Increased sensitivity to nitrazepam in old age

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Summary

The effects of a single 10 mg oral dose of nitrazepam were compared with those of a placebo in healthy young and old people. Both the young and the elderly slept better on three successive nights after nitrazepam but they felt less awake at 12 and 36 hours ($P < 0.01$). Elderly people made significantly more mistakes in a psychomotor test than did the young, despite similar plasma concentrations of nitrazepam and half lives in the two groups. This difference in response to psychomotor testing is probably explained by an increased sensitivity of the ageing brain to the action of nitrazepam.

Introduction

The elderly are more likely to develop adverse reactions to drug treatment than are the young.[1] One explanation for this may lie in changes in drug pharmacokinetics that occur with ageing. In animals increased plasma levels and pharmacological actions of drugs correlate well with their slower rates of elimination in old age. Thus the longer duration of carisprodol paralysis and pentobarbitone narcosis in older rats is associated with a slower rate of oxidation of these drugs by the liver microsomes.[2,3] More recently studies in man have confirmed that the metabolism of antipyrine, phenylbutazone, and amylobarbitone is impaired in the elderly.[4-7] Renal excretion is also diminished with advancing age.[8,9] If drugs such as digoxin that are not metabolised to any great extent are given in conventional doses to elderly patients they therefore tend to accumulate and cause an increased incidence of toxicity.[10]

A second explanation is a changed sensitivity of the target organ in the elderly. But opinions diverge on this possibility: some workers, including Harman[11] and Chouinard,[12] suggest that elderly tissues are hypersensitive to drugs, while Hall[13] has argued that tissue sensitivity is reduced. In an attempt to resolve this controversy we compared the effects of nitrazepam in elderly and young subjects by relating its pharmacological effects to the plasma concentration.

Subjects and methods

The subjects were divided into two groups according to age: the elderly included those over 69 years (mean 74·7), while those under 40 years (mean 25·3) were classed as young. Each group contained 10 subjects, three of whom were men. The average weight of the two groups was similar, but the young were taller (165·5 ± (1 SD) 8·6 cm) than the elderly (155·6 ± 5·0 cm). All subjects were apparently in good health. There was no clinical or biochemical evidence of cardiac, pulmonary, hepatic, renal, or mental disease. The elderly were self-sufficient and living in the community, and none had seen their general practitioner within a year of the study. All subjects gave their consent to the study, which had been approved by the local ethical subcommittee.

Design of study—Each subject received nitrazepam 10 mg and an identical placebo on separate occasions a week apart. The two treatments were administered double-blind and the order was randomised and balanced. Samples of venous blood were drawn 12, 36, and 60 hours after each treatment, and the plasma was analysed for nitrazepam. At the same time each subject carried out a simple psychomotor test and indicated on separate visual analogue scales how well he had slept (perfectly to not at all), and how awake he felt (wide awake to almost asleep). All the elderly were visited in their homes.

Psychomotor test—This consisted of crossing out the letter "e" every time it occurred on a single page of prose. Three different sheets were used and were submitted in the same order to each subject in both the first and second weeks. The time taken to complete the test and number of mistakes made were recorded.

Estimation of plasma nitrazepam—Samples of plasma were analysed for nitrazepam by gas-liquid chromatography using a Pye 104 chromatograph equipped with a ^{63}Ni electron-capture detector. The assay was essentially that of de Silva and Bekersky[14] except that toluene replaced benzene in the extracting solvent and an ammonium chloride buffer pH 9·2 was used.

Statistical analysis—An analysis of variance was used to compare the results of the two groups in the psychomotor test. A preliminary analysis showed that there was no effect due to the order in which the active and placebo tablets were administered. Order of administration was therefore not included as a treatment condition in the main analysis. The results were compared using an analysis of variance design with one between-block treatment (age) and two within-block treatments (active *v* placebo, and time). Student's *t* test for unpaired data was used to compare the plasma nitrazepam concentration and the apparent volume of distribution of the two groups, and the Wilcoxon matched pairs signed rank test was used to compare the data from the visual analogue scales.

Results

Pharmacokinetic data—There was no evidence of any difference between the elderly and the young in the plasma nitrazepam concentrations at 12, 36, and 60 hours (table I). The half life of nitrazepam in the elderly group (mean 32·5 hours) was essentially the same as that in the young group (mean 33·0 hours), and the apparent volume of distribution of the groups was also similar (mean 2·7 and 2·9 l/kg respectively) ($P > 0.05$ in every case).

TABLE I—*Mean (± 1 SD) plasma nitrazepam concentrations (nmol/l) in old and young subjects after single oral dose*

Time (h)	Old	Young	Probability
12	168 ± 36	149 ± 18	> 0·05
36	105 ± 21	94 ± 23	> 0·05
60	59 ± 13	53 ± 13	> 0·05

Conversion: SI to traditional units—Nitrazepam: 1 nmol/l ≈ 0·28 ng/ml.

Errors in psychomotor test—The elderly made more mistakes than the young even on placebo tablets ($P < 0.01$). Although the young seemed to be less accurate at 12 and 36 hours after nitrazepam than they were after placebo, this difference was not statistically significant ($P > 0.05$). The elderly made more mistakes at both 12 and 36 hours after nitrazepam ($P < 0.01$) than they did after placebo and still appeared to do so at 60 hours, although the difference then was not statistically significant ($P > 0.05$) (fig 1).

Speed on psychomotor test—All subjects took longer to complete the test at 12 and 36 hours after nitrazepam ($P < 0.05$ in each case), but

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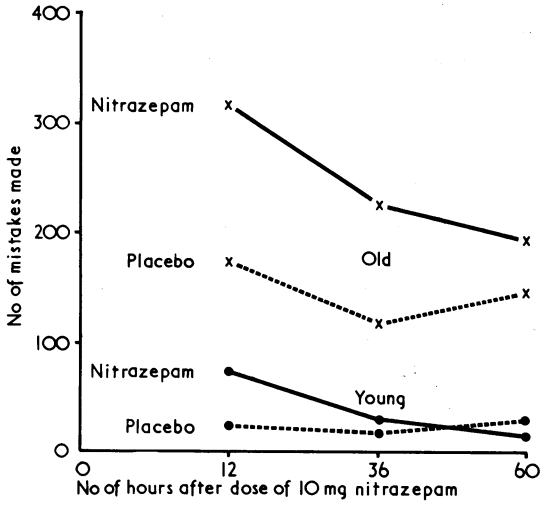

FIG 1—Total number of mistakes made by each group after 10 mg nitrazepam and placebo.

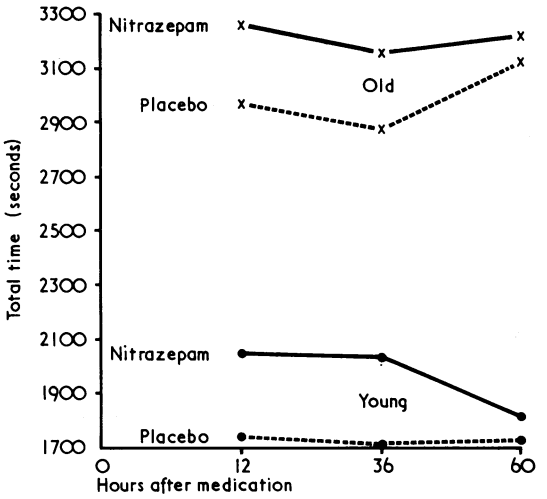

FIG 2—Total time taken by each group to complete psychomotor test after 10 mg nitrazepam and placebo.

there was no evidence of an effect at 60 hours ($P < 0.05$). The elderly took longer than the young to complete the test at all times, but the drug did not affect their speed more than it did in the young (fig 2).

Subjective assessment—As there was no difference between the groups in the type or number of complaints of side effects, the results were pooled for comparing nitrazepam and placebo (table II). Without using the visual analogue scale, the subject's detection of any impairment was less accurate (fig 3). At 36 and 60 hours the mean plasma concentrations for all subjects were 106 nmol/l (27·9 ng/ml) and 57 nmol/l (15·9 ng/ml) respectively, and only the person with the highest level 149 nmol/l (42 ng/ml at 36 hours) reported any adverse effect at this time. Analysis of the visual analogue scales, however, showed that subjects slept better on all three nights after a single dose of nitrazepam ($P < 0.01$ in every case), but they felt less awake at 12 and 36 hours ($P < 0.01$ in both cases) (table III). Sixteen out of 20 subjects reported an effect of nitrazepam at 12 hours the commonest symptom being sedation: their plasma concentration at this time was 165 nmol/l (46·4 ng/ml) compared with 132 nmol/l (37·0 ng/ml) in the three subjects who were unaffected.

Steady-state concentration of plasma nitrazepam—The mean half life of nitrazepam in 20 subjects was 32·8 hours. Thus 10 mg of nitrazepam daily would be expected to produce a steady state concentration of 367 nmol/l (104 ng/ml).

TABLE II—*Numbers of subjects complaining of side effects 12 hours after 10 mg oral nitrazepam*

	Sleepy	Unsteady/ dizzy	Nausea	Headache	Abnormal dreams	None
Old ..	5	5	1	1	1	2
Young ..	7	4	1	0	0	2
Total	12	9	2	1	1	4

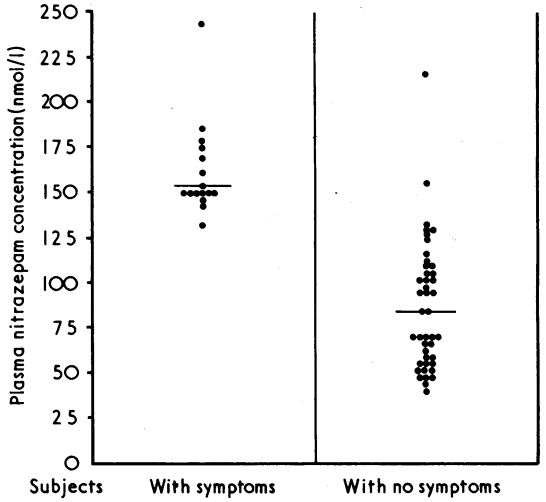

FIG 3—Plasma nitrazepam concentrations of people with side effects compared with those of people who had no side effects.

Conversion: SI to traditional units—Nitrazepam: 1 nmol/l ≈ 0·28 ng/ml.

TABLE III—*Mean results of all subjects in visual analogue scales for subjective assessment of sleep and alertness after 10 mg nitrazepam and placebo*

	Score		
	Placebo	Nitrazepam	Probability
Sleep*			
12 h	32·0	4·2	$<<0.01$
36 h	21·0	9·1	<0.01
60 h	14·1	8·7	<0.01
Alertness†			
12 h	12·9	42·2	<0.01
36 h	8·2	12·8	<0.01
60 h	8·7	14·3	>0.05

*High scores indicate worse sleep. †High scores indicate less alertness.

Discussion

Although it is recommended that nitrazepam should be prescribed at a reduced dose in patients over 65,[15] no satisfactory explanation has been offered for this. Nitrazepam is extensively metabolised in the body,[16] and it has been suggested[17] that adverse effects in the elderly may be due to slower clearance of the drug. A similar argument was used to explain why drowsiness after diazepam and chlordiazepoxide was almost twice as common in patients over 70 as in those under 40 years.[18] Recently Klotz *et al*[10] found that the clearance of diazepam was the same in old and young subjects but the apparent volume of distribution increased linearly with age, and the half-life was also prolonged. In our present study, however, similar plasma concentrations were found in both young and elderly subjects, and the half lives were almost identical in the two groups. As the mean volume of distribution was also similar in the two groups, the disposition of nitrazepam did not seem to be affected by age in the manner shown for diazepam. Thus any differences between our groups in the effects of nitrazepam on psychomotor function were likely to be due to variation in its effects on the ageing brain.

The psychomotor test consisted of two components. Bond and Lader[20] regard the speed with which such a test is completed as largely a motor effect, while the accuracy depends on

cognitive factors. Of the two indices tested, speed and accuracy, only accuracy showed an age and drug effect. Nitrazepam depressed motor function irrespective of age while its depressive effects on cognitive function were greater in the elderly. Clinically this is borne out by a syndrome described only in elderly people, in which considerable confusion and disorientation result from chronic administration of nitrazepam.[17] This increased sensitivity of the ageing brain to the action of nitrazepam can most readily be explained on present evidence by a change in the normal compensatory mechanisms.[21] The fact that the elderly performed less well overall in the psychomotor test than the young, even on placebo, reflects a general deterioration that accompanies ageing, especially when speed of performance is emphasised.[22]

Malpas *et al*[23] have shown psychomotor impairment the next morning and electroencephalogram abnormalities up to 18 hours after a single dose of nitrazepam. Our results suggest that the effects of this drug last considerably longer, however—even up to 60 hours after a single dose. This is not surprising in view of the long half life, which makes it unlikely that sleep can be induced without producing side effects the next day. The effects of repeated doses remain to be studied, but the mean steady state concentration of nitrazepam calculated from our data would have produced considerable adverse effects in our subjects unless tolerance occurred.

In conclusion, our findings support the concept that the dose of nitrazepam should be decreased in elderly patients but suggest that this is due to a change in the ageing brain and not a change in pharmacokinetics, as has been suggested.

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Antimicrobial proteins in sterilised human milk

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Summary

Human milk contains factors such as IgA and lactoferrin that increase the newborn infant's resistance to infection. Preterm infants are fed pooled milk, which is normally sterilised by heating. After standard heat sterilisation IgA and lactoferrin were undetectable in milk samples. Pasteurisation also sterilised milk samples even after heavy artificial contamination and did not damage the proteins. Gamma-irradiation sterilised equally effectively but caused some denaturation of IgA and lactoferrin. Since most of the milk samples were sterile or had only light contamination with skin bacteria, there seems to be no need for routine sterilisation. If sterilisation is necessary, the method used should be chosen to minimise damage to milk proteins.

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Introduction

The breast-fed infant appears to have greater resistance to infection than the artificially fed child.[1] Hence it is logical to use human milk to feed infants who are particularly at risk of infection. It is common practice to feed pooled expressed breast milk to preterm babies,[2] and it is desirable that these infants should receive the milk with its protective properties intact. To obtain information about the effect of a standard sterilisation procedure on milk proteins we examined the effect on two proteins (IgA and lactoferrin) known to have important antimicrobial functions. Antibody titres to *Escherichia coli* were also measured, and the effects of alternative methods of sterilisation were investigated.

Methods

Samples of human milk obtained by manual expression or the Humalactor breast pump during routine collections on the wards were obtained from the central milk kitchen of the Simpson Memorial Maternity Pavilion. Part of each sample was sterilised in the standard way by heating to 105°C, freezing, and thawing, the cycle then being repeated. Part of the remainder was stored at −40°C for immunological studies after bacteriological cultures had been made using blood agar, McConkey agar, and mannitol salt agar plates. Aliquots of the unsterilised samples were stored at room temperature for a maximum of six hours before being subjected to pasteurisation (62·5°C for 30 minutes) or gamma-irradiation with 2·5 Mrads from a cobalt-60 source. The samples were cultured again within one hour