

Trend of Memory Recovery after Benzodiazepine Overdose

NASTARAN EIZADI-MOOD, ALI MOHAMMAD SABZGHABAEI, KAMRAN MONTAZERI, FARZAD GHESHLAGHI, AHMAD YARAGHI, BEHZAD NAZEMORRAYA and SHADI KAZEMI

For author affiliations, see end of text.

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ABSTRACT

Because of difference in the toxicokinetic and pharmacokinetic characteristics of drugs and with respect to the high rate of benzodiazepine abuse in suicidal attempts, the trend of possible anterograde amnesia after recovery from benzodiazepine overdose were evaluated in Iranian patients. This was a prospective descriptive/analytic clinical trial, which was conducted, in Noor general teaching hospital. Patients 18-50 years old, who attempted suicide with long acting benzodiazepines, were tested for memory at 3 times: immediately after waking up (time 0, t0), 12 (time 12, t12) and 24 hours (time 24, t24) after time 0. Memory was assessed using the Wechsler Memory Scale. The mean of memory score was 44.6 ± 7.1 immediately after waking up (t0). This score was 76.9 ± 3.5 and 93.3 ± 8.18 in t12 and t24 respectively. The difference between the means of memory scores of t0 and t12 was statistically significant and this was the same between t12 and t24. There was a statistically significant relationship between memory score and drug dosage. It is concluded the memory status following waking up in benzodiazepine overdose is different in the course of recovery and ascending in an approximately linear way.

Keywords: *Benzodiazepine, Overdose, Amnesia*

Memory impairment due to use of benzodiazepines in contemporary medical practice is well defined in previous studies [1, 2]. The type of this side effect is commonly referred to as anterograde amnesia, the phenomenon whereby information presented after benzodiazepines have been taken is poorly remembered [3]. Type of individual benzodiazepine, the route of administration, the dose ingested, the time elapsed from the ingestion and finally the individual characteristic of the population which the subject belongs to are all important in the duration and severity of this amnesia [4-7]. In a previous study, it was shown that only partial tolerance to the amnesic effects develops; in verbal recall tests, tolerance to the effects of benzodiazepines was found on immediate but not delayed recall in normal volunteers [8]. Chronic benzodiazepine users have already reported this impaired delayed recall after acute administration of the medication [9]. In certain medical situations (e.g. as premedication in some surgeries) anterograde amnesia is beneficial for the patient and in some others (e.g. patients under psychotherapy), it may interfere with the therapy [10].

Because of the difference in toxicokinetic and pharmacokinetic characteristics of drugs [11] and also with

respect to the high rate of benzodiazepine abuse in suicide attempts [12], the trend of possible amnesia after recovery from benzodiazepine overdose, in Iranian patients was evaluated.

MATERIALS AND METHODS

Study Specifications

This work is from Anesthesiology Research Department, Isfahan University of Medical Sciences (IUMS). The protocol was reviewed and approved by the Institutional Ethics Committee of the Faculty of IUMS. It was a prospective descriptive/analytic clinical trial, which was conducted, in Noor general teaching hospital. Patients 18 to 50 years old, who had attempted with long acting benzodiazepines (Diazepam, Clonazepam or Flurazepam) were included into the study. Mixed drug ingestion, use of benzodiazepines for more than 6 months, history of memory disorders (Alzheimer disease) and need for mechanical ventilation due to apnea were considered as exclusion criteria. Fifty one patients have completely met the inclusion criteria for the study.

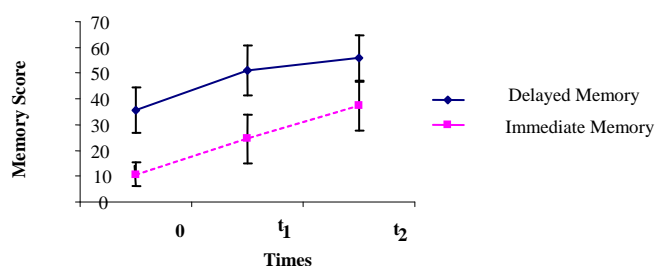


Fig 1. Trend of immediate and delayed memory scores in patients. t₀, immediately after waking up; t₁₂, 12 hours after time 0; t₂₄, 24 hours after time 0

Assessment

All the patients were tested for memory functional status at 3 times: immediately after waking up (time 0, t₀), 12 (time 12, t₁₂) and 24 hours (time 24, t₂₄) after time 0. Memory was assessed according to test manual guidelines using the Wechsler Memory Scale (WMS-III) [13]. The subtests of WMS-III are grouped into immediate memory both auditory and visual, general memory both auditory and visual, and working memory both auditory and visual. Many of the subtests are separated into two conditions: The immediate condition and the delayed condition which is administered approximately 35 to 45 minutes after the immediate condition. The following subtests, sums of scaled scores and index scores were derived and achieved: Auditory Immediate Memory, Visual Immediate Memory (Immediate Memory); Auditory Delayed Memory, Visual Delayed Memory, Auditory Recognition Delayed Memory (Delayed Memory); and Working Memory [13, 14]. At Noor Hospital, all patients admitted because of a suicide attempt, are seen by a psychiatrist for a routine clinical interview following waking up, provided the patient is sufficiently alert for psychiatric consultation. For this study, at the end of the interview, a psychiatric resident informed the patients about the study and asked them to participate. The patients were interviewed and tested by a research assistant (an experienced consultation-liaison medical student), formally trained in the procedures by the department of psychiatry. An informed consent was obtained from each person after the nature of the procedure(s) had been fully explained and the research assistant immediately started assessments according to the study protocol.

Statistical Analysis

Data are presented as mean ± SD. Data were analyzed by two-way analysis of variance (ANOVA) using repeated measures followed by the test of least significant difference. For comparison within the groups, one-way ANOVA was used. For the assessment of relationship between memory score and drug dosage, the Spearman Correlation test was used. The statistical test was 2-tailed, and a $P < 0.05$ was considered significant. The data were analyzed using the SPSS software.

Table 1. Mean of memory score in benzodiazepine poisoned patients during deterrent times

Time	Memory Score
t ₀	44.6 ± 7.1
t ₁₂	76.9 ± 3.5 *
t ₂₄	93.3 ± 8.2 * ⁺

All values are expressed as mean ± SD (n=51); t₀, immediately after waking up; t₁₂, 12 hours after time 0; t₂₄, 24 hours after time 0; * $p < 0.05$ comparison of values at different times with respect to value at "0" time within groups; ⁺ $p < 0.05$ comparison of t₂₄ vs. t₁₂.

RESULTS

Fifty one patients completely met the inclusion criteria for the study (24 Clonazepam, 26 Diazepam and 1 Flurazepam cases). Five patients had at least 1 missed evaluation process that was excluded. In 7 cases, the patient was intoxicated with more than 1 kind of benzodiazepine and 3 others had multi-drug poisoning who was excluded as well.

The average score of memory immediately after waking up (t₀) was 44.6 ± 7.1. This score was 76.9 ± 3.5 and 93.3 ± 8.18 in 12 and 24 hours after waking up (t₁₂, t₂₄) respectively (Table 1). The difference between the average memory score of t₀ and t₁₂ was statistically significant and this was the same between t₁₂ and t₂₄. The absolute trend of mean value changes for all three occasions was definitely ascending.

The average immediate and delayed subsets of WMS score in all three stages of assessment were also (statistically) significantly different (p value = 0.003). (Fig 1)

The Correlation Spearman test shows that there is a relationship between memory score and drug dosage (p value < 0.001).

DISCUSSION

Impairments in memory appear to be induced by benzodiazepines not only after long-term use, but also after administration of a single dose [3, 4, and 9]. However, there are few studies to evaluate this effect in overdose patients [15, 16]. This study was conducted to clarify the trend of memory improvement following poisoning with long acting benzodiazepines. Our analysis suggests that long acting benzodiazepines play a major role in memory impairment in suicide attempters who took an overdose of these agents. Results show that the memory status following waking up is definitely different in the course of recovery and ascending in an approximately linear way. Our results with respect to memory are in concordance with the previous study [15, 16]. In a verbal recall test, patients performed more poorly on the first day of admittance to the hospital than on the second day in immediate and delayed recall [15]. Memory impairment has been also found in a photo recognition task [17].

Although we used WMS-III for evaluating amnesia, our results are in agreement with the existing investigations in which different test results demonstrate memory impairment after the intake of benzodiazepines [5, 15-17].

Our results also show there is a statistically significant relationship between memory score and drug dosage. In the study by Mintzer and Griffiths in 2005, the dose-related amnesia by lorazepam has been reported [18]. In another study by Ghonim and co-workers, 120 healthy volunteers were randomly assigned to four treatments of diazepam and three testing times. Immediate and delayed free recall of word lists revealed consistent decreases in performance as oral diazepam dose increased [19]. However, it should be noted suicide attempters are often unable to give reliable information about the dosage they have taken and considerable inter individual 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. Although the drug plasma levels of benzodiazepines were not evaluated in our study, the relationship between anterograde amnesia, and plasma levels of benzodiazepines was studied prospectively by Verwey et al. in a group of 24 patients who took an overdose of diazepam [16]. In their study amnesia was tested by using a verbal recall and photo recognition tests. The change in anterograde amnesia was strongly related to change in cumulative amount of diazepam equivalents.

It is concluded the memory status following recovery from benzodiazepine overdose is different in the course of recovery and ascending in an approximately linear way. It may be recommended that psychiatric consultation after suicidal attempts should be postponed for at least 24 hours after wake-up of patients.

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CURRENT AUTHOR ADDRESSES

- Nastaran Eizadi-Mood, Associate Professors of Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: izadi@med.mui.ac.ir (corresponding author)
- Ali Mohammad Sabzghabaei, Assistant Professor of Isfahan University of Medical Sciences, Isfahan, Iran.
- Kamran Montazeri, Associate Professors of Isfahan University of Medical Sciences, Isfahan, Iran.
- Farzad Gheshlaghi, Associate Professors of Isfahan University of Medical Sciences, Isfahan, Iran.
- Ahmad Yaraghi, Assistant Professor of Isfahan University of Medical Sciences, Isfahan, Iran.
- Behzad Nazemorraya, Anesthesiologist, Isfahan University of Medical Sciences, Isfahan, Iran.
- Shadi Kazemi, General Physician, Isfahan University of Medical Sciences, Isfahan, Iran