Recovery of dynamic balance after additional small divided doses of midazolam given intravenously for sedation

Abstract

We have previously reported that a dynamic balance test with perturbation stimuli and computerised dynamic posturography sensitively reflected the inhibitory effect on balance of intravenous midazolam sedation given intravenously as a single dose, and recovery time was within 80 minutes. The purpose of this study was to investigate the recovery of dynamic balance after additional doses of midazolam.

Eighteen young adult male volunteers were sedated with midazolam given intravenously. The initial dose was given until the Wilson sedation score reached 3, and an additional dose was given until the same score was obtained 40 minutes later. They were tested with perturbation stimuli 40, 80, 100, and 120 minutes after the additional doses had been given. Their recovery time was recorded.

The mean (SD) initial dose of midazolam was 0.07(0.005) mg kg^{-1}, and additional doses were 41 (7)% of the initial dose. The serial changes in bispectral index after initial and additional doses were similar. The recovery time for the dynamic balance test (within 80 minutes) was the same as that recorded in the previous single-dose study. The recovery time of the psychomotor function test was within 75 minutes.

Additional doses of midazolam aiming for a Wilson sedation score of 3 at a dose about 40% of the initial dose and given 40 minutes after the initial dose are valid in terms of the maintenance of sedation and recovery of dynamic

balance. Complete recovery time, including psychomotor function, was within 80 minutes of the additional dose of the drug.

Key words: Conscious sedation, Midazolam, Additional administration, Recovery of function, Dynamic balance

Introduction

Many oral operations that were previously done under general anaesthesia can now be done under local anaesthesia with intravenous sedation.[1,2] The assessment of recovery of dynamic balance involving movement of the centre of gravity after intravenous sedation, is important for ensuring safe discharge particularly walking. In a previous study,[3] we recorded the recovery of static and dynamic balance after a single dose of midazolam, and reported that the dynamic balance test with perturbation stimuli using an unstable platform is a useful method that reflects sensitively the disturbance of balance by sedation; the recovery time is less than 80 minutes. The sedative effects of midazolam continue for only a short period (20-47 minutes),[2,4-7] so additional doses are necessary when the duration of treatment is prolonged. Acute tolerance may result in a reduction in effects of the drug or in the promotion of recovery,[8-10] while deterioration of metabolism and excretion may also result in delayed recovery.[11,12] However, there have been no studies on the influences of additional doses on the recovery of dynamic balance. We therefore gave additional doses of midazolam 40 minutes after the initial dose, and evaluated the recovery of dynamic balance.

Subjects and methods

Eighteen healthy young male volunteers were given midazolam intravenously. Before the study, the ethics committee had approved the protocol and subjects had given informed consent. Midazolam was given intravenously in small divided doses (total, about 0.07 mg kg^{-1} as the standard initial dose)[13] until the Wilson sedation score reached 3 (the eyes are closed, but the subject responds to one or two calls).[14] Forty minutes after this, 0.5-1 mg increments were given until the same degree of sedation was achieved. As an objective index of sedation, bispectral index was recorded using a BIS monitor A1050 TM(Aspect Medical Systems, Newton, MA, USA). [15,16] The electroencephalographic (EEG) signal was acquired using BIS sensor electrodes applied to the forehead and temple. The segments of the EEG were computed for individual bispectral and power-spectral features. The subjects were stimulated by having their names called and their shoulders tapped 1 minute before the recording of the bispectral index.

The dynamic balance was tested using computerised dynamic posturography, before (baseline) as well as at 40, 60, 80, 100, and 120 minutes after additional midazolam had been given.[3] Briefly, an unstable platform tilts in all directions according to the changes in body weight applied by the tips of the toes and the heels. The subjects were asked to keep the platform horizontal for 20 seconds. The degree of tilt from the horizontal

in all directions during the test was expressed as the stability index. A simple psychomotor function test, the Trieger dot test (in which a geometrical figure was drawn by connecting a series of dots with a ball-point pen),[17] and an addition test in which double figures selected from a table of random numbers were added,[18] were done before as well as 35, 55, 75, 95, and 115 minutes after the additional doses. The increase in each variable (except the addition test) indicates reduction of function.

The study was designed to have an 80% power for detecting a difference of 0.32° (which is equivalent to 20% of the baseline value in the previous study[3]) between the baseline value and the value at each time point in the stability index of the dynamic balance test. The recovery time was defined as the time until the difference between the mean value at each time point and the baseline value ceased to be significant. Friedman's test was used for analysis of the data, and subsequent multiple comparisons were made by the Wilcoxon signed-ranks test with Bonferroni correction. Probabilities of less than 0.05 were accepted as significant. Values are expressed as mean (SD).

Results

Details of subjects and doses are given in Table 1.

Serial changes in the bisprectral index after the initial and additional doses

were similar, showing similar changes in the levels of sedation (Table 2). The difference in values at each time point between the initial and additional doses in each subject was relatively small (median; 3, range; 0 to 14), and for two thirds of the time points the difference was 5 or less.

Serial changes in values of the dynamic balance test and simple psychomotor function tests are shown in Tables 3 and 4. The recovery times after the dynamic balance test and the psychomotor function tests were within 80 minutes and 75 minutes, respectively.

Discussion

Previous studies using similar initial doses of midazolam have shown an effective duration of 20-47 minutes: [2,4-7] the duration of amnesia after an intravenous injection (5 mg), 20 minutes;[4] duration of amnesia after intravenous injection, 25 minutes;[2] time to recovery of psychomotor function judged by the peg board test after intravenous injection (5 mg) in volunteers, 34 minutes;[5] interval between intravenous injection of midazolam 5.9 mg combined with fentanyl (100 μg), and additional doses of midazolam in clinical cases, 45min;[6] and of time that eyes were closed after intravenous injection (0.05 mg kg^{-1}) under spinal anaesthesia, 47 minutes.[7] Additional doses are therefore often necessary if the duration of treatment is

prolonged, and the additional dose has been reported to be a third[4,7] or half[6] of the initial dose. The additional time and dose given in the present study seem to be valid when compared with these reports.

The previous studies evaluated mainly the level of sedation from clinical findings, which tends to be subjective. We added the bispectral index to our conventional clinical findings. This index is an indicator of the patient's hypnotic state and ranges from 100 (fully awake) to 0 (no cerebral activity). Ranges of 80-90 and 70-80 indicated light to moderate sedation, and arousable but moderate to deep sedation, respectively.[19]To evaluate the purely sedative effects of midazolam, it is desirable to assess certain stimuli. However, when they are resting supine, volunteers sometimes sleep spontaneously, which may result in overestimation of its purely sedative effects. [20] We used slight arousal stimuli and measured the index one minute after stimulation. Changes in the index after the additional doses were therefore similar to those after the initial dose. Of the 20 subjects in our previous study of a single dose,[3] 18 were included in this study. The dose of midazolam (0.07 mg kg^{-1}) that we used previously was similar to that given initially (0.069 mg kg^{-1}) in this study, so we think that recovery of dynamic balance from a level of sedation similar to that in the previous study could also be evaluated here.

Acute tolerance of midazolam given intravenously has been reported to be observed with the blood concentration of midazolam at 55-66 ng ml^{-1}, [8] or with the conscious sedation level 20 minutes after the start of injection of midazolam. [9] The blood concentration after giving midazolam intravenously 5 mg has been reported to be 50-150 ng ml^{-1}, [21] and in the presence of the anti-anxiety and amnesic effects without sleep after an intramuscular injection of midazolam 0.13 mg kg^{-1}, 70 μg l^{-1}. [22] These results suggest that tolerance may develop after a short time even when only mildly sedated. Some studies have shown that acute tolerance develops more readily with more pronounced initial effects, and so is more common after a single dose than after a continuous intravenous injection. [23,24] Re-transfer from the distribution phase should also be considered, particularly in elderly people after the additional doses and their influences on delay in metabolism/excretion. [11,12] In younger people, it is unlikely that any additional doses will induce a delay in the reduction in the concentration. As we did not measure concentrations of midazolam in blood we can only speculate about the influences of tolerance and delayed excretion. Additional doses of midazolam in young people once they have been sedated may not delay the recovery of dynamic balance if the timing and dose are appropriate.

Before patients can return home safely, evaluation of the recovery of psychomotor function and balance are necessary. The test that we used is widely employed to assess recovery from sedation or general anaesthesia, [17, 25] and as the recovery time was 55-75 minutes, the recovery of psychomotor function was probably similar to that of dynamic balance.

In summary, additional doses of midazolam aimed to achieve Wilson sedation score 3 at a dose of about 40% of the initial dose 40 minutes after the initial dose had been given is valid to maintain the level of sedation and recovery of dynamic balance. Total recovery time including psychomotor function was within 80 minutes of the additional doses of midazolam.

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Table 1. Details of subjects and doses.

Variable	Mean (SD)	Range
Age (years)	23 (2)	20 - 27
Height (cm)	171 (6)	164 - 184
Weight (kg)	65 (9)	53 - 85
Body mass index (kg m^{-2})	22 (3)	19 - 29
Initial dose of midazolam (mg/kg)	0.07 (0.005)	0.05 - 0.08
Additional dose (mg/kg) (% of initial dose	0.03 (0.006) 41 (7)	0.01 - 0.04 22 – 50)

Table 2. Serial changes in mean (SD) bispectral index after the initial and additional doses of midazolam (n = 18).

		Time afterwards (minutes)			
	Immediately	5	15	25	35
After initial dose	72.0 (4.7)	80.4 (7.1)	84.9 (5.8)	89.5 (5.2)	90.4 (7.9)
After additional doses	73.5 (5.1)	83.6 (5.9)	86.5 (5.7)	90.1 (4.5)	Not measured

Baseline value 95.9 (2.0)

Table 3. Serial changes in mean (SD) values in computerised dynamic posturography after additional doses of midazolam (n=18).

Test	Measure	Baseline	Time afterwards (minutes)					Recovery time (min)
			40	60	80	100	120	
Dynamic balance test	Stability index	1.4 (0.4)	2.7 (1.2) **	1.8 (0.7)**	1.6 (0.5)	1.4 (0.4)	1.4 (0.4)	60 - 80

** 0.01 (compared with baseline)

Table 4. Serial changes in mean (SD) values of psychomotor function after additional doses of midazolam (n = 18).

			Time afterwards (minutes)					
Test	Measure	Baseline	35	55	75	95	115	Recovery time (min)
Trieger dot test	Number of dots left outside the line drawn	1.2 (1.3)	5.8 (4.2)**	3.4 (3.2)**	2.0 (2.2)	1.2 (1.3)	1.3 (1.2)	55 - 75
Addition test	Number of correct answers	24.2 (4.7)	19.3 (5.6)*	22.7 (5.0)	23.5 (5.6)	25.4 (4.4)	25.3 (4.4)	35 - 55

* 0.05; ** 0.01 (compared with baseline)