ORIGINAL ARTICLE

Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients

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Summary

To date, the dosing of sugammadex is based on real body weight without taking fat content into account. We compared the reversal of profound rocuronium-induced neuromuscular blockade in morbidly obese patients using doses of sugammadex based on four different weight corrections. One hundred morbidly obese patients, scheduled for laparoscopic bariatric surgery under propofol-sufentanil anaesthesia, were randomly assigned four groups: ideal body weight; ideal body weight + 20%; ideal body weight + 40%; and real body weight. Patients received sugammadex 2 mg.kg^{-1}, when adductor pollicis monitoring showed two responses. The primary endpoint was full decurarisation. Secondary endpoints were the ability to get into bed independently on arrival to the post-anaesthetic care unit and clinical signs of residual paralysis. There was no residual paralysis in any patient. Morbidly obese patients can safely be decurarised from rocuronium-induced neuromuscular blockade T1-T2 with sugammadex dosed at 2 mg.kg^{-1} ideal body weight + 40% (p < 0.0001).

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The incidence of morbid obesity (defined as body mass index (BMI) > 40 kg.m^{-2}) is 2–5% in Western populations. The introduction of bariatric surgery has been a considerable breakthrough in the treatment of these patients [1]. For such patients, calculation of an appropriate drug dose is a problem. Pharmacokinetic studies show that weakly lipophilic drugs such as rocuronium should be dosed on ideal body weight (IBW), rather than real body weight (RBW) [2]. The pharmacokinetic profile of sugammadex is similar to that of rocuronium, despite the fact that sugammadex has no affinity for plasma proteins. Sugammadex dosage is usually based on RBW without taking fat content into account. Morbidly obese patients have a large amount of fat. Drug dosage according to total body water may lead to overdose for this group. We compared the reversal of profound rocuronium-induced neuromuscular blockade in morbidly obese patients using doses of sugammadex adjusted on the basis of three different weight corrections in addition to real body weight.

Methods

The study was approved by the AZ Sint-Jan Brugge-Oostende AV Hospital Ethical Committee. One hundred morbidly obese patients (BMI > 40 kg.m^{-2}) scheduled for laparoscopic bariatric surgery gave written informed consent to participate. Patients were aged between 19 and 60 years old. They were randomly assigned into four groups: (1) IBW; (2) IBW + 20%; (3) IBW + 40% and (4) RBW. Ideal body weight is defined as (height (cm)–110) for women and (height − 100) for men [3].

Exclusion criteria were a history of neuromuscular disease, use of drugs interfering with neuromuscular transmisstion, allergy to neuromuscular blocking agents, known intubation problems, and a creatinine level > 159 μmol.l^{-1}.

During anaesthesia and surgery, routine monitoring included an automated blood pressure cuff, ECG, pulse oximetry, capnography and nerve stimulation to monitor neuromuscular blockade.

Before induction, all patients were given 100% oxygen and baseline haemodynamic variables were recorded. Induction of anaesthesia consisted of IV sufentanil 1 μg.kg^{-1} followed by IV propofol 2.5 mg.kg^{-1} administered over 2 min. Tracheal intubation was facilitated with rocuronium 0.6 mg.kg^{-1} and anaesthesia was maintained with propofol by continuous infusion, and 66% nitrous oxide in oxygen. Propofol maintenance was started at 200 μg.kg^{-1}.min^{-1} and was adjusted according to blood pressure and heart rate. All drug doses were calculated based on IBW. Additional doses of 5–10 mg rocuronium were given to keep a single twitch (T1) response at the adductor pollicis on train of four (TOF) stimulation of the ulnar nerve.

All neuromuscular monitoring was conducted according to the guidelines established by Good Clinical Research Practice in pharmacodynamic studies of neuromuscular blocking drugs [4]. To monitor neuromuscular activity, the patients' study arm was immobilised with a splint. An accelerator transducer was taped to the distal interphalangeal joint of the thumb. The study arm was positioned so that free movement of the thumb occurred during nerve stimulation. Supramaximal (50-mA) square-wave TOF stimulation was delivered to the ulnar nerve via surface electrodes at 15-s intervals. Core temperature was measured and maintained with blankets applied to the arm. Forced-air warming of the arm was used if necessary. Temperature was maintained between 35.5 and 37.0 °C.

After surgery, when TOF responses were T1–T2, sugammadex was given for reversal of rocuronium-induced muscular blockade. Patients received sugammadex 2 mg.kg^{-1} as determined by randomisation group (IBW, IBW + 20%, IBW + 40%, RBW) independent of the total amount of rocuronium administered. Anaesthetists were not blinded to group identity or sugammadex dose because they were responsible for the correct dosage of drugs. The primary endpoint was full decurarisation. Recovery was defined as a TOF ratio > 0.9. The period of time from injection of sugammadex to TOF ratio > 0.9 is named 'sugammadex time' in this study.

Tracheal extubation was performed only when patients met the following criteria: able to protect their airway; opening eyes; acceptable oxygen saturations; tidal volumes of more than 10 ml.kg^{-1} IBW; and minute volumes of more than 100 ml.kg^{-1} IBW. The period of time between injection of sugammadex and extubation is named 'extubation time' in this study.

During the patient's stay in the post-anaesthetic care unit (PACU), nurses blinded to the study drug dosage recorded the following parameters: independent or assisted transfer from the theatre-table to bed; clinical signs of residual paralysis upon arrival to the PACU (head tilting and hand squeezing); incidence of nausea or vomiting; visual analogue scale pain scores (0 = no pain, 10 = worst possible pain); and recovery scores based on the 6-point scale described by Steward [5]. A score of 0, 1, or 2 was assigned to each of three parameters: (1) level of sedation; (2) adequacy of ventilation; and (3) motor activity. The patients were assessed on arrival to the PACU, and every 15 min thereafter for 45 min.

Patients received 1 g paracetamol IV and 200 mg prophylactic alizapride on arrival. Patients who reported a pain score > 3 received rescue analgesia consisting of piritramide IV in 5-mg increments. Patients who suffered from nausea or vomiting received rescue antiemetics consisting of ondansetron 4 mg IV. Patients were discharged from PACU only if they had a Steward score of 6 and pain, nausea and vomiting were under control. They stayed in the PACU for at least 2 h.

Preliminary power analysis revealed that for one-way ANOVA with four groups, a sample size of 25 subjects in each group was required to establish the statistically significant difference in 'sugammedex time'. One-way ANOVA statistical analysis was used with significance level $p < 0.05$ for analysis of time intervals between groups.

Results

Baseline characteristics of the patients are shown in Table 1. Patients in the four groups were similar with respect to sex, age, RBW, BMI, lean body mass (fat-free mass) and fat mass (Table 1). The times from administration of sugammadex until appearance of TOF ratio > 0.9, extubation and eye opening are shown in Table 2. There was no statistically significant difference in reversal time between IBW + 40% and

Table 1 Baseline patient characteristics. Ideal body weight (IBW) was determined using the formula of Broca [3]. Fat-free mass and fat mass were measured using electrical impedance. Values are number or mean (SD).

	IBW	IBW + 20%	IBW + 40	RBW
Female∕male	18∕7	17∕8	17∕8	19∕9
Age; years	44.3 (12.9)	46.4 (10.1)	41.8 (14.2)	43.2 (7.4)
RBW; kg	115.8 (22.6)	120.6 (17.7)	120.5 (16.7)	118.8 (15.1)
BMI; kg.m^{-2}	43.6 (3.8)	43.6 (4.1)	44.2 (4.2)	41.4 (2.4)
IBW; kg	60.6 (15.4)	59.3 (12.8)	60.0 (10.3)	63.4 (12.0)
Fat-free mass; kg	66.7 (18.8)	62.2 (13.7)	64.3 (11.9)	64.5 (13.0)
Fat mass; kg	46.3 (5.7)	47.9 (5.1)	45.5 (5.7)	45.4 (5.1)

RBW, real body weight; BMI, body mass index.

Table 2 Comparison of sugammadex time, extubation time and time to opening eyes. Values are mean (SD).

	IBW	IBW + 20%	IBW + 40%	RBW	F	p-value
Sugammadex time; s	188.9 (84.4)	154.6 (59.7)	112.5 (30.3)	128.8 (47.0)	8.042	< 0.0001
Extubation time; s	318.4 (122.0)	306.9 (184.7)	255.1 (119.9)	326.8 (107.9)	1.381	0.253
Eye opening; s	358.9 (150.9)	330.4 (229.2)	285.9 (147.4)	345.8 (123.9)	0.897	0.446

RBW, real body weight.

Table 3 Ideal body weight (IBW), IBW + 20%, IBW + 40%, RBW, actual dose and calculated dose real body weight (RBW) in the four groups. Values are mean (SD).

	IBW	IBW + 20%	IBW + 40%	RBW
IBW; kg	60.6 (15.4)	59.3 (12.8)	60.0 (10.3)	63.4 (12.0)
IBW + 20%; kg		65.5 (24.6)		
IBW + 40%; kg			73.9 (31.0)	
RBW; kg	115.8 (22.6)	120.6 (17.7)	120.6 (16.8)	119.0 (15.1)
Actual dose; mg	119.6 (31.0)	143.1 (32.8)	162.3 (20.8)	236.4 (35.5)
Calculated dose RBW; mg	231.8 (48.0)	243.3 (37.1)	241.0 (34.2)	236.5 (33.5)

RBW. Reversal times in IBW and IBW + 20% were prolonged compared to IBW + 40% and RBW (IBW and IBW + 40%, p = 0.0001; IBW and RBW, p = 0.004; and IBW + 20% and IBW + 40%, p = 0.003). Table 3 shows IBW, RBW, actual dose of sugammadex and calculated dose based on RBW in each of the four groups. There is no statistical significant difference between IBW in the four groups. The administered doses (actual dose) in group IBW, IBW + 20% and IBW + 40% are respectively 50%, 40% and 33% lower compared to the calculated doses.

Upon arrival in the PACU, 91 patients had a Steward score of more than 3 and were considered well oriented. All patients had a Steward score of 6 at the time of discharge from the PACU. None of the patients complained of muscle weakness during their PACU stay. Analysis of these variables did not show any statistically significant difference among the four groups.

On arrival in the PACU, 42% of the patients in the IBW group, 59% in the IBW + 20% group, 50% in the IBW + 40% group and 52% in the RBW group were able to get into bed by themselves. There were no statistically significant differences among the groups.

Discussion

Sugammadex is a drug with a weakly lipophilic pharmacokinetic profile. The distribution of the drug between fat and lean body mass may influence pharmacokinetics in obese patients. Lean body weight is the difference between RBW and fat mass (weight of all organs, bone and muscles without fat). Obese patients have both an increased amount of fat and lean body weight compared with non-obese patients of similar age, height and sex. The increase in lean body weight (LBW) can account for as much as 20–40% of the excess RBW [6, 7]. This suggests that LBW is the ideal weight scalar for drug administration in morbidly obese patients. Nevertheless, accurately measuring LBW is relatively difficult under normal clinical circumstances.

Similar to other water-soluble molecules, such as lithium and rocuronium [2], the sugammadex dose should be based on IBW. There are numerous formulae and height–weight tables available to determine IBW. The ideal weight of a person is the weight believed to be optimal for health. Primarily, it is based on height but other considerations include sex, age, body frame size and lean body mass. The BMI or Quetelet index, obtained when body weight is divided by the square of its height, is a widely used diagnostic tool to identify weight problems. A BMI of 18.5–25 $kg.m^{-2}$ indicates optimal weight. However, BMI is not ideal for drug dosage for obese patients as it leads to overdosing. Numerous equations exist to calculate IBW, all of which show general agreement. Table 1 shows that the differences between IBW using Broca's formula and LBW (or fat free mass) using electrical impedance were 6.6% and not in accordance with the results of Savarese et al. [6], or Forbes and Welle [7]. We used the method of Broca [3] that easily calculates IBW for men and women. For the IBW group and the IBW + 20% group, the time from T1 to T2 to T4/T1 > 0.9 is significantly longer than in the IBW + 40% group and the RBW group; suggesting that IBW + 40% is the ideal formula for the dosage of sugammadex in obese patients.

Sorgenfrei et al. [8] found a median time for reversal of rocuronium-induced blockade of 78 s in non-obese patients at a sugammadex dose of 2 $mg.kg^{-1}$. In this study, we observed longer times. As stated by Savarese et al. [6], this can be explained by differences in LBW and body composition of obese patients compared to non-obese patients, or by differences in methodology.

There is conflicting evidence concerning the effects of obesity on pharmacodynamics of other medications with poor lipophilic profiles. Weinstein et al. [9] found no prolonged action of atracurium in obese patients when the dose was based on RBW, whereas Kierkegaard and Nielsen [10] found a prolonged action of atracurium. Body composition and fat deposition may differ within individuals with the same BMI, and differences can also be explained by the limited number and large inter-individual differences of the patients studied by Weinstein et al. In this study, inter-individual differences in weight were controlled as we included only patients with a BMI > 40 $kg.m^{-2}$. Upper boundary was BMI 55.8 $kg.m^{-2}$ and 32 patients had BMI > 45 $kg.m^{-2}$.

Approximately 50% of the patients in each group were able to get into bed by themselves on arrival in the PACU. This finding is of clinical importance because transfer of morbidly obese patients is often difficult and requires special lifting devices. It was also clinically evident that these patients were fully decurarised and fully mobile.

Obese patients are at higher risk for postoperative pulmonary complications [11]; therefore, tracheal extubation must be carefully considered. A conservative approach is strongly recommended to achieve maximum stability before proceeding to tracheal extubation. For this reason, patients' tracheas were only extubated when they met the criteria as described in the Methods section. No free airway or extubation problems were seen in this study.

Even for patients in the IBW group, the sugammadex dose of 2 $mg.kg^{-1}$ IBW succeeded in producing full decurarisation. One of our major concerns was the detection of recurarisation. Eleveld et al. [12] described recurarisation as the result of inadequate sugammadex dosage. In their study, 0.5 $mg.kg^{-1}$ was given instead of 4 $mg.kg^{-1}$ as recommended based on post-tetanic count response. At 0.5 $mg.kg^{-1}$ dosing, sugammadex is sufficient to form complexes with rocuronium molecules in the central compartment, but insufficient to sustain redistribution of rocuronium from the peripheral to the central compartment. We did not experience recurarisation in our study. Presumably, the doses of sugammadex under the study conditions were large enough to prevent muscle relaxation rebound.

In conclusion, morbidly obese patients can be safely decurarised from rocuronium-induced neuromuscular blockade with IBW-based sugammadex dosage. This study suggests optimal dosing of sugammadex at 2 $mg.kg^{-1}$ IBW + 40%.

Competing interests

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