J Anesth (2012) 26:790–793
DOI 10.1007/s00540-012-1395-5

SHORT COMMUNICATION

Ideal body weight-based remifentanil infusion is potentially insufficient for anesthetic induction in mildly obese patients

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Received: 3 January 2011 / Accepted: 9 April 2012 / Published online: 3 May 2012
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Abstract We evaluated whether the effect of remifentanil treatment differs between normal weight (NW) patients with real body weight-based remifentanil and mildly obese (Ob) patients with ideal body weight based-remifentanil during short-term anesthetic induction. We enrolled 20 patients aged between 20 and 64 years in each group (NW group: 18.5 kg/m^2 $\leq$ BMI $<$ 25 kg/m^2; Ob group: BMI $\geq$ 25 kg/m^2). Tracheal intubation (TI) was performed after administration of 0.5 μg/kg/min remifentanil for 5 min, including 2 min of antecedent administration, with propofol and rocuronium. Hemodynamic parameters (SBP, DBP, and HR) were measured. Percent changes in hemodynamics resulting from anesthetic induction and TI were calculated, and effect-site concentration (ESC) in each patient was calculated by performing pharmacokinetic simulation. All hemodynamic values in the Ob group after TI were significantly higher than those in the NW group. Percent increases in SBP and HR in the Ob group were significantly higher than the corresponding values in the NW group. ESC of remifentanil at the time of TI in the NW group was higher than that in the Ob group. Remifentanil treatment with anesthetic induction based on the Japanese package insert might have insufficient effects in obese patients.

Keywords Remifentanil · Mildly obese patient · Anesthetic induction

Presented at the American Society of Anesthesiologists, San Diego, CA, on October 19, 2010.

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The pharmacokinetics of remifentanil are well known, and the effect-site concentration (ESC) of remifentanil is determined according to age and lean body mass (LBM) of the patient [1, 2]. Therefore, remifentanil dose for obese patients is determined on the basis of their ideal body weight (IBW), because the dose determined on the basis of total body weight (TBW) might be an overdose for these patients (Package_insert; Ultiva, GlaxoSmithKline UK, Brentford, UK. Package_insert; Ultiva, Abbott Laboratories, Abbott Park, IL, USA. Package_insert; Ultiva, Janssen Pharmaceutical, Tokyo, Japan). The criteria for obese patients in the package insert are more strict in Japan [body mass index (BMI) 25 kg/m^2 or more, which on conversion is greater than approximately 11.4 % over IBW] than in the United States (BMI greater than 30 % over IBW) (Package_insert; Ultiva, Abbott Laboratories. Package_insert; Ultiva, Janssen Pharmaceutical). Although the strict criteria minimize the variation in ESC, there may be an increase in the ratio of patients in whom remifentanil treatment during short-term anesthetic induction (AI) produced insufficient effects. Thus, we evaluated whether administration of remifentanil treatment to obese patients based on the Japanese package insert during AI is likely to produce an insufficient effect.

The study was approved and monitored by the Research Ethics Committee of Asahikawa Medical College, and

informed consent was obtained from each patient. The study population consisted of 40 patients [20 patients each from the following two groups: normal weight group (NW group) of patients with 18.5 kg/m^2 $\leq$ BMI $<$ 25 kg/m^2 and obesity group (Ob group) of patients with BMI of 25 kg/m^2 or more]. The patients were aged between 20 and 64 years and were scheduled to undergo ophthalmological or otolaryngological surgeries; their American Society of Anesthesiologists (ASA) physical status was I or II. Patients with arrhythmias, such as atrial fibrillation or disturbance in the conduction system, and those receiving α-methyldopa or clonidine treatment, were excluded from this study.

No patients received premedication after 12 h of fasting. After arrival of the patient in the operating room, standard monitoring for general anesthesia was performed using IntelliVue M8010A (Philips Electronics Japan, Tokyo, Japan). Each patient was administered 1.5 mg/kg propofol (dose based on actual body weight) for AI 2 min after starting continuous infusion of 0.5 μg/kg/min remifentanil (dose based on actual body weight in the NW group and IBW in the Ob group). Then, 0.9 mg/kg rocuronium was administered, and tracheal intubation (TI) was performed by certificated anesthesiologists 3 min after AI. Hemodynamic parameters [systolic and diastolic blood pressures (SBP and DBP, respectively) and heart rate (HR)] during AI were assessed, and the percent changes were calculated after both AI and TI. Blood pressure (BP) was measured in the repeatedly measured mode using a cuff, and HR was measured by electrocardiography (EKG). Hemodynamic parameters measured during a stable state immediately before the administration of remifentanil were recorded as values in the pre-induction period. The lowest value of a hemodynamic parameter after AI and the highest value 5 min after TI were recorded as values in the post-induction period and in the post-intubation period, respectively. The percent changes in the hemodynamic values caused by AI or TI were calculated by using the following formula: post–pre)/pre values. ESC in each patient was calculated using TIVA Trainer version 8 (http://www.eurosiva.org) with Minto's parameter [1], and the results were compared between the two groups.

Gender and ASA physical status (ASA-PS) score were analyzed using the Mann–Whitney *U* test. Other demographic parameters, percent changes in hemodynamic values from AI or TI, and ESC of remifentanil were analyzed using unpaired *t* test. The hemodynamic values were analyzed using repeated-measures analysis of variance (ANOVA); subsequently, multiple comparisons within the group were performed using the Tukey–Kramer test, and intergroup comparison was performed using unpaired *t* test. Data were expressed as mean ± standard deviation, and a *p* value $<$0.05 was considered statistically significant.

There were no intergroup differences in the patients' demographic characteristics, except in body weight and BMI (Table 1).

The hemodynamic values in each period are presented in Fig. 1. After anesthesia was induced, all hemodynamic parameters significantly decreased in both groups. There were no significant differences in the hemodynamic values in the post-induction period. SBP significantly increased after TI in both groups. Because the degree of SBP increase in the Ob group was higher than that in the NW group, SBP after TI was significantly higher in the former than in the latter (126 ± 23 vs. 107 ± 9 mmHg). Similar results were obtained for DBP (76 ± 16 vs. 63 ± 11 mmHg) and HR (78 ± 11 vs. 68 ± 8 beats/min).

The percent changes in hemodynamic values caused by AI and TI are shown in Fig. 2. There was no intergroup difference in the percent decrease in SBP or DBP or HR as a result of AI. The percent increase in SBP resulting from TI was significantly higher in the Ob group (38 ± 27 %) than in the NW group (14 ± 15 %). The percent increase in HR was also significantly higher in the Ob group (29 ± 15 %) than in the NW group (15 ± 11 %).

ESC of remifentanil increased with time in both groups. ESC of remifentanil in the NW group was higher than that in the Ob group throughout the procedure. ESC of remifentanil 5 min after starting administration was significantly higher in the NW group than in the Ob group (7.0 ± 0.6 vs. 6.4 ± 0.5 ng/ml).

Pharmacokinetics of remifentanil are affected by age and LBM, which is calculated by height and body weight in

Table 1 Patient demographics

	NW group	Ob group	*p* value
Number of patients	20	20	
Age (year)	41 ± 15	50 ± 14	0.135
Gender (M/F)	11/9	9/11	0.539
Weight (kg)	59 ± 10	73 ± 12	0.007*
Height (cm)	167 ± 9	161 ± 9	0.08
Body mass index (kg/m^2) (range)	21.2 ± 2.5 (16.4–24.9)	28.1 ± 3.9 (25.1–39.5)	$<$0.001*
ASA physical status (I/II)	16/4	13/7	0.300
Hypertension (+/−)	16/4	14/6	0.471

Data are presented as mean ± standard deviation or number of patients

ASA American Society of Anesthesiologists, *NW* normal weight, *Ob* obesity

* *p* value $<$0.05 was considered statistically significant

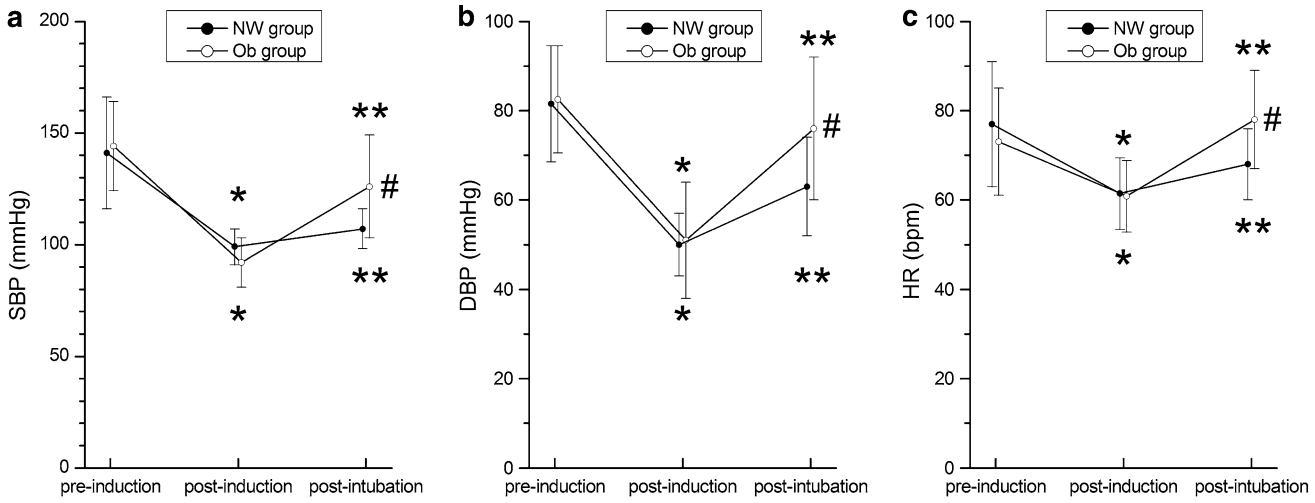

Fig. 1 Hemodynamic data for each period. **a** Systolic blood pressure (*SBP*) significantly decreased as a result of anesthetic induction (AI) in both groups and significantly increased as a result of tracheal intubation (TI) in both groups. SBPs in the obesity (*Ob*) group at the post-intubation period were significantly higher than those in the normal weight (*NW*) group. **b** There was a significant decrease in diastolic blood pressure (*DBP*) and heart rate (*HR*) (**c**) due to AI and a significant increase due to TI in both groups. DBP and HR in the Ob group at the post-intubation period were significantly higher than those in the NW group. $*p < 0.05$, when compared with pre-induction within the same group; $**p < 0.05$, when compared with post-induction within the same group; $\#p < 0.05$, when compared with NW group in the same period

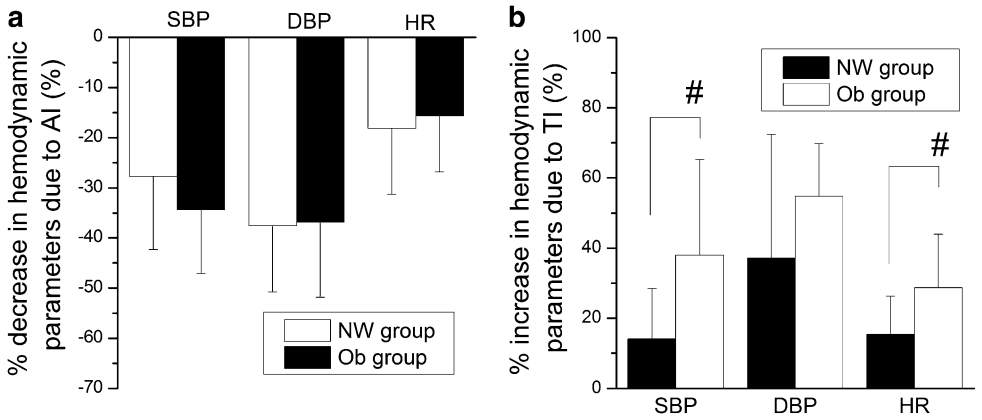

Fig. 2 Percent changes in the hemodynamic values resulting from anesthetic induction and tracheal intubation. **a** There are no significant differences in percent decrease in the systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), and heart rate (*HR*) from anesthetic induction (*AI*) between the two groups. **b** The percent increases in the SBP and HR due to tracheal intubation (*TI*) in the obesity (*Ob*) group were significantly higher than the corresponding values in the normal weight (*NW*) group. There was no significant intergroup difference in the percent increase in DBP. $\#p < 0.05$, when compared with the NW group

each gender, of the patient [1, 2]. Therefore, a dose based on TBW can be an overdose for obese patients, as reported by Egan et al. [3] for their study in which average BMI in the obese group was 38.6 ± 3.6 kg/m^2. Moreover, the following was described in the US package insert (Package_insert; Ultiva, Abbott Laboratories) on the basis of Egan's report [3]: there is no difference in the pharmacokinetics of remifentanil in non-obese versus obese patients when normalized to IBW. Therefore, it has been recommended in many countries that the dose of remifentanil for obese patients should be adjusted on the basis of their IBW (Package_insert; Ultiva, GlaxoSmithKline. Package_insert; Ultiva, Abbott Laboratories. Package_insert; Ultiva, Janssen Pharmaceutical). Thus, it is reasonable that the dose for obese patients is determined on the basis of the IBW.

However, the criteria for the adjustment of remifentanil dose may vary among countries. Because the criteria for the adjustment of remifentanil dose in Japan are stricter

(BMI of 25 kg/m^2 or more, which is approximately 11.4 % over IBW) than those in the US (BMI greater than 30 % over IBW), the ratio of Japanese patients receiving reduced doses of remifentanil might be higher than that of American patients. This difference might increase the number of Japanese patients in whom remifentanil treatment produces an insufficient effect under some conditions; for example, when the concentration of remifentanil used is similar to that required for blunting cardiovascular response during some invasive procedures such as during short-term AI. In the present study, there was a difference in the ESC of remifentanil at the TI; consequently, there were significant intergroup differences in the hemodynamic values and response to TI.

The results of this study do not suggest that the dose recommended on the Japanese package insert is always insufficient. First, induction methods may vary with the package insert. The induction period can be extended, and an initial bolus injection can be selected. Moreover, propofol dose, which was determined on the basis of the required dose in the previous study [4], can be increased. Because these modifications increase the ESC of remifentanil or propofol, intergroup differences may be prevented. Second, we can use propofol or inhalation drug after loss of consciousness on the usual clinical situation. These drugs may compensate for the insufficient effect of remifentanil.

The association between dose and ESC of remifentanil is noteworthy. Because the amount of drug per unit of time is proportional to body weight, ESC of remifentanil will decrease with decrease in BMI without dose adjustment of remifentanil based on body weight if other body characteristics (height, age, and gender) do not differ. If the body weight of participants in the control group had been less than that in the present study, meaning that ESC of remifentanil in the control group decreased, different results would have been obtained.

In contrast, if remifentanil had been administrated on the basis of TBW, not IBW, in obese patients as well, what results would have been obtained? The ESC of remifentanil 5 min after starting administration is calculated to be 7.9 ± 0.8 ng/ml, and this value is higher than that (7.0 ± 0.6 ng/ml) in the NW group. Different results for hemodynamic change would be obtained; however, we cannot discuss these results because we did not perform such a study.

A limitation of the present study is that only one protocol was evaluated. We are unsure whether other protocols will yield the same result. It is necessary to conduct a study in the future to determine the optimal remifentanil dose for obese patients during AI.

Remifentanil treatment during AI based on the Japanese package insert might produce insufficient effects in mildly obese patients.

Acknowledgments Support was provided solely from institutional and/or departmental sources.

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