Confusion and hypnotics in demented patients

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SUMMARY. Eleven elderly confused patients were given a single dose of chlormethiazole, temazepam and placebo on separate nights within a 10-day period. There was no statistically significant difference between the three treatments the next morning in any of the tests, which included subjective and objective measures of mental ability, orientation and hangover effect. These results mirror those previously found in normal, healthy, elderly patients, and do not therefore support the contention that hypnotics increase confusion in demented patients, or that such patients are more sensitive to their actions. Indeed, plasma drug concentrations were on average twice as high in demented as in normal elderly subjects, thus raising the possibility of decreased sensitivity in the demented group. There was little correlation between plasma concentration and pharmacological effect.

Introduction

IT is well established that acute toxic confusional states in elderly patients are precipitated by drugs. It is claimed also that chronically confused patients are more sensitive to hypnotics than elderly patients with normal brain function (Stedeford, 1978; Davison, 1980). While the evidence supporting the first statement is clear to every practising physician and well established in the literature (Church and Marriott, 1959; Evans and Jarvis, 1972; Schentag *et al.*, 1979), there are almost no data on the second, apart from one report showing that demented parkinsonian patients exhibit abnormal CNS reactions to L-dopa (Sacks *et al.*, 1970). Since nocturnal wandering and wakefulness are poorly tolerated by relatives of demented patients (Sanford, 1975), hypnotics are frequently used and compliance is assured. However, the patients' problems to others may be aggravated because of increased confusion, sedation, unsteadiness and incontinence the next day (Evans and Jarvis, 1972).

Aim

To establish whether confused patients are especially sensitive to the action of chlormethiazole and temazepam.

Methods and subjects

Subjects were female inpatients at Leicester General Hospital with a mean age of 80 (range 73-92 years); all had been in hospital for at least one week before the study, and were healthy apart from their confusion, which was stable. They scored between 5 and 9 out of 12 on the Clifton Scale for orientation and information (Clarke *et al.*, 1981). None took regular medication apart from laxatives (three cases). Full blood counts, urea, electrolytes, creatinine, liver function tests and plasma viscosity were within the normal range for the local laboratory. The consent of the nearest relative was obtained and the study had Local Ethical Committee approval.

The study was a double blind crossover within-patient comparison which was randomized and balanced by an independent observer. Each subject received 20 mg temazepam, 384 mg chlormethiazole edisylate and an identical placebo orally on three occasions, separated by at least two days, over a 10-day period; these drugs were chosen because they have been shown to lack hangover effects in normal elderly subjects (Briggs *et al.*, 1980). The patients slept in their own hospital bed, and 11 hours after administration of medication the following tests were carried out:

1. Tests of mental ability and orientation. Each subject was asked a number of standard questions to assess their degree of confusion (Blessed *et al.*, 1968).

2. EEG Sleep Score. A 30-minute EEG recording was taken at 11 hours and scored blind by two independent observers (Malpas *et al.*, 1970).

3. 'E' Deletion Test. Subjects crossed out the letter 'e' on a page of standard prose for two minutes (Briggs *et al.*, 1980). The score was the total number of 'e's correctly deleted.

4. Sway Test. Subjects had their cumulative sway over one minute measured by a Codoc Ataxiameter, one unit equalling one third of a degree arc (Overstall *et al.*, 1977).

5. Subjective assessment. Each subject was asked to assess their own sleep in terms of latency (went straight to sleep = 0; went to sleep in the first half of the night = 1; did not sleep until the second half of the night = 2; did not sleep at all = 3), duration (slept right through = 3; slept half the night = 2; slept less than half the night = 1; did not sleep at all = 0), and sedation (felt wide awake = 0; felt slightly drowsy = 1; felt very drowsy = 2; felt almost asleep = 3).

6. Venous blood sample for estimation of plasma drug concentration (Huggett *et al.*, 1980).

The Wilcoxon Matched Pairs Signed Rank Test was used to compare the results of the tests between each drug and placebo.

Psychomotor tests after chlormethiazole, temazepam and placebo in elderly confused patients.

	Chlormethiazole (mean ±SEM)	Temazepam (mean ±SEM)	Placebo (mean ±SEM)
Mental test score ($n=11$)	15.4±1.7	17.4±1.4	16.9±1.5
EEG sleep score ($n=11$)	25.6±11.1	40.4±21.2	29.6±12.1
E deletion ($n=7$)	13.3±2.3	12.1±2.7	14.3±3.4
Subjective assessment ($n=11$)			
Latency	6	5	4
Duration	26	29*	21*
Sedation	8	15	14

*All differences between drugs and between drugs and placebo N.S. except subjective impression of duration of sleep (temazepam *v.* placebo $p<0.025$).

Results

Eleven patients completed the study.

1. Mental test score

There was no effect of either hypnotic on the mental test score compared to placebo (see Table).

2. EEG Sleep Score

Although there was no significant difference in the sleep scores between the three treatments, one patient with a sleep score of 232 could not be roused after temazepam; her sleep scores were 26 and 19 after chlormethiazole and placebo respectively.

3. 'E' Deletion Test

Only seven patients successfully completed the 'E' Deletion Test and no difference was found between either drug or placebo. One subject was unrousable the next morning, one had lost her glasses and two could not see the print even though large, clear type was used.

4. Sway Test

This test was abandoned because of inability of most of the patients to co-operate.

5. Subjective assessment

There was no significant difference between treatments in the patients' assessment of sleep latency or of their degree of sedation 11 hours after dosing. However, temazepam significantly increased the duration of sleep ($p<0.025$).

6. Plasma drug concentrations

The mean plasma temazepam and chlormethiazole concentrations 11 hours after dosing were 177.2 μg/l and 65.8 ng of base/ml respectively (range 47–294 μg/l and 12–183 ng of base/ml). There was no correlation between values of the plasma concentration of chlormethiazole and of temazepam within patients, and also no correlation between plasma concentrations of either drugs and performance in any test.

Discussion

Our results suggest that hangover effects can be avoided to a large extent in demented patients by using short-acting hypnotics. The results thus agree with those found in normal young and elderly subjects after the same drugs (Briggs *et al.*, 1980). Although the number of subjects in this study was small, sedation and impaired psychomotor performance the next day have been clearly demonstrated in other similar studies in normal subjects after a single dose of drugs with longer half-lives (Malpas *et al.*, 1970; Castleden *et al.*, 1977; Castleden *et al.*, 1979).

The lack of impaired psychomotor performance lends no support to the contention that confused patients are more sensitive to sedative drugs. We also found no evidence of increased confusion in our patients. It is possible that the reverse may be true, since the plasma concentrations of chlormethiazole and temazepam 11 hours after dosing (mean ± SEM 65.8 ± 20 ng/ml and 177.3 ± 54 μg/l respectively) were almost twice as high as found previously in the same centre in normal elderly subjects (mean ± SEM 34.4 ± 9 and 82.0 ± 6) (Briggs *et al.*, 1980). Such results support the ample published evidence of impaired hepatic drug metabolism in hospital patients, even though their hepatic function is apparently normal by conventional tests (Vestal, 1980). It is also well established that drugs metabolized by different hepatic pathways are affected to differing degrees by ageing and disease (Castleden, 1980), and thus it was not surprising that there was no correlation between the plasma concentration of the two drugs within individuals. Although there was no overall correlation between

the pharmacokinetics and pharmacodynamics of either drug, one patient was unrousable until midday following temazepam and her plasma concentration was 288 μg/l, the second highest of any subject.

We thought it important to investigate these drugs in the patients who often receive them. However, this study identified some of the problems of studying any drug in confused patients. Informed consent by the patients themselves was impossible, and often there were no relatives or they objected; thus recruitment was slow. The study design was also probably too complicated, although justified by our attempt to make it the same as a previous study in normal subjects. A simple comparison between placebo and drug will be used in future. Certain tests which required more than minimal co-operation were difficult and probably not worth attempting. For example, the sway test required the patient to stand still for one minute; this proved largely impossible and the test was abandoned. Other defects such as poor vision hampered attainment in the 'e' deletion test, although within a patient this should not affect the detection of any drug effect. Finally, the results of subjective assessment are unreliable, since chlormethiazole is known to be an effective hypnotic (Briggs *et al.*, 1980).

Although our study is a preliminary report, it lends no support to the contention that confused patients are more sensitive to hypnotics than normal subjects. Considerably higher plasma concentrations were found overall than in normal elderly subjects, and individual variation in response varied in confused patients as in any other group. It therefore seems wise, when prescribing hypnotics to confused patients, to use the customary precaution of starting with the smallest available dose.

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Words our patients use

'Set-fast'—the 'core' of a boil or abscess (Lakeland).

'Daubment'—ointment (Lakeland).

'Up t' stick'—pregnant (Lakeland).

'Cravicked'—still (for example, a leg) or bent double with arthritis (Lakeland).

'Quackle'—to interrupt breathing, 'Quackled'—throttled: "I'll quackle yer" (East Anglia).

'Bush'—thorn: "I've got a bush in my hand" (East Anglia).

'Push'—boil; furuncle (East Anglia).

"I'm in dodgy fettle", or "dowley fettle"—I'm not feeling so well (Cumbria).

"I'm not worth a lite"—I'm not feeling so well (Cumbria).

"I'm lite as a kite"—I'm not feeling so well (Cumbria).

To be 'fuzzey'—to be not so well (Cumbria).