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Evaluation of single-dose hypnotic treatment before elective operation

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Summary and conclusions

A prospective randomised double-blind controlled trial was carried out to evaluate the place of a single dose of triazolam, flurazepam, and placebo on the evening before an elective operation in 96 patients. Features of sleep were recorded by patients and nurses on questionnaires. Onset of sleep was delayed and duration of sleep reduced in two-thirds of patients allocated placebo compared with their normal sleep pattern. Two-thirds of these patients also complained of waking more than twice during the night. Both hypnotics significantly improved the duration and time of onset of sleep and reduced the frequency of waking when compared with the placebo. Patients who took triazolam, however, fell asleep faster and woke less often than those who took flurazepam. Furthermore, triazolam appeared to have advantages over flurazepam before major surgery.

Thus giving a single dose of a hypnotic on the night before an elective operation improves the patient's sleep, and greater benefit was derived from triazolam than flurazepam.

Introduction

Little is known about the influence of hospital admission on sleep before operation. We have found, however, that many patients complain that sleep is disturbed before even minor operations. Alterations in preoperative sleep have been reported before open heart surgery, but severe disruption of sleep occurred only after operation.¹ Data on patients undergoing non-cardiac operations are sparse. Detailed observations on 10 patients undergoing elective herniorrhaphy showed decreased sleep time and reductions in the durations of rapid eye movement and deep sleep before operation.² These minor changes were attributed to anxiety, fear, and the presence of a new environment that inhibited the duration and depth of sleep. In

view of the lack of knowledge concerning disturbance of sleep and the value of hypnotics before operation we undertook a randomised double-blind controlled trial to compare a hypnotic with a short half life (triazolam)³ and one with a long half life (flurazepam)⁴ against a placebo before elective operation.

Patients and methods

All patients under the care of one surgeon admitted to two surgical wards were included in the trial provided that they were undergoing elective operation and were aged 18-65 years. Patients were excluded if they had recently been prescribed anticonvulsants, antihistamines, or appetite suppressants; if they had been habitually taking 5 mg or more of nitrazepam or 15 mg or more of flurazepam; and if they had taken any hypnotic or benzodiazepine within three days of the operation. We explained to all patients that a capsule was being prescribed that might improve the duration and quality of sleep on the night before operation.

A questionnaire was given to the patients before the trial drug was administered so that they could study the document and were aware of the questions that they had to answer the next morning. Patients considered suitable for inclusion in the trial were allocated at random to receive one of the following: triazolam 0.25 mg, flurazepam 15 mg, and placebo. These were all presented in identical capsules. The medication was administered half an hour before lights out. The night nurses who dispensed the drugs were also given a simple questionnaire for each patient enrolled in the trial. The patients were checked hourly to ascertain whether they were asleep. Nurses were asked to assess the overall quality of the patients' sleep as bad, reasonable, or very good.

The patient questionnaire asked the following questions: (1) Did the capsule help you sleep? (2) How often did you wake during the night? (3) How quickly did you fall asleep? (4) How long do you think you slept? (5) How do you feel this morning? (6) Were you satisfied with your night's sleep?

The study was confined to the immediate preoperative period, and we did not attempt to evaluate the long-term effects of single-dose treatment.

Results

The study included 108 patients, but 12 had to be excluded because they had been habitually taking hypnotics or had taken a hypnotic within three days of admission; thus we present data on 96 patients. Table I shows the distribution of patients and compares the groups for age, sex, and operation.

The results of the nurses' questionnaire indicated that eight patients given placebo (26% of those for whom data were complete) were considered to have had a poor night's sleep compared with two (6%) given flurazepam and two (6%) given triazolam. When the data were analysed using a Mann Whitney U test for ranked scores only the patients who had received triazolam were considered by the nurses

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to have slept significantly better than the patients given placebo (table II).

In answer to the question "Were you satisfied with your night's sleep?" only 13 of the 33 patients who had received placebo had had a good night's sleep (39%) compared with 22 (71%) of the 31 who had received flurazepam ($p < 0.05$) and 29 (91%) of the 32 who had received triazolam ($p < 0.001$) (table III). Patients given triazolam had fallen asleep faster than those given flurazepam ($p < 0.05$), even though flurazepam had induced more rapid onset of sleep than placebo ($p < 0.01$). Of the patients given placebo, 21 (64%) said that they had taken longer to go to sleep than usual compared with nine (29%) given flurazepam and three (9%) given triazolam (table IV).

When duration of sleep was evaluated 22 patients who had received placebo (67%) said that they had slept for a shorter time than usual compared with 12 (40%) who had received flurazepam ($p < 0.05$) and nine (29%) given triazolam ($p < 0.001$) (table IV). Frequency of waking differed appreciably between the groups, such that 18 of the 27 patients given placebo for whom data were complete woke more than twice (67%) compared with 14 out of 29 patients given flurazepam (48%) and nine out of 31 patients given triazolam (29%). The differences between each group achieved significance. There were no significant differences in answer to the question "How did you feel on awakening?" (table V). On the other hand, even in the group given placebo 13 patients complained of drowsiness and four of headaches (table VI).

Whether the patients had been satisfied with their night's sleep was also analysed according to whether they were to have had a major or minor operation (table I). For both major and minor operations triazolam was found to provide significantly better results than placebo ($p < 0.05$ and $p < 0.0005$ respectively), whereas flurazepam was shown to be significantly better than placebo ($p < 0.05$) only before minor operations (table III).

TABLE I—Details of each group

	Triazolam (n = 32)	Flurazepam (n = 31)	Placebo (n = 33)
No of men	17	21	20
No of women	15	10	13
Mean age (years) ..	47.4	49.9	50.6
No undergoing major operation	13	7	10
Gastric	3	2	2
Mastectomy	2	1	1
Biliary	6	4	5
Colorectal	2		2
No undergoing minor operation	19	24	23
Herniorrhaphy ..	8	10	8
Minor anorectal ..	4	5	4
Others	7	9	11

TABLE II—Response obtained from nurses to question on the quality of patients' sleep

	Triazolam	Flurazepam	Placebo
Bad	2	2	8
Reasonably good ..	17	19	15
Very good	12	10	8
Data incomplete ..	1		2

Significance of differences (Mann Whitney U test): triazolam *v* placebo $p < 0.05$; triazolam *v* flurazepam NS; flurazepam *v* placebo NS.

TABLE III—Numbers of patients who answered "Yes" to the question "Were you satisfied with the night's sleep?" related to severity of operation they were about to undergo

	Triazolam (n = 32)	Flurazepam (n = 31)	Placebo (n = 33)
Total answering "Yes" ..	29	22	13
Major operation ..	12	6	5
Minor operation ..	17	16	8

Significance of differences—All patients answering "Yes": triazolam *v* placebo $p < 0.001$; triazolam *v* flurazepam NS; flurazepam *v* placebo NS (χ^2 test). Patients undergoing major operations: triazolam *v* placebo $p < 0.05$; triazolam *v* flurazepam NS; flurazepam *v* placebo NS (Fisher's exact test). Patients undergoing minor operations: triazolam *v* placebo $p < 0.0005$; triazolam *v* flurazepam NS; flurazepam *v* placebo $p < 0.05$ (Fisher's exact test).

TABLE IV—Responses of patients to three questions relating to sleep kinetics

	Triazolam (n = 32)	Flurazepam (n = 31)	Placebo (n = 33)
<i>A: How quickly did you fall asleep?</i>			
Slower than usual ..	3	9	21
As usual	16	14	9
Quicker than usual ..	13	8	3
<i>B: How did the duration of sleep compare with usual?</i>			
Shorter	9	12	22
Same	12	14	8
Longer	10	4	3
Data incomplete ..	1	1	
<i>C: How often did you wake in the night?</i>			
> 4 times	2	4	9
3-4 times	7	10	9
1-2 times	13	11	7
Never	9	4	2
Data incomplete ..	1	2	6

Significance of differences (Mann Whitney U test)—Question A: triazolam *v* placebo $p < 0.0001$; triazolam *v* flurazepam $p < 0.05$; flurazepam *v* placebo $p < 0.01$. Question B: triazolam *v* placebo $p < 0.001$; triazolam *v* flurazepam NS; flurazepam *v* placebo $p < 0.05$. Question C: triazolam *v* placebo $p < 0.001$; triazolam *v* flurazepam $p < 0.05$; flurazepam *v* placebo $p < 0.05$.

TABLE V—Responses of patients to the question "How did you feel on awakening?"

	Triazolam (n = 32)	Flurazepam (n = 31)	Placebo (n = 33)
Complaints	14	12	18
Refreshed and alert ..	18	17	13
Not recorded		2	2

Significance of differences (χ^2 test): triazolam *v* placebo NS; triazolam *v* flurazepam NS; flurazepam *v* placebo NS.

TABLE VI—Numbers of patients in each group complaining of drowsiness, headaches, and nausea on awakening

	Triazolam	Flurazepam	Placebo
Drowsiness	11	10	13
Headaches	3	1	4
Nausea		1	1

Discussion

This study was designed to answer two questions: How badly is normal sleep affected by admission to hospital for elective surgery? and, To what extent do hypnotics with long and short half lives improve this sleep deficit? In answer to the first question, 61% of the patients who had received placebo were dissatisfied with their night's sleep, particularly before elective minor operations. Two-thirds of patients given placebo complained that they had taken longer to get to sleep than usual, their duration of sleep had been impaired, and they had woken more than twice in the night. Giving a hypnotic significantly improved these changes in sleep pattern. Furthermore, in certain respects—particularly the time of onset of sleep and frequency of waking—triazolam was superior to flurazepam.

There was no evidence that either hypnotic was associated with any increased incidence of side effects compared with placebo. Interestingly, even when placebo was given 13 of the 31 patients complained of drowsiness and four of headaches. No adverse reactions to either hypnotic were recorded. Rebound insomnia has been recorded, particularly with short-term hypnotics,⁵ but the present study was conducted immediately before operation and no follow-up was undertaken. Even if we had followed up the patients it is unlikely that we could have evaluated rebound insomnia since the effect of operation itself has such a pronounced influence on sleep.⁶ Nevertheless,

Nicholson⁷ reported that rebound insomnia is uncommon even after administration of hypnotics with short lives, and we question the relevance of this phenomenon.

We accept that the results of the present study are based on rather subjective data and that we did not measure the period of rapid eye movement, obtain electroencephalograms, or assess any other objective neurophysiological indices. Nevertheless, many of the same questions were asked in different ways. Hence the additional questions "Did the treatment help you sleep?" and "How long did you sleep?" provided results that were exactly the same as those elicited by the questions "Were you satisfied with the night's sleep?" and "How did the length of sleep compare with usual?"

Remarkably few studies have been carried out on the value of single-dose hypnotic treatment for patients before major and minor operations, although two studies have suggested that hypnotics improve the duration and quality of sleep before operation.^{8,9} The results of the present study leave us in no doubt that triazolam is safe and effective for patients before elective operation.

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Effect of bile on vitamin B₁₂ absorption

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Summary and conclusions

The standard double-isotope Schilling test was used to study vitamin B₁₂ absorption in seven patients with obstructive jaundice and 10 with T-tube bile duct drainage after cholecystectomy and bile duct exploration. In three and five of these patients respectively absorption was impaired. In the second group six patients were restudied after removal of the T tube, and in each case absorption was improved. Similar results were obtained after bile duct ligation in rats. Bile exclusion produced a 50-60% reduction in renal and hepatic uptake of vitamin B₁₂ from the intestinal lumen. The malabsorption was corrected by replacing bile.

These studies suggest that bile plays a part in the normal absorption of vitamin B₁₂.

Introduction

In man both vitamin B₁₂ and bile acids are absorbed in the ileum^{1,2} but the relation between these processes has not been defined. We have therefore tried to determine whether bile acids play a part in the absorption of vitamin B₁₂.

Materials and methods

Human studies—A standard double-isotope Schilling test was performed on seven patients with obstructive jaundice and 10 patients with T-tube drainage of the common bile duct for biliary calculi.

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The project was approved by the hospital ethics committee and informed consent obtained from all patients. After an overnight fast patients swallowed capsules containing ⁵⁷Co-vitamin B₁₂ bound to intrinsic factor and ⁵⁸Co-vitamin B₁₂; non-radioactive vitamin B₁₂ (1 mg) was given intramuscularly at the same time. The fast was maintained for a further two hours and the urine output collected for 24 hours. Absorption of vitamin B₁₂ was expressed as the percentage of the oral dose excreted in the urine over 24 hours. In a patient with carcinoma of the common bile duct (case 7) the test was repeated with oral chenodeoxycholic acid 250 mg given hourly for the first three hours. In the patients with T-tube drainage the test was done between the fifth and seventh postoperative days with the T-tube still in situ. In six patients the test was repeated, in three (cases 8, 10, and 17) within a week and in the other three (cases 11-13) one month after the tube had been removed.

Rat experiments—Vitamin B₁₂ absorption was studied in three groups of eight female albino Wistar rats weighing 150-200 g. A sham operation was performed on the animals in group 1 and the bile duct ligated in groups 2 and 3. On the day after operation each animal was given 0.005 µg ⁵⁷Co-cyanocobalamin in 0.2 ml physiological saline directly into the stomach. One and three hours later 1 ml rat bile was infused into the stomach of the animals in group 3. All animals were killed at seven hours. At the end of the experiment the kidneys, liver, stomach, colon, and small intestine were removed. The small intestine was divided into three segments, the lumen of each flushed with 15 ml deionised water, and the washings collected. The radioactivity of the organs and intestinal contents were counted in a Packard gamma counter.

Results

Human studies—Of the patients with obstructive jaundice (table I), the three with carcinoma of the head of the pancreas had severe cholestasis, plasma bilirubin concentrations exceeding 170 µmol/l (9.9 mg/100 ml). Absorption of vitamin B₁₂ was abnormal in two of these patients and at the lower limit of normal in one. The patient with carcinoma of the common bile duct had abnormal absorption, and at operation his pancreatic duct was noted to be normal. When the Schilling test was repeated with 750 mg chenodeoxycholic acid his urinary excretion of ⁵⁷Co-vitamin B₁₂ and ⁵⁸Co-vitamin B₁₂ improved