laboratory evidence of maternal infection in which neither virus excretion nor persistence of antibody can be demonstrated in the infant though the congenital abnormalities are typical of congenital rubella.

It must be concluded that clinical rubella in the first trimester confirmed by the laboratory means an infected fetus. It also appears that termination of a pregnancy for suspected rubella without laboratory support for the diagnosis is destroying many fetuses unnecessarily.

Our thanks are due to those clinicians who sent us material from their cases; to Dr. B. W. Barton, Derby, Dr. A. M. R. Mackenzie, Oxford, Dr. H. S. Lawy, Grimsby, and Dr. Pauline M. Poole, Chester, who forwarded material collected in their areas; to Dr. E. R. Mitchell, Nottingham, who isolated virus from the fetus of a case diganosed by us and allowed us to include his findings in our results; and to Miss Wendy Bagguley and Miss Lesley Robinson for laboratory assistance.

This work was supported by a grant from the Department of Health and Social Security to the Public Health Laboratory Service for the study of rubella in pregnancy.

REFERENCES

Alford, C. A., jun., Neva, F. A., and Weller, T. H. (1964). *New England Journal of Medicine*, **271**, 1275.
Beale, A. J., Christofinis, G. C., and Furminger, I. G. S. (1963). *Lancet*, **2**, 640.
Best, Jennifer M., Banatvala J. E., and Watson, D. (1969). *Lancet*, **2**, 65.
Brown, G. C., Baublis, J. V., and O'Leary, Theresa (1969). In *Proceedings of the 23rd Symposium on Rubella Vaccines, London, 1968*, edited by R. H. Regamey *et al.*, p.95. Basel, Karger.
Cooper, L. Z. (1968). *Birth Defects Original Article Series*, **4**, No. 7, p.23.
Dudgeon, J. A. (1969). *American Journal of Diseases of Children*, **118**, 35.
Field, Anne M., Vandervelde, Elise M., Thompson, K. M., and Hutchinson, D. N. (1967). *Lancet*, **2**, 182.
Hardy, B., McCracken, G. H., Gilkeson, Mary R., and Sever, J. L. (1969). *Journal of the American Medical Association*, **207**, 2414.
Heggie, A. D. (1967). *Journal of Pediatrics*, **71**, 777.
Horstmann, D. M., *et al.* (1965). *American Journal of Diseases of Children*, **110**, 408.
Hutchinson, D. N., and Thompson, K. M. (1965). *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, **24**, 385.
Monif, G. R. G., Sever, J. L., Schiff, G. M., and Traub, Renee G. (1965). *American Journal of Obstetrics and Gynecology*, **91**, 1143.
Norrby, E. C. J. (1969). In *Polyma Virus* by B. E. Eddy, p.115. Vienna, Springer.
Rawls, W. E., Desmyter, J., and Melnick, J. L. (1968). *Journal of the American Medical Association*, **203**, 627.

Chlordiazepoxide (Librium) and Tests of Thyroid Function

FREDERICK CLARK,* M.B., B.S., M.R.C.P. ; REGINALD HALL,† M.D., B.SC., M.R.C.P.

British Medical Journal, 1970, 2, 266-268

Summary: The effect of chlordiazepoxide (Librium) on thyroid function was examined in 14 euthyroid patients who required the drug for psychiatric reasons and in six patients with clinically mild thyrotoxicosis. There was no significant difference in results from tests of thyroid iodide trapping (thyroid radioiodine uptake, thyroid clearance, and absolute iodine uptake) or of thyroid hormone release (protein-bound iodine, T3 resin uptake, and free thyroxine index) carried out before and during treatment with the drug over a four-week period. It is suggested that chlordiazepoxide need not be withdrawn before thyroid status and function are assessed in any patient taking the drug.

Introduction

The list of drugs known to affect laboratory tests of thyroid function becomes more formidable year by year (Hall, 1967), and the clinician must be alert to the possibility that his patient has taken such agents, otherwise diagnostic confusion or error may result and inappropriate or unnecessary therapy instituted. Furthermore, even if the offending drug is withdrawn, diagnosis may have to be delayed until the metabolic effects of the drug have ceased, often a period of some weeks.

Recently it was reported that treatment with chlordiazepoxide (Librium) causes alterations in certain tests of thyroid function, in particular a low thyroid radioiodine uptake, in patients with clinical thyrotoxicosis (Baron, 1967; Harvey, 1967). The results of these reports appear to have been widely accepted (Today's Drugs, 1967; Walton and Thompson, 1969), though earlier studies by Oberman *et al.* (1963) did not show any effect of chlordiazepoxide (40-80 mg. daily for 7 to 30 days) on the level of protein-bound iodine (P.B.I.), red cell uptake of ^{131}I-labelled triiodothyronine, or 24-hour thyroid ^{131}I uptake. Animal studies, using comparatively huge doses of the drug, showed depression of thyroid radioiodine uptake and release (Caprino, 1963), which, it was suggested, might be due to interference with pituitary release of thyroid-stimulating hormone (T.S.H.). Nevertheless, Boris *et al.* (1961) and Schindler *et al.* (1966) failed to find any evidence of impairment of T.S.H. release by chlordiazepoxide in animals.

Chlordiazepoxide is often prescribed for anxiety and emotional disorders, and it is not uncommon to find that patients who are in fact thyrotoxic have been given the drug on the mistaken and possibly hazardous assumption that their illness is of psychiatric origin (Ashford and Ross, 1968). Other patients with psychiatric symptoms are taking the drug when it is suggested that thyrotoxicosis could be a cause of their complaint. In both situations laboratory investigation may be necessary for confirmation of the diagnosis.

With this background it appeared important to examine the problem further and ascertain the effect, if any, of chlordiazepoxide on tests of thyroid function in euthyroid and thyrotoxic patients.

Subjects and Methods

Euthyroid Group.—Fourteen patients (2 men and 12 women) aged 23 to 57, most of whom were referred from a group general practice, were tested before and after four weeks of continuing therapy with chlordiazepoxide in a dosage of 10 mg. three times a day. The patients, none of whom showed clinical evidence of thyroid disease, were selected on psychiatric grounds and were asked if they would take part in the trial. Those who agreed had their initial assessment within the next 48 hours, so there was little delay in starting treatment.

Thyrotoxic Group.—Six patients (all women) aged 37 to 55 with clinically apparent but relatively mild thyrotoxicosis (Graves' disease) were investigated. After standard initial diagnostic studies the patients were asked if they were prepared to defer definitive antithyroid therapy for a four-week period in order to determine any effect of chlordiazepoxide (10 mg. three times a day) on their symptoms and tests of thyroid function. All agreed, and after this time interval the tests were repeated. Subsequently, treatment with carbimazole was started.

Thyroid Function Tests.—Two measurements of thyroid function were assessed—thyroid iodide trapping and thyroid hormone release. In addition, the patients' sera were tested for the presence of thyroid autoantibodies by standard tanned red cell agglutination and complement fixation tests (W.H.O. 1966).

* Consultant Physician, Newcastle General Hospital; Lecturer in Clinical Medicine, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP.
† Consultant Physician, Royal Victoria Infirmary; Senior Lecturer in Medicine, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP.

TABLE I.—*Thyroid Function Tests in Euthyroid Patients Before and During Treatment with Chlordiazepoxide**

	% ^{131}I Thyroid Uptake				Thyroid Clearance (ml./min.)	Renal Clearance (ml./min.)	Urinary Inorganic Iodide (μg./100 ml.)	Plasma Inorganic Iodide (μg./100 ml.)	Absolute Iodine Uptake (μg./hour)	P.B.I. (μg./100 ml.)	T3 Resin Uptake Ratio	Free Thyroxine Index
	1 hour	2½ hours	6 hours	24 hours								
No.	12	12	5	9	12	11	11	11	11	12	12	12
Before treatment:												
Mean	8·70	16·19	31·22	38·38	20·64	30·24	2·69	0·21	2·34	6·91	0·96	6·61
S.D.	3·20	5·44	9·61	8·47	13·49	5·89	1·76	0·06	1·15	1·49	0·08	1·36
During treatment:												
Mean	10·18	17·22	27·10	39·23	19·73	27·72	2·44	0·21	1·93	6·88	0·96	6·59
S.D.	3·66	5·27	11·13	8·45	13·19	7·93	1·90	0·11	0·80	1·15	0·07	1·14
Mean of individual differences	+1·48	+1·03	−4·12	+0·86	−0·91	−2·52	−0·26	0·0	−0·41	−0·03	0·0	−0·02
S.E. of mean difference	1·27	1·29	2·01	1·83	1·57	2·24	0·72	0·33	0·42	0·43	0·02	0·39
P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = Not significant. *The statistical tests are based on within-patient comparisons.

TABLE II.—*Thyroid Function Tests in Thyrotoxic Patients Before and During Treatment with Chlordiazepoxide**

	% ^{132}I Thyroid Uptake		Thyroid Clearance (ml./min.)	P.B.I. (μg./100 ml.)	T3 Resin Uptake Ratio	Free Thyroxine Index
	2 minutes	20 minutes				
No.	6	6	6	6	6	6
Before treatment:						
Mean	10·08	45·07	397·00	13·12	1·37	18·65
S.D.	2·77	11·15	173·21	2·95	0·32	8·89
During treatment:						
Mean	11·92	42·80	410·50	12·73	1·36	17·89
S.D.	5·34	8·35	251·52	2·21	0·35	7·91
Mean of individual differences	+1·83	−2·27	+13·50	−0·38	−0·01	−0·76
S.E. of mean difference	1·69	4·34	108·19	0·52	0·03	0·52
P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = Not significant. *The statistical tests are based on within-patient comparisons.

Thyroid Iodide Trapping.—(*a*) Carrier-free ^{131}I iodide was used for the euthyroid group and most patients had thyroid uptake measured at 1, 2½, and 24 hours after a dose of 10 μCi, by mouth. In a few cases six-hour values were also obtained. Thyroid and renal clearances of the radioisotope were performed between 1 and 2½ hours and plasma inorganic iodide and absolute iodine uptake by the thyroid were determined (Wayne *et al.*, 1964). (*b*) Carrier-free ^{132}I iodide was used for the thyrotoxic group. Thyroid uptake was measured at 2 and 20 minutes after intravenous injection of 20 μCi, as was the thyroid clearance at 2 to 20 minutes (Alexander *et al.*, 1967).

Thyroid Hormone Release.—The level of circulating thyroid hormone was indicated by the P.B.I. (μg./100 ml.) (Riley and Gochman, 1964) (S.D. Exp. in our laboratory, ± 0·15 – 0·32 μg./100 ml.), the T3 resin uptake ratio (T3 resin) (S.D. Exp. ± 0·04 as ratio) (Clark, 1963), and by their mathematical product the free thyroxine index (FT_4) (Clark and Horn, 1965).

Results

The results obtained in the euthyroid group are shown in Table I. There was no significant difference in any of the tests between results obtained before and during treatment with chlordiazepoxide. The values for thyroid and renal clearance, plasma inorganic iodide, and absolute iodine uptake approximate to those obtained by Wayne *et al.* (1964). The mean of the P.B.I. (6·9 μg./100 ml.) and of the FT_4 (6·6) are each in the high normal range (3-8 μg./100 ml. and 2·2-7·1 respectively), and the mean of the T3 resin (0·96) is also within the normal range (0·82-1·28). Thyroid autoantibodies were not detected in any patient's serum before chlordiazepoxide and none appeared during treatment with this drug.

The results of the thyrotoxic group are shown in Table II. Values for all tests were in the thyrotoxic range, and again there was no significant change in any after chlordiazepoxide. It was of some interest that no deterioration occurred in the patients' clinical condition during the four-week period of observation. Thyroglobulin antibodies (tanned red cell test) were detected originally in high titre in two of the six patients but were not looked for subsequently. Complement fixing antibodies were not found.

Discussion

The findings obtained in the euthyroid group agree with and extend, by inclusion of measurements of early thyroid uptake and clearances, plasma inorganic iodide, and absolute iodine uptake, those of Oberman *et al.* (1963), who found that chlordiazepoxide had no effect on tests of thyroid function. We were unable to confirm the reports by Baron (1967) and Harvey (1967) that the drug depresses thyroid uptake, or in fact affects any measure of thyroid activity, in patients with thyrotoxicosis. An explanation for this discrepancy is not apparent, but our results do not exclude the possibility that mixed drug therapy (including chlordiazepoxide) could act as a thyroid suppressant.

A compound closely related to chlordiazepoxide, diazepam (Valium), has also been incriminated as causing changes in thyroid function tests (Harvey, 1967; Today's Drugs, 1969), though a double-blind crossover investigation by Mazzaferri and Skillman (1969) in normal volunteers has exonerated the drug from any action on thyroid function. We are currently re-examining this problem, with relevance particularly to patients with thyrotoxicosis.

It is concluded that chlordiazepoxide does not alter the commonly used tests of thyroid function and need not be withdrawn before diagnostic studies are made.

We wish to thank Dr. H. Holgate, of Roche Products Ltd., Professor F. T. Farmer, Professor G. A. Smart, and Professor D. J. Newell, of the University of Newcastle upon Tyne, for advice and help; members of the Prospect House Medical Group, Newcastle upon Tyne, for referring the euthyroid patients; and Mrs. M. A. Beck for technical help.

REFERENCES

Alexander, W. D., Harden, R. McG., Shimmins, J., McLarty, D., and McGill, P. (1967). *Journal of Clinical Endocrinology and Metabolism*, **27**, 1682.

Ashford, A., and Ross, J. W. (1968). *British Medical Journal*, **2**, 217.

Baron, J. M. (1967). *British Medical Journal*, **1**, 699.
Boris, A., Costello, J., Gower, M. M., and Welsch, J. A. (1961). *Proceedings of the Society for Experimental Biology and Medicine*, **106**, 708.
Caprino, L. (1963). *Bolletino della Società Italiana di Biologia Sperimentale*, **39**, 671, 674.
Clark, F. (1963). *Lancet*, **2**, 167.
Clark, F., and Horn, D. B. (1965). *Journal of Clinical Endocrinology and Metabolism*, **25**, 39.
Hall, R. (1967). *Journal of Clinical Pathology*, **20**, 407.
Harvey, R. F. (1967). *British Medical Journal*, **2**, 52.
Mazzaferri, E. L., and Skillman, T. G. (1969). *American Journal of the Medical Sciences*, **257**, 388.
Oberman, H., Buse, J., Herbert, E. G., Ellison, H. S., and Buse, M. G. (1963). *Journal of the American Medical Association*, **184**, 342.
Riley, N., and Gochman, N. (1964). Technicon Symposium.
Schindler, W. J., Matthews, M. G., and McHorse, T. S. (1966). *Federation Proceedings*, **25**, 380.
Today's Drugs (Benzodiazepines) (1967). *British Medical Journal*, **2**, 36.
Today's Drugs (Thyroid Hormones) (1969). *British Medical Journal*, **2**, 561.
Walton, J. G., and Thompson, J. W. (1969). *British Dental Journal*, **127**, 379.
Wayne, E. J., Koutras, D. A., and Alexander, W. D. (1964). *Clinical Aspects of Iodine Metabolism.*, Oxford, Blackwell Scientific.
World Health Organization (1966). Booklet on Immunology Techniques. Geneva, W.H.O.

Electrocardiographic Changes and Plasma Potassium Levels in Patients on Regular Haemodialysis

M. PAPADIMITRIOU,* M.D. ; R. R. ROY,† M.B., F.R.C.S., F.R.C.S.ED. ; M. VARKARAKIS,‡ M.D.

British Medical Journal, 1970, **2**, 268–269

Summary: Two out of four patients who had severe ischaemic E.C.G. changes when first accepted on to the dialysis programme showed much improvement after six months. From an analysis of 40 electrocardiograms (20 before and 20 after dialysis) of a further 17 patients it was found that the height of the T wave is a good index of the plasma potassium level. The tolerance of higher plasma potassium levels by these patients compared with patients with acute renal failure may be explained by the fact that the former do not have a hypercatabolic process and have a lesser degree of acidosis.

Introduction

Haemodialysis removes excess salt and water, urea, creatinine, urate phosphate, and other toxic substances accumulated in the plasma between dialyses. Hyperkalaemia is a great danger since it may cause sudden cardiac arrest in any oliguric patient with acute or chronic renal failure (Shaldon, 1966; Douglas and Kerr, 1968). During dialysis potassium loss is controlled by using a low concentration of potassium in the dialysate. Hypokalaemia with associated electrocardiographic (E.C.G.) changes has been noted during potassium-free dialysis (Klutsch, 1965).

Though there is no exact correlation between the serum potassium level and E.C.G. changes, the sequence of changes in the E.C.G. pattern is characteristic (Douglas and Kerr, 1968), particularly with a raised level of serum potassium (Black, 1968). We frequently noted that some of our patients had very high serum potassium levels before dialysis, without symptoms. We decided to investigate early E.C.G. changes in these patients, because it is known that the E.C.G. pattern is a more sensitive indicator of cardiotoxicity than the serum potassium level (Bellet, 1963).

Patients and Methods

Twenty-one patients on regular haemodialysis were studied; each patient had twice weekly 12-hour overnight haemodialysis by a modified Kiil two-layered parallel flow machine with a warm single pass automatic dialysate supply (Papadimitriou and Kulatilake, 1970). So far as possible all patients received a carefully controlled diet containing 0·7—0·9g. of protein per kg. body weight with intake of about 25 mEq of sodium, 70 mEq of potassium, and 300 mg. of calcium per day. No patients were on digitalis.

* Honorary Registrar and N.A.T.O. Scholar.
† Registrar to Professor R. Shackman, and Tutor in Surgery.
‡ Honorary Registrar.
Urological Unit, Department of Surgery, Hammersmith Hospital and Royal Postgraduate Medical School, London.

The blood samples for biochemical analysis were taken from the arterial side of a modified Scribner arteriovenous shunt immediately before or after dialysis, or both. Serum sodium and potassium were measured by an EEL-flame photometer, serum calcium by a Zeiss flame spectrophotometer, and total CO_2 by a phenolphthalein autoanalyser. During the period of study all patients had a normal serum calcium. Serum sodium ranged between 128 and 140 mEq/l. and predialysis TCO_2 between 21 and 24 mmole/litre. Electrocardiograms were taken by a Sanborn 500 visocardiette electrocardiograph (standard deflection 1 cm. to 1 mV), lead II being studied and the height of the P and T waves in millimetres and the length of QRS in seconds measured to the nearest 0·5 mm. Though the results are grouped at 0·5-mm. intervals, statistical analysis is made as for ungrouped data.

Results

Four out of 21 patients had severe ischaemic E.C.G. changes when accepted on to the haemodialysis programme; one of these also had angina. At the end of six months' regular haemodialysis two of these patients showed normal E.C.G. recordings and two still had abnormal recordings but showed moderate improvement toward a normal pattern. During this period angina in one of these cases disappeared completely. In 40 electrocardiograms taken in the remaining 17 patients a highly significant negative correlation ($r=-0{\cdot}46$; $P=0{\cdot}001$) was found between the pulse rate per minute and the plasma potassium (Fig. 1). The negative correlation between the height of P wave and the plasma potassium (Fig. 2) was also significant ($r=-0{\cdot}43$; $P=0{\cdot}003$). The length of QRS (Fig. 3) was only marginally correlated with the plasma potassium ($r=0{\cdot}29$; $P=0{\cdot}035$), while the correlation between the height of T wave and the plasma potassium was highly significant ($r=0{\cdot}68$, $P=0{\cdot}001$) (Fig. 4).

The pre-dialysis plasma potassium levels corresponding to 20 of the 40 electrocardiograms studied ranged between 4·4 and 8·8 mEq/l.; the post-dialysis plasma potassium corresponding to the remaining 20 electrocardiograms ranged between 2·7 and 4·6 mEq/l. During the period of study only two examples of arrhythmia were observed. In one patient transient supraventricular extrasystoles were noted at the beginning of dialysis. The biochemical values were normal at that time. During the reinsertion of an arteriovenous shunt into another patient cardiac monitoring showed sudden onset of idioventricular rhythm. Serum potassium was measured and found to be 9·2 mEq/l. Sodium bicarbonate, calcium gluconate, and glucose with insulin were given intravenously at once and the patient was transferred to the kidney unit for haemodialysis. His E.C.G. 30 minutes later was as shown in Fig. 5 and his plasma potassium was 8·8 mEq/l. Finally, no significant E.C.G. changes were found in patients with low plasma potassium levels immediately after dialysis.