Benzodiazepines and postoperative cognitive dysfunction in the elderly

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Postoperative cognitive dysfunction (POCD) has been attributed to long-acting sedatives. We hypothesized that diazepam and its active metabolites could be detected in blood after surgery and correlated with POCD, 1 week after surgery in elderly patients. We studied 35 patients, 60 yr or older, undergoing abdominal surgery with general anaesthesia, including diazepam. Neuropsychological tests were performed before surgery and at discharge, where blood concentrations (free fraction) of benzodiazepines were also measured. POCD was found in 17 patients (48.6%). Diazepam or desmethyldiazepam was detected in 34 patients; median postoperative blood concentrations were 0.06 and 0.10 μmol kg^{-1}, respectively. In a multiple regression analysis considering age, duration of anaesthesia and blood concentrations of diazepam and desmethyldiazepam, only age was found to correlate with the composite z-score (*F* test, *P*<0.01). The postoperative cognitive dysfunction we found in elderly patients after operation could not be explained by benzodiazepine concentrations detected in blood.

Postoperative cognitive dysfunction (POCD) has been described after cardiac and non-cardiac surgery.[1] [2] In the ISPOCD1 study (International Study of Postoperative Cognitive Dysfunction), 1218 elderly patients were studied who underwent major non-cardiac surgery with general anaesthesia.[2] No relation was found between POCD and anaesthetic technique. However, deterioration of memory and concentration have been attributed to benzodiazepines[3] and in a study of elderly patients undergoing cataract surgery, a statistically significant correlation was found between reduction in memory performance and amount of nitrazepam administered during the postoperative week.[4] Some benzodiazepines, such as diazepam, are long-acting and their metabolites may be active. The terminal half-life of diazepam is approximately 30 h.[5] Hydroxylation of diazepam leads to formation of 3-hydroxydiazepam and demethylation to desmethyldiazepam, which has an elimination half-life of approximately 60 h.[5–7] The terminal metabolite of diazepam is oxazepam, which is metabolized much more rapidly.

We hypothesized that diazepam and its active metabolites in blood after operation could be correlated with POCD, 1 week after surgery in elderly patients.

Patients and methods

After obtaining approval from the Ethics Committee and written informed consent, we studied patients aged more than 60 yr undergoing major abdominal surgery with general anaesthesia. The patient group was a subset of patients in the ISPOCD1 study.[2] Patients with diseases of the central nervous system were excluded, as were those who were already receiving benzodiazepines or other sedatives. A standard general anaesthetic was used. Diazepam 0.15 mg kg^{-1} orally was given as premedication and the same dose i.v. at induction of anaesthesia. In addition, thiopental 3–5 mg kg^{-1} and fentanyl 5 μg kg^{-1} were given and pancuronium 0.1 mg kg^{-1} was administered to achieve neuromuscular block. The trachea was intubated in all patients and the lungs were ventilated with oxygen–

nitrous oxide, adjusting ventilation to achieve normocapnia. Thoracic epidural analgesia was used routinely.

Neuropsychological testing

Psychometric testing was performed before surgery and 7 days after operation. The neuropsychological test battery took approximately 45 min to administer and measured memory, sensimotor speed and cognitive flexibility. Testing was performed by trained examiners, supervised by neuropsychologists.

A brief description of the test battery is given below. More detailed information is available in Moller and colleagues.[2] The battery comprised the following tests:

- *Mini-mental state examination* as a screening test for dementia.[8] All patients had to obtain a preoperative score greater than 23 points to be included
- *Visual verbal learning test*[9]
- *Concept shifting test*, based on the *trail making test*[10]
- *Stroop colour word interference test*[11]
- *Paper and pencil memory scanning test*[12]
- *Letter–digit coding*[13]
- *The four boxes test*[14]

We used seven variables to assess cognitive function. From the visual verbal learning test, cumulative learning in three trials and delayed verbal recall; from the concept shifting test, time and errors for part C; from the stroop colour word interference test, time and errors for part 3; and finally the score from the letter–digit coding. Normative data were available for an elderly population and were used to calculate z-scores that express by how many standard deviations the patient's performance deviates from the expected performance in the control population.[2] First, we calculated mean (SD) changes in performance among control subjects for each test from baseline. The mean change may be taken as estimated learning effects. For individual patients, we compared preoperative test results with postoperative test results, subtracted the average learning effect form these changes, and divided the result by the standard deviation of the control group to obtain a z-score for each test with an appropriate sign + or –. Large positive z-scores showed a deterioration in cognitive function from baseline in patients compared with controls. We defined a composite z-score from the total z-scores for the controls. The standard deviation of the total was used to normalize patients' composite z-scores. Patients had cognitive dysfunction when two z-scores in individual test variables or the composite z-score was greater than 1.96. This deterioration is encountered in less than 4% of the control population.[2]

Measurement of blood concentrations of benzodiazepines

A venous blood sample was obtained after the postoperative psychometric test and concentrations (free fraction) of diazepam, desmethyldiazepam, 3-hydroxydiazepam and

Table 1 Patient characteristics (median (range) or number)

Age (yr)	68 (60–84)
Sex (M/F)	24/11
Weight (kg)	71 (44–106)
Height (cm)	172 (156–184)

oxazepam were measured. If other benzodiazepines had been given between the pre- and postoperative psychometric test, concentrations of these drugs were measured also. The initial screening for benzodiazepines was performed using a radioreceptor assay.[15] In all samples positive in the radioreceptor assay, identification and quantitative analyses were performed by gas chromatography with an electron capture detector, using a 25-m HP-5 capillary column. Benzodiazepines were isolated from blood by extracting at pH 9 with toluene containing asolectin 0.01 mg ml^{-1}. The cut-off concentration is 0.01 µmol kg^{-1} for diazepam, desmethyldiazepam, 3-hydroxydiazepam, oxazepam, nitrazepam and midazolam.

Statistical analysis

Values are reported as median (range or interquartile range where stated) or proportions (95% confidence intervals).

Comparison of benzodiazepines between groups was performed using Mann–Whitney's non-parametric rank sum test. Blood concentrations of benzodiazepines were correlated with z-scores using multiple linear regression analysis. $P < 0.05$ was considered statistically significant. The sample size calculation was based on a pilot study with measurements of benzodiazepine concentrations and a power of 80%. We found that a patient group of 30 subjects would enable us to detect a difference in neuropsychological test results corresponding to 1 SD between patients with benzodiazepine concentrations greater than or less than 0.1 µmol kg^{-1}, respectively.

Results

We included 35 patients; characteristics are given in Table 1.

For premedication, patients were given a median dose of diazepam 0.13 (0.05–0.21) mg kg^{-1} orally, and during surgery, the median dose of i.v. diazepam was 0.10 (0–0.23) mg kg^{-1}. Surgical procedures included intestinal (15), vascular (14), urological (five) and gynaecological (one). Median duration of anaesthesia was 250 (75–525) min. Postoperative complications were recorded in six patients: two had pneumonia, two had wound infections, one had pneumonia and suffered from delirium, and one had a minor pulmonary embolus. After operation, 12 patients received zopiclone as a hypnotic and four of those were also given diazepam orally as a sedative. Six patients were given zopiclone less than 24 h before the postoperative neuropsychological test.

Diazepam was detected in 31 patients and desmethyldiazepam in 31. In only one patient was neither benzodiazepine detected. Oxazepam was found in one patient

Table 2 Psychometric test results for seven variables used in the evaluation of cognitive function (median (interquartile range))

	Before operation	After operation
Cumulative learning (No. of words)	26 (21–29)	21 (16–28)
Delayed verbal recall (No. of words)	8 (5–11)	6 (4–10)
Time in concept shifting task, part C (s)	39.9 (33.1–48.8)	47.5 (35.5–61.5)
Errors in concept shifting task, part C (No.)	0 (0–1)	0 (0–2)
Time for Stroop part 3 (s)	50.1 (44.3–58.9)	52.5 (44.4–64.6)
Errors for Stroop part 3 (No.)	0 (0–1)	1 (0–1)
Letter–digit coding (No. of correct answers)	27 (21–32)	24 (19–28

Table 3 Regression coefficients between change in psychometric test result (z-score) and age, blood concentrations of diazepam and desmethyldiazepam, and duration of anaesthesia
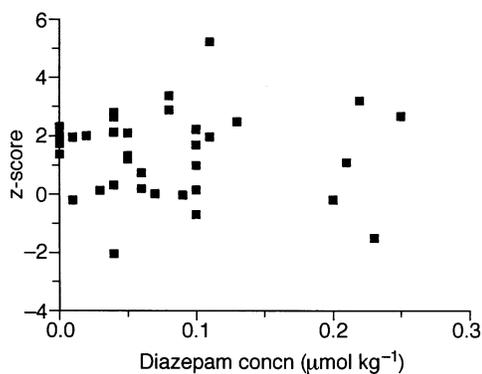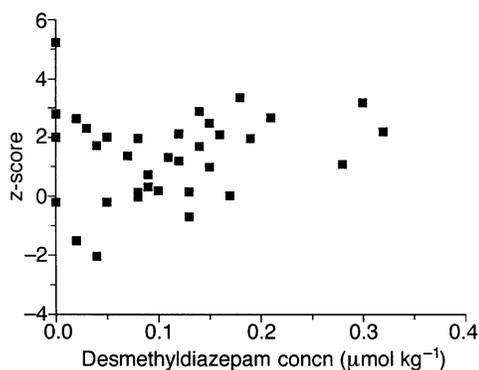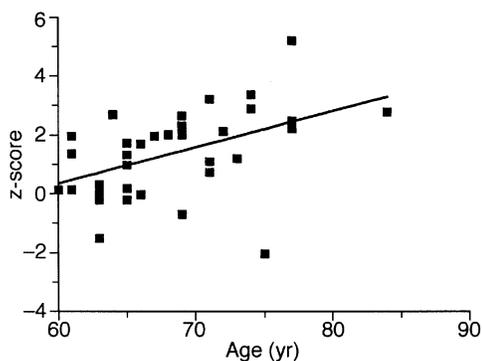
	Regression coefficient	P
Age	$0.124 \ yr^{-1}$	0.0046
Diazepam	$0.0728 \ kg \ \mu mol^{-1}$	0.98
Desmethyldiazepam	$2.63 \ kg \ \mu mol^{-1}$	0.35
Duration of anaesthesia	$0.00296 \ min^{-1}$	0.22

Fig 1 Postoperative blood concentration (free fraction) of diazepam *vs* change in neuropsychological test result (expressed as a z-score), 1 week after major abdominal surgery in elderly patients.

Fig 2 Postoperative blood concentration (free fraction) of desmethyldiazepam *vs* change in neuropsychological test result (expressed as a z-score), 1 week after major abdominal surgery in elderly patients.

Fig 3 Age *vs* change in neuropsychological test result (expressed as a z-score), 1 week after major abdominal surgery in elderly patients.

who had received this drug as a sleeping pill on the third postoperative night. The concentration of 3-hydroxy-diazepam was below the limit of detection in all patients. Fifteen patients received midazolam during surgery and three of those also in the PACU. Four patients received nitrazepam after operation. However, concentrations of both midazolam and nitrazepam were below the limit of detection in all cases.

Median postoperative blood concentration of diazepam was 0.06 (0–0.25) $\mu mol \ kg^{-1}$. Blood concentration of diazepam was 0.1 $\mu mol \ kg^{-1}$ or higher in 13 patients. Median postoperative blood concentration of desmethyl-diazepam was 0.10 (0–0.32) $\mu mol \ kg^{-1}$. Blood concentration of desmethyldiazepam was 0.1 $\mu mol \ kg^{-1}$ or higher in 18 patients.

The postoperative test was performed a median of 7 (2–13) days after surgery. POCD was found in 17 patients (48.6% (31.4–66.0%)) and deterioration was seen in all tests (Table 2). Five of 17 patients had postoperative complications. Blood concentrations of diazepam and desmethyldiazepam in patients with and without POCD were not significantly different (Mann–Whitney test, $P>0.4$).

In a multiple linear regression analysis considering age, duration of anaesthesia and blood concentrations of diazepam and desmethyldiazepam, only age was found to correlate with the composite z-score (F test, $P<0.005$). Table 3 shows the regression coefficients and corresponding P values and Figures 1–3 show graphical presentations of the relationships between composite z-score and age and concentrations of diazepam and desmethyldiazepam. The multiple regression analysis was also performed after excluding patients who had received zopiclone within 24 h before testing. Only age correlated significantly with z-score.

Discussion

Our patient population was a subset of patients in the ISPOCD1 study where the incidence of POCD was 25.8%, 1 week after surgery.[2] In that study, multiple logistic regression analysis revealed a significant relationship between POCD after 1 week and age, duration of anaesthesia, level

of education, second operation, postoperative infection and respiratory complications. Our study examined the influence of long-acting benzodiazepines in a selected group undergoing abdominal surgery with diazepam-based anaesthesia. The incidence of POCD was 48.6% and therefore these patients appeared to be at greater risk. We found no significant relationship between blood concentrations of benzodiazepines and change in cognitive function, 1 week after surgery.

Diazepam or desmethyldiazepam was detected in blood in nearly all patients, 1 week after surgery, and measured blood concentrations represent the free fraction of the drug. Late after administration, the free fraction is in equilibrium with the concentration in the cerebrospinal fluid and brain.[16] Blood concentrations greater than 0.1 μmol kg^{-1} (free fraction) are considered forensically important.[15] This concentration was exceeded in approximately 50% of our patients. Thus even though benzodiazepines were detected, concentrations appeared to be too small to affect cognitive function. Concentrations of oxazepam and 3-hydroxy-diazepam were less than the detection limit in nearly all patients. This supports the more rapid metabolism of these drugs and the findings of another study.[17]

In young patients and healthy volunteers, a significant correlation has been found between plasma concentrations of diazepam and slowing of reaction time, but only very shortly (i.e. 1 h) after i.v. administration.[6 18] When the assessment is performed after several hours or days, the correlation between blood concentrations of benzo-diazepines and objective measures of cognitive function is much less clear.[19] However, in elderly surgical patients, we expected a major susceptibility to be present.[20 21] Many drugs with effects on the central nervous system are more potent in the elderly and metabolism may be slower. In previous studies addressing the correlation between cognitive functioning and blood concentrations of benzo-diazepines, total plasma concentrations have generally been reported, but at least 90% is protein bound.[19 22] Variations in plasma protein content, especially in surgical patients, may make total plasma concentrations unsuitable for assessing the influence on cognitive functioning. Finally, our neuropsychological test battery comprised several tests with proven sensitivity, such as the Stroop colour word interference test.[23] Accordingly, we believe that both evaluation of cognitive function and benzodiazepine blood concentrations enabled us to perform a reliable analysis. The cause of POCD is not known but it is possible that the trauma of operation is more important than any modifiable aspect of the anaesthetic procedure.

We found age to be a risk factor for postoperative cognitive function, even in this small group of patients. The number of subjects was too small to make more complex statistical analyses, for example concerning the combined effects of benzodiazepine blood concentrations and postoperative complications. The postoperative neuropsychological test was performed after patients had recovered from their complications but still five of six patients with complications had POCD. This is in accordance with previous data confirming postoperative complications to be important risk factors for POCD.[2] A limitation of our study was that postoperative administration of benzodiazepines and other drugs was not standardized and this could contribute to cognitive deficits. However, exclusion of patients who had received the very short-acting hypnotic zopiclone within 24 h before neuropsychological testing did not change the result of the regression analysis.

Lack of statistical power should always be considered when analysing a limited number of subjects but the graphical presentations do not indicate that a larger study is necessary. Instead, blood sampling and neuropsychological testing at other times may allow a statistically significant correlation but the clinical relevance of such a relationship 1 or 2 days after surgery can be questioned.

In summary, cognitive dysfunction 1 week after surgery in elderly patients could not be explained by blood concentrations of benzodiazepine at the time of neuropsychological testing.

Acknowledgements

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