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## **Don't forget : contributions to the assessment and management of suicide attempters in the general hospital**

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## *Chapter 6* – Clinically relevant anterograde amnesia and its relationship with blood levels of benzodiazepines in suicide attempters who took an overdose

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### ABSTRACT

The relationship between anterograde amnesia, sedation and plasma levels of benzodiazepines was studied prospectively in a group of 24 patients who took an overdose of benzodiazepines. Patients were tested on two consecutive days after having taken an overdose. Anterograde amnesia was tested by using a verbal recall test and a photo recognition test. Sedation was scored on a visual analogue scale (VAS) by the patient and the interviewer. The concentration of benzodiazepines in plasma was measured by using a radioreceptor assay that adds benzodiazepines and their active metabolites. The cumulative amount of benzodiazepines was expressed as diazepam equivalents (DZE). Diazepam equivalents determined by this radioreceptor assay were significantly higher on the first day than on the second day. Ratings on the verbal recall test were significantly lower on the first day than on the second day. There was a significant relation between decrease of diazepam equivalents and increase of verbal recall: more than 30% of increase of verbal recall was explained by decrease of diazepam equivalents. There was not a strong relation between decrease of diazepam equivalents and reduction of level of sedation as scored by the patients. There was almost no relation between decrease of diazepam equivalents and reduction of level of sedation as scored by the interviewer. No relation was found between verbal recall, sedation and diazepam equivalents. There was no relation between diazepam equivalents and photo recognition. It was concluded that anterograde amnesia was strongly associated with benzodiazepines in patients who take benzodiazepines in an overdose. Sedation does not predict the degree of anterograde amnesia.

## INTRODUCTION

Anterograde amnesia is a well known side effect of benzodiazepines (Curran, 1991), albeit desirable in situations like perioperative surgical periods and during procedures like endoscopies. In volunteers who took one or more standard doses of benzodiazepines the degree of anterograde amnesia correlated with dosage of benzodiazepines (Ghoneim et al., 1984). In a previously published, prospective study anterograde amnesia was investigated in a group of 43 suicide attempters who had taken an overdose of benzodiazepines (Verwey et al., 2000) by assessing them on two sequential days. The results of a verbal recall test were analyzed, as well as the degree of sedation and the result of a photo recognition test. Anterograde amnesia was demonstrated, that is to say the scores of the immediate and delayed recall on two consecutive days differed significantly: patients forgot more words on the first than on the second day after benzodiazepine overdose. There was a low correlation between ratings of recall and patient's ratings of sedation. On the second day, only half of the patients were able to recognize, from photographs, the resident in psychiatry with whom they had spoken the day before. So anterograde amnesia was found in this group of suicide attempters, but whether the benzodiazepines are the causative factor of this memory impairment was not established. The stressful circumstances of these patients recently admitted to a hospital could also have deteriorating effects on memory functions. The role of benzodiazepines as a causative factor would be more probable if a dose-response relationship could be demonstrated in this patient group. However, suicide attempters are often unable to give reliable information about the dosage they have taken and considerable interindividual differences in metabolism of benzodiazepines exist, which makes it necessary to investigate the relationship between the degree of amnesia and the dosage taken via drug plasma levels. Therefore we decided to study this relationship in the group of patients who took an overdose by using the blood samples we had taken. These blood samples had already been taken to check whether the patients had used benzodiazepines and to exclude those who had alcohol in their blood.

A problem in the study of the effects of overdoses of benzodiazepines is that suicide attempters differ in the types of benzodiazepines they use. Many use more than one benzodiazepine. Moreover, many benzodiazepines are metabolised in compounds that act as benzodiazepines themselves. With high-performance liquid chromatography (HPLC), it is possible to determine, in plasma samples, different benzodiazepines and their active metabolites. However, all these benzodiazepines and metabolites have their own affinity to the receptor, making it impossible to study the relationship of the overall benzodi-

azepine level on the one hand and amnesia and sedation on the other simply by adding up the levels of all benzodiazepines and metabolites involved. Using a radio receptor assay solves this problem because the total amount of benzodiazepines and metabolites can be measured and expressed in equivalents of a standard benzodiazepine. Using this method, we studied the relationships between anterograde amnesia, sedation and the amount of benzodiazepines at the receptor site.

Our first hypothesis was that in this group of patients the change in anterograde amnesia is related to the change in the amount of benzodiazepines.

In most studies amnesia could not be related to the sedative effect of benzodiazepines. Even when patients are not sedated, amnesia can clearly be established (Hennessy et al., 1991; Veselis et al., 2001). Higher concentrations of benzodiazepines might be needed to cause sedation than to produce memory impairment as has been established in one study comparing different plasma levels of flunitrazepam (Bareggi et al., 1998). We expected to find high levels of benzodiazepines in the group of suicide attempters even more than 24 hours after having taken the overdose.

Our second hypothesis was that, in patients who took an overdose, change in anterograde amnesia is more related to change in levels of benzodiazepines than to change in sedation.

## METHOD

### *Material and procedure*

We used data from our previously published study including 24 suicide attempters with blood samples available, to investigate the relations between changes in anterograde amnesia, sedation and changes in benzodiazepine plasma concentrations. Below follows a description of the study methods.

### *Subjects*

All patients with benzodiazepines in their blood were included. The additional use of other drugs (except alcohol) or non-drug methods in the suicide attempt was not a reason for exclusion.

Patients with the following criteria were excluded: younger than 18 (because the tests used were not developed for younger people); a DSM IV (American Psychiatric Association, 1994) diagnosis of dementia or amnesic disorder before admission (cognitive dysfunction may interfere with the drug effects); alcohol dependence or abuse (cognitive dysfunction and impaired liver function may interfere with the drug effects); a positive screening on alcohol; delir-

ium, according to DSM IV criteria; inability to read or understand test instructions and items on the verbal recall test. Patients that used benzodiazepines during their stay in the hospital were also excluded.

The medical ethics committee of the hospital approved the study and written informed consent was obtained from all patients.

### *Assessments*

- 1 The '15-woorden test' (15-words test) is the Dutch equivalent of the Rey Auditory Verbal Learning test, a verbal recall test often used in research on anterograde amnesia caused by benzodiazepines (Lezak, 1983). Free recall is considered the most taxing of memory tests (Buffett-Jerrott and Stewart, 2002). We adapted the procedure slightly by administering the list of words only once on day 1 and once on day 2. On both days, the research assistant instructed the patient in the use of a computerized version of the test. The patient was asked to remember words that were presented successively on the computer screen for a period of 2 s each. Immediately after the presentation of 15 unrelated words, the patient was asked to recall as many words as possible (immediate recall). After 15 minutes the patient was asked again to recall as many words as possible (delayed recall). The patient was assessed on day 1 and day 2. To prevent learning (Ryan & Geisser, 1986), patients were presented different but equivalent lists on these days.
- 2 A photo recognition test was used as a visual recognition test. The patient was presented with a series of 6 photographs of faces with a variety in features such as hair, spectacles, etc., one of which showed the resident in psychiatry who had examined the patient. This procedure is used in formal police investigations in the Netherlands. The patient had to answer three questions: [1] Do you recognize anyone? [2] Who do you recognize? [3] How do you know this person? This test was administered on day 2 only. Patients who were known to the resident, possibly because of earlier suicide attempts, were excluded from this test.
- 3 Degree of sedation was rated on a 10-cm Visual Analogue Scale (VAS). On day 1, the patient as well as the resident in psychiatry filled in this scale. A low score indicates a high level of sedation.
- 4 Blood alcohol concentration was measured with gas liquid chromatography.
- 5 Determination of benzodiazepines was measured by a radio receptor assay (Hunt et al., 1979). Radio receptor assays are based upon competition between an analyte and a radioactive labeled ligand for binding to a certain receptor. In the absence of competing analytes, the radioactive labeled ligand is bound to the receptor. When another benzodiazepine is added, this

compound will replace a portion of the receptor-bound radioactive-labeled ligand. The concentration of benzodiazepine from a sample is indirectly measured by determination of the receptor radioactive-labeled ligand. Since in most samples mixtures of benzodiazepines and active metabolites are present, calibration will be based on a single compound, diazepam. Cumulative concentrations will therefore be expressed as diazepam equivalents (DZE). The radio receptor assay was developed by MERSKA, Research and Consultancy Centre of the University of Groningen. The method to measure the amount of benzodiazepines used in this study, has been compared with measuring the benzodiazepine concentrations by high performance liquid chromatography and is described elsewhere (De Jong et al., 2004).

#### PROCEDURE

All patients admitted after a suicide attempt were seen by a psychiatric resident for a routine clinical interview at least 12 hours after admittance, provided the patient was sufficiently alert for psychiatric consultation. At the end of the interview, the psychiatric resident informed patients who had used benzodiazepines in the suicide attempt about the study and asked them to participate. When written informed consent was obtained, a research assistant (an experienced psychiatric consultation-liaison nurse) immediately started assessments (day 1). Twenty-four hours later, the research assistant repeated the assessments. Blood samples were collected from patients on both days directly after the assessments.

#### STATISTICAL ANALYSIS

Cumulative amount of diazepam equivalents on day 1 and day 2 were analysed using the paired *t* test; the level of significance was  $p \leq 0.05$ . The same was done to analyse ratings on the verbal recall test and ratings of sedation. Linear regression analysis was used to investigate relationships between changes in verbal recall, sedation and cumulative amount of diazepam equivalents. This method was chosen to exclude the influence of patient characteristics. Logistic regression was used to study relations between photograph recognition and cumulative amount of diazepam equivalents.

## RESULTS

There were 70 blood samples from 43 patients. From the first 16 patients, blood was taken only on day 1, but during the study, we decided to take blood on days 1 and 2. Originally, we planned only to check blood on day 1 to be sure patients used benzodiazepines and to exclude patients who had alcohol in their blood, but later we realized that blood taken on both days could be used to investigate changes across patients. For the present analyses, we decided to use only samples of patients who were tested twice. Three samples could not be used because there was not enough sample material or it was of insufficient condition to analyse. This resulted in 48 blood samples of 24 patients that could be analysed.

### *Cumulative amount of diazepam equivalents determined by radioreceptor assay*

The diazepam equivalents (DZE) determined with the radioreceptor assay on day 1 were significantly higher than those collected on day 2 (mean  $\pm$  SD DZE =  $938.96 \pm 808.23$  and  $701.42 \pm 837.07$ , respectively;  $p = 0.02$ ).

### *Verbal recall with the 15-word test*

Immediate recall on day 1 was significantly lower than on day 2 (means respectively  $4.96 \pm 1.57$  and  $6.50 \pm 2.02$ ,  $p = 0.003$ ). Delayed recall was also significantly lower on day 1 than on day 2 (means respectively  $3.21 \pm 1.74$  and  $4.54 \pm 2.11$ ,  $p = 0.001$ ).

Regression analysis showed a significant association between change of scores in immediate recall on day 1 and day 2 and the change in diazepam equivalents determined by radioreceptor assay on day 1 and day 2 (immediate recall change =  $-0.83 - 0.30 \times$  DZE change;  $R$ -square = 0.37). (Fig. 2). This means that an average decrease of 100 ng/ml diazepam equivalents leads to an average increase of immediate recall rating of 1.13. The change in DZE explained 37% of the variance in change in immediate recall.

There was also a significant relation between change in scores of delayed recall and change in diazepam equivalents determined by radioreceptor assay on day 1 and day 2 (delayed recall change =  $-0.82 - 0.22 \times$  DZE change;  $R$ -square = 0.34) (Fig. 3). This means that an average decrease of 100 ng/ml diazepam equivalents leads to an average increase in delayed recall rating of 1.04. The change in DZE explained 34% of the variance in change of delayed recall.



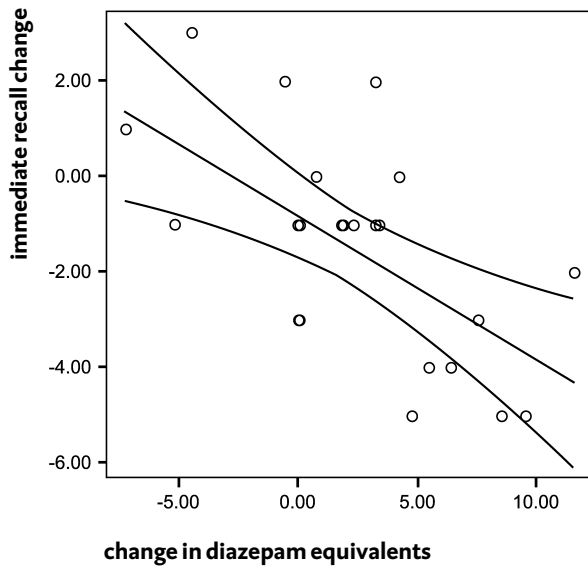


Figure 2 Relation between change in immediate recall and change in diazepam equivalents

immediate recall change =  
 $-0.83 - 0.30 \times \text{diazepam change}$   
R square = 0.37

1 'diazepam change' means a change of 100 ng/ml diazepam equivalents

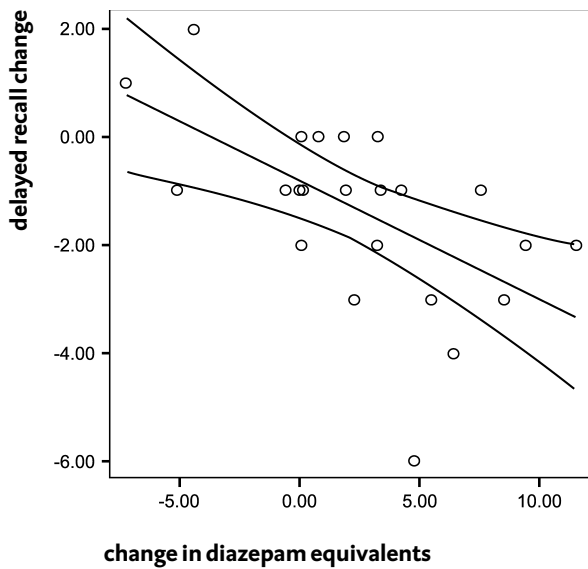


Figure 3 Relation between change in delayed recall and change in diazepam equivalents

delayed recall change =  
 $-0.82 - 0.22 \times \text{diazepam change}$   
R square = 0.34

1 'diazepam change' means a change of 100 ng/ml diazepam equivalents

### *Visual recall with the photograph recognition test*

Less than half of the patients recognized the psychiatric resident from the photograph and knew that he was the one formally spoken to the day before.

On day 1 the diazepam equivalents of patients who were not able to recognize the psychiatric resident were higher than those of patients who were able to do so, but the difference was not significant (mean  $\pm$  SD DZE =  $897.23 \pm 754.82$  and  $512.45 \pm 622.01$ , respectively;  $p = 0.08$ ). Furthermore, the logistic regression showed that levels of diazepam equivalents on day 1 did not predict recognition.

### *Sedation*

VAS scores of patients on day 1 were significantly lower than on day 2 (means respectively  $6.27 \pm 1.66$  and  $8.68 \pm 1.03$ ,  $p = 0.000$ ). VAS scores of patients rated by the interviewer were also significantly lower on day 1 than on day 2 (means respectively  $5.19 \pm 2.02$  and  $7.27 \pm 2.44$ ,  $p = 0.001$ ).

Regression analysis showed a low correlation between change in scores of the patients on the VAS and change in diazepam equivalents determined by radio receptor assay on day 1 and day 2 (patient VAS change =  $-1.66 - 0.18 \times$  DZE change;  $R$ -square = 0.11; Fig. 4) There was also almost no relation between change in VAS scores of the interviewer and change in diazepam equivalents determined by radio receptor assay on day 1 and day 2 (interviewer VAS change =  $-2.30 - 0.05 \times$  DZE change;  $R$ -square = 0.01; Fig. 5). There was not a statistically significant relation between change in verbal recall scores and VAS scores of the patients (immediate recall change =  $-0.53 + 0.28$  patient VAS change;  $R$ -square = 0.09) (delayed recall change =  $-0.95 + 0.14$  patient VAS change;  $R$ -square = 0.04; Figs. 6 and 7).

## DISCUSSION

### *Change in Anterograde amnesia and change in diazepam equivalents*

The main finding of this study is that the change in anterograde amnesia is strongly related to change in cumulative amount of diazepam equivalents: 37% of increase of immediate recall and 34% of increase of delayed recall across patients was explained by decrease of diazepam equivalents. This implies that our hypothesis on the effects of benzodiazepines on memory was confirmed. Our analysis suggests that the benzodiazepines play a major role in the presence of anterograde amnesia in suicide attempters who took an overdose of these agents.

Of course, the stressful circumstances of the patient related to the admis-

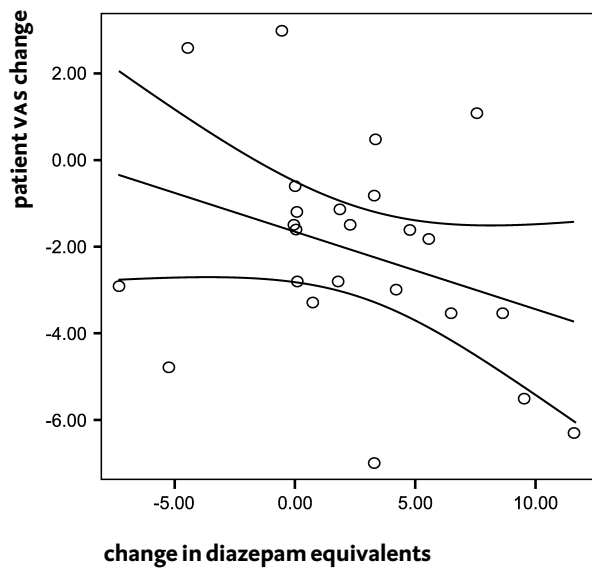


Figure 4 Relation between change in scores of visual analogue scale rated by the patients and change in diazepam equivalents

patient VAS change =  
 $-1.66 - 0.18 \times \text{diazepam change}$   
R square = 0.11

1 'diazepam change' means a change of 100 ng/ml diazepam equivalents

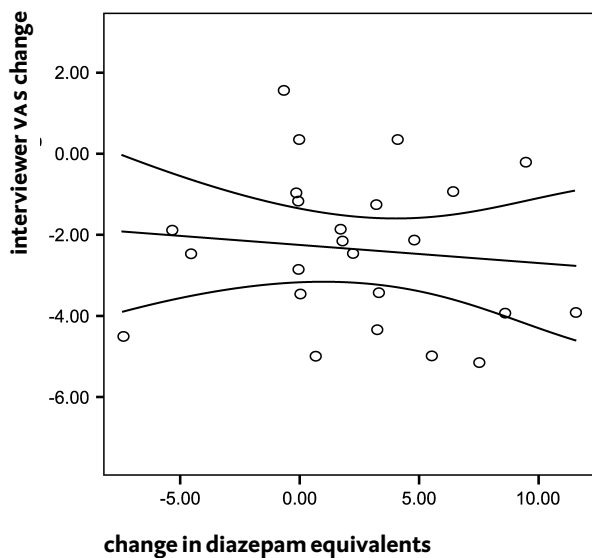


Figure 5 Relation between change in scores of visual analogue scale rated by the interviewer and change in diazepam equivalents

interviewer VAS change =  
 $-2.30 - 0.05 \times \text{diazepam change}$   
R square = 0.01

1 'diazepam change' means a change of 100 ng/ml diazepam equivalents

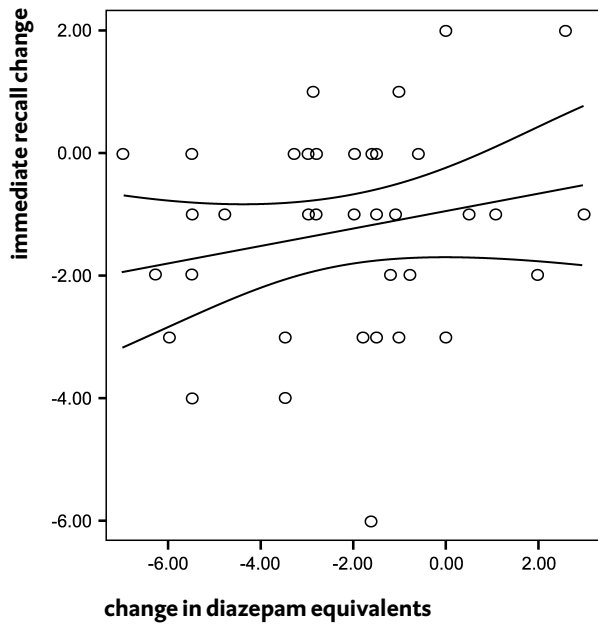


Figure 6 Relation between change in immediate recall and change in scores of visual analogue scale rated by the patients

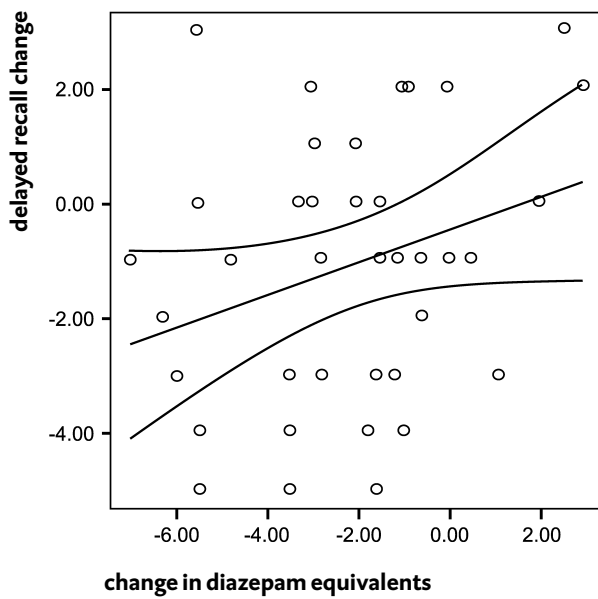


Figure 7 Relation between change in delayed recall and change in scores of visual analogue scale rated by the patients

sion to hospital might have added to the amnesia as well as the influence of other drugs not investigated by us. However, it is improbable that these are major factors since on the second day, in much more quiet conditions and with lower levels of other drugs, significant anterograde amnesia was still present. It could also be argued that the increase in scores of the verbal recall test was due to a practice effect. This is not likely because on day 1, patients were presented different but equivalent wordlists than on day 2.

Analysis of the results on the other memory task, the visual recall test, showed that recognition of the resident from photographs was not predicted by levels of diazepam on day 1. It should be mentioned that the interview with the patients was not always done by the same resident. We did not study whether some were more easily recognizable than others, and so, we cannot rule out that this could have influenced the results. What also has to be mentioned is the fact that visual recognition is a more implicit memory task while verbal recall is a typically explicit memory task. Benzodiazepines do impair explicit memory, and the influence on implicit memory is doubtful. It seems, however, that implicit memory is impaired by benzodiazepines when levels of benzodiazepines are close to peak plasma concentrations (Buffett-Jerrott et al., 1998). Perhaps this explains why the diazepam equivalents on day 1 of patients who were not able to recognize the psychiatric resident on day 2 were higher than those of patients who were able to do so, although the difference was not statistically significant.

In this study the results on tests of every patient on day 1 were compared with those on day 2. To rule out the possibility of stress or use of psychoactive drugs that could have influenced the results, we would recommend a study with a control group of suicide attempters that did not use benzodiazepines or other psychoactive drugs.

#### *Change in sedation and change in diazepam equivalents*

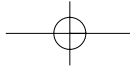
Our second hypothesis was also confirmed in this patient group: although the ratings of sedation were higher on the first day, there was almost no relation between change in diazepam equivalents and change in scores of sedation by the interviewer. The relation between change in diazepam equivalents and change in scores of sedation by the patient was somewhat stronger, although not statistically significant. Linear regression showed no relevant relation between verbal recall, sedation and amount of diazepam equivalents. It is likely that a dose-response relationship exists between benzodiazepines and the presence of amnesia and sedation, but our analyses suggest that anterograde amnesia and sedation are not strongly related. An explanation could be that amnesia occurs already at lower levels of benzodiazepines than does sedation.

The very low ratings on the verbal recall tests on day 2, i.e., more than 24 hours after intake of benzodiazepines, are remarkable and suggest that amnesia is already present at low levels of benzodiazepines.

#### *Clinically relevance*

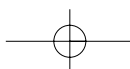
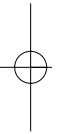
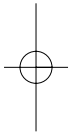
This study is the first to examine in a clinical situation the relationship between plasma levels of benzodiazepines and memory impairment in patients who attempted suicide. In addition, our study is unique in using an assessment method that allows for a summation of the concentrations of benzodiazepines and their metabolites, corrected for their binding potentials. We believe this technique will facilitate studies on the relationship between clinical effects and levels of benzodiazepines in other groups and other circumstances.

This study underlines again that patients who have taken an overdose of benzodiazepines are likely to forget information offered to them after the suicide attempt, even if they are interviewed as late as 12 hours after admittance to the hospital. Even with low plasma levels of benzodiazepines anterograde amnesia is likely to occur. In our study, patients who took an overdose without having used benzodiazepines before, as well as chronic users were included, and both showed anterograde amnesia. Therefore it is improbable that oral agreements made during an interview within 24 hours after the suicide attempt with benzodiazepines will be remembered by the patient. If necessary, flumazenil might be useful to circumvent the amnesia (Bishop and Curran, 1995; Nagelhout et al., 1999; The Flumazenil in Intravenous Conscious Sedation with Diazepam Multicenter Study Group I, 1992), although the potential is limited because of its short duration of action and precipitation of acute withdrawal effects. In any case, in routine daily practice it is reasonable to adjust the interview and arrangements for care of suicide attempters because of the possible presence of anterograde amnesia. For instance, the patient can be interviewed again at another time, significant others (relatives, partners, etc.) can be present during the interview and the patient can be provided with written information about arrangements for aftercare.



## CONCLUSIONS

Patients who attempt suicide by taking an overdose of benzodiazepines are likely to have memory impairment, i.e., anterograde amnesia. In this group of patients, a strong relation was established between change in cumulative amount of benzodiazepines and change in scores on a verbal recall test. The relation between change in cumulative amount of benzodiazepines and change in sedation was less impressive. Therefore it can be concluded that assessment of suicide attempters in clinical practice should take into account the forgetfulness of these patients, even if they do not seem to be sedated.



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