Titrated sedation with propofol or midazolam for flexible bronchoscopy:
a randomized trial

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ABSTRACT

In this study, we questioned whether propofol provided clinical benefits compared with midazolam in terms of neuropsychometric recovery, safety profile and patient tolerance.

Patients > 18 years of age were randomized to receive midazolam or propofol, given by non-anesthetist physicians to achieve moderate levels of sedation as assessed by the electroencephalographic bispectral index (BIS between 70 and 85). The primary endpoint was the time delay until recovery of the BIS index above 90. Other endpoints included a neuropsychometric continuous performance test (CPT), serious respiratory adverse events, patient tolerance and physician satisfaction.

Neuropsychometric recovery was improved in the propofol compared to the midazolam group as evidenced by faster normalization of BIS index (5.4 ± 4.7 min vs 11.7 ± 10.2 min, p = .001) and better results at the CPT. In the midazolam group, 15% of patients presented profound sedation precluding CPT completion and one patient required mechanical ventilatory support. Patient's tolerance was significantly better in the propofol group whereas the operator's assessment was comparable in both groups.

Compared with midazolam, propofol provided a higher quality of sedation in terms of neuropsychometric recovery and patient's tolerance. BIS-guided propofol administration represents a safe sedation technique that can be performed by the non-anaesthesiologist.

INTRODUCTION:

Sedative techniques using hypnotic and /or analgesic drugs are currently used during flexible bronchoscopy (FB) to facilitate the diagnostic procedure and to improve patient comfort [1, 2]. Operators often tend to minimize patient discomfort [3-5] and, although FB can be performed without sedation [6-8], a recent survey revealed that 80% of patients prefer to be sedated during FB [4].

Benzodiazepines are frequently used for sedation given their ease of administration, speed of action and availability of an antidote. Although they undoubtedly enhance operator satisfaction and patient's tolerance during FB[1, 2, 4, 9], their major drawbacks are related to numerous drug-drug interactions and variability in metabolic clearance at the level of the CYP3A4 and CYP3A5 (approximately five-fold). Consequently, prolonged sedation, respiratory depression, memory disturbances and other cognitive impairments may occur, particularly in the elderly and patients with liver or renal dysfunction[10].

In contrast to these long-lasting and poorly predictable sedative effects, propofol (P), - a lipid formulation of 2,6 di-isopropylphenol -, provides a more rapid onset of sedation after delivery and a faster recovery. Several clinical studies have demonstrated the superiority of propofol compared to midazolam regarding recovery of alertness, memory and motor function [11, 12]. Thus, there is a keen interest in the use of P in ambulatory practice. While P is commonly and safely used in gastro-enterological endoscopic procedures, its use by the pneumologist is currently hampered by minimal experience with the drug and lack of collaboration with the anaesthesia team [13-17].

The main purpose of this study was to compare patient's subjective tolerance, recovery of brain function and safety of use after intravenous administration of P and M by bolus during FB using bispectral index as an objective tool for measuring the depth of sedation.

METHOD

Study design

This was a prospective, randomised and controlled study. The institutional review board at each study site approved the protocol. Written informed consent was obtained from all participants before inclusion in the study. The study protocol has been registered at clinical trials.gov (Number NCT00839371)

Subjects

From May 5 2006 until June 3 2007, 124 patients referred for diagnostic FB were recruited at the Centre Valaisan de Pneumologie in Montana and at the University Hospitals of Geneva. Patients undergoing endoscopic procedures such as trans-bronchial biopsies or advanced techniques (endo-bronchial ultrasound [EBUS], auto-fluorescence, etc.) were excluded because of important technical and procedural differences between the two centres and their time-consuming character. Patients $\geq$ 18 and < 80 years of age and with an American Society of Anaesthesiology (ASA) class of risk I to III (ASA) were considered eligible for study enrolment. Exclusion criteria included the following items: psychological disorders, female patients of child-bearing age, hypersensitivity or allergy to soya, anaesthetic drugs or benzodiazepine, severe chronic obstructive pulmonary disease (FEV_1 < 50% of predicted value, requirement for oxygen therapy), unstable haemodynamic status (defined as a heart rate [HR] < 60 or $\geq$ 120 and/or a systolic blood pressure [BP] < 100 or > 180 mmHg) and any signs of systemic or pulmonary infection. Other exclusions were patients with predictable difficult upper airways (Mallampati classification score of III or IV).

Study procedures

Following completion of the preprocedural assessments, eligible patients were randomly assigned to the M or P group using sealed and opaque envelopes in a 1:1 allocation ratio.

All patients were equipped with an intravenous line for fluid infusion and were monitored by continuous ECG for heart rate (HR) and rhythm, pulsed arterial oximetry (SaO_2) and non-invasive blood pressure. Processed EEG parameters were acquired with a BIS monitor, using Zip prep surface electrodes, with impedance maintained at less than 5kΩ to ensure adequate signal quality (AXP-2000 monitor, 3.11 version software; Aspect Medical Systems, Newton, MA). Raw EEG data from two channels (F_7-C_Z and F_8-C_Z) were processed by company proprietary software and the BIS values (calculated for each 4-sec epoch) were continuously displayed along with the trend line. A study nurse, blinded to the study drug allocation was trained for proper use of all monitoring devices, including the BIS monitor.

For each procedure, the staff consisted of a chest physician trained in FB (operator), a physician in charge of sedation and two nurses for technical assistance and proper data recording. The operator was unaware of the study drug administration as the syringes and connecting lines were masked. Oxygen was administered only if SaO_2 was < 92%.

Before starting sedation, lidocaïne was administered topically on the pharynx and upper airways and intravenously (50 mg) to prevent drug-induced pain upon injection. Thereafter, sedation was started by injecting a 4 ml drug bolus (40 mg of P or 2 mg of M). Supplemental doses of drugs (20 mg of P or 2 mg of M) were administered at an interval of $\geq$ 2 min to achieve and maintain BIS index between 70 and 85 [18, 19]. This 2-min time interval between each bolus was based upon previous studies[12, 20]. The operator inserted the bronchoscope when the target sedation level was reached. The patient's level of sedation was assessed using the BIS index and the 5-grade Observer Assessment of Alertness/Sedation score (OAA/S; 5=appropriate verbal response to patient's name, 4=lethargic response, 3=response only after name is spoken loudly and/or repeatedly, 2=response after mild prodding or shaking, 1=response after painful stimuli, 0=no response at all).

Besides BIS index and OAA/S score, blood pressure, SaO_2, and HR, were recorded every 3 minutes during the procedure and at 5, 15, 30, 45 and 60 minutes thereafter.

The time necessary to achieve the targeted BIS value after drug injection, the duration of FB, the BIS index recovery time (defined as the time to reach a BIS value > 90) and total doses of M and P were all noted. The cardiopulmonary safety profile was determined by collecting the following adverse events during FB: hypotension (systolic BP < 100 mmHg or mean arterial blood pressure (MAP) < 60 mmHg), tachycardia (HR > 100/min and/or a variation of > 20% from baseline value), oxygen desaturation (SaO_2 decrease < 90% for > 30 s), bradycardia (HR < 50/min).

At 1 hour and 24 hours after FB, the operator and patient, both blinded to the allocation group evaluated 1) the global tolerance to the procedure and 2) the intensity of 4 key symptoms during FB (pain, nausea, breathlessness and cough) using a visual analogic scale (VAS: 1 mm: excellent tolerance, 100 mm very low tolerance)

Recovery of neuropsychometric capacities was also assessed 15 min and 60 min after the end of the procedure by a continuous performance test (CPT) [21, 22]. In this standardized computer generated test, the subject was instructed to respond by pressing a computer key, to a specified visual stimulus or target (letters A to Z) appearing randomly on a computer screen. Each letter was shown during 250 ms and the interval between the two letters was 1 sec. Over the course of the test (7 minutes), the subject was asked to press a key only when the letter appearing on the screen was the same as the previous one. Each subject was exposed to 335 letters with 170 successful changes. The maximum number of missed targets or omissions errors (OE) possible was 170. The maximum number of false hits or commission errors (CO) possible was 335-170 = 165. These values were recorded by the computer and a score ranging from 0 and 100 was calculated by dividing OE by 170 and CO by 165. A higher score indicated a greater degree of error. These scores define CPT results used in this study.

Reaction time (RT) was also recorded. It measured the amount of time between the presentation of the stimulus and the patient's response. A slow reaction time with high commission and omission errors indicates patient inattention.

Study endpoints

The primary endpoint was the time delay from the end of the procedure until recovery of BIS index > 90. Previous studies have demonstrated a good correlation between the BIS index (linear scale from 100 to 0) and clinical sedation scores as assessed by the OAA/S score during the administration of P or M [18, 19, 23, 24].

The secondary endpoints were the patient's subjective tolerance, operator evaluation of patient tolerance and cardiopulmonary adverse events rate.

Statistical analysis

The sample size was calculated for a two-sided significance α level of 0.05 and a power of 0.8 to detect a 35 percent difference in recovery time between the two groups. In previous studies comparing M and P for outpatient fibroscopy, the average (±SD) recovery time was around 10-12 min (±5 min); thus the minimum number of subjects was 35-40 per group [12, 20]. Results are expressed as mean values with standard deviation, and median values with interquartile range. Parametric tests and Wilcoxon test, when appropriate, were used to assess differences between the groups. Analysis of the differences between the M and P groups were carried out with robust linear regression models for CPT and tolerance to FB results at 15 min and 60 min and a logistic mixed model for OAAS scores. We applied fixed effects for the sedation group and a random effect for patients. A p value < .05 was considered as statistically significant. Recovery time after FB was compared between groups with t-test for unequal variances. It must be emphasized that some patients were unable to complete CPT at 15 min (6 patients) and 60 min (1 patient) after the procedure, and their score of correct,

wrong or missed answers is thus not included in the analysis. For these cases, we attributed a reaction time value of 1000 milliseconds to consider them in the analysis of the reaction time. We evaluated the overall correlation between OAAS and BIS score with an R-squared value obtained from linear regression models with the study patients as a random effect variable. Statistical analyses were performed with STATA 10 (College Station, Texas, USA).

RESULTS

Baseline characteristics

Out of 124 patients, 84 were randomized (**figure 1**). Two patients in the M group were excluded from the final analysis because of emergency intubation (n=1) and gag reflex precluding the introduction of the bronchoscope in the trachea (n=1). At baseline there was no difference between both groups (**table 1**).

The time necessary to achieve the targeted BIS value (70-85) after the injection of the sedative drug before starting the FB (T_{IB}), duration of FB and mean dose of M and P necessary to achieve and maintain the chosen sedation depth according to BIS during FB are shown in **table 2**.

Overall, the R-Squared value between OAA/S score and BIS measurements was 0.49 for both groups during the procedure.

Recovery parameters after bronchoscopy

The electroencephalographic recovery time (BIS value > 90) was shorter in the P group than in the M group (5.4 ± 4.7 min vs 11.7 ± 10.2 min, p = .001). In addition, the rate of patients with a BIS value > 90 or an OAA/S score = 5 (i.e. awake) at any time after the FB was significantly higher after P than M sedation (**figure 2 and 3**).

The cognitive recovery evaluated by CPT at 15 min after FB also showed striking and significant differences for all tested items in favour of the P group. At 60 min, no difference was apparent between the groups except the rate of incorrect responses and the reaction time, which remained statistically lower in the P group (**table 3**). In the M group only, 6/39 (15 %) and 1/39 (3 %) patients at 15 and 60 minutes after FB respectively were unable to complete the CPT trial because of profound sedation. We performed additional comparisons between M and P using non parametric tests, which yielded a similar interpretation on the differences between groups.

Tolerance

The immediate tolerance of FB, as assessed by the patient, was better on most items with P than M and significantly better on the items "Pain", "Nausea" and "breathlessness" (**table 4**). At 24 hours after the procedure global patient satisfaction was still better in the P group, whereas the operator's assessment was similar in the two groups.

Adverse events

Two patients in the M group required ventilatory support due to oxygen desaturation. A 77-year old obese woman with moderate chronic obstructive lung disease required intubation. One other patient with an important gag reflex needed manual ventilation and the endoscopic procedure was postponed. All other desaturation events were transient and easily corrected with nasal oxygen administration. Apart from the two cases above, there was no difference between the two groups (**table 5**).

DISCUSSION

In this trial, we found that propofol is superior to midazolam to enhance patient tolerance, to shorten recovery time and to facilitate return to baseline neurological function after FB. Indeed, recovery time after sedation is impressively faster after P compared to M. Both sedation techniques appear safe and enhance the completion rate of the procedure.

Propofol sedation guided by BIS during FB proved to be safe, confirming results from previous studies[12, 14, 15, 17, 20, 25]. However, the good correlation between OAA/S score and BIS monitoring during the procedure suggests that the OAA/S alone may be sufficient to estimate level of sedation in clinical practice.

The complication rate was similar in both groups, consisting mainly of easily remedied temporary episodes of O_2 desaturation and tachycardia. Indeed, O_2 had been weaned rapidly at the end of the FB in most cases or within 60 minutes for the remaining patients. The causes of O_2 desaturation during FB are manifold (e.g., ventilation-perfusion mismatch due to fluid instillation, and excessive secretions) and were not exclusively due to hypoventilation secondary to sedation, since this has also been observed during procedures without sedation [4]. The time to reach the target value of sedation (BIS value 70 to 85) before starting the FB was not faster for P than for M, contrary to what drug pharmacokinetics and some studies might suggest[10, 11, 20], yet in agreement with other findings[12]. Further, the use of BIS did not induce a change in the average doses of P and M (1.9 mg / kg and 0.08 mg / kg respectively) used in our study, when compared to other studies using only clinical scores as assessment of sedation depth[2, 12, 20, 26]. The slower recovery time and the relatively persistent confusional state after M (15% of patients were unable to perform the cognitive tests after FB in the M group and none in the P group) cannot be explained by an exaggerated use of M as the dose we used was in the lower range of that recommended in previous guidelines and lower than certain prescription habits in other institutions [2, 27].

We have also shown the intravenous administration of initially lower doses of sedatives by bolus followed by regular increments, to be a simple and safe option, not requiring the use of an infusion pump or target controlled infusion device, as used in other studies [12]. Our study confirms previous findings obtained using clinical sedation scores by incorporating objective measurements of brain activity using the BIS technology: The average recovery time was significantly faster for P than for M. All patients were alert very quickly after P contrasting with the slower time of recovery after M. Within 10 minutes after the end of the procedure, nearly 90% of patients had recovered in the P group versus 50% in the M group. As most endoscopic procedures are performed on an outpatient basis, the use of P may increase cost-effectiveness as the duration of monitoring after FB is much shorter when using P, counterbalancing its higher cost.

In addition, measuring the objective time of recovery using the BIS index and performing repeated CPT may enrich further studies, as they allow the objective testing of neurological recovery after sedation [21]. The comparison of both groups showed this clear advantage for P on all items tested at 15 minutes and for some at 60 minutes. That study was not designed to evaluate attentional deficits on usual daily tasks such as driving or working after FB. These are most probably only measurable with other more precise and specific neuropsychological tests

Patient's tolerance to the procedure was excellent in both groups with a slight but significant advantage for P. Our study confirms that sedation offers a high degree of satisfaction for the patient without compromising safety.

Interestingly, the assessment related to the tolerance of the procedure differed between patient and operator. In other words, physicians tended in our study to underestimate the tolerance of FB, emphasizing the amnesic properties of both drugs.

Some aspects of our study need to be addressed. First, sedation was performed by a second physician trained in the use of P and not by a nurse as is usual practice with M. This may result in additional costs. Managing BIS-guided sedation by trained nurses seems to be safe for gastroenterologic procedures provided adequate protocols are established in collaboration with the anaesthesia team [28-30] Another limitation of our study relates to the short time of most procedures. This may preclude conclusions regarding longer procedures such as ultrasound guided trans-bronchial needle aspiration or autofluorescence.

In conclusion, this study shows that, with appropriate training, titrated sedation with P using BIS index for FB in an ambulatory setting is safe, can be performed by the non-anaesthetist and allows for greater patient satisfaction. The better neurological recovery with P may allow shorter stay in hospital, representing a potential economical benefit. We believe that P could be the first choice drug for providing sedation in patients undergoing bronchoscopic procedures.

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TABLES

Table 1:
Baseline clinical characteristics, anthropometric data and Continous Performance Test results before bronchoscopy.

		Midazolam (n=39)	**Propofol (n=43)**
sex	Male, n (%)	28 (72)	27 (63)
	Female, n (%)	11 (28)	16 (37)
ASA class	I, n (%)	18 (46)	14 (33)
	II, n(%)	17 (44)	26 (60)
	III, n (%)	4 (10)	3 (7)
Base	Age	55.2 (14.3)	57.9 ± 11.4
	Weight (kg)	71.6 ± 12.4	74.9 ± 15.6
	Systolic BP (mmHg)	136.5 ± 18.5	135.8 ± 16.6
	Diastolic BP (mmHg)	80.1 ± 10.1	82.1 ± 11.7
	Heart Rate(min^{-1})	79.5 ± 17.8	73.6 ± 12.3
	SaO_2 (%)	96.0 ± 3.7	95.8 ± 2.9
CPT results	CE score	8.2 (14.8)	8.1 (15.7)
	OE score	13.4 (15.0)	10.7 (8.9)
	Reaction time (ms)	463.9 ± 73	452.9 ± 128.0

Baseline data are presented as mean±SD. CPT results: CE and OE score and reaction time as are expressed as mean±SD.
BP = blood pressure; CPT = continuous performance test; OE = omission error or missed target; CE = commission error or false hit; ms = millisecond. For CE and OE score: 0 = best score and 100 worst score.

Table 2:
Bronchoscopy and sedation parameters

	Midazolam (n=39)	**Propofol (n=43)**	p value*
T_{IB}	2.3 (1.3)	2.4 (1.7)	0.731
FB duration	12.2 (9.9)	12.4 (9.6)	0.368
Recovery time after FB (BIS > 90)	9.5 (15.6)	3.8 (7.2)	0.010
Drug dose (mg)	6.2 ± 2.7	135.1 ± 71.7	----

*Wilcoxon test.
Data are presented as median and interquartile range in parentheses for T_{IB}, FB duration and recovery time and mean with standard deviation for drug dose; Time value are expressed in minutes. T_{IB} = Time from sedative drug injection to start of bronchoscopy, FB = flexible bronchoscopy.

Table 3:
Continuous performance test results at 15 and 60 minutes after bronchoscopy in both groups

		Midazolam (n=39)	Propofol (n=43)	Difference (95%CI)	p value
CPT results 15 min after bronchoscopy	CE score	22.5 (13.1)	12.2 (10.7)	-10.3 (-15.7 ; -0.5)	<0.001*
	OE score	22.7 (16.1)	15.2 (13.6)	-7.5 (-14.2 ; -0.6)	0.032*
	Unable to complete, n	6	0		
	Reaction time, ms	486 (161)	450 (114)		0.011†
CPT results 60 min after bronchoscopy	CE score	19.2 (16.7)	12.0 (12.9)	-7.2 (-13.7 ; -0.6)	0.032*
	OE score	16.6 (11.8)	13.1 (11.4)	-3.4 (-0.9 ; 1.7)	0.186*
	Unable to complete, n	1	0		
	Reaction time, ms	464 (96)	429 (136)		0.043†

* Differences between groups and p values derived from robust linear regression using score as dependent variable and group as independent variable.
†: Wilcoxon test.
CPT results: CE, OE scores are expressed as mean and standard deviation. Reaction time is expressed as median and interquartile range in parentheses. CPT = continuous performance test; CE = commission error or false hit, OE = omission error or missed target; ms = millisecond. For CE and OE score: 0 = best score and 100 worst score.

Table 4:
Tolerance to bronchoscopy as assessed by the patient and the operator with a visual analogic scale (VAS)

		Midazolam (n=39)	Propofol (n=43)	Difference (95%CI)	p value*
Global tolerance	Patient 60 min	15.2 (18.7)	8.4 (11.1)	-6.8 (-13.5; 0.1)	0.051
	Patient 24 h	14.3 (16.7)	7.9 (8.7)	-6.4 (-0.4; -12.2)	0.036
	Operator	16.2 (17.4)	22.7 (24.9)	+6.5 (-2.9; 15.9)	0.171
Pain	Patient 60 min	8.8 (13.0)	3.9 (4.1)	-4.9 (-9.2; -0.6)	0.026
	Patient 24 h	8.1 (12.0)	4.8 (4.8)	-3.4 (-7.4; 0.7)	0.106
Nausea	Patient 60 min	7.7 (13.4)	3.2 (4.7)	-4.6 (-9.0; -0.1)	0.047
	Patient 24 h	8.9 (15.7)	4.3 (7.0)	-4.6 (-10.0; 0.8)	0.097
Breathlessness	Patient 60 min	13.3 (23.6)	4.4 (5.9)	-9.0 (-16.4; -1.2)	0.024
	Patient 24 h	12.3 (20.6)	5.9 (8.2)	-6.4 (-13.4; 0.64)	0.074
Cough	Patient 60 min	18.4 (23.5)	18.0 (20.9)	-0.3 (-10.2; -9.5)	0.946
	Patient 24 h	16.4 (19.1)	18.1 (21.3)	+1.6 (-7.3; -10.5)	0.715

Visual analogic scale: 0 mm corresponds to excellent tolerance and 100 mm to very low tolerance.
* p values derived from robust linear regression using VAS score difference as dependent variable and group as independent variable.
Results are expressed as mean and standard deviation in parentheses.

Table 5:
Adverse events for both groups during bronchoscopy

	Midazolam (n=39)	Propofol (n=43)	p value*
Hypotension (%)*	0	2 (4.7)	0.495
Tachycardia (%)[+]	11 (28.2)	7 (16.3)	0.285
Hypoxemia (%)[§]	14 (35.9)	15 (34.9)	1
Bradycardia (%)	0	0	1

*: Systolic BP < 100 mmHg or mean arterial blood pressure (MAP) < 60 mmHg), +: HR > 100/min and/or a variation of > 20% from baseline value. §: SaO_2 decrease < 90% for > 30 second. HR < 50/min. * Fischer's exact test
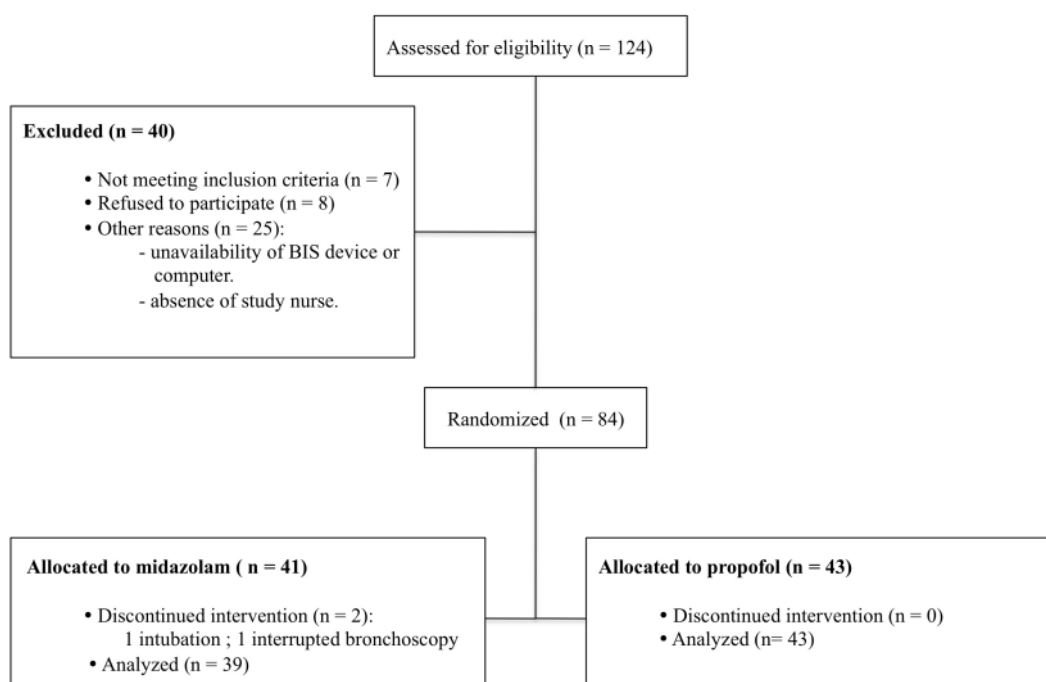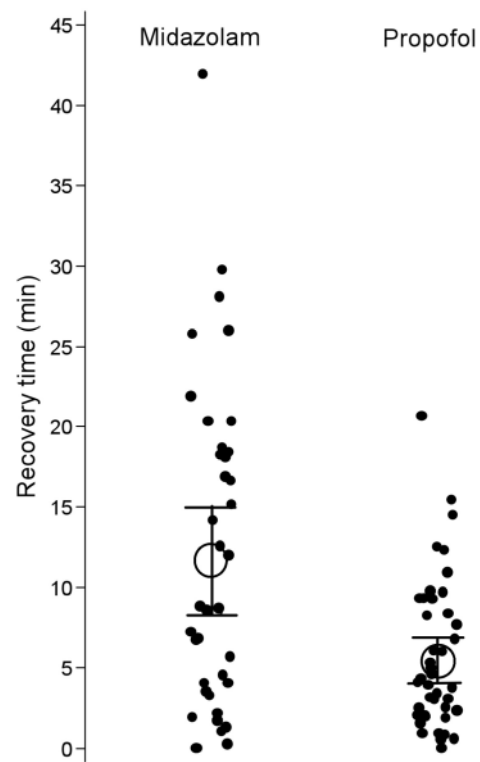
Figure 1

Figure 2

Figure 3