Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Different conflicting reports have been published for the use of atracurium in morbidly obese patients. Dosing of atracurium based on lean body mass, total body weight, and total body weight with a dose reduction for every 10 kg more than 70 kg have been proposed.

WHAT THIS STUDY ADDS

- The current prospective randomized double-blind study compares atracurium 0.5 mg kg⁻¹ ideal body weight vs. 0.5 mg kg⁻¹ total body weight when used as a muscle relaxant in morbidly obese patients undergoing bariatric surgery. Based on our results in patients with body weights varying from 112 to 260 kg, we have concluded that atracurium 0.5 mg kg⁻¹ ideal body weight results in a predictable profile of muscle relaxation allowing for adequate intubation conditions and recovery of muscle strength within 60 min with lack of need for antagonism. A dose-dependent prolongation of action is shown when dosing is based on total body weight.

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AIMS

This double-blind randomized study evaluated atracurium dosing based on ideal body weight vs. total body weight for muscle relaxation in morbidly obese patients undergoing bariatric surgery.

METHODS

Twenty patients (body weight 112–260 kg, BMI 38–79 kg m⁻²) were randomized to receive atracurium 0.5 mg kg⁻¹ ideal body weight vs. 0.5 mg kg⁻¹ total body weight. Primary endpoint was neuromuscular blockade using train-of-four ratios (TOF ratios) and secondary endpoints were intubation conditions and need for antagonism with neostigmine.

RESULTS

In the ideal body weight group, times to recovery of TOF ratio from 0 to 5%, 50% and 75% were significantly shorter [TOF ratio from 0 to 5%: mean difference 30 min (95% CI 23, 39 min)] and with lower variability compared with the total body weight group. In the total body weight group there was a significant correlation between atracurium dose and time to a TOF ratio of 5% ($r = 0.82$, $P < 0.001$), which was absent in the ideal body weight group ($r = 0.24$). In both groups, intubation conditions were good while 70% of the patients in the total body weight group needed neostigmine at the end of surgery compared with 0% in the ideal body weight group.

CONCLUSION

In morbid obesity (112–260 kg), atracurium 0.5 mg kg⁻¹ ideal body weight results in a predictable profile of muscle relaxation allowing for adequate intubation conditions and recovery of muscle strength to a TOF ratio >90% within 60 min with lack of need for antagonism. A dose-dependent prolongation of action is shown when dosing is based on total body weight.

Introduction

Atracurium is a commonly used non-depolarizing neuromuscular blocking agent whose disposition depends on Hofmann elimination and non-specific esterase hydrolyses, and is independent of liver and kidney function. Different conflicting reports have been published for the use of atracurium in morbidly obese patients. As a result, dosing of atracurium based on lean body mass [1, 2], total body weight [3] and total body weight with a dose reduction for every 10 kg more than 70 kg have been proposed [4].

While a muscle relaxant is used to obtain adequate intubation conditions, at the time of recovery muscle strength should be recovered fully to allow for spontaneous respiration. This is of special importance in morbidly obese patients, as these patients are prone to desaturation and apnoea. A relevant question in this respect is whether higher doses of atracurium are needed in morbidly obese patients, and if so, how this dose should be elevated with increasing body weight.

Therefore, the aim of this randomized double-blind study was to evaluate the time course of atracurium effect when atracurium is dosed on ideal body weight vs. total body weight in morbidly obese patients, who were stratified in five body weight groups (100–120, 120–140, 140–160, 160–180 and >180 kg). The effects of these two doses were evaluated by the use of the neuromuscular train-of-four (TOF) monitor and by intubation conditions and need for antagonism with neostigmine.

Methods

Patients

Twenty morbidly obese patients scheduled to undergo bariatric surgery were prospectively studied. Inclusion criteria were age between 18 and 60 years, American Society of Anaesthesiologists (ASA) physical status classification II or III, a BMI of over 35 kg m⁻² at inclusion together with an indication for weight-reducing surgery and normal renal and hepatic function assessed by routine laboratory testing. Exclusion criteria were pregnancy, neuromuscular disease, treatment with medication known to interfere with neuromuscular transmission and known allergy to atracurium besylate or benzene sulphonic acid. The study was approved by the hospitals ethics committee and written informed consent was obtained for all patients.

Study design and procedure

In this prospective randomized double-blind study, in all patients, before induction, an antecubital infusion line, an indwelling arterial blood pressure line and a three-lead ECG were installed. No pre-anaesthetic medication was given and all patients were fasting from midnight in the evening of the day before surgery to minimize the risk of

reflux aspiration during induction. At the time of induction, patients were randomized to receive either atracurium 0.5 mg kg⁻¹ based on ideal body weight or based on total body weight as a bolus injection. Ideal body weight was calculated by the following formulae:

Male: $50 + ((2.3 \times \text{length in inches}) - 60)$, female: $45.5 + ((2.3 \times \text{length in inches}) - 60)$ [5].

Following propofol injection (2.5 mg kg⁻¹) a neuromuscular train-of-four (NMT) (type M-NMT-00 = 00, Datex Engstrom) was applied over the ulnar nerve by use of surface electrodes. The NMT was calibrated and the resultant force of contraction of the adductor pollicis muscle was recorded after fixing the arm. Patients were positioned in a semi-fowler position and there was no change in positioning of the arm on which the TOF watch was attached after calibration. Fentanyl and cefazolin were given in a fixed dose of 250 µg and 2 g, respectively, followed by the randomized and blinded atracurium dose, which was prepared by an unblinded nurse. The unblinded nurse filled a 20 ml syringe with either the dose of atracurium based on ideal body weight or total body weight after which NaCl 0.9% was added to a total volume of 20 ml just prior to administration. Except for this unblinded nurse all medical personnel as well as the patients were blinded for the dose of atracurium. The attending blinded anaesthesiologist was allowed to give an additional bolus of atracurium when the neuromuscular block was inadequate in his opinion. After atracurium administration, the trachea was intubated and mechanical ventilation was initiated by the attending blinded anaesthesiologist. Anaesthesia was maintained with continuous infusions of propofol and remifentanyl after induction of anaesthesia by the attending blinded anaesthesiologist according to routine clinical practice. Body temperature was measured using a nasal probe.

Primary endpoint

The primary endpoint of the study was the time course of neuromuscular train-of-four (TOF) blockade exerted by the two different doses of atracurium. TOF was measured using depression of the twitch response of T1, the first stimulation in the TOF, and expressed as a percentage of the pre-atracurium value. The time to a decrease from 100% to 0% of twitch response after the bolus dose of atracurium and the times from 0 to 5%, to 25%, to 75% and 90% recovery of twitch response were recorded for each patient. Recovery times and indexes were compared between the two groups.

Secondary endpoints

Secondary endpoints of the study were intubation conditions and need for antagonism in the two groups. For quality of intubation the blinded anaesthesiologist was asked to qualify the intubation conditions as good or poor.

At the end of surgery the effect of atracurium could be antagonized with neostigmine in combination with atro-

pine by the blinded anaesthesiologist when the TOF ratio was <90%. The percentage of patients needing this antagonism was evaluated and compared between the two groups.

Statistical analysis

For the statistical analyses, the SPSS statistical package (PASW Statistics 18.0 for Mac; IBM, Chicago, IL) was used. Patient baseline characteristics, primary and secondary endpoints were compared between patients receiving atracurium 0.5 mg kg⁻¹ based on ideal body weight or atracurium 0.5 mg kg⁻¹ based on total body weight. Continuous data are expressed as the mean $\pm$ SD or as the median (interquartile range) where appropriate. Categorical data were analyzed by χ^2 and continuous data by Student's *t*-test or rank tests when appropriate. Linear regression analyses and Student's *t*-test were applied to analyze time to specific TOF ratios between both groups. For all tests, $P \leq 0.05$ was considered significant.

Results

Patient characteristics

Table 1 shows the patient characteristics of both groups. In one patient in the ideal body weight group, registration of the TOF ratio was lacking and this patient was not considered in the results. The mean age of the patients was 44 years and 53% were female. The range in ideal body weight was 50–86 kg, the range in total body weight was 112–260 kg and the range in BMI was 38–79 kg m⁻². All patients were classified as ASA physical status II–III. No differences in patient characteristics were noted between the groups studied. Duration of anaesthesia was not significantly different between the two groups. Mean doses of atracurium were significantly different ($P < 0.001$). The type of surgery for both groups is shown in Table 1. None

Table 1

Patient characteristics of morbidly obese patients receiving a bolus injection of atracurium 0.5 mg kg⁻¹ total body weight (TBW) vs. 0.5 mg kg⁻¹ ideal body weight (IBW)

	TBW (<i>n</i> = 10)	IBW (<i>n</i> = 9)	<i>P</i> value
Age [median (IQ-range)]	51 (41–56)	38 (32–49)	0.59
Female [<i>n</i> (%)]	6 (60)	5 (56)	0.66
TBW (kg) [mean (SD)]	155 (42)	150 (26)	0.78
IBW (kg) [mean (SD)]	65 (12)	70 (10)	0.35
BMI (kg m ⁻²) [mean (SD)]	54 (13)	48 (6)	0.28
Duration of anaesthesia (min) [mean (SD)]	89 (30)	91 (22)	0.86
Dose of atracurium (mg) [mean (SD)]	77 (20)	35 (5)	<0.001
Gastric bypass	4	3	
Laparoscopic banding	4	5	
Laparoscopic sleeve resection	2	1	

BMI, body mass index.

of the patients had a body temperature below 36°C and there was no difference in body temperature between the two groups studied.

Neuromuscular train-of-four-ratio

Figure 1 shows the percentages of twitch response of the neuromuscular TOF ratio vs. time after a bolus injection of atracurium 0.5 mg kg⁻¹ for the ideal body weight group (*n* = 9) and the total body weight (*n* = 10) group. In this figure, data after administration of neostigmine, which was judged necessary by the blinded anaesthesiologist in seven patients in the total body weight group, are not shown. One patient in the ideal body weight group needed two additional boluses of atracurium after 54 and 98 min during the unexpectedly prolonged surgical procedure and the full TOF ratio profile is shown in Figure 2. In Figure 1, the TOF ratios of this patient are depicted until the first re-dose of atracurium at 54 min. In one patient in the ideal body weight group, there was evidence for a slightly reduced signal of the TOF monitor showing a prolonged recovery profile, despite adequate muscle recovery at 60 min (Figure 1, open squares). Figure 1 shows that in the total body weight group, time to recovery of muscle relaxation was prolonged and showed more variability compared with the ideal body weight group.

Table 2 shows mean times for the TOF ratio to decrease from 100% to 0% and recover from 0% to 5%, 25%, 50%, 75% and >90% for both groups. Muscle relaxation (from a TOF ratio of 100% to 0%) was more rapid in the total body weight group (mean difference 1.5 min, 95% CI 0.4, 2.6 min), while patients in the ideal body weight group showed shorter times to recovery. Additionally, it is shown that the number of patients decreased in the total body weight group because of the need for antagonism with neostigmine due to TOF ratios lower than 90% at the end of the procedure. This decrease in number of patients was not found in the ideal body weight group as none of the patients in this group needed neostigmine. Due to technical failure of the TOF monitor in one patient in the ideal body weight group this patient was excluded from the data analysis and for one patient only the decrease from a TOF ratio of 100% to 0% was available. Mean difference between the total body weight and the ideal body weight group in time to recovery to 5% was 30 min (95% CI 23, 39 min). Similar results were obtained for higher TOF ratios (Table 2).

In Figure 3, time to reach a TOF ratio of 5% was plotted vs. dose of atracurium for all patients in both groups. In both the ideal body weight group and the total body weight group, one patient could not be evaluated because time to a TOF ratio of 5% was not available due to technical errors. A positive correlation between the dose of atracurium and time to reach a TOF ratio of 5% ($r = 0.82$; $P = 0.001$, $n = 9$) was found in the total body weight group, while in the ideal body weight there was no correlation ($r = 0.24$; $P = 0.566$, $n = 8$).

Figure 1

Neuromuscular train-of-four ratio (TOFratio, ■ with solid line) after a bolus injection of atracurium 0.5 mg kg^{-1} ideal body weight (IBW, $n = 9$, A) and 0.5 mg kg^{-1} total body weight (TBW, $n = 10$, B) vs. time. In one patient of the ideal body weight group, TOF ratios were unavailable during time = 40 min and time = 50 min due to a temporary technical error (dotted line). In another patient in the ideal body weight group, TOF equipment was not working fully (□)

Quality of neuromuscular block and need for antagonism

Table 3 shows the characteristics of neuromuscular block. Quality of intubation was good in all patients in both groups. All patients could be ventilated by bag-mask after induction of anaesthesia and none of the patients desaturated to values lower than 90%. At the end of the procedure, seven patients in the total body weight group needed antagonism with neostigmine vs. no patients in the ideal body weight group ($P = 0.003$).

Discussion

The present study evaluated atracurium dosing based on total body weight vs. ideal body weight when used as a muscle relaxant in twenty morbidly obese patients with body weights up to 260 kg undergoing bariatric surgery.

Our findings strongly suggest that atracurium should be dosed based on ideal body weight instead of total body weight, as this leads to a predictable profile of muscle relaxation and full recovery of muscle strength within 60 min allowing for adequate intubation conditions and lack of need for antagonism.

There are several explanations for our finding that atracurium should be based on ideal body weight in morbidly obese patients. First, an increase in body weight may not necessarily imply an increase in muscle tissue. Furthermore, atracurium is a hydrophilic neuromuscular blocking agent, and therefore a correlation between total dose and effect is to be expected. Such a relation is confirmed by our finding that a positive correlation ($r = 0.82$) was observed between total atracurium dose and the TOF ratio recovery to 5% in the patients dosed on total body weight. As the range in dose in the ideal body weight group was relatively small, this correlation was absent in the ideal body weight

Figure 2 Neuromuscular train-of-four ratio (TOF ratio) in a patient of the ideal body weight group, who received after the initial dose of atracurium 38 mg at time = 0, two additional boluses of atracurium; 20 mg at time = 54 min, lowering the TOF ratio to nearly 0%, and 10 mg at time = 98 min, lowering the TOF ratio to around 50%. Duration of surgery was longer than expected and was 125 min. TOF ratios were unavailable between time = 5 min and time = 54 min due to a temporary technical error

Table 2 Time to specific percentages of decrease and recovery of the twitch response of the neuromuscular train-of-four ratio (TOF ratio) after bolus injection of atracurium 0.5 mg kg⁻¹ total body weight (TBW) vs. 0.5 mg kg⁻¹ ideal body weight (IBW)

	TBW <i>n</i>	Mean (SD)	IBW <i>n</i>	Mean (SD)	Mean difference (95% CI)
Time from 100% to 0 %	10	3 (1)	9	4 (1)	1.5 (0.4, 2.6)
Time to 5 % of recovery	9	60 (10)	8	30 (4)	30 (23, 39)
Time to 25 % of recovery	7	75 (8)	8	36 (3)	40 (33, 47)
Time to 50 % of recovery	5	82 (9)	8	43 (4)	39 (31, 47)
Time to 75 % of recovery	5	91 (8)	8	51 (6)	40 (31, 49)
Time to 90% of recovery	1	116	8	60 (10)	56 (31, 82)

Time in min; *n* represents number of patients in whom the effect of atracurium was not antagonized with neostigmine. Mean values are based on data from patients in whom the effect of atracurium was not antagonized with neostigmine, as this directly leads to a TOF ratio >90%.

group. This finding partly confirms the findings from Varin *et al.* [3], who reported that in obese patients atracurium distributes in a total volume equivalent to non-obese patients. However, these authors also concluded that obese patients need higher plasma concentrations of atracurium to obtain the same effect as non-obese patients [3]. This latter result was not reported in our study, because plasma concentrations of atracurium were not available. As the method of collecting plasma atracurium concentrations is very expensive, is time -and resource-consuming (due to Hofmann’s elimination) and the fact that Fisher *et al.* [6] suggests there is limited utility for plasma concentration data, in the current study the TOF ratio was used as primary endpoint and no atracurium plasma concentrations were considered. Even though we have not measured atracurium concentrations, it seems from our study that the finding that ideal body weight is the key determinant of time to recovery of the TOF ratio can mainly be

Figure 3 Time to recovery of the twitch response of the neuromuscular train-of-four ratio (TOF ratio) to 5% vs. dose of atracurium based on total body weight (x, *n* = 9) and ideal body weight (♦, *n* = 8)

Table 3

Characteristics of neuromuscular block after a bolus injection of atracurium 0.5 mg kg⁻¹ based on total body weight (TBW) vs. ideal body weight (IBW)

	TBW n = 10	IBW n = 9	P value
Good quality of intubation [n (%)]	10 (100)	9 (100)	N/A
Need for antagonism [n (%)]	7 (100)	0 (0)	0.003

N/A, not applicable.

explained by an unchanged muscle mass in morbidly obese patients and an unchanged volume of distribution [3] in morbidly obese patients compared with normal weight patients. In addition, due to organ-independent degradation of atracurium through Hofmann's elimination, clearance is also expected to remain unchanged in morbidly obese patients. Thus, no changes in half-life, being the quotient of these two parameters, of atracurium can be expected in obese patients. This is reflected in Figure 1 as duration of effect, which does not change in obese patients compared with non-obese patients. This indicates that dosing of atracurium should not be based on total body weight, but ideal body weight instead.

In our study, we report a positive correlation between total atracurium dose and duration of effect in the total body weight group. A prolonged duration of action when dosing is based on total body weight was also shown in a study by Kirkegaard-Nielsen *et al.* [4]. They studied 127 patients (mean weight 69 kg, range 46–119 kg) and also found a prolonged duration of action in obese patients when an induction dose of atracurium 0.5 mg kg⁻¹ was based on total body weight. Even though the body weights in our study were higher than in the study of Kirkegaard-Nielsen *et al.*, we think that the results of these two studies are in good agreement. However, Kirkegaard-Nielsen *et al.* [4] proposed, based on their study results, a dose reduction of atracurium by 2.3 mg for each 10 kg total body weight more than 70 kg, when using an induction dose expressed in mg kg⁻¹ total body weight [4]. In our opinion, our study shows an even more simple way to dose atracurium in morbidly obese patients that is based on ideal body weight.

In our study, morbidly obese patients with a mean body weight of 155 kg with individuals up to 260 kg were studied. Additionally, patients were stratified in five body weight subgroups in order to obtain balanced groups with regard to body weight distribution and to adequately study differences when dosing on total or ideal body weight. While this stratification of body weights may be considered a strength of our study, the mean body weight in our study was also higher than in other studies. Weinstein *et al.* [7], for instance, studied recovery times from neuromuscular blocks induced by atracurium (dose 0.5 mg kg⁻¹ of total body weight) in obese (mean weight

80 kg, range 61–95 kg) and non-obese patients (mean weight 60 kg, range 48–77 kg). While they found no difference in recovery times, it is questionable whether these results can be extrapolated to morbidly obese patients, as the difference in body weight between obese and non-obese patients was rather small. Similarly, Beemer *et al.* [2] evaluated body build variables to scale clearance of atracurium and to dose atracurium. They found that dosing of atracurium should be based on lean body mass. Again, in this study no morbidly obese patients were included (maximum weight 116 kg) and they did not evaluate a bolus injection of atracurium, only a continuous infusion of atracurium following a bolus injection of succinylcholine.

According to the RxList, the internet drug index, a dose of 0.4–0.5 mg kg⁻¹ leads to good or excellent conditions for non-emergency intubation in 2 to 2.5 min in non-obese patients, with a maximum neuromuscular block achieved approximately 3 to 5 min after injection. Clinically, the neuromuscular block typically lasts 20 to 35 min under balanced anaesthesia and recovery to 25% of control may be achieved approximately 35 to 45 min after injection, while recovery is usually 95% complete approximately 60 min after injection. The results of the ideal body weight group in our study largely approach these times of recovery, indicating that a dose of atracurium of 0.5 mg kg⁻¹ ideal body weight also applies for morbidly obese patients in comparison with non-obese patients.

A weakness of the study is that some data are missing. In one patient in the ideal body weight group registration of the TOF ratio was lacking and this patient was not included in the results. In two other patients some data from the TOF ratio registration were lacking due to failure of equipment at specific time points, even though the remaining data were still usable for evaluation. Other data points in the total body weight group could not be evaluated because neostigmine was administered at the end of the surgical procedure, thereby directly reversing the effect of atracurium, resulting in an immediate baseline TOF ratio. However, the number of patients who needed reversal of the effect of atracurium (seven in the total body weight group vs. none in the ideal body weight group) can also be considered an endpoint of the study as it shows that the effect of atracurium was longer in the total body weight group compared with the ideal body weight group. As the values of reversal of the TOF ratio from 0 to 5% could be evaluated in almost all individuals of both groups, we can still conclude on the effects of both dosing regimens.

The current study shows that when using a dose of atracurium based on ideal body weight in morbidly obese patients, monitoring of the TOF ratio is important to decide when to administer additional boluses of atracurium. Titrating can easily be done, as shown by one patient who received two additional boluses because of a relatively long surgical procedure, one of 20 mg lowering the TOF ratio to nearly 0%, and one of 10 mg, lowering the TOF ratio to around 50% (Figure 2). The advantage of

dosing based on ideal body weight is that recovery is as described for non-obese patients, meaning full recovery after 60 min, while when dosing is based on total body weight recovery is unpredictable and duration of action is prolonged excessively (Figure 1). Although the time to reach a TOF ratio of 0% at induction of anaesthesia is faster in the total body weight group, dosing of atracurium on a total body weight basis resulted in a need for antagonism with neostigmine. If the goal is to reach a TOF ratio of 0% as fast as possible, other neuromuscular agents such as rocuronium or succinylcholine can be considered. Succinylcholine, however, has many adverse side-effects (muscle soreness, excessive salivation and cardiovascular effects like bradycardia), and therefore atracurium remains the drug of choice in our clinic.

Based on the findings in this study in morbidly obese patients, we conclude that dosing of atracurium is most appropriate when based on ideal body weight, as this gives predictable levels of neuromuscular blockade, good intubation conditions and fast recovery of muscle strength. For re-dosing of atracurium during maintenance of anaesthesia the TOF monitor showed very good applicability. Dosing based on total body weight leads to an unwanted, dose-dependent prolongation of action of atracurium.

Competing Interest

There are no competing interests to declare.

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