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]

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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.

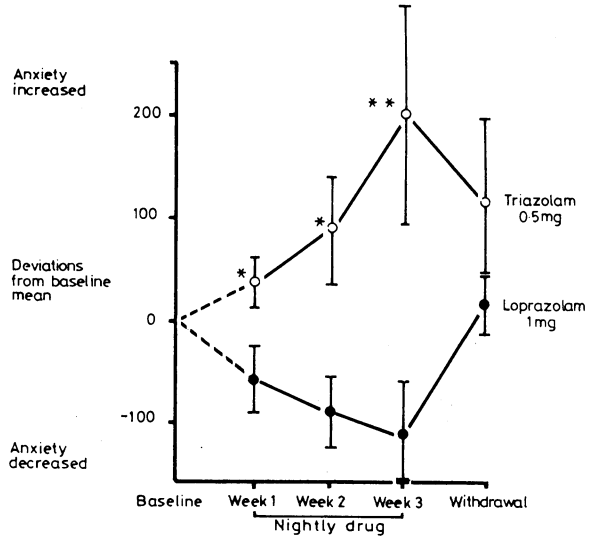
Subjects, methods, and results

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.

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