Comparison of Thyroid Suppressibility by Triiodothyronine and Calcium Acetylsalicylate

J. MYHILL,* M.Sc.; I. B. HALES,* M.B., M.R.C.P., M.R.C.P.BD.

Brit. med. J., 1966, 1, 145-146

Measuring the suppressibility of the thyroïdal radioiodine uptake during the administration of some form of thyroid hormone is a well-established method of distinguishing between a thyrotoxic and a euthyroid radioiodine thyroïdal uptake in doubtful cases (Werner *et al.*, 1952; Morgans *et al.*, 1952; Greer and Smith, 1954; Spencer *et al.*, 1958). The degree of suppression of the thyroïdal clearance rate during the administration of either thyroxine or triiodothyronine (T3) has also been assessed in an Australian population (Oddie *et al.*, 1960a; Hales *et al.*, 1961), where the dietary intake of iodide is lower than that generally obtaining in Great Britain or the United States. Calcium acetylsalicylate also reduces thyroïdal radioiodine uptake in euthyroid subjects (Austen *et al.*, 1958), but fails to reduce appreciably the uptake in hyperthyroid patients (Myhill and Hales, 1963). Thyroid suppressibilities during T3 and calcium acetylsalicylate administration are here compared.

Methods

Thyroidal clearance rates were calculated by methods previously described which involve accurate corrections of the observed neck counts for extrathyroidal radioactivity in the neck tissues and allowance for the renal excretion rate (Oddie *et al.*, 1955). Patients were classified as euthyroid or hyperthyroid on the basis of clinical examination and the initial radioiodine clearance rate measurement, for which diagnostic borderlines are available (Oddie *et al.*, 1960b). For measurement of the T3 suppression test a dose of 120 µg./day was given for seven days and the clearance rate again measured. For assessment of the suppression on calcium acetylsalicylate a dose of 1 g./day was given for four days and the clearance rate again measured.

Results

The clearance rates were measured before and during calcium acetylsalicylate administration in eight euthyroid subjects. The ratio of the uptake before salicylate to the uptake during salicylate was calculated for each patient. The mean value of this quantity for the eight patients was 2.81, and the standard deviation of an individual observation was 1.12. Results previously published (Hales *et al.*, 1961) for T3 suppression values in 109 euthyroid patients gave four patients who had clearance rates which suppressed to zero, and the remaining 105 patients had a mean ratio of 7.41; the standard deviation of an individual value was 8.38. Although the statistical distribution of the ratio was skew, the distribution of the mean would be more normal, and a Student's *t* test of the significance of the difference between the mean values yielded $P < 0.001$.

If the fall of the clearance rates from before to during suppression, rather than their ratio, was analysed then the mean fall for the calcium acetylsalicylate patients ($2.84 \times 10^{-3} \text{ min.}^{-1}$) was significantly different from that for T3 patients ($7.30 \times 10^{-3} \text{ min.}^{-1}$), $P < 0.001$.

Five euthyroid patients were assessed on both calcium acetylsalicylate and T3. In each patient the fall of the clearance rate

(min.^{-1}) on T3 was greater than the fall on calcium acetylsalicylate. The mean difference in the fall was 1.09, which is significant at the 5% level. T3 is thus the superior suppressing agent for euthyroid subjects.

Eight hyperthyroid patients were measured on calcium acetylsalicylate, with a mean ratio close to unity; the previously reported results for patients assessed on T3 gave a similar mean ratio.

Five hyperthyroid patients were also assessed on both calcium acetylsalicylate and T3. On the administration of T3 all the five clearance rates rose slightly, whereas only one rose on calcium acetylsalicylate, the rest falling. The mean difference between the two sets of results was $2.58 \times 10^{-3} \text{ min.}^{-1}$, which is significant at the 5% level. This is evidence that calcium acetylsalicylate may cause a slight fall in the thyroïdal clearance rate in hyperthyroid patients, whereas T3 causes a lesser fall or a rise.

Discussion

On the basis of these results diagnostic borderlines have been drawn for the calcium acetylsalicylate suppression test, a normal statistical distribution fitted to the logarithms of the ratios being used. With regard to the euthyroid results, only 1% of patients from the fitted distribution would have a ratio (of clearance rate before calcium acetylsalicylate to clearance rate

Percentage of patients falling in different diagnostic zones with triiodothyronine (T3) or calcium acetylsalicylate (C.A.S. suppression).

during calcium acetylsalicylate) less than 1.26. In regard to the hyperthyroid results, only 1% of patients would have a ratio greater than 1.82. With these borderlines we obtain the diagnostic zones depicted in the Chart. Here it is seen that, with these borderlines, 78% of hyperthyroid and 88% of euthyroid patients are correctly diagnosed with the calcium acetylsalicylate suppression test. Doubtful results are obtained with 21% of hyperthyroid patients and 11% of euthyroid

* Institute of Medical Research and Thyroid Investigation Clinic, Royal North Shore Hospital of Sydney, and Department of Surgery, University of Sydney, Australia.

subjects. Wrong results would be expected to be obtained in 1% of hyperthyroid patients and 1% of euthyroid subjects. When compared with similar diagnostic borderlines for the T3-suppression test, where 82% of hyperthyroid patients and 97% of euthyroid patients are correctly diagnosed, and 16% of hyperthyroids and 2% of euthyroids remain doubtful, it is seen that calcium acetylsalicylate is inferior, as would be expected.

Results on the 10 patients who underwent both calcium acetylsalicylate and T3-suppression tests are shown in the Table. If these patients were diagnosed on the basis of the initial thyroïdal clearance rate alone (Oddie *et al.*, 1960b), only three would have been diagnosed correctly, the remaining seven

Differential Diagnosis (by Laboratory Tests) of Doubtful Cases of Hyperthyroidism

Patient	Diagnosis	Initial Clearance Rate* (min. ⁻¹) × 10 ³	Diagnosis†	Ratio on T3‡	Diagnosis§	Ratio on C.A.S.¶	Diagnosis
1	Euthyroid	2.65	Euthyroid	4.57	Euthyroid	2.65	Euthyroid
2	"	4.12	"	51.5	"	2.22	"
3	"	5.67	Doubtful	∞	"	2.73	"
4	"	6.44	"	2.57	"	2.01	"
5	"	7.36	"	2.23	"	1.94	"
6	Hyperthyroid	5.45	"	0.953	Hyperthyroid	1.40	Doubtful
7	"	7.07	"	0.876	"	1.07	Hyperthyroid
8	"	7.73	"	0.712	"	1.27	Doubtful
9	"	17.59	"	0.957	"	1.25	Hyperthyroid
10	"	36.44	Hyperthyroid	0.958	"	0.973	"

* Thyroïdal clearance rate is here defined as the fraction of the circulating inorganic iodide cleared per minute by the thyroid (Oddie *et al.*, 1955).

† Borderlines of Oddie *et al.* (1960b).

‡ Borderlines of Hales *et al.* (1961).

§ Ratio of the thyroïdal clearance rate before commencing T3 or calcium acetylsalicylate to the rate during T3 or calcium acetylsalicylate administration.

|| Borderlines of this paper.

having clearance rates in the doubtful range. After a T3-suppression test all patients would have been correctly diagnosed. But had the diagnosis been made on the basis of a calcium acetylsalicylate suppression two of the 10 patients would have been undiagnosed, their suppressions falling in the doubtful range. On the basis of a serum-protein-bound-iodine determination (Radcliff *et al.*, 1954) two out of five would have remained undiagnosed.

Salicylates are often used, and in large doses, for conditions such as rheumatoid arthritis. An increased incidence of thyrotoxicosis and non-toxic goitre in patients with rheumatoid arthritis has been reported (Short *et al.*, 1957; Gibberd, 1964). It is often necessary to assess thyroid function in patients on large doses of salicylate. A euthyroid patient will have a lower uptake than prior to starting on salicylate, though, owing to the wide variation in clearance rates for euthyroid subjects

(0.5×10^{-3} to 15×10^{-3} min.⁻¹ in Sydney), the uptake on salicylate may still be relatively high. Hyperthyroid patients will maintain their high uptake on salicylate (in Sydney a hyperthyroid patient has a clearance rate greater than 5×10^{-3} min.⁻¹). If the physician is unaware of the effects of salicylate, and a standard T3-suppression test is performed while an undiagnosed euthyroid patient is on calcium acetylsalicylate, a wrong result may be obtained, since the initial "control" value may be depressed and hence less apparent suppression may occur on T3. There is the possibility of irreversible therapy being instituted in this circumstance. For accurate assessment of thyroïdal function the patient merely ceases salicylate for a few days and the thyroïdal clearance is measured both then and during salicylate. The ratio of the rates is diagnostic.

Summary

Thyroïdal clearance rates were measured in hyperthyroid and euthyroid patients before and during the administration of calcium acetylsalicylate (1 g./day for four days) and compared with measurements before and during triiodothyronine (120 µg./day for seven days). Triiodothyronine proved to be the superior suppressing agent for the diagnosis of thyrotoxicosis, and statistical borderlines for the two diagnostic tests are compared. Knowledge of the thyroid's suppressibility on salicylate is useful when the diagnosis of thyroid disease is obscured by treatment with salicylates.

REFERENCES

- Austen, F. K., Rubini, M. E., Meroney, W. H., and Wolff, J. (1958). *J. clin. Invest.*, **37**, 1131.
- Gibberd, F. B. (1964). Private communication.
- Greer, M. A., and Smith, G. E. (1954). *J. clin. Endocr.*, **14**, 1374.
- Hales, I. B., Myhill, J., Oddie, T. H., and Croydon, M. (1961). *Ibid.*, **21**, 189.
- Hetzel, B. S., Good, B. F., Wellby, M. L., and Begg, M. W. (1962). *Aust. Ann. Med.*, **11**, 34.
- Morgans, M. E., Oldham, A. K., and Trotter, W. R. (1952). *J. Endocr.*, **8**, 250.
- Myhill, J., and Hales, I. B. (1963). *Lancet*, **1**, 802.
- Oddie, T. H., Meschan, I., and Wortham, J. (1955). *J. clin. Invest.*, **34**, 95, 106, 1044.
- Rundle, F. F., Thomas, I. D., Hales, I. B., and Catt, B. (1960a). *J. clin. Endocr.*, **20**, 1146.
- Thomas, I. D., Rundle, F. F., Myhill, J., and Catt, B. (1960b). *Ibid.*, **20**, 389.
- Radcliff, F. J., Baker, J. M., Croydon, M. J., Hart, M. J., and Hales, I. B. (1964). *Ibid.*, **24**, 883.
- Short, C. L., Bauer, W., and Reynolds, W. E. (1957). *Rheumatoid Arthritis*, p. 371. Harvard University Press, Cambridge, Mass.
- Spencer, R. P., Henkelmann, C. R., and King, E. R. (1958). *Metabolism*, **7**, 119.
- Werner, S. C., Hamilton, H., and Nemeth, M. (1952). *J. clin. Endocr.*, **12**, 1561.