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Evaluation of saccadic eye movements as an objective test of recovery from anaesthesia

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Saccadic eye movements have been previously used to assess residual effect of anaesthetics, but this test is seldom compared to other psychomotor tests. The aim of the present study was to validate saccades as a recovery index in relation to frequently referred subjective and psychometric tests.

Eight healthy subjects were tested before and after intra-muscular injection of either placebo or 0.15 mg · kg^{-1} of midazolam. Each session consisted of a saccadic test (recorded by electro-oculography), a choice-reaction-time test (CRT), a subjective state-of-alertness test (11 visual analogic scales) and blood sampling (to monitor midazolam plasma concentration), before and 30 (t30), 60 (t60), 120 (t120), 180 (t180), 240 (t240) minutes after drug administration.

In the placebo group, there was no change in subjective assessment, saccade characteristics (latency, peak velocity and duration) or CRT results. In the midazolam group, 6 subjective items changed with different time-courses, when compared to baseline: from t30 to t120 (*drowsy, in shape, tired, clumsy, strong*) and at t120 (*woolly*). Saccade latency and duration were significantly different from t30 to t120 and until t180 for peak velocity. CRT performance was significantly altered from t30 to t120. Midazolam plasma concentration decreased from 177±33 ng · ml^{-1} at t30 to 47±12 ng · ml^{-1} at t240. At this latter time, sensorimotor functions returned to the baseline. All subjects fulfilled the clinical conditions for home discharge 4 hours after administration.

These results suggest that a saccadic eye movement test is a sensitive and reliable tool for the assessment of residual effect of anaesthetics. This test was found to be more sensitive than CRT test since peak saccadic velocity was the last psychometric parameter to be returned to baseline after midazolam injection. This study also confirms the poor reliability of subjective assessment, as subjects tended to underestimate the alteration of their performance immediately following drug injection.

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The development of ambulatory anaesthesia leads anaesthesiologists to redefine criteria for home discharge of the outpatient (1). Several studies relying on psychomotor tests have been carried out to evaluate psychomotor function during recovery from anaesthesia. Among these tests, Maddox wing, reaction-time, critical flicker fusion and tracing tests are the most commonly used (2). Saccadic eye movements may provide an appropriate test to assess recovery from anaesthesia. Changes in saccade velocity profile have been observed after propofol (3), halothane, cyclopropane (4) and isoflurane (5) administration, suggesting that the saccade velocity profile is a sensitive indicator of central nervous system alteration.

Saccades are rapid eye movements, triggered in an attempt to fixate a visual target. The pattern of muscle activation responsible for this gaze shift is under the control of a brainstem generator. Fuchs & Kaneko (6) have described a saccade generator, based on the activities of several brainstem neurones which are located around the oculomotor nuclei. This saccade generator receives a burst of activation (at constant, high discharge frequency), which has a duration proportional to the saccade amplitude. The sequential output of the generator (agonist pulse) drives the eye muscles at high velocity, stops the eyeball when the desired position is reached (antagonist pulse) and maintains the position by a constant (step) activation. The step activation is derived from the pulse and is proportional to the new position of the eye in the orbit. The Fuchs & Kaneko model predicts that the saccade duration and peak velocity are proportional to the eye position change. This has been shown by Bahill & Stark (7) who described for the first time the so-called "main-sequence" of saccadic eye

movements as a way to characterise normal saccades. Since saccades are directly under brainstem neural control, rapid eye movements have been used to test the state of this region of the central nervous system. Administration of drugs such as alcohol, diazepam, temazepam, methadone or GABA have been shown to produce changes in the relationship between saccadic amplitude, duration and peak velocity (8–12). Saccadic eye movement characteristics are objective measurements that can be recorded readily. They are free of cognitive control and sensitive to the effects of psychoactive drugs. Also, they show characteristic changes as a result of neurodegenerative disorders., To date, no direct comparison of saccadic eye movement alterations and psychomotor changes in the course of recovery from anaesthesia or sedation is available in the literature.

The aim of this study was to assess the validity, sensitivity, and reliability of saccadic eye movements as an anaesthesia recovery index, as compared to other subjective and objective tests, in patients receiving a premedicament intramuscular injection of midazolam.

METHODS

This prospective, randomised, cross-over, double-blind, placebo-controlled study was approved by the ethical committee of the University.

Subjects

Eight healthy male volunteers aged 25.4±3.8 years, weighing 76±5.8 kg, and 181±9 cm tall participated in the study, after giving their informed consent. Non inclusion criteria were: age >45 years or <18 years; weight >10% from the ideal weight (defined by the Metropolitan Life Insurance tables); any organ system abnormalities, particularly neurologic diseases; history of allergy; treatment during the month before inclusion and involvement in any other study in the past 3 months. All volunteers were trained with the apparatus one week before the first session. They were requested to abstain from medication and alcohol for a week before test day. On the test day, they fasted from midnight until discharge.

Procedure

The testing schedule included six test periods: before injection (t0), and 30 min (t30), 60 min (t60), 120 min (t120), 180 min (t180), 240 min (t240) after injection.

The subjects were randomly assigned to receive, intramuscularly, the same volume of either midazolam (0.15 mg · kg^{-1}) or isotonic sodium chloride (placebo). In a cross-over manner, they received the two drug regimens during two sessions separated by at least a one-week interval. Midazolam doses ranged from 10.2 to 13.5 mg.

Environmental parameters were maintained at a stable level, with particular emphasis on the darkness and silence. Between experimental periods, the subjects rested in the laboratory room, and if they wished to do so, they could lie down on a bed. Each session, run in the morning, lasted approximately 5 h.

Experimental session

Subjective assessments

Eleven Visual Analogic Scales (VAS) were used for subjective evaluation. Subjects were asked to assess their own state of alertness on 100 mm lines labelled with the following adjectives: "anxious", "tired", "happy", "relaxed", "drowsy", "woolly", "clumsy", "in shape", "strong", "sad", "depressed'.

Choice-reaction-time (CRT) test

The subjects were asked to scan two light bulbs of different colours which were turned on at random. The task was to press one of the two corresponding buttons, in order to turn off the light source. Each test consisted of 50 trials and data were expressed as an average reaction time in ms.

Saccadic eye movement test

Experimental set-up. The subject was seated 114 cm in front of a horizontal linear array of 11 yellow LED targets. The angle between two consecutive targets, as seen from the subject's eyes, was 5°. The subject's head was immobilized by a chin rest and a forehead support.

Experiment control and recording system. A personal computer was used to control the experiment. A single trial consisted of a target jump and the subject's corresponding eye movement. The experimenter triggered each trial while the computer programme controlled the illumination of the LEDs via a digital input/output interface. The subject was instructed to rapidly step from the central fixation to the randomly illuminated eccentric target. The total duration of each trial was 2 s. Trials followed at a pace of about one every 5 s. Eye movements were recorded by electro-oculographic (EOG) technique; two silver-silver chloride surface electrodes were applied to each eye's outer-cantus, while a reference electrode was located in the middle of the forehead. The EOG electrodes were connected to a battery-powered DC amplifier, which low-pass filtered the signal (200 Hz at −3 dB, 12 dB/octave). The EOG signal was digitised at 500 samples/s with a 12-bit A/D converter. EOG and target position signals were displayed in real-time on a graphic screen. Sections of 2 s were saved on a disk for off-line analysis. Since EOG is linear within the ±30° range, no linearisation procedure was necessary. The calibration session started and ended the recording period. A typical recording period consisted of a series of 30 steps, from the central target towards one of the eccentric targets (5, 10, 15, 20 and 25° in each direction).

Data analysis

Off-line signal analysis started with digital low-pass filtering of the recorded signal (running average using 7 coefficients and providing a cut-off frequency of 30 Hz) and differentiation with respect to time (saccade velocity profile). The saccades were manually detected using an interactive, graphic, cursor-based method (13). Four parameters were extracted to characterise each saccade: saccade amplitude, latency (time between the target jump and the onset of the saccade), saccade duration and peak velocity.

The effects of the drug on saccades were quantified in terms of average changes in the population of single saccades collected from each test period and each subject. Raw data were pre-processed, as follows: all saccades collected during a test (same subject, standard time after injection) were used to plot peak saccadic velocity and saccade duration *vs* actual saccadic amplitude. A least-square linear regression was applied to these data. The slope of the regression line was used to characterise the population saccades. For each test, the following statistical parameters were derived: average latency, slope of the saccade duration *vs* amplitude regression line, and slope of the peak saccadic velocity *vs* amplitude regression line.

Midazolam assay

Blood samples were collected at the above test intervals, through a vein cannula placed in the forearm. They were immediately centrifuged for plasma isolation which was stored at 4°C until midazolam extraction. Midazolam plasma concentrations were measured as described by Cre-

vat-Pisano (14) and Drouet-Coassolo (15) using a HP 5710A gas chromatograph (Hewlett Packard, Les Ulis, France).

Monitoring

Non invasive measurements of heart rate, blood pressure and SpO_2 were carried out throughout the experimental session, so that the protocol could have been immediately interrupted if the subject had developed any respiratory or haemodynamic alterations.

Statistical analysis

Results are expressed as the mean±standard deviation. Two-ways ANOVA for repeated-measures was used to assess pooled variance of the two groups. In each group, data were compared to baseline (t0) using post-hoc paired *t*-test with Bonferroni's correction with $P<0.05$ considered as significant.

RESULTS

General considerations. Each set of measurements was performed in 5 to 7 min. All the subjects completed the protocol. Only one subject felt drowsy during the placebo session. This was probably related to the quietness of the environment. All the subject felt drowsy during midazolam treatment and fell asleep approximately 15 min after injection. They needed to be awakened to perform the t30 evaluation, and were not always able to completely carry out the saccadic test and/or the CRT test. At the end of the recording sessions (4 h after injection) all the subjects reported feeling in good physical condition. Clinical examination confirmed they could be safely discharged home.

Midazolam plasma concentrations

Midazolam group. Peak plasma concentration was achieved at t30 (177±33 ng · ml^{-1}), followed by a monotonic decrease of the plasma concentration: 144±23 ng · ml^{-1} at t60, 93±20 ng · ml^{-1} at t120, 67±15 ng · ml^{-1} at t180 and finally 47±12 ng · ml^{-1} at t240 (Fig. 1A).

Visual analogic scales (VAS)

Placebo group. No significant difference was detected for any of the tested items.

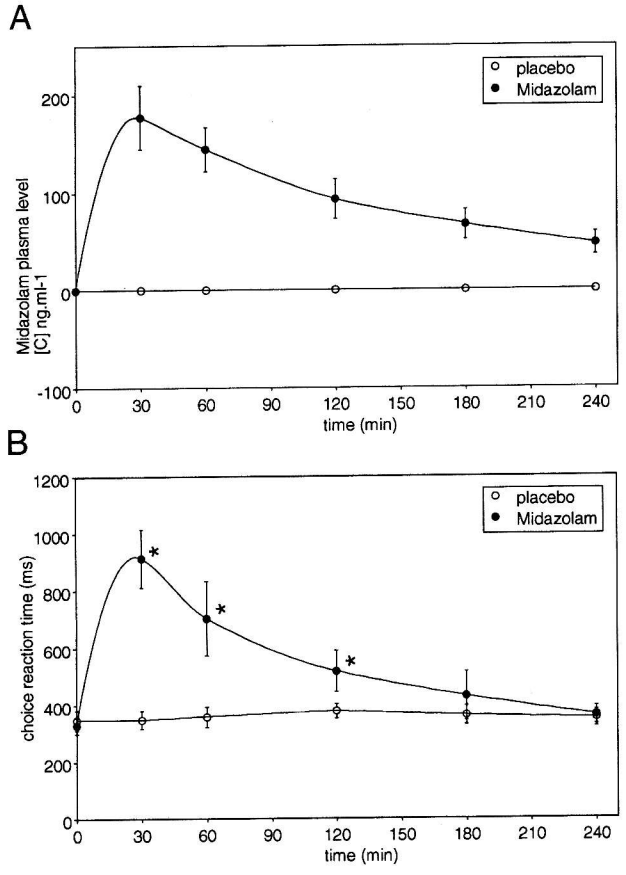


Fig. 1A. Midazolam plasma concentration as a function of time after injection. 1B: Choice-reaction-time as a function of time after injection. Data are the mean value and standard deviation over all eight subjects. Open circles (○) correspond to placebo tests, black filled circles (●) correspond to midazolam tests. (*) $P<0.05$ in comparison to baseline (t0) by repeated measures ANOVA and paired *t*-test with Bonferroni's correction.

Table 1

Time-course of subjective assessment using Visual Analogic Scales. For each tested item, values are compared to the baseline of placebo (PLA) or midazolam (MDZ) session, obtained before injection (t0).

		t0	t30	t60	t120	t180	t240
Anxious	PLA	50.5	51.5	51.3	51.4	51.5	51.3
	MDZ	48.9	45.5	49.8	48.6	50.5	52.5
Tired	PLA	51.9	48.8	49.8	52.3	51.4	50.6
	MDZ	47.4	73.5*	68.4*	72.5*	57	44.8
Happy	PLA	48.6	50	49.5	50	50	55.4
	MDZ	42.1	53.9	51.6	51.3	51.8	49.6
Relaxed	PLA	48	44.9	42.9	47.3	47.3	47.3
	MDZ	50.5	43.5	48.1	41.9	47.1	46.9
Drowsy	PLA	50.1	51.1	49.2	51.6	50.6	49.2
	MDZ	49.7	75.4*	75.6*	80*	61.2	43.9
Woolly	PLA	48.8	49.1	50	48.8	50	50
	MDZ	51	61.1	61.8	69*	49.6	45.4
Clumsy	PLA	50	49.3	49	48.9	49.1	48.8
	MDZ	51.4	62*	65*	66.4*	54.5	50
In shape	PLA	50.2	49	49.4	51.2	47.9	53.1
	MDZ	51.2	33.4*	36.1*	34*	43.7	51.9
Strong	PLA	49.9	49.8	48.3	45.4	47.9	48.8
	MDZ	49.4	36.1*	35.1*	33.3*	42.4	49
Sad	PLA	51	51.3	51	51.9	51.4	51.4
	MDZ	51.9	53.5	50.6	51.4	50.8	52.5
Depressed	PLA	51.4	51.9	51.4	52.5	52.3	57
	MDZ	53.9	48.6	50.8	50.4	51.8	52.3

* $P<0.05$ for comparison with control (t0) in each group by repeated measures ANOVA and paired *t*-test with Bonferroni's correction.

Midazolam group. Six items were not significantly different from the baseline: "anxious", "happy", "relaxed", "strong", "sad", "depressed". Five items, with variable time-course, were significantly different from baseline. Subjects reported feeling more tired, clumsy and drowsy and less in shape from t30 to t120, and more "woolly" at t120 only (see Table 1).

Choice reaction-time

Placebo group. Relative to the baseline, no significant difference was shown during any session.

Midazolam group. As compared to baseline (329±29 ms), performance deterioration was maximal at t30 (912±103 ms, $P<0.05$). CRT was still significantly increased at t60 (703±131 ms, $P<0.05$), t120 (517±73 ms, $P<0.05$). No statistical difference was observed at t180 (429±85 ms) and t240 (362±31ms) (see Fig. 1B).

Saccadic eye movements

Saccade morphology. Fig. 2 shows the time-course of typical saccades after administration of midazolam or placebo. Following placebo injection, saccade latency, duration and peak velocity remained equivalent to control. Conversely, after midazolam administration, both saccade latency and duration were increased, while peak velocity was decreased. These changes were maximal at t30. Saccade characteristics returned progressively to baseline values which were reached for all parameters at t240.

Saccadic eye movement parameters

Fig. 3 illustrates how the saccade peak velocity and duration were computed. For all saccades collected with a given subject at a time relative to drug administration, peak velocity and duration were plotted against saccade amplitude. The linear regression applied to data provided a slope, which was averaged over all subjects. Changes in regression slope are particularly evident between t0 and t30, as shown in Fig. 3. In fact, the performance of the subjects decreased to a point where some target jumps did not systematically result in eye motion. It follows that t30 to t60 graphs contain a slightly more limited number of data than the other time recording tests.

Fig. 4 shows the time-course of mean saccade latency (Fig. 4A), peak-velocity (Fig. 4B) and duration (Fig. 4C), for both the placebo and midazolam groups.

Placebo group. No statistically significant difference was found between the various post-injection tests and pre-injection controls, for duration, peak velocity and average latency.

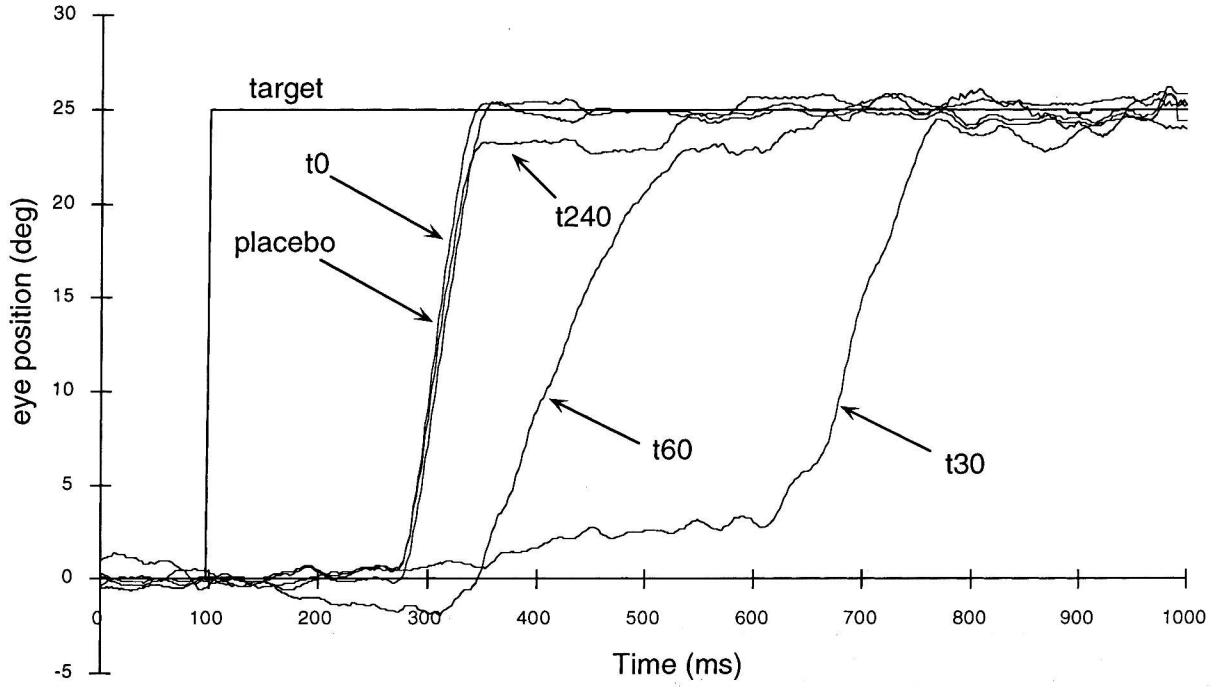


Fig. 2. Typical saccades recorded during periods pre- and post-drug administration for a 25° target jump to the right. Five saccades are represented: 30 min after administration of the placebo, prior to midazolam administration (t0), then 30 min (t30), 1 hour (t60) and 4 hours (t240) after midazolam administration. The thick line represents the target position signal.

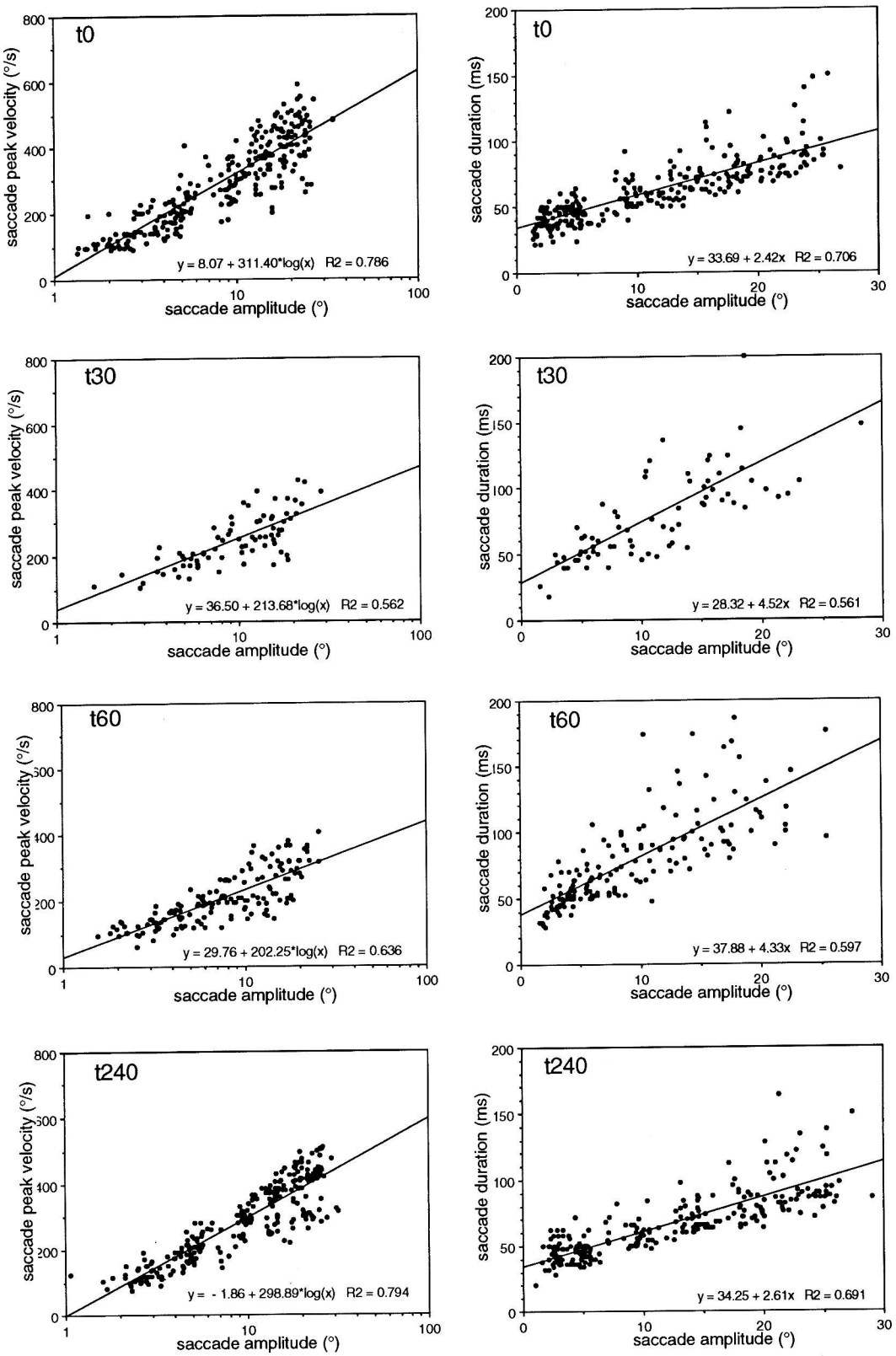


Fig. 3. Relationships between saccade amplitude and saccade peak velocity (left hand graphs) and saccade duration (right hand graphs), before (t0), 30 min (t30), 1 hour (t60) and 4 hours (t240) after administration of midazolam.

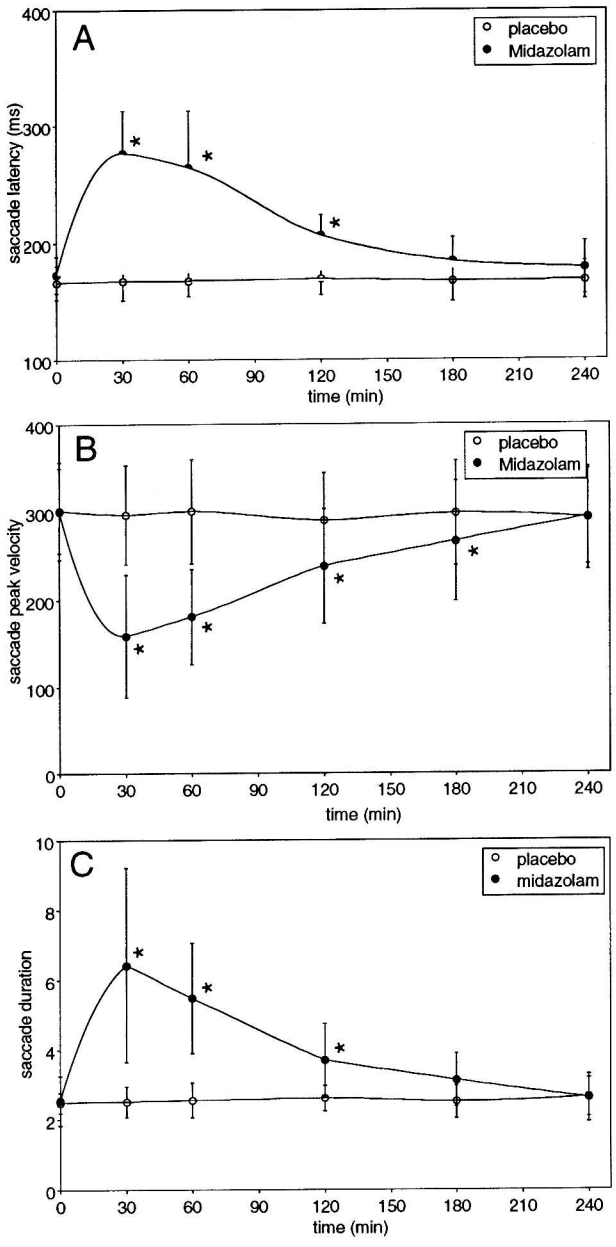


Fig. 4. Time-course of saccade characteristics after injection. Conventions are the same as in Fig. 1. A: average saccadic latency vs time after injection. B: average slope of peak velocity and amplitude vs time after injection. C: average slope of saccade duration and amplitude vs time after injection.

Midazolam group. Saccade duration increased significantly, as seen from the rise of regression slope at t30 (6.58±2.19, $P<0.05$), at t60 (5.48±1.59, $P<0.05$), and at t120 (3.69±1.69, $P<0.05$). No statistical difference was found at t180 (3.1±0.76) and at t240 (2.59±0.68) as compared to baseline (2.53±0.71). Saccade latency was significantly increased at t30 (286.21±52 ms, $P<0.05$), t60 (264±49.6 ms, $P<0.05$) and at t120 (206±17.3 ms, $P<0.05$); no statistical difference was found at t180 (184.1±19.9 ms) and at t240 (178.7±22 ms), relative to baseline (173±15.5 ms). Peak-velocity was affected, from t30 to t180 [t30: 160.4±54.8, $P<0.05$; t60: 180.3±54.4, $P<0.05$; t120: 237.7±65.9, $P<0.05$; t180: 266.5±68.5, $P<0.05$]. However, there was no statistical difference at t240 (293.8±54.5) as compared to baseline (301.3 deg±55.5).

DISCUSSION

The aim of post-operative mental function assessment is to determine the residual effects of anaesthetics or to detect mental changes resulting from the process of anaesthesia or surgery (16). The discrepancy between subjective and objective assessments, and the substantial development of outpatient anaesthesia during the last two decades has motivated researchers to find a recovery test, well adapted to ambulatory settings. For this purpose, several psychomotor tests have been developed (2, 16). The usefulness and pertinence of psychomotor tests depend on how they are applied.

In experimental or clinical research, psychomotor tests evaluate the speed of post-operative recovery from new drugs or new anaesthetic procedures (2, 17). In this case, residual effects are readily assessed using one of the available recovery tests, or a battery of tests. In clinical practice, psychomotor tests assist the anaesthesiologist in his or her decision to discharge the patient from the hospital after day-care surgery. However, studies have shown that the patient's auto-evaluation during recovery from anaesthesia is not reliable (5). In our study, the VAS results confirmed that the subject's auto-evaluation is not a valid method of assessment. This suggests that the clinician should not take the patient's own assessment into account. Presently, a reliable standard test is not available and the physician makes the decision to discharge the patient on clinical examination grounds (18). Yet, clinical recovery does not correlate with psychomotor function recovery. In a recent study, Korttila et al. (19) showed that one hour after brief anaesthesia, all the volunteers met the clinical discharge criteria, while impairment of psychomotor function was still present. For this reason, Korttila recommended further studies to validate psychomotor tests for "home readiness" after outpatient surgery (18).

Drug-induced changes in saccadic eye movements appear to offer a direct, sensitive and minimally invasive means of investigating human central nervous system function (20). Saccadic eye movements are altered by alcohol (21) and benzodiazepines (9, 10, 22). Other psychotropic drugs such as barbiturates and narcotics have also been shown to modify saccadic characteristics (see references 20 and 23 for a detailed review).

In recent literature, the effects of anaesthetics on sac-

cadic eye movements have drawn attention. Gao et al. (3) showed that saccade peak-velocity decreased linearly with increasing $\log_{10}$ propofol concentration. In a later study, the same authors (5) showed that low concentrations of nitrous oxide (5%, 10%) did not affect peak-velocity, while low concentrations of isoflurane (0.06%, 0.12%) significantly altered peak-velocity. A similar study, conducted by Yoshizumi et al. (4), found that low concentrations of cyclopropane and halothane (4.7% MAC and 5.3% MAC, respectively) significantly depressed peak-velocity, in a dose-related manner.

Saccadic eye movements have been widely used by psychopharmacologists to assess psychomotor effects of psychoactive drugs, but only a few studies have compared saccadic eye movements with other tests. In 1984, Tedeschi et al. (21) showed that oral meptazinol and ethanol significantly impaired saccade peak-velocity, duration and latency, while critical flicker fusion and CRT tests showed no significant effect. They concluded that the eye movement technique is a more sensitive tool for detecting the influence of centrally acting drugs. Other studies relied on either saccade tests or other psychomotor tests to evaluate psychoactive drugs. These studies covered a period longer than a regular anaesthesia recovery period (days instead of hours) (24–26). In our experimental conditions (recovery from anaesthesia or sedation), CRT is known to be a sensitive tool (27) and, for this reason, we compared the saccade test and the CRT test results.

Our study evaluated the reliability and sensitivity of a saccadic eye movement test during recovery from an intra-muscular dose of midazolam. Our data confirmed the previous report by Tedeschi et al. (21). That is saccadic eye movement changes correlate well with CRT readings. Two characteristics of saccades, latency and duration, showed a maximal impairment at t30 and returned progressively to baseline at t180 and, as a matter of fact, had the same time-course as CRT. Saccade peak-velocity was altered longer, and returned to baseline at t240. Our results also confirmed Mandema and co-workers' data (28), showing that a premedicant dose of midazolam significantly alters all saccade characteristics.

In clinical research, saccadic eye movement test is a potent tool for the assessment of residual effects caused by anaesthetics. There is no doubt that this test will be widely used, in the future, to evaluate new protocols or new drugs and their effects on psychomotor function. Can saccadic movements be assessed as a clinical routine test? Presently, the goal of the anaesthesiologist in ambulatory anaesthesia practice is to discharge the patient providing he or she is accompanied home. The patient is further counselled to abstain from drinking alcohol, driving a car and making important decisions for 48 h ("home readiness"). Therefore, the goal is not to let the patient leaving the hospital be alone ("street fitness"). In addition, a potential risk remains for the patient at home, which could result in medico-legal exposure for the physician. A further aspect is the social and economic cost of job interruption, which could be reduced if the patient quickly regained work capacity. All these reasons make psychomotor tests a matter of permanent interest.

New methods for assessing psychomotor performance during recovery have recently been described (29), but unfortunately no psychomotor test could be recommended in ambulatory anaesthesia settings (30). At the present time, a saccadic test cannot be recommended in clinical practice because saccade analysis has to be carried out manually (EOG signal/noise ratio is too low). However, computer programmes have recently been developed which both simplify the recording procedure and increase data accuracy. Infrared monitoring of eye position may be used to decrease the noise level and permit automatic measurement of saccade characteristics (31).

In addition to being reliable, the saccadic test is objective. Indeed, it allows the evaluation of the voluntary control of a major sensorimoter function (saccade reaction-time) and noncognitive control (saccade duration and peak-velocity). In several other tests, such as the Maddox wing test or the critical flicker fusion test, the subject's contribution (and honesty) is requested. Nevertheless, further studies are needed to evaluate saccadic eye movements in day care anaesthesia.

In conclusion, this study confirmed that saccadic eye movement measurement is a reliable psychomotor test for detecting residual effects of anaesthetics. Among the parameters studied, saccade peak-velocity was shown to be the most sensitive parameter to detect psychomotor dysfunction. This measure is therefore a precious tool for the assessment of recovery from anaesthesia and in the future its use is warranted in clinical research. Our study also showed that a premedicant dose of midazolam (0.15 $mg \cdot kg^{-1}$) altered psychomotor functions for 3 hours after injection and that psychomotor impairment was strongly correlated to midazolam plasma concentrations.

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