Preliminary Communications

Metabolism of ^{35}S-labelled Antithyroid Drugs in Man

British Medical Journal, 1969, 2, 290–291

Summary: Differences in the metabolic fate of antithyroid drugs influence the optimal frequency of administration and their therapeutic efficacy. ^{35}S propylthiouracil differed from the ^{35}S imidazoles (carbimazole and methimazole) in the more rapid absorption and excretion and the shorter biological half-life in the plasma of the former. Renal function may have a more important influence on the biological half-life of the drugs than thyroid status. Further work is required to determine the optimal frequency of administration for each compound.

Introduction

Antithyroid drugs are widely used to treat thyrotoxic patients because of their blocking action on thyroid hormone synthesis (Astwood, 1949). Recent work has suggested that antithyroid drugs may also have some beneficial effect on the underlying cause of thyrotoxicosis (Alexander *et al.*, 1967). We have therefore studied the metabolism of ^{35}S-labelled antithyroid drugs of the type most widely used to treat thyrotoxicosis—that is, propylthiouracil, methimazole, and carbimazole.

Methods

Two patients were studied. One had frank thyrotoxicosis and inoperable carcinoma of the cervix. The other had a large non-toxic goitre and myelomatosis associated with renal failure. Both patients were judged suitable for treatment with ^{131}I and volunteered for the drug studies, which were carried out before ^{131}I was given. ^{35}S-labelled methimazole and carbimazole were prepared by Dr. J. G. Allen at the Nicholas Research Institute Ltd., and ^{35}S propylthiouracil was obtained from Amersham. ^{35}S methimazole was given by mouth, and after an interval of some days intravenously; ^{35}S propylthiouracil was given only by mouth. The oral doses were 25 mg. of drug and the intravenous doses were 10 mg. Purity of the compounds before administration was established by infrared spectroscopy as a potassium bromide disc and by thin-layer chromatography.

Samples of plasma and urine were taken and 1-ml. aliquots added direct to 10 ml. of Bray's (1960) solution. An automatic scintillation counter was used, and an appropriate correction for quenching was made. The distribution space of the drug was obtained by extrapolation of the plasma radioactivity curve to zero time. Chromatography of urine samples was carried out on silica-gel plates 500 μ thick with chloroform 160: methanol 40: water 25.

The 50-μCi dose of ^{35}S used was estimated to give at most a whole-body dose of 18 millirads and a thyroid dose of 360 millirads.

Results

The distribution space of ^{35}S methimazole in the two patients studied approximated the total body water, whereas that of propylthiouracil averaged 12 litres (see Table). In Case 1 the half-life of plasma radioactivity after ^{35}S methimazole was about five times that of ^{35}S propylthiouracil (Fig. 1). Both absorption and excretion of the label after ^{35}S propylthiouracil were more rapid (Fig. 2). Excretion was mainly in the urine; only 3% of the counts from the ^{35}S methimazole could be recovered in the faeces. The half-life of the plasma radioactivity after ^{35}S methimazole was the same whether the patient was toxic (thyroxine iodine 9·4 μg./100 ml., half-life 13·0 days) or euthyroid (thyroxine iodine 4·2 μg./100 ml., half-life 12·8 days). In Case 2, with renal failure (creatinine clearance 23 ml./min.), the plasma half-life after both ^{35}S propylthiouracil and ^{35}S methimazole was considerably prolonged. The blood radioactivity curve after oral administration of ^{35}S carbimazole was very similar to that of methimazole. Both imidazole drugs were more slowly absorbed than ^{35}S propylthiouracil.

Distribution and Excretion of ^{35}S After Administration of Labelled Antithyroid Drugs

		Distribution Space (litres)	Half-life in Plasma (hours)	Renal Clearance (ml./min.)
Case 1	Methimazole	34·2	13·8	20·0
	Propylthiouracil	12·8	2·5	
Case 2	Methimazole	35·7	20·7	11·9
	Propylthiouracil	11·2	8·5	9·0

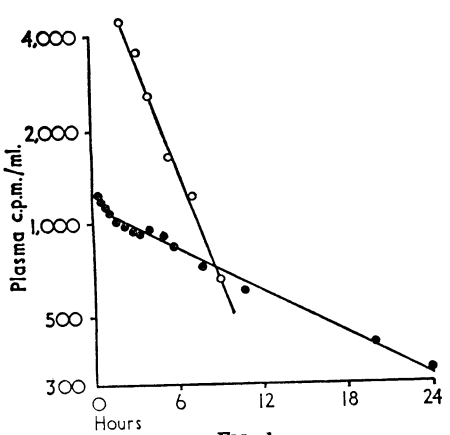

FIG. 1

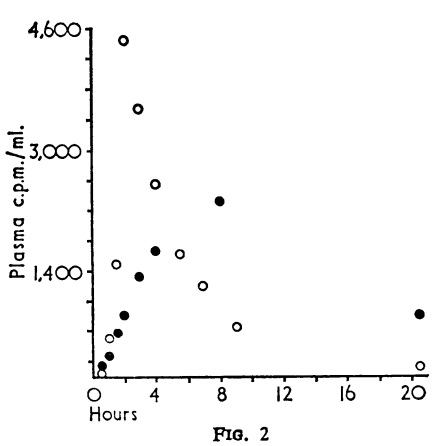

FIG. 2

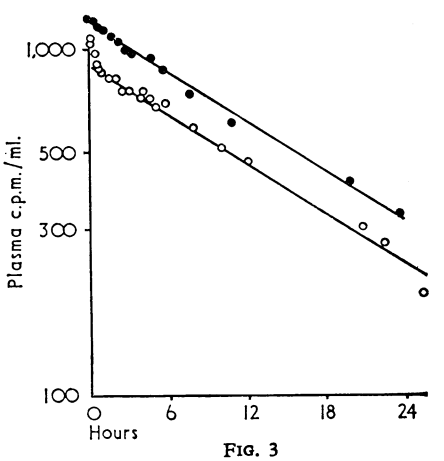

FIG. 3

FIG. 1.—Case 1. Plasma radioactivity after ^{35}S propylthiouracil (○) (given by mouth) and ^{35}S methimazole (●) (given intravenously). FIG. 2.—Case 1. Plasma radioactivity after oral administration of ^{35}S propylthiouracil (○) and ^{35}S methimazole (●). FIG. 3.—Plasma radioactivity after ^{35}S methimazole given intravenously when thyrotoxic (○) and when euthyroid (●).

Three radioactive compounds could be detected in chromatograms of the urine after administration of ^{35}S methimazole, of which two were probably ^{35}S methimazole and $^{35}SO_4$. The third compound could be detected at the origin after the urinary sulphate had been removed by precipitation with barium chloride. After administration of propylthiouracil chromatographs of the urine showed that the ^{35}S label remained at the origin with the chromatographic system used, and few or no counts running as propylthiouracil could be detected.

COMMENT

Propylthiouracil and methimazole are generally thought to be equivalent drugs for the treatment of thyrotoxicosis. Our results reflect differences in metabolism of the drugs, including distribution space, plasma half-life, absorption, and excretion. Intrathyroid metabolism may also differ. Thus we have found (Gallagher, Londono, and Alexander, to be published) that the T/S (thyroid/serum radioactivity) ratio in rats reaches ~3 after administration of ^{35}S methimazole, and ~40 for ^{35}S propylthiouracil. The differences in drug metabolism may influence their therapeutic efficacy. The latter may also be influenced by host factors such as renal failure.

These preliminary results provide measurements of plasma radioactivity only. Studies to determine the chemical form of the antithyroid drug in the plasma are in progress. Nevertheless, if the ^{35}S is split off it is unlikely that the residue of the molecule would have antithyroid activity, and the label would probably be rapidly excreted, mainly as $^{35}SO_4$. In the rat thyroid the ^{35}S label is present mainly as $^{35}SO_4$ after administration of ^{35}S thiourea (Schulman, 1950 ; Maloof and Spector, 1959).

We wish to thank Dr. E. B. Astwood for advice and help throughout this study. The Medical Department of British Schering provided the ^{35}S-labelled methimazole and carbimazole.

W. D. ALEXANDER, M.D., F.R.C.P.ED.
VIRGINIA EVANS
A. MACAULAY, M.SC.
T. F. GALLAGHER, JR., M.D.
J. LONDONO, M.D.

New England Medical Centre Hospitals and Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts 02111.

REFERENCES

Astwood, E. B. (1949). *Annals of the New York Academy of Science*, **50**, 419.
Alexander, W. D., Harden, R. McG., Shimmins, J., McLarty, D., and McGill, P. (1967). *Journal of Clinical Endocrinology and Metabolism*, **27**, 1682.
Bray, G. A. (1960). *Analytical Biochemistry*, **1**, 279.
Maloof, F., and Spector, L. (1959). *Journal of Biological Chemistry*, **234**, 949.
Schulman, J. (1950). *Journal of Biological Chemistry*, **186**, 717.

Medical Memoranda

Atypical Cushing's Syndrome Associated with Bronchial Carcinoid

British Medical Journal, 1969, **2**, 291–292

Adrenocortical hyperactivity associated with neoplasms arising outside the pituitary-adrenal system has been increasingly recognized in recent years. Allott and Skelton (1960) reviewed 38 reports of this association and suggested a causal relationship. The mechanism of this relationship was elucidated by Liddle *et al.* (1963) when they demonstrated the presence of a corticotrophin-like substance in the associated neoplasm. Similar evidence has been provided by many others.

Further reports have been reviewed by O'Riordan *et al.* (1966) and Friedman *et al.* (1966), and the neoplasm most commonly concerned is an oat-cell bronchial carcinoma. Nevertheless, the condition has occurred with other neoplasms, particularly of the thymus, pancreas, and, more rarely, with bronchial adenomas or carcinoids. Some of the carcinoids have been of an unusual type (Cohen *et al.*, 1960). We wish to report a further case of atypical Cushing's syndrome due to adrenocortical hyperplasia in which at necropsy only a small (1 cm. in diameter) subepithelial bronchial adenoma or carcinoid was found.

CASE REPORT

A man aged 48 first attended the diabetic clinic in January 1966. He complained of a dry salty taste, thirst, polyuria, and nocturia present for the previous month. His doctor had found glycosuria. Physical examination at that time was normal (B.P. 140/80), but urine analysis showed glycosuria and albuminuria. The fasting blood sugar was 110 mg./100 ml. One week later, on simple dietary restriction, the glycosuria had disappeared. During the next three weeks he developed profound weakness and had to give up work. He then noticed puffiness of his face and ankle oedema, and was admitted to hospital for further investigation.

His main symptoms were as already described, but, in addition, he mentioned considerable loss of weight despite an apparently good appetite. He was a non-smoker. Re-examination showed evidence of considerable muscle wasting, weakness, and loss of weight. He had ankle oedema and his skin was covered with numerous petechiae. In contrast to his bodily appearance there was a superficially healthy look to his face. The blood pressure was 200/110. The rest of the examination was normal.

Investigations.—Haemoglobin 13·7 g./100 ml. ; W.B.C. 19,000/cu. mm., due to neutrophil leucocytosis ; E.S.R. 3 mm. in one hour ; platelets 360,000 ; blood urea 33 mg./100 ml. ; serum sodium 139, potassium 1·6, chloride 80, and standard bicarbonate 37 mEq/litre ; *p*H 7·537 ; random blood sugars 200 to 350 mg./100 ml. ; serum calcium 10·3 and phosphorus 3·1 mg./100 ml. ; alkaline phosphatase 7·5 K.A. units/100 ml. Urine analysis again showed glycosuria and albuminuria, with an acid reaction ; E.C.G. was consistent with hypokalaemia ; clotting-time was normal ; bleeding-time was over 20 minutes ; prothrombin ratio was 1·03. Two 24-hour urine specimens were examined for electrolyte output. Average volumes were 3,000 ml./24 hours. Both showed excessive kaluria (114 mEq/24 hours) and excessive calciuria (700 and 900 mg./24 hours). Sodium and chloride outputs were normal. Screening tests for catecholamines, vinyl mandelic acid, and 5-hydroxyindole-acetic acid showed no increase. Three further urine specimens were examined for 17-hydroxycorticosteroid output: 17 February 36 mg., 3 March 157 mg., and 4 March 212 mg./24 hours. Further analysis of the last two specimens by gas chromatography showed that nearly a third of the 17-hydroxycorticosteroids were "free" steroids. This was reported by the rheumatism research unit at Sheffield as similar to previously investigated cases associated with bronchial carcinoma. Plasma cortisol was 88 μg./100 ml. Chest *x*-ray examination, including