Br. J. Surg. Vol. 69 (1982) 638–640 Printed in Great Britain

# Nadolol and potassium iodide in combination in the surgical treatment of thyrotoxicosis

*With the two aims of rapidly reducing circulating thyroid hormone levels and controlling the symptoms of thyrotoxicosis, we have prepared 17 thyrotoxic patients for subtotal thyroidectomy, using a combination of potassium iodide administered for 10 days and the long acting beta-adrenoceptor antagonist nadolol. All 17 patients had normal serum thyroxine levels after 10 days of such treatment although 10 still showed elevation of serum tri-iodothyronine and considerable elevation in the most severely toxic patient. All patients were, however, clinically euthyroid preoperatively.*

*Nadolol was adminstered once daily, hence avoiding the problems of drug administration in the immediate postoperative period, and plasma nadolol concentrations were high throughout the perioperative period. Serum thyroxine and tri-iodothyronine levels were significantly lower and reverse tri-iodothyronine levels higher 24 h postoperatively than before operation. All patients remained stable throughout the perioperative period.*

*We conclude that this regimen has a number of advantages in the preparation of patients for thyroidectomy, in reducing the degree of thyrotoxicosis, in convenience of drug administration and in ensuring adequate circulating concentrations of beta-adrenoceptor antagonist whilst still retaining a relatively short preoperative phase of drug treatment.*

**N. R. PEDEN, A. GUNN, M. C. K. BROWNING, J. CROOKS, A. L. FORREST, W. F. HAMILTON AND T. E. ISLES**

Departments of Anaesthesia, Biochemical Medicine, Surgery and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY

*Correspondence to*: Mr. A. Gunn, Department of Surgery, Ninewells Hospital.

Subtotal (partial) thyroidectomy is widely performed as definitive treatment for thyrotoxicosis (1, 2). While propranolol alone may be adequate preoperative preparation (3–7) the perioperative course, particularly in severely thyrotoxic patients, can be complicated despite large doses (8). Oral administration in the immediate postoperative period may be difficult and adequate plasma levels can be guaranteed only by giving propranolol via nasogastric tube (9). In patients prepared with propranolol the metabolic and endocrine response to surgical stress is abnormal with impairment of the normal rise in blood glucose and cortisol levels during and after thyroidectomy (10).

Propranolol was first used as a preparation for surgery in association with potassium iodide (Lugol's iodine) (3, 11, 12) and 10 days' preoperative treatment produced a significant fall in circulating thyroid hormones and allowed operation on patients who were euthyroid or with only minor elevations of serum tri-iodothyronine (T3) (13).

The non-selective beta-adrenoceptor antagonist nadolol controls the symptoms and signs of thyrotoxicosis, gives a modest reduction in circulating serum T3 concentrations (14, 15) and produces prolonged beta-adrenoceptor blockade in thyrotoxic patients at a dose of 160 mg given once daily (14). In addition the drug is poorly lipid soluble and might be expected to be free from centrally mediated neuroendocrine effects.

A combination of potassium iodide and nadolol (administered once daily) might therefore overcome the problems encountered when operating on thyrotoxic patients using propranolol alone and we report our experience using this combination in 17 patients including some with severe thyrotoxicosis.

## Patients and methods

Seventeen patients (1 male, mean age 35·8 years) of whom 16 had Graves' disease and 1 a toxic multinodular goitre, consented to the study which had local Ethical Committee approval. Sixteen patients received nadolol alone for a mean of 16·2 days (range 3–28) including 8 patients taking part in a 3-week study of the dose–response relationships of nadolol in thyrotoxicosis (14). The dose of nadolol, 80 mg initially, was increased to 160 mg daily after 3–7 days treatment. In 1 patient the dose was subsequently reduced again to 80 mg because of the development of ankle oedema in association with bradycardia. All 17 patients then received nadolol and potassium iodide 60 mg three times daily for a further 10 days and were then admitted to hospital for subtotal thyroidectomy the following day. Surgery was deferred for 5 days in 1 patient because of an acneiform rash on the upper chest possibly related to iodide allergy. Iodide was discontinued, nadolol 160 mg continued and oxytetracycline administered.

On the morning of operation nadolol 160 mg (80 mg in 1 patient referred to above) was administered at 6 a.m. With one exception who received no premedication, patients were premedicated with papaveretum 10–20 mg and hyoscine 0·2–0·4 mg and anaesthesia was induced with thiopentone 5 mg/kg and alcuronium 0·25 mg/kg. Maintenance anaesthesia was with $N_2O/O_2$ (70/30 per cent) with supplementation using halothane 0·5 per cent. During the operation patients received Hartmann's solution, 500 ml during the first hour and 500 ml during the subsequent 2 h, followed by 5 per cent dextrose in water—1500 ml during the following 18 h. Postoperative analgesia was with methadone 7·5 mg or cyclimorph (cyclizine 50 mg + morphine 10 mg) and antiemetic therapy was with prochlorperazine 12·5 mg. The surgical technique was comparable in all patients, with the thyroid remnant being left equal in size to a 10-g section of the excised gland. Patients were followed closely postoperatively and in addition to regular pulse, blood pressure and temperature recordings, all patients were reviewed after 1, 4, 8 and 24 h. Nadolol was continued for 5 days.

Blood was taken at the time of diagnosis (all), before starting on iodide (12 cases), on the day of admission (all), and 24 h postoperatively (13 cases) and serum was frozen at −20 °C for estimation by radioimmunoassay of serum tri-iodothyronine (T3) and thyroxine (T4) (16) and reverse tri-iodothyronine (rT3) (17). Blood was also withdrawn, in 12 patients, 12 h post-dosing on the day of admission and during the perioperative period, and plasma was frozen at −20 °C for subsequent assay of nadolol (18). Blood glucose was measured by a glucose oxidase method at intervals before, during and after operation.

Comparisons in individual patients have been made using the Student's *t* test for paired observations and correlations obtained by the method of least squares regression. Data throughout are presented as mean values ±s.e. of the mean.

## Results

*Changes induced by treatment preoperatively*

*Effect on thyroid status*: Seven patients were considered to be severely thyrotoxic at initial assessment with the Crooks–Wayne diagnostic index for thyrotoxicosis (19) (i.e. $\geqslant 30$ and serum T3 $\geqslant 8$ nmol/l). No patient was clinically thyrotoxic when admitted to hospital 1 day before operation. Changes in serum T3 and T4 are shown in *Table I*. On the day of admission for operation all patients had a normal serum T4 although only 7 had a normal serum T3, with the remainder of the patients therefore exhibiting biochemical T3 toxicosis. In most cases the serum T3 was modestly elevated (up to 3·95 nmol/l) but one patient, initially severely thyrotoxic, had a serum T3 of 5·80 nmol/l (T4, 111 nmol/l).There was no correlation between the initial serum thyroxine and the preoperative serum thyroxine but there was a weak correlation ($r = 0{\cdot}68$, $P < 0{\cdot}01$) between initial serum T3 and preoperative serum T3 (*Fig.* 1).

*Effects on heart rate*: Mean casual sitting pulse was $114 \pm 5$ beats/min at time of diagnosis and $69 \pm 2$ beats/min at 12 h post-dosing on the day of admission with all patients having a casual sitting pulse of <90 beats/min at this time. The mean reduction in casual sitting pulse rate was $39 \pm 3$ per cent. One patient initially in atrial fibrillation had reverted to sinus rhythm with nadolol alone.

*Operative course*

*Clinical state*: Recordings of pulse rate and systolic blood pressure at predetermined time intervals are shown in *Fig.* 2 (readings at intermediate times did not differ significantly) and were stable during the 24-h postoperative period. Four patients developed bradycardia (<50 beats/min) within 30 min of the induction of anaesthesia and in all cases this responded rapidly to intravenous atropine 0·3–0·6 mg. One patient was hypertensive and agitated immediately postoperatively but showed no sweating, tachycardia or pyrexia. Her condition settled rapidly with sedation and she was thereafter stable. Mean blood loss was $102 \pm 20$ ml due to thyroidectomy.

No case of thyrotoxic crisis or exaggeration of the thyrotoxic state (tachycardia, temperature >38 °C, sweating, mental confusion and agitation) was seen and the mean temperature 24 h postoperatively was $37 \pm 1$ °C. Two patients, both cigarette smokers, developed evidence of postoperative chest infections. Patients were mobilized on the first postoperative day and the mean period of hospitalization was 7 days.

*Biochemical parameters*: Changes in thyroid hormones in the perioperative period are shown in *Table I*. T4 fell slightly but significantly ($P < 0{\cdot}05$) while there was a marked reduction in serum T3 ($P < 0{\cdot}001$) associated with a significant rise in serum reverse T3 ($P < 0{\cdot}001$). Of the 13 patients in whom serum T3 was measured 24 h postoperatively, 2 had an elevated serum T3 concentration (2·63 and 3·17 nmol/l). In the patient in whom potassium iodide was discontinued for 5 days before operation the serum thyroid hormones rose briskly with serum T3 rising from 3·22 to 7·34 nmol/l on the preoperative day. This patient also showed the pattern of fall in T3 and rise in rT3 on the day of operation but the data are not included in the values in *Table I* for the 24-h postoperative column.

Mean serum calcium reached its nadir on the first postoperative day at $2{\cdot}15 \pm 0{\cdot}03$ mmol/l and no patient showed evidence of tetany. Blood glucose estimations in the perioperative period are shown in *Fig.* 2 and no patient was hypoglycaemic.

Plasma nadolol concentrations in the perioperative period are shown in *Table II*. Plasma nadolol was maximal during the operation and decayed slowly thereafter. Plasma nadolol concentrations 12 h post-dosing on the day of operation (i.e. approximately 8 h postoperatively) were strikingly and significantly higher than on the day before operation ($P < 0{\cdot}001$).

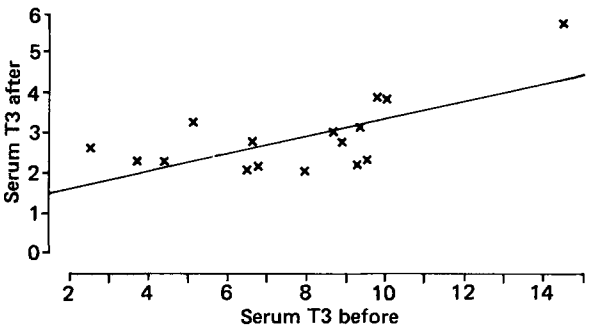


**Fig. 1.** *Relationship between serum T3 before any treatment and serum T3 after 10 days of nadolol + KI.*

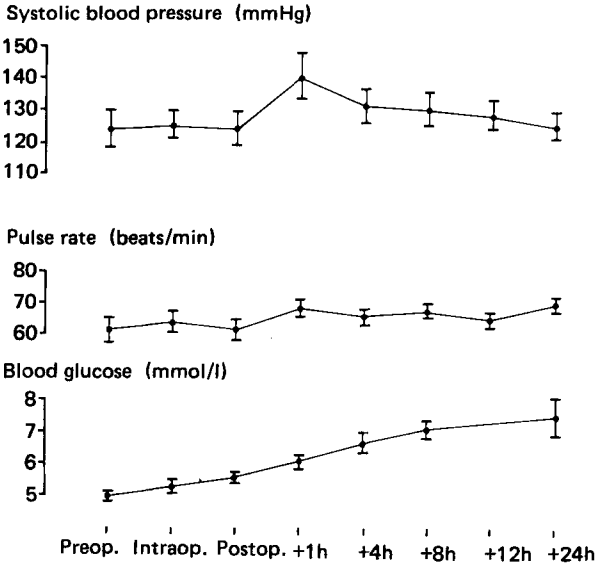


**Fig. 2.** *Changes in systolic blood pressure, pulse rate and blood glucose during the perioperative period.*

**Table I:** *VALUES OF THYROID HORMONES*

| | *T4 (nmol/l)* | *T3 (nmol/l)* | *rT3 (nmol/l)* |
|---|---|---|---|
| At diagnosis | 230 ± 18 | 7·72 ± 0·74 | 1·26 ± 0·12 |
| On nadolol | 225 ± 17 | 6·95 ± 0·43 | 1·55 ± 0·30 |
| After 10 d nadolol + KI | 91 ± 7 | 2·85 ± 0·24 | 0·59 ± 0·06 |
| 24 h postop. | 85 ± 7 | 1·53 ± 0·23 | 1·22 ± 0·16 |
| Normal range | 75–140 | 0·9–2·4 | 0·15–0·48 |

Postop., postoperatively.
Values are means ± s.e.m.

**Table II:** *PLASMA NADOLOL CONCENTRATIONS*

| | *1 d preop.* | *Before premed.* | *Intra-op.* | *Postop. 4 h* | *Postop. 8 h* | *Postop. 24 h* |
|---|---|---|---|---|---|---|
| Plasma nadolol (ng/ml) | 134 ± 34 | 338 ± 55 | 602 ± 68 | 531 ± 56 | 438 ± 45 | 305 ± 44 |

Preop., preoperatively; premed., premedication; intra-op., intra-operatively; postop., postoperatively.
Values are means ± s.e.m.

## Discussion

We had two main aims in embarking on the present study. First, to overcome the problems associated with propranolol administration in the perioperative period by using nadolol administered once daily and secondly to avoid the potential hazards of operating on severely thyrotoxic patients by using a 10-day course of potassium iodide to block thyroid hormone secretion while still retaining a relatively short period of preoperative preparation.

The second of these aims was partially achieved with all patients showing a normal serum T4 at the time of operation. Ten patients, however, still had elevated serum T3 and this

comparatively large number remaining thyrotoxic after 10 days of potassium iodide is at variance with the findings of Feek et al. (13). There was a weak correlation between serum T3 levels before and after treatment with nadolol and potassium iodide and such a correlation was also found by Emerson (20, 21) who in addition noted that a rebound increase in serum T3 may occur as early as 4 days after introduction of iodide. The finding of a correlation between serum T3 levels before and after treatment and the potential for early escape from iodide control suggests that it is the very toxic patient with a high initial serum T3 value who may be inadequately controlled by iodide or escape from iodide control. We therefore feel that the thyroid status of an initially very severely toxic patient cannot be confidently predicted after 10 days of beta-blocker and iodide and that it is preferable to render such a patient euthyroid with antithyroid drugs before embarking on surgery.

Since many of our patients were biochemically thyrotoxic at the time of operation this emphasizes the need for adequate circulating levels of beta-adrenoceptor antagonist during and after operation. The present study has shown that plasma nadolol levels are high throughout the perioperative period and are indeed higher than expected postoperatively. The likely explanation for this is that nadolol is poorly absorbed (22) and the effects of premedication and surgery may increase bioavailability by inhibiting gut motility.

The high plasma nadolol levels were reflected in patients' pulse rates in the perioperative period, which were in general very stable. The only problem encountered was bradycardia which developed in 4 patients shortly after induction of anaesthesia and was responsive to atropine. Hyoscine, which was used as premedication in all these patients, is known to cause secondary bradycardia (23) and it is clear that caution should be exercised in its use in a patient with a high degree of beta-adrenoceptor blockade. One further advantage of sustained high circulating drug concentrations is that the timing of surgery on the day of operation in relation to the timing of drug administration is not critical.

While the dose of nadolol used in this study (160 mg in all but one patient) has previously been shown to be necessary to produce 24-h beta-blockade in the majority of thyrotoxic patients (14), it may be that patients who have been rendered less thyrotoxic by potassium iodide and in whom the drug pharmacokinetics are strikingly altered during the operative period will require a smaller dose of nadolol. The use of the higher dose does, however, add some flexibility to the timing of the operation in relation to the course of potassium iodide treatment, particularly if for any reason such as intercurrent illness the timing of operation has to be delayed.

The changes in thyroid hormones over the course of operation are similar to those previously described during thyroidal and non-thyroidal surgery (10, 13, 24, 25) with a striking fall in serum T3 and rise in serum rT3. Since serum T4 fell significantly in the 24 h postoperatively there appears to be no excessive release of stored thyroid hormone, thus allaying the fears expressed by Pimstone (26). The rise in blood glucose in response to surgical stress in all patients appeared to be normal despite fasting and a high degree of beta-adrenoceptor blockade. Short term alleviation of the thyrotoxic state may therefore allow repletion of hepatic glycogen reserves which are known to be depleted in thyrotoxicosis (27).

In summary, we feel that this regimen has a number of advantages, particularly in rapidly reducing the levels of circulating thyroid hormones and in overcoming the problems associated with propranolol and its administration in the perioperative period. Surgery and anaesthesia appear to alter the pharmacokinetics of nadolol to increase plasma concentrations and the present study suggests that the dose of nadolol (160 mg) administered on the day of operation may be higher than is necessary in some patients. Further work will be necessary to clarify this point.

**Acknowledgements**

We thank Susan Fitzpatrick and Alan Anderson for skilled technical assistance and Lynn Connolly for secretarial help. Dr David Jackson (Squibb Laboratories Ltd) kindly provided supplies of nadolol.

**References**

1. Michie W.: Whither thyrotoxicosis? *Br. J. Surg.* 1975; **62**: 673–82.
2. Klementschitsch P., Shen K. and Kaplan E. L.: Reemergence of thyroidectomy as treatment for Grave's disease. *Surg. Clin. North Am.* 1979; **59**: 35–44.
3. Michie W., Hamer-Hodges D. W., Pegg C. A. S. et al.: Beta blockade and partial thyroidectomy for thyrotoxicosis. *Lancet* 1974; **1**: 1009–11.
4. Toft A. D., Irvine W. J., McIntosh D. et al.: Propranolol in the treatment of thyrotoxicosis by subtotal thyroidectomy. *J. Clin. Endocrinol. Metab.* 1976; **43**: 1312–16.
5. Caswell M. T., Marks A. D. and Channick B. J.: Propranolol for the preoperative preparation of patients with thyrotoxicosis. *Surg. Gynecol. Obstet.* 1978; **146**: 908–10.
6. Anderberg B., Kagedal B., Nilsson O. R. et al.: Propranolol and thyroid surgery for hyperthyroidism. *Acta Chir. Scand.* 1979; **145**: 297–303.
7. Zonszein J., Santangelo R. P., Mackin J. F. et al.: Propranolol therapy in thyrotoxicosis. A review of 84 patients undergoing surgery. *Am. J. Med.* 1979; **66**: 411–16.
8. Feely J., Crooks J., Forrest A. L. et al.: Propranolol in the surgical treatment of hyperthyroidism including severely thyrotoxic patients. *Br. J. Surg.* 1981; **68**: 865–9.
9. Feely J., Forrest A., Gunn A. et al.: Influence of surgery on plasma propranolol levels and protein binding. *Clin. Pharmacol. Ther.* 1980; **28**: 759–64.
10. Feely J., Crooks J., Forrest A. L. et al.: Altered endocrine response to partial thyroidectomy in propranolol prepared hyperthyroid patients. *Clin. Endocrinol.* 1981; **14**: 597–601.
11. Vinik A. I., Pimstone B. L. and Hoffenberg R.: Sympathetic nervous system blocking in hyperthyroidism. *J. Clin. Endocrinol. Metab.* 1968; **28**: 725–7.
12. Pimstone B. and Joffe B.: The use and abuse of β adrenergic blockade in the surgery of hyperthyroidism. *S. Afr. J. Med.* 1970; **44**: 1059–61.
13. Feek C. M., Sawers S. A., Irvine W. J. et al.: Combination of potassium iodide and propranolol in preparation of patients with Grave's disease for thyroid surgery. *N. Engl. J. Med.* 1980; **302**: 883–5.
14. Peden N. R., Isles T. E., Stevenson I. H. et al.: Nadolol in thyrotoxicosis. *Br. J. Clin. Pharmacol.* 1982; (In the press).
15. Wilkinson R. and Burr W. A. In: F. Gross (ed): *International Experience with Nadolol.* Royal Society of Medicine International Congress and Symposium Series No. 37. London: Academic Press, 1981: 51–5.
16. Seth J., Toft A. D. and Irvine W. J.: Simple solid phase radioimmunoassays for total triiodothyronine and thyroxine in serum and their clinical evaluation. *Clin. Chim. Acta* 1976; **68**: 291–301.
17. Ratcliffe W. A., Marshall J. and Ratcliffe J. G.: The radioimmunoassay of 3,3'5'-triiodothyronine (reverse T3) in unextracted human serum. *Clin. Endocrinol.* 1976; **5**: 631–41.
18. Ivashnik E.: Fluorometric determination of nadolol in human serum and urine. *J. Pharm. Sci.* 1977; **66**: 1168–72.
19. Crooks J., Murray J. P. C. and Wayne E. J.: Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Q. J. Med.* 1959; **28**: 211–34.
20. Emerson C. H., Anderson A. J., Howard W. J. et al.: Serum thyroxine and triiodothyronine concentrations during iodide treatment of hyperthyroidism. *J. Clin. Endocrinol. Metab.* 1975; **40**: 33–6.
21. Emerson C. H. and El-Zahiri M. M. S.: Potassium iodide and propranolol in Grave's disease. *N. Engl. J. Med.* 1980; **303**: 527–8.
22. Dreyfuss J., Brannick L. J., Vukovich R. A. et al.: Metabolic studies in patients with nadolol: oral and intravenous administration. *J. Clin. Pharmacol.* 1977; **17**: 300–7.
23. List W. F. and Gravenstein J. S.: Effects of atropine and scopolamine on the cardiovascular system in man 2. Secondary bradycardia after scopolamine. *Anesthiology* 1965; **26**: 299–304.
24. Burr W. A., Griffiths R. S., Black E. G. et al.: Serum T3 concentrations after surgical operations. *Lancet* 1975; **2**: 1277–9.
25. Brandt M. R., Kehlet M., Skorsted L. et al.: Rapid decrease in plasma triiodothyronine during surgery and epidural anaesthesia independent of afferent neurogenic stimuli and of cortisol. *Lancet* 1976; **2**: 1333–6.
26. Pimstone B.: Propranolol in thyrotoxicosis: invited commentary. *World J. Surg.* 1977; **1**: 256–7.
27. Piper J. M. and Poulsen E.: Liver biopsy in thyrotoxicosis. *Acta Med. Scand.* 1947; **127**: 439–47.

Paper accepted 18 May 1982.