Pharmacokinetic mass of fentanyl for postoperative analgesia in lean and obese patients

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Background. We previously proposed dosing weights for fentanyl, termed ‘pharmacokinetic mass’, that span the total body weight (TBW) range from 40 to 210 kg. In this study, we examined the relationships among fentanyl doses needed to achieve postoperative analgesia, corresponding plasma fentanyl concentrations, and pharmacokinetic mass in lean and obese patients undergoing abdominal surgery.

Methods. A total of 69 patients were studied, with TBW ranging from 48 to 181 kg. Fentanyl infusion was used during surgery. After surgery, fentanyl infusion rates were titrated to achieve analgesia without significant respiratory depression. Plasma fentanyl concentrations were measured when an apparent steady analgesic state was obtained. Comparisons were made for dosing requirements and effective plasma concentrations for 37 lean patients (body mass index <30, TBW <85 kg) and 33 obese patients (body mass index >30, TBW ≥85 kg).

Results. The average fentanyl dose (µg h⁻¹) required to achieve and maintain analgesia over the 4 h postoperative period had a non-linear relationship to TBW; in comparison, fentanyl dose had a strong linear relationship to pharmacokinetic mass: dose (µg h⁻¹) = 1.22 × pharmacokinetic mass/7.5; r = 0.741, P < 0.001. Based on results from our earlier study, the corresponding values of TBW and pharmacokinetic mass are: 52 kg – 52 kg; 70 kg – 65 kg; 100 kg – 83 kg; 120 kg – 93 kg; 140 kg – 99 kg; 160 kg – 104 kg; 180 kg – 107 kg; 200 kg – 109 kg. In the group comparisons, there was no statistically significant difference in the postoperative fentanyl dose per unit of pharmacokinetic mass between lean and obese patients. The plasma concentration of fentanyl required for analgesia was approximately 1.5 ng ml⁻¹, and was similar in the two groups.

Conclusion. The relationship between dose and pharmacokinetic mass, compared with that of dose vs TBW, may provide confidence for the use of pharmacokinetic mass as a dosing approximation for fentanyl. Fentanyl dose based on TBW may cause overdosing in obese patients.


Keywords: analgesics, fentanyl; complications, obesity; pharmacokinetics, fentanyl

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In recent years anaesthetists have been caring for an increasing number of obese patients. Obese patients, especially morbidly obese patients, are vulnerable to airway- and ventilatory-related adverse effects of sedative and analgesic drugs following surgery.1 There is a need for improved understanding of dose requirements of opioids in relation to body weight.

Previously,2 we proposed derived dosing weights for fentanyl that spanned the total body weight (TBW) range from 40 to 210 kg; we termed these dosing weights ‘pharmacokinetic mass’. Pharmacokinetic mass was derived by application of a correction to the non-weight-scaled pharmacokinetic model described by Shafer and colleagues.3 The correction was based on the error that was found between predicted and measured plasma concentrations of fentanyl in relation to TBW as body weight increased.4 The pharmacokinetic mass vs TBW relationship

has an exponential association expressed as:

\[
\text{pharmacokinetic mass} = \frac{52}{\left[1 + (196.4 \times e^{-0.025 \text{TBW} - 53.66})/100\right]}
\]

A nomogram and a table for this relationship are presented in the Appendix.

In the present study, we examined the relationships between the fentanyl doses required to achieve analgesia and (i) total body weight and (ii) pharmacokinetic mass, as well as corresponding effective plasma fentanyl concentrations.

**Methods**

A total of 69 patients with a TBW range of 48–181 kg who were undergoing major elective abdominal surgery were studied after the approval of the Institutional Review Board of New York Medical College, Valhalla, NY, USA. Informed consent was waived by the Institutional Review Board because plasma fentanyl concentrations were determined on blood that remained after blood-gas analyses had been completed, in patients who would routinely require arterial cannulation for monitoring and blood gas analysis. The patients received standard anaesthetic management; therefore, no additional risks would have been expected.

The types of surgery included abdominal aortic aneurysmectomy, major abdominal surgery, and open abdominal gastric bypass surgery. Only patients undergoing open abdominal surgery were included, in order to standardize a relatively uniform intensity of postoperative pain. The subjects were essentially a subgroup of the patients reported in the previous study, which comprised patients that had undergone a variety of procedures, including thoracic and orthopaedic surgeries; the latter procedures may have been associated with a greater intensity of pain than that following abdominal surgery. Patients with liver disease, renal disease and those requiring chronic analgesic medication were not included in the study. Patients who were not extubated in the operating room were excluded from the study. Also, patients who received naloxone and analgesics other than fentanyl were not included. Patients with cardiac disease, chronic obstructive pulmonary disease or morbid obesity with a history of sleep apnoea were not excluded.

Anaesthesia was induced with fentanyl 1–2 µg kg⁻¹, propofol 1.5–2.5 mg kg⁻¹, sevoflurane 2% and atracurium 0.5 mg kg⁻¹. After the initial bolus dose of fentanyl, a continuous infusion of fentanyl was started at the rate of 0.05–0.07 µg kg⁻¹ min⁻¹ for 60–75 min, followed by 0.03–0.05 µg kg⁻¹ min⁻¹ for the next 1–2 h, and then at a reduced rate of 0.02–0.03 µg kg⁻¹ min⁻¹. The exact infusion rate of fentanyl, however, was adjusted by the participating anaesthesiologists to meet the clinical need in each case. The infusion of fentanyl was discontinued approximately 30–40 min before the estimated end of surgery. Inhaled anaesthetic agents used for maintenance of anaesthesia were either sevoflurane or desflurane at a concentration of approximately 1 MAC. When an increase in heart rate or blood pressure was observed, the infusion rate of fentanyl was increased rather than raising the concentration of the inhalation agent.

Titration of the infusion rate of fentanyl for postoperative analgesia by the postanaesthesia care unit (PACU) nurses or postoperative care unit (POCU) nurses was routine at the time of this study for patients who had undergone major open abdominal surgery. The patients were told that they would be expected to do deep breathing and coughing exercises as part of routine postoperative procedures, and that the nurse would adjust the infusion rate of fentanyl to make them reasonably comfortable regarding pain. The ratio of nurses to patients was one to one, and a protocol had been established. After arrival in the PACU or POCU, pain relief at rest, pain relief during deep breathing and coughing exercises and the state of wakefulness were rated on a scale of 1–5 (pain relief score: 5, no pain; 4, minimal pain; 3, tolerable pain; 2, uncomfortable pain; 1, severe intolerable pain; wakefulness score: 5, alert; 4, drowsy with open eyes; 3, eyes closed, opened in response to light touch or voice; 2, eyes closed, eyes opened briefly in response to touching; 1, closed eyes, no response to touch). These relatively simple scales were chosen over those with more subtle gradations because they were familiar to our PACU and POCU personnel for clinical monitoring, and more practical to apply in our setting. When patients started to complain of pain, a continuous fentanyl infusion was started by the participating anaesthetist who had administered anaesthesia during surgery. Usual starting infusion rate was approximately 1 µg kg⁻¹ h⁻¹, with a range of 0.5–2.0 µg kg⁻¹ h⁻¹. However, the subsequent actual infusion rate of fentanyl in an individual patient was titrated by nurses according to the following sets of criteria. If a patient was uncomfortable with pain (pain score ≤2), the infusion rate was increased by 20–30% so that the patient became comfortable and willing to breathe deeply and cough with some tolerable pain (pain relief score 3 or 4). The patients were expected to respond promptly to a soft voice or gentle touch. The infusion rate of fentanyl was decreased when the pain relief score for coughing became 5, or when a patient became sluggish in response to gentle touch, or if the respiratory rate decreased to less than 10 per min. All patients received oxygen supplementation. Respiratory rate, pulse oximetry (S\textsubscript{PO}_2), heart rate (HR), systolic and diastolic arterial pressure (SAP and DAP, respectively), pain relief score and consciousness score were regularly observed by nurses and recorded every 30 min during the first 2 h and then every hour thereafter. Nausea or any other untoward incident was recorded. All of the subjects received i.v. infusion of fentanyl for at least 4 h after surgery. Changes in infusion rates were tracked, and the total dose administered was divided by the time period (4 h) to yield the average postoperative dose in µg h⁻¹.

Arterial blood gas analyses were obtained at the end of surgery, within 1 h after arrival at the PACU or POCU, and
later as needed. The residual blood was allowed to partially clot and was centrifuged within 2 h; plasma (serum) was stored at −70°C until radioimmunoassay for fentanyl concentration. Radioimmunoassay was performed at the Department of Anatomy, Physiological Sciences and Radiology of North Carolina State University, Raleigh, NC, using a fentanyl radioimmunoassay kit from Janssen Pharmaceutica (Olen, Belgium). The assay had a lower limit of quantification of 0.1 ng ml⁻¹. The inter-assay coefficient variation averaged 8.42% at a plasma fentanyl concentration of 0.25 ng ml⁻¹.

In order to more fully examine the general effects of ‘obesity’ on the fentanyl requirements for postoperative analgesia, the patients were divided retrospectively into two groups using common criteria for the designation of obesity. Thus, comparisons were made for dosing requirements and effective plasma concentrations for 37 lean patients (group L; body mass index <30, TBW <85 kg) and 33 obese patients (group O; body mass index >30, TBW ≥85 kg).

PK Analyst (MicroMath Scientific Software, Salt Lake City, UT, USA) was used to derive the non-linear regression equation for the relationship between postoperative analgesic dose (µg h⁻¹) and TBW. A bi-exponential model of the general form

\[ \text{dose} (\mu g \ h^{-1}) = A \cdot e^{-\alpha \cdot \text{TBW}} + B \cdot e^{-\beta \cdot \text{TBW}} \]

was fitted to the data.

Non-parametric Mann–Whitney tests were used to determine the significance of differences in the mean values of variables between group L and group O. Fisher’s exact test was used for confirmation of statistical inferences when the parameters were represented as ordinal data (ASA class, wakefulness scores and pain scores). The \( \chi^2 \)-test was used to compare types of surgery between the groups and the ratios of males to females in group L vs group O. The coefficient of determination was used to describe the goodness of fit for the non-linear relationship between postoperative analgesic dose and TBW, and the Pearson correlation coefficient (\( r \)) was used to characterize the linear relationship between postoperative analgesic dose and pharmacokinetic mass. Statistical significance was considered to be \( P<0.05 \).

**Results**

Analgesic endpoints were usually reached within 1 h after arrival at the PACU or POCU. The relationship between average postoperative fentanyl dose (µg h⁻¹) over the 4 h postoperative period and TBW (Fig. 1A) had a non-linear profile, similar to that observed previously for the relationship between pharmacokinetic mass vs TBW (Appendix, Fig. A1). The equation for the non-linear regression in Fig. 1A was as follows:

\[ \text{dose} (\mu g \ h^{-1}) = -167 \cdot e^{-0.011 \cdot \text{TBW}} + 149 \]  
\[ \text{coefficient of determination} = 0.551; \ P<0.001 \]

\[ \text{dose} (\mu g \ h^{-1}) = 1.22 \times \text{pharmacokinetic mass} - 7.5 \]  
\[ r = 0.741, \ P<0.001 \]

The second exponent of this bi-exponential equation, \( \beta \), was essentially zero, so the entire term, \( e^{-\beta \cdot \text{TBW}} \), was dropped from the equation.

In comparison, the average fentanyl dose had a strong linear relationship to pharmacokinetic mass, with the intercept approaching zero on the y-axis:

\[ \text{dose} (\mu g \ h^{-1}) = 1.22 \times \text{pharmacokinetic mass} - 7.5 \]  
\[ r = 0.741, \ P<0.001 \]

(Fig. 1B). Approximately 90% of the actual analgesic doses that were delivered were within ±30% of the average relation between dose (µg h⁻¹) vs pharmacokinetic mass (Fig. 1B).

Patient characteristics for the subjects of groups L and O are presented in Table 1. There were statistically significant differences between group L and group O in age [mean 69 (sd 13) yr vs 49 (17) yr]. Also, as expected, all of the body measurements, TBW [70 (9) vs 116 (28) kg], height [166 (9) vs 173 (13) cm], body mass index [26 (4) vs 40 (12)], body surface area [1.8 (0.1) vs 2.3 (0.2) m²] and pharmacokinetic
mass [64 (6) vs 88 (11) kg] were statistically different between groups L and O. The median values for ASA class for group L and group O were III and II, respectively, and were statistically different. Duration of surgery was approximately 5 h in both groups.

Table 2 lists the types of surgery in the patients studied. Group L had statistically more abdominal aortic surgery than group O; group O had more gastric bypass surgery than group L.

Although not the principal focus of this study, data were also collected on the intraoperative analgesic dosing requirements for fentanyl (Table 3). The average doses for that period were 212 and 275 μg h⁻¹ for group L and group O, respectively (P < 0.001). The measured plasma concentration of fentanyl at the end of surgery was not statistically different between the groups (1.67 and 1.51 ng ml⁻¹ for groups L and O, respectively) (Table 3). This result is not unexpected, since fentanyl dosing was titrated in each patient to the responses of heart rate and blood pressure to surgical stimuli. Before extubation, most of the patients were awake and followed verbal commands (Table 3). After extubation, patients were asked if they were experiencing pain; 86% in group L and 81% in group O reported no pain. The incidence of nausea during the early postoperative period was 33 and 22% for groups L and O, respectively (Table 3).

Analgesic endpoints were reached after surgery within 1 h after arrival at the PACU or POCU in more than 85% of the patients, and within the next 1–2 h in the remaining patients. Fentanyl doses (average for the 4 h postoperative period) are compared between group L and group O in Table 4. Fentanyl doses are designated as dose (μg h⁻¹), dose normalized to TBW, i.e. μg h⁻¹ kg⁻¹ (dose-TBW), and dose normalized to pharmacokinetic mass, μg h⁻¹ kg⁻¹ pharmacokinetic mass (dose-PK mass). The mean values of non-normalized doses in group L and group O [73 (18) and 98 (24) μg h⁻¹, respectively] were statistically different, as were doses normalized to TBW (dose-TBW) [1.04 (0.21) and 0.86 (0.17) μg h⁻¹ kg⁻¹, respectively] (Table 4). However, the mean values of doses normalized to pharmacokinetic mass (dose-PK mass) were essentially identical [1.12 (0.23) and 1.10 (0.21) μg h⁻¹ kg⁻¹ pharmacokinetic mass, respectively] (Table 4).

Plasma fentanyl concentrations (Cpm-analg) and other parameters that were determined in the PACU or POCU at the time when analgesic endpoints were achieved are listed in Table 5. Cpm-analg was not statistically different between groups L and O [1.58 (0.47) ng ml⁻¹ and 1.38 (0.54) ng ml⁻¹, respectively]. There were small statistical differences in respiratory rate and pain relief scores on coughing between group L and group O (Table 5).

No incidence of SpO₂ less than 85% was recorded during the period of postoperative analgesic titration, or overnight. In one obese patient with sleep apnoea, fentanyl infusion was discontinued after midnight because of increased lethargy.
and rising $P_{a\text{CO}_2}$. No serious respiratory morbidity requiring re-intubation or resuscitation occurred in any patient.

**Discussion**

Total body weight-based dosing assumes that fentanyl pharmacokinetics are influenced by TBW in a proportional manner, but there has been no proof for this.\(^2\) Previously,\(^2\) we described a non-linear dosing weight adjustment (pharmacokinetic mass), which proposes that the dose of fentanyl should be determined per kg of pharmacokinetic mass, rather than TBW. The relationship between pharmacokinetic mass and TBW is non-linear, and is shown as a nomogram in the Appendix (Fig. A1A), and for selected body weights in Table A1 of the Appendix. Total body clearance was also measured in the previous study,\(^2\) and it had a similar non-linear relationship to TBW (Appendix Fig. A1B). Our previous findings suggested that pharmacokinetic mass is the dosing weight for fentanyl that reflects the influence of TBW on clearance.\(^2\)

In the present study, the fentanyl dose required to achieve and maintain analgesic endpoints during the 4 h postoperative period had a non-linear profile related to TBW (Fig 1A), similar to that observed previously for the relationship between pharmacokinetic mass and TBW.\(^2\) Also, the dose had a strong linear relationship to pharmacokinetic mass, the intercept approaching zero on the y axis (Fig 1B). This linear relationship between dose and pharmacokinetic mass implies that dosing recommendations for fentanyl to achieve postoperative analgesia can be based on pharmacokinetic mass. The least-squares fit for this relationship indicates a dose of 1.22 $\mu$g h\(^{-1}\) per unit of pharmacokinetic mass = 7.5. If the relationship is forced through the origin, the sums of squares of deviations from linear regression is only increased by 0.7%, and the dose for postoperative analgesia is 1.12 $\mu$g h\(^{-1}\) (or simply 1.1 $\mu$g h\(^{-1}\)) per unit of pharmacokinetic mass.

Although the principal focus of this investigation was an analysis of postoperative analgesic fentanyl requirements over a broad continuum of body weight, and in relation to the derived pharmacokinetic mass, the data afforded the opportunity to compare a number of parameters when the patients were grouped as lean and obese. With comparisons of patient characteristics and types of surgery (Tables 1 and 2), several characteristics, other than obvious body mass measurements, were found to be statistically different between the groups. This included differences in age, ASA class and types of surgery. Therefore, we tested whether any of these factors could have contributed to the slope of the relationship between postoperative analgesic fentanyl requirements and pharmacokinetic mass (Fig. 1B). The Pearson correlation coefficient between fentanyl dose ($\mu$g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass) and age for all of the patients was $-0.199$, and was not statistically significant. The Spearman rank correlation coefficient between fentanyl dose ($\mu$g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass) and ASA class for all patients was $-0.041$; this was not statistically significant. Group L patients had a predominance of abdominal aortic aneurysm surgery, while group O consisted predominantly of gastric bypass cases. The mean (SD) postoperative fentanyl dose ($\mu$g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass) for abdominal aortic aneurysm surgery was 1.13 (0.23); the same measure in gastric bypass cases was 1.11 (0.18) (not statistically different). Although the ratio of male:female patients was not statistically different between lean and obese patients (Table 1), we also examined the analgesic fentanyl differences for our entire patient population. The fentanyl dose in males [mean (SD)] was 1.13 (0.23) $\mu$g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass (the same as above by chance alone) and 1.08 (0.21) for females (not statistically different). It would appear that none of the factors listed above contributed disproportionately to the slope of the relationship between postoperative fentanyl analgesic dose and pharmacokinetic mass (Fig. 1B). It is of interest to note that the mean values for doses listed immediately above all round to 1.1 $\mu$g h\(^{-1}\) per unit of pharmacokinetic mass, which is the value that was obtained when the regression relationship presented in Fig. 1B was forced through the origin.

The apparent advantage of basing dose on pharmacokinetic mass was borne out by the data that were obtained for dose comparisons when the patients were grouped as lean and obese (Table 4). The mean dose normalized to TBW was significantly higher in group L vs group O (1.04 vs 0.86 $\mu$g h\(^{-1}\) kg\(^{-1}\), respectively), but was essentially identical when normalized to pharmacokinetic mass (1.12 vs 1.10 $\mu$g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass, respectively).

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**Table 5** Plasma fentanyl concentrations and analgesic and respiratory endpoints obtained by continuous infusion of fentanyl. *P<0.05 vs group L. Group L, lean group; group O, obese group; Cpm-analg, plasma fentanyl concentration at a time that most closely approximated when analgesic endpoints were achieved; RR, respiratory rate. Wakefulness score: 1, no response to shake; 3, eyes closed, response to voice; 5, awake and eyes open. Pain relief score: 1, intolerable pain; 3, tolerable pain; 5, no pain

<table>
<thead>
<tr>
<th>Cpm-analg (ng ml(^{-1}))</th>
<th>$P_{a\text{CO}_2}$ (mm Hg)</th>
<th>RR (min(^{-1}))</th>
<th>$Sp_{\text{O}_2}$ (%)</th>
<th>Wakefulness (median)</th>
<th>Pain relief at rest (median)</th>
<th>Pain relief on coughing (median)</th>
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<td>Group L (n=36)</td>
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<tr>
<td>Mean</td>
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<td>sd</td>
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<tr>
<td>Mean</td>
<td>1.38</td>
<td>44</td>
<td>20(^a)</td>
<td>97</td>
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<td>3</td>
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<td>sd</td>
<td>0.54</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3(^a)</td>
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Plasma concentrations at the end of surgery (Cpm-end-surg; Table 3) were only slightly higher than those found when the postoperative analgesic endpoints had been reached (Cpm-analg; Table 5); the mean values were 1.67 and 1.58 ng ml\(^{-1}\), respectively, for group L patients and 1.51 and 1.38 ng ml\(^{-1}\), respectively, for group O patients (Tables 3 and 5). A majority of the patients answered ‘no pain’ when queried after extubation (Table 3), and it appears that a quasi-steady state in plasma fentanyl concentrations existed in the early postoperative period and that a stable analgesic state was easily achieved, usually within 1 h after admission to the PACU or POCU.

Although the average plasma fentanyl concentrations required for postoperative analgesia without significant respiratory depression approximated 1.5 ng ml\(^{-1}\) in both lean and obese patients, there were relatively large inter-individual variations, as evidenced by the standard deviations in Cpm when analgesic endpoints had been reached (Table 5).

As noted above, we did not find a significant influence of age on the fentanyl dose required for postoperative analgesia during the 4 h postoperative period. The literature generally supports the notion that elderly patients should receive lower doses of opioids.\(^5\) Recently, Aubrun and colleagues\(^6\) reported that the doses of intravenous morphine titrated by nurses for postoperative analgesia were not significantly different between the younger and elderly patients. The authors commented that their study did not disprove the hypothesis that elderly patients are more sensitive to opioids. Our present study was not designed to study the influence of age on fentanyl dosing, and the intersubject variation in Cpm-analg, as evidenced by the standard deviations, was substantial (Table 5). Therefore, we also do not believe that our data disprove the perceived association of increased sensitivity to the analgesic effects of fentanyl in the elderly. However, age did not appear to be a significant determinant of fentanyl dosing for postoperative analgesia in the immediate postoperative period. Likewise, as also noted above, analgesic requirements for fentanyl in our relatively small patient population were found to be independent of ASA class, gender, and type of surgery, and would be expected to be satisfied on average by an infusion of 1.1 \(\mu\)g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass. (The pharmacokinetic mass equivalent for TBW can be estimated from the nomogram, Fig. A1, or Table A1 in the Appendix.)

Although the optimal blood concentration of fentanyl for adequate analgesia may vary in each patient, our data suggest that a postoperative infusion rate of 1.1 \(\mu\)g h\(^{-1}\) kg\(^{-1}\) pharmacokinetic mass, on average, would serve as a starting point for individual titration, thus avoiding a gross overdose or undertose. It might be expected that a refinement of preemptive analgesia to prevent exposure to the stress response of pain would be advantageous.

In summary, we observed that the relationship between the fentanyl doses (\(\mu\)g h\(^{-1}\)) required to achieve and maintain postoperative analgesic endpoints and TBW had a non-linear profile (Fig. 1A). This profile is similar to those reported previously for the relationships between pharmacokinetic mass \(vs\) TBW, and total body clearance \(vs\) TBW (Appendix).\(^2\) In comparison, a strong linear relationship was found between fentanyl dose and pharmacokinetic mass over the entire body weight range (Fig. 1B). The slope of this relationship would be expected to be steeper (i.e. higher dose requirements) during surgery, but it is our expectation that it would remain linear in relation to pharmacokinetic mass. This relationship may provide confidence that fentanyl dose normalized to pharmacokinetic mass may be more useful clinically than that based on TBW. Also, from our findings, TBW-based dosing would be predicted to mediate towards overdosing in obese patients.

Acknowledgement

Financial Support was provided solely from institutional and departmental sources.

Appendix

Data derived from our previous publication\(^2\) are presented as background material and for reference (Table A1).
Table A1  Pharmacokinetic mass (PK) weights for selected total body weights. PK mass is calculated from the formula: PK mass=52/[1+(196.4e^{0.025 TBW_}-53.66)/100], as described in reference 2. The data are rounded to whole numbers for convenience; rounding errors are <1% in all cases. TBW, total body weight; PK mass, pharmacokinetic mass.

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