimazole compared with the other values observed in the group.

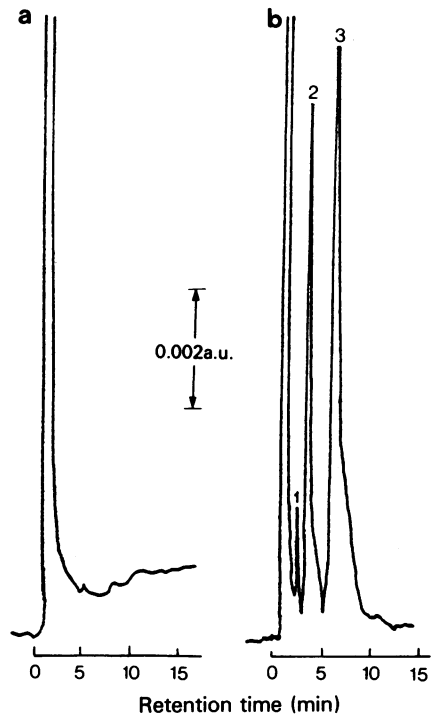

Figure 2 A typical high-pressure liquid chromatogram from a patient receiving oral carbimazole (60 mg). a) extract of control plasma; b) extract of test plasma with internal standard. 1, 3-methyl-2-thiohydantoin; 2, methimazole; 3, *p*-toluamide (internal standard).

Table 2 The pharmacokinetic parameters of methimazole in female hyperthyroid patients following oral administration of 60 mg methimazole.

	Patient number					
	11	*12*	*13*	*14*	*15*	*Mean* ± s.e. mean
Body weight (kg)	53.0	54.4	50.8	49.4	61.7	53.9
Age (years)	30	45	42	39	31	37.4
β (h^{-1})	0.249	0.352	0.308	0.172	0.251	0.266 ± 0.030
± s.e. mean	±0.055	±0.114	±0.129	±0.069	±0.066	
$T_{\frac{1}{2}}$ (h)	2.79	1.97	3.25	4.03	2.76	2.96 ± 0.34
Apparent $V_d\beta$ (l)	21.5	17.2	20.8	17.2	22.1	19.8 ± 1.1
Apparent clearance (ml min^{-1})	89	101	107	49	92	92 ± 9.8
T_4 (nmol l^{-1})*	305	232	191	264	264	251
Liver function	N	N	N	Abnormal	N	
Serum creatinine (mg/100 ml)	0.88	0.92	1.04	1.2	0.51	0.91

*Normal T_4 range: 55 to 144 nmol l^{-1}.

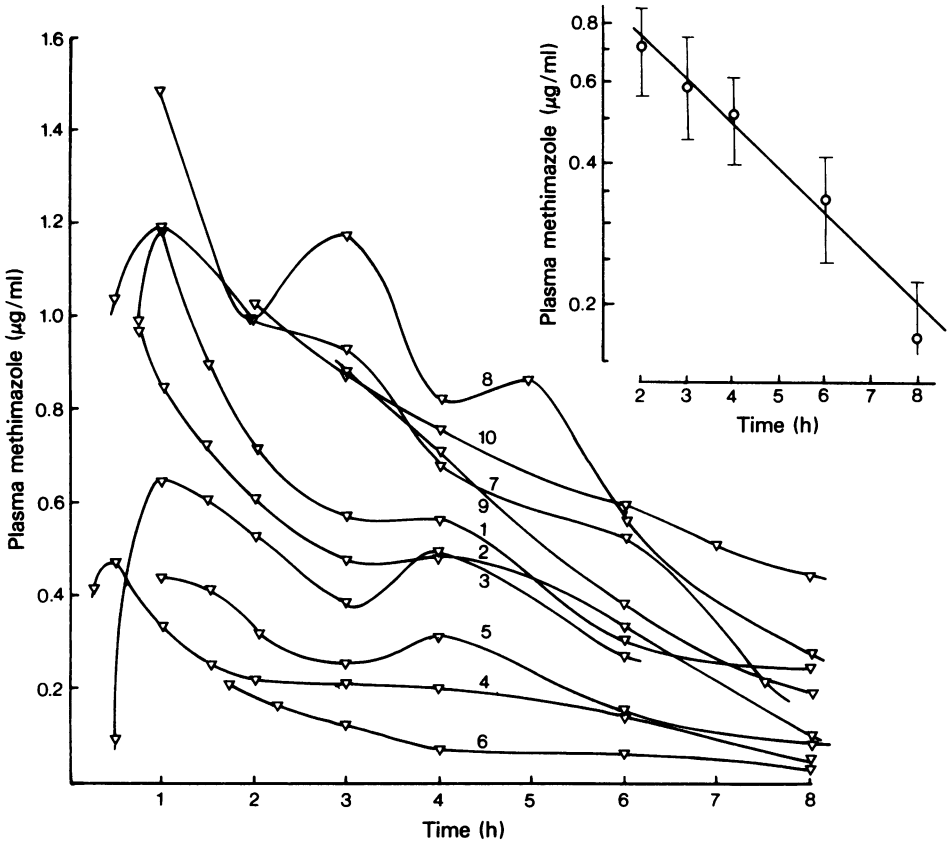

Figure 3 The methimazole plasma concentration *v* time curves from patients receiving oral carbimazole (60 mg). Insert: Semilogarithmic plot of the mean methimazole plasma concentrations (±s.e. mean) *v* time.

Discussion

The replacement of the internal standard in the published method (Skellern *et al.*, 1976) with *p*-toluamide resulted in a slightly shorter analysis time. Also, since the molar absorptivity of *p*-toluamide is higher, lower concentrations were required. With certain alumina columns it was found that theophylline was eluted at a retention time similar to that of the internal standard, and would often interfere with the analyses. Silica columns were tried as an alternative to alumina, but on silica caffeine elutes at a retention time similar to methimazole. Because of the problem of interference by these substances, patients were asked to abstain from tea and coffee for 8 h before and during the time that blood samples were being taken.

The second inflexion at 4 h on the methimazole plasma concentration-time curves were much less pronounced after methimazole (Figure 4) than after carbimazole (Figure 3) administration, but have been drawn in so as to be consistent with the presentation of the carbimazole data. A secondary absorption phase from the intestine could explain this inflexion; in both cases, however, it is not possible to say whether, after carbimazole administration, the inflexion is due to carbimazole or methimazole absorption. Carbimazole is stable *in vitro* for 2 h in gastric juice (unpublished results), whereas, at alkaline pHs it is hydrolysed to methimazole. The initial plasma peak concentration after carbimazole administration, therefore, is probably due to the partial absorption of intact carbimazole from the stomach, followed by its rapid conversion to methimazole in the blood, while the inflexion at 4 h may be due to the absorption from the small intestine of either intact carbimazole, or methimazole after hydrolysis of carbimazole, following stomach emptying. A more rapid absorption of carbimazole compared to methimazole would be expected because of the much higher lipid/water partition coefficient of carbimazole (unpublished results), and may explain

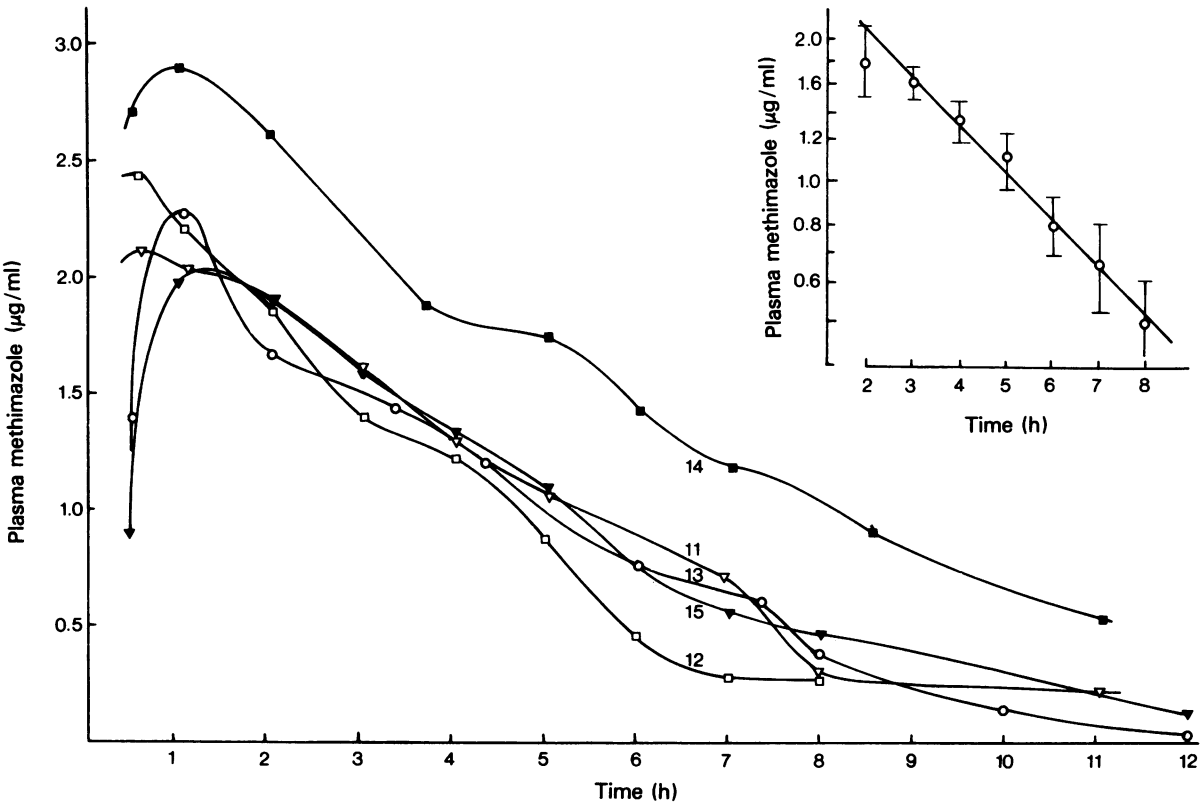

Figure 4 The methimazole plasma concentration *v* time curves from patients receiving oral methimazole (60 mg). Insert: Semilogarithmic plot of the mean methimazole plasma concentrations (±s.e. mean) *v* time.

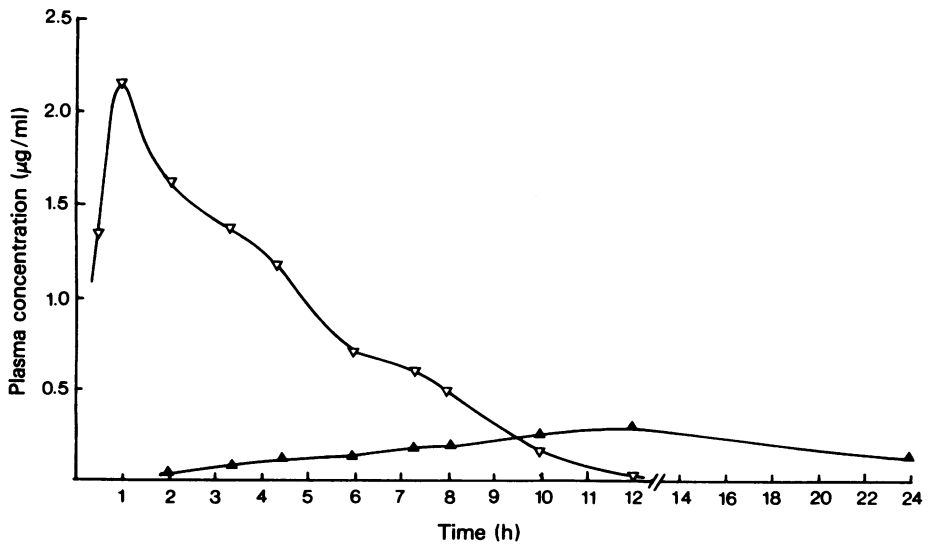

Figure 5 The methimazole (▽) and 3-methyl-2-thiohydantoin (▲) plasma concentration *v* time curve from patient 13 receiving oral methimazole (60 mg).

the more pronounced inflexion in the case of carbimazole administration.

There is only one report in the literature on the bioavailability of methimazole. Shimmins, Gillespie, Orr, Smith & Alexander (1969) found ratios of the area under the curve for total radioactivity after administration of ^{35}S-methimazole orally and intravenously in two patients, of 0.99 and 0.81. From studies in man (Alexander *et al.*, 1969; Marchant, Lees & Alexander, 1978) it is known that carbimazole and methimazole are rapidly absorbed after oral administration, and that a cumulative 24-h faecal excretion of less than 1% of the administered radioactivity was found after ^{35}S-carbimazole and only 3% after ^{35}S-methimazole administration. While these data indicate that the extent of absorption of both drugs would seem to be high, if not complete, the use of total radiolabel data can give no indication whether the drug has been metabolized in the gut or during its first passage through the liver to the systemic circulation. Two studies which have reported that about 7% of a dose of methimazole and carbimazole (Marchant *et al.*, 1978; Pittman *et al.*, 1971) is excreted as unchanged drug in the urine indicate that the drugs are extensively metabolized. The large difference in the area under the curves (Figures 3 and 4) would seem to indicate large interindividual differences in the amount of the dose absorbed, particularly within the carbimazole group (Figure 3). These large interindividual differences may explain the variability of the response to antithyroid therapy in hyperthyroid patients which is so commonly observed in clinical practice. However, other factors may also be important (Low, Hilditch & Alexander, 1979), and detailed kinetic analysis of thyroid radio-iodide uptake and pharmacokinetic studies of the drug in individual patients will greatly contribute to our understanding and management of patients who show no response to the usual recommended therapy.

If the assumption is made that all the dose of the drug was absorbed from the gut, and in the case of carbimazole that there was complete hydrolysis to methimazole, i.e. 60 mg carbimazole is equivalent to 36.7 mg methimazole, apparent clearances and apparent volumes of distribution can be calculated (Tables 1 and 2). The apparent clearance was calculated from the quotient of the dose of drug administered and the area under the methimazole plasma concentration-time curve, whilst the apparent volume of distribution was obtained from the quotient of the apparent clearance and the elimination rate constant, β.

As would be anticipated, there are considerable interindividual variations in the apparent volume of distribution in the carbimazole study ranging from 17.6 l to 153 l, whilst the results are more homogeneous in the methimazole group with a mean apparent volume of distribution of 20 ± 2.4 l (mean $\pm$ s.d.). The apparent volumes of distribution and clearance values for the methimazole group may be a reasonable estimate of these parameters based on Shimmins *et al.* (1969) report of a bioavailability of nearly unity.

There are no statistical differences (t-test, $P > 0.05$) in the pharmacokinetic parameters between the carbimazole and methimazole groups, and in the interindividual variation in area under the curve between the two groups (F-test, $P > 0.05$); although the variation within the methimazole group is due chiefly to the high area under the curve of patient 14, which may be atypical because of the patients liver disorder. This patient also had a longer methimazole half-life compared to other patients in the group. The lower areas under the curves in the carbimazole group are expected because of the lower equivalent dose of methimazole administered.

Melander *et al.* (1978) have also reported large interindividual variations in the kinetics of methimazole after carbimazole and methimazole administration to healthy volunteers.

The semi-logarithmic plots of the mean methimazole plasma concentrations *v* time (Figures 3 and 4 insert) illustrate that a one-compartment model is a reasonable representation of methimazole distribution in man, after oral administration of methimazole and carbimazole.

Various half-lives have been reported for methimazole after methimazole and carbimazole administration. With euthyroid patients, methimazole half-lives of 6.4 h (Pittman *et al.*, 1975) and 9.3 h (Vesell *et al.*, 1975) have been reported, and in hyperthyroid patients 7.9 h (Crooks *et al.*, 1973; McNee, Hedley, Stevenson & Crooks, 1973), 6.9 h (Vesell *et al.*, 1975) and, using HPLC, 4 h (Skellern *et al.*, 1974) have been observed. However, none of these studies considered the possible presence of methimazole metabolites in the assay procedure. From a recent GLC study (Bending & Stevenson, 1978) with plasma from a patient who had received a 60 mg oral dose of carbimazole, it was possible to calculate the methimazole half-life as 3.7 h (from the data given).

In this present study the mean half-life of methimazole after carbimazole administration was 3.18 h and after methimazole administration it was 2.96 h. These half-lives are less than half those observed in the majority of other reports in the literature, and is undoubtedly due to the more specific assay for methimazole which is possible by HPLC.

Methimazole is accumulated by the thyroid and its effect on the inhibition of iodination of thyroid protein may last up to 24 h (Wartofsky & Ingbar, 1971), however since its plasma half-life is short, and that of its metabolite, 3-methyl-2-thiohydantoin is 3 times longer, the prolonged duration of action

observed may be partially attributable to the antithyroid activity of this metabolite. 3-Methyl-2-thiohydantoin has antithyroid activity in rat (Searle, Lawson & Morley, 1951), which remains to be demonstrated in man.

The observed protein-binding of methimazole reported in an earlier study (Skellern *et al.*, 1974) has since been shown to be artefactual owing to the procedure used.

A logical extension of this present study which is planned would be intravenous studies on the drugs to determine their bioavailabilities.

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