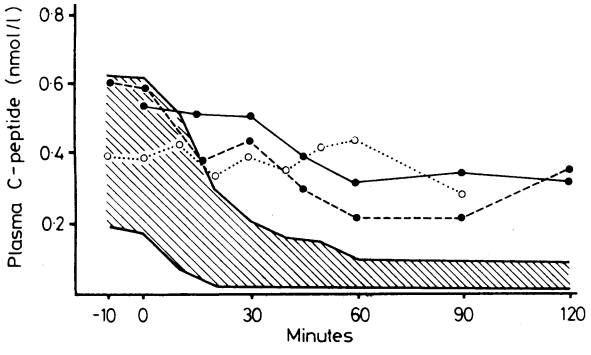
tumour; a second oral glucose tolerance test 21 months later again indicated reactive hypoglycaemia.

*Case 2*—A 43-year-old man was admitted to hospital in a coma and sweating profusely. His blood glucose concentration was 1·9 mmol/l (34 mg/100 ml) and he responded to intravenous dextrose. His wife had diabetes and was taking glibenclamide; he strenuously denied taking any of her tablets. He had had four milder episodes of drowsiness and sweating over the previous seven weeks. After overnight fasting on two occasions he remained normoglycaemic, but after two further fasts his blood glucose concentration fell to 2·9 mmol/l (52 mg/100 ml) and 1·9 mmol/l (34 mg/100 ml) with a plasma insulin concentration on the second occasion of 10 mU/l (assay sensitivity 3 mU/l, 95% confidence limits). Insulin-induced hypoglycaemia indicated abnormal C-peptide suppression (see figure). Several episodes of drowsiness with sweating occurred over the next month. Subselective arteriography of the pancreatic arteries showed a tumour blush in the body of the pancreas which measured 2·5 × 4 × 4 cm. No insulinoma was found at laparotomy, and distal pancreatectomy was performed; no tumour was identified in the resected pancreas. A postoperative C-peptide suppression test again suggested autonomous insulin production (see figure). Repeat pancreatic arteriography




Plasma C-peptide responses to bolus intravenous insulin (at 0 minutes) in case 1 (● ··· ●) and in case 2 before (●——●) and after (●- - -●) distal pancreatectomy. Hatched area indicates normal response (n = 8).

showed no evidence of a tumour. A further hypoglycaemic episode responded to 1 mg glucagon iv with normal blood glucose and insulin responses. A calcium infusion, however, was associated with a fall in blood glucose concentration to 1·9 mmol/l (34 mg/100 ml) and a rise in plasma insulin concentration from 16 to 24 mU/l, thus suggesting an insulinoma.[4] Radioimmunoassay for sulphonylurea-type drugs in samples from the various investigations showed plasma concentrations of glibenclamide ranging from 107 to 352 μg/l on five of six separate occasions. The patient then admitted to taking his wife's glibenclamide tablets.

## Comment

The C-peptide suppression test was particularly useful in case 1, in which the patient had undergone gastric surgery and had evidence of reactive hypoglycaemia. Plasma insulin concentrations at the time of fasting hypoglycaemia suggested a tumour of low functional activity, and his plasma C-peptide concentration was unsuppressed by hypoglycaemia. The C-peptide response in case 2, however, was similar to that in case 1. The value of C-peptide measurements in the diagnosis of hypoglycaemia has recently been reviewed.[5] Our second case shows that chronic glibenclamide ingestion may lead to failure of normal C-peptide suppression. This, together with difficulties in interpreting pancreatic arteriography,[5] emphasises that the offending drug must be measured to confirm or refute factitious hypoglycaemia due to sulphonylureas. A high index of suspicion is essential when patients with hypoglycaemia and access to antidiabetic drugs are assessed.

We thank Dr L G Heding, Novo Research Institute, Bagsvaerd, Copenhagen, Denmark, for providing reagents for C-peptide radioimmunoassay and Dr J McEwen and Dr J D Robinson, Hoechst UK Ltd, for glibenclamide determinations.

[1] Jordan RM, Kammer H, Riddle MR. Sulfonylurea-induced factitious hypoglycaemia. *Arch Int Med* 1977;**137**:390-3.
[2] Service FJ, Horwitz DL, Rubenstein AH, *et al.* C-peptide suppression test for insulinoma. *J Lab Clin Med* 1977;**90**:180-6.
[3] Rubenstein AH, Block MB, Starr J, Steiner DF. Proinsulin and C-peptide in blood. *Diabetes* 1972;**21**:661-72.
[4] Kaplan EL, Rubenstein AH, Evans R, Lee CH, Klementschitsch P. Calcium infusion: a new provocative test for insulinomas. *Ann Surg* 1979;**190**:501-7.
[5] Anonymous. Insulinomas. *Br Med J* 1981;**282**:927-8.

(*Accepted 15 December 1981*)

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# Importance of thyroxine in suppressing secretion of thyroid-stimulating hormone after thyroidectomy

Serum concentrations of triiodothyronine (T3) correlate well with clinical indices of thyroid hormone activity[1] and are generally considered to be of greater functional importance than thyroxine (T4) concentrations. The inhibition of thyroid-stimulating hormone release by thyroid hormones, however, correlates better with serum concentrations of T4 than with those of T3 in hypothyroid patients receiving T4 replacement therapy.[2] We have observed two cases which indicate that T3 alone, in serum concentrations close to the upper normal limit, may not be sufficient to suppress the secretion of thyroid-stimulating hormone.

## Case reports

Both patients were women who had had total thyroidectomies because of follicular or papillary cancer of the thyroid gland. Owing to supposed side effects their T4 replacement therapy was changed to T3 in daily doses of 60 μg (case 1) and 40 μg (case 2). This treatment produced clinical euthyroidism in both patients. The first patient was investigated with the thyrotropin-releasing hormone test (200 μg thyrotropin-releasing hormone intravenously) after 38 months of receiving T3 replacement therapy and the second after 19 months. The results are summarised in the table.

*Determination of thyroid function in two patients receiving T3 replacement therapy after thyroidectomy*

| | Serum concentrations of thyroid-stimulating hormone (mU/l) after administration of thyrotropin-releasing hormone* | | | Serum concentrations* (nmol/l) | |
|---|---|---|---|---|---|
| | 0 | 20 minutes | 30 minutes | T4 | T3 |
| Case 1 | 28 | 100 | 100 | 1 | 2·8 |
| Case 2 | 75 | 390 | 350 | | 3·2 |
| Normal range | 1–7 | | | 5–154 | 0·9–3·2 |

*Samples drawn before daily administration of T3.

When the replacement therapy was changed back to T4 both patients had basal serum thyroid-stimulating hormone concentrations of 1 mU/l or less, which did not increase after administration of thyrotropin-releasing hormone. With T4 replacement therapy the serum T4 concentrations were 163 nmol/l (case 1) and 194 nmol/l (case 2) and the serum T3 concentrations 1·8 nmol/l (case 1) and 2·0 nmol/l (case 2). Thus, T4 replacement therapy suppressed the secretion of thyroid-stimulating hormone more effectively despite a lower serum T3 concentration.

## Comment

Total thyroidectomy is a special situation in which the effect of T3 on the secretion of thyroid-stimulating hormone can be studied

selectively. Apparently T3 replacement regimens that lead to clinical euthyroidism and serum concentrations close to the upper normal limit may not always be sufficient to suppress the secretion of thyroid-stimulating hormone in the absence of T4. This agrees with the results of Wahner and Gorman,[3] who found above normal serum concentrations of T3 to be necessary to achieve normal values of serum thyroid-stimulating hormone in hypothyroid patients receiving T3 replacement therapy. The occupancy of nuclear receptors for T3 in the pituitary gland correlates well with the suppression of thyroid-stimulating hormone secretion,[4] which contrasts with its apparent dependence on circulating T4. The difference may be explained by a much higher capacity of local intracellular monodeiodination of T4 in the pituitary gland compared with other tissues, providing T3 for the nuclear receptors.[4]

These observations indicate that T4 is important for the feedback suppression of thyroid-stimulating hormone. Therefore T3 should be avoided as replacement therapy after thyroidectomy for follicular or papillary cancer of the thyroid gland as the prognosis of these diseases is worse if the serum concentration of thyroid-stimulating hormone is not adequately reduced.[5]


[1] Bantle JP, Dillman WH, Oppenheimer JH, Bingham C, Runger GC. Common clinical indices of thyroid hormone action: relationships to serum free 3,5,3'-triiodothyronine concentration and estimated nuclear occupancy. *J Clin Endocr Metab* 1980;**50**:286-93.

[2] Ryder S, Gollapudi M, Varma A. Relationship of serum T4 and T3 to TSH in primary hypothyroidism. *Arch Intern Med* 1980;**140**:1290-1.

[3] Wahner HW, Gorman CA. Interpretation of serum tri-iodothyronine levels measured by the Sterling technic. *N Engl J Med* 1971;**284**:225-30.

[4] Silva JE, Larsen PR. Contributions of plasma triiodothyronine and local thyroxine monodeiodination to triiodothyronine to nuclear triiodothyronine receptor saturation in pituitary, liver, and kidney of hypothyroid rats. *J Clin Invest* 1978;**61**:1247-59.

[5] Clark OH. TSH suppression in the management of thyroid nodules and thyroid cancer. *World J Surg* 1981;**5**:39-47.


(*Accepted 16 December 1981*)


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# Anxiety caused by a short-life hypnotic

The Committee on the Review of Medicines[1] and others have commended hypnotic drugs that have a short duration of action in preference to those that are cumulative and persistent all day. We, however, describe a potential disadvantage of a benzodiazepine derivative with a very short half life, used in large dosage.

The recommended dose of triazolam in Britain is 0·125 to 0·25 mg, though in other European countries up to 1 mg has been used. It is rapidly eliminated, about half within four hours. In contrast, we have also used loprazolam, which has a half life of eight hours or longer.

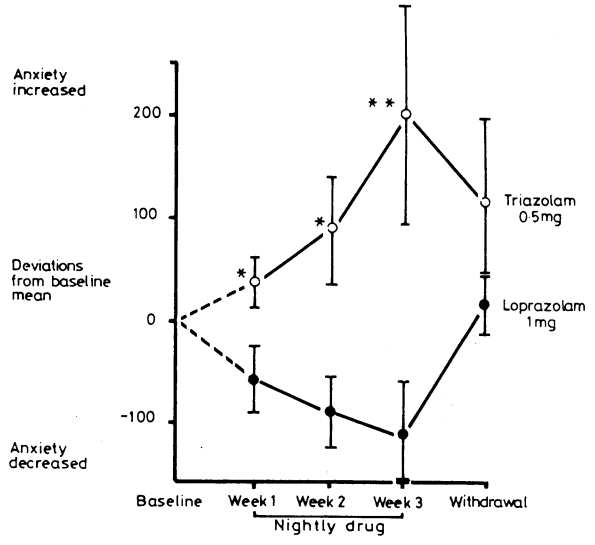
## Subjects, methods, and results

As part of a larger double-blind study 16 women and five men, all poor sleepers, with a mean age of 56 years took matching capsules nightly for two periods of six weeks. In one period each took inert capsules in an adaptation week, then inert capsules in a second (baseline) week, triazolam 0·5 mg nightly for the next three weeks, and inert capsules for a withdrawal week. In another six-week period they received loprazolam 1 mg instead of triazolam. The periods were separated by at least four weeks, and 12 subjects took the triazolam and nine the loprazolam first. Each evening and with visual analogue scales they rated how anxious they had felt that day.

Loprazolam taken at night was associated with a mean decrease of daytime anxiety, and triazolam with increased anxiety. Comparing the two (see figure), the subjects, acting as their own controls, were significantly more anxious when taking triazolam in each of the three weeks (repeated measures analysis of variance and subsequent $t$ tests: $p<0.05$ in weeks 1 and 2, $p<0.01$ in week 3).

Examination of mean raw scores in each week and comparison with subjects' own baseline weeks showed loprazolam to be associated with a significant reduction of anxiety in each of the three drug weeks ($p<0.05$, $p<0.03$, $p<0.02$). Patients taking triazolam showed a mean increase of anxiety each week compared with baseline, not reaching significance by the second week ($p=0.09$) but significant in the third week ($p=0.038$).

On withdrawal days in the withdrawal week mean anxiety was greatest on the day after three nights without loprazolam (patients had also slept badly on the third night) and greatest on the day after the first night without triazolam (on which night they had slept very badly): on only that day did the data, in which there was a high variance, reach significance ($p<0.01$).




Comparison of mean anxiety with two benzodiazepine derivatives. Units are deviations from baseline mean expressed as percentage of baseline standard deviation for each subject. Bars indicate standard errors. *$p<0.05$. **$p<0.01$.

## Comment

Drugs used as hypnotics are the same as those used to diminish anxiety—for example, alcohol, barbiturates, and benzodiazepines—and their presence leads to adaptive changes in the central nervous system, as if to counteract the drug. When the drug is stopped the induced changes persist, with resultant insomnia and anxiety. These rebound phenomena are features of the first few weeks after stopping benzodiazepines.[2,3] The more rapidly the drug is eliminated the earlier the rebound. A measurable rebound in sleep may occur within a single night[4]; indeed, a bottle of gin each evening causes early awakening, with anxiety, because alcohol is rapidly metabolised.

We presume that the large dose of triazolam each evening was rapidly metabolised and so led to daytime rebound anxiety, in contrast to the more familiar reduction of anxiety by the longer-persisting loprazolam. Withdrawal of anxiety-relieving drugs often causes paranoid ideas, and a report of paranoid ideas associated with triazolam[5] might have arisen from a dose of 1 mg. Dosage is clearly crucial, and the merits of very rapidly metabolised drugs like triazolam, at optimal dosage, should continue to be recognised.

We thank Roussel UCLAF for the capsules. Loprazolam is an investigative drug for which there is a clinical trials certificate.


[1] Committee on the Review of Medicines. Systematic review of the benzodiazepines. *Br Med J* 1980;**280**:910-2.

[2] Petursson H, Lader MH. Withdrawal from long-term benzodiazepine treatment. *Br Med J* 1981;**283**:643-5.

[3] Allen S, Oswald I. Anxiety and sleep after fosazepam. *Br J Clin Pharmacol* 1976;**3**:165-8.

[4] Ogunremi OO, Adamson L, Březinová V, *et al.* Two anti-anxiety drugs: a psychoneuroendocrine study. *Br Med J* 1973;ii:202-5.

[5] Van Der Kroef C. Reactions to triazolam. *Lancet* 1979;ii:526.


(*Accepted 7 December 1981*)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