Original article

Clinical evaluation of target controlled infusion system for sufentanil administration

ZHAO Yan, ZHANG Li-ping, WU Xin-min, JIANG Jian-yu, DUAN Jing-li, HU Yong-fang, LI Min, LIU Wei, SHENG Xiao-yan, NI Cheng, XU Mao and GUO Xiang-yang

Keywords: *anesthesia; analgesic; sufentanil; target-controlled infusion; tandem mass spectrometry*

Background Sufentanil target controlled infusion (TCI) provides stable analgesia, better hemodynamic control than a bolus injection of intravenous anesthetics, anticipated recovery and improved quality of anesthesia during perioperative period. This study evaluated the accuracy and feasibility of TCI system for sufentanil at high concentrations in Chinese surgical patients.

Methods Twelve low risk adult patients undergoing elective surgery under general anesthesia were included in this study. Sufentanil was administered with a specific TCI system incorporating the population pharmacokinetic data of sufentanil previously reported, using a target effect-site concentration of sufentanil 4 or 6 ng/ml. Sufentanil TCI duration was 30 minutes. Frequent arterial blood samples were taken during and up to 24 hours after sufentanil TCI for determination of plasma sufentanil concentrations by liquid chromatography-mass spectrometry/mass spectrometry. The changes of circulatory system function during the procedure, recovery profile and adverse effects were recorded. Measured plasma sufentanil concentrations were compared with the values predicted by the TCI system. The bias (median performance error, MDPE), precision (median absolute performance error, MDAPE) and wobble (variability of performance error) of the sufentanil TCI system were determined.

Results All patients had stable cardiovascular variables during induction and maintenance of anesthesia. Time to eye opening and extubation were (5.6±1.7) minutes when TCI set to 4 ng/ml and (7.2±2.3) minutes when set to 6 ng/ml. There was no episode of agitation, muscle rigidity or intraoperative awareness. The bias (MDPE), precision (MDAPE) and wobble of the sufentanil TCI system were –3.7%, 18.9% and 19.6% respectively during TCI, and the MDPE, MDAPE and wobble were –29.1%, 31.7% and 15.0% respectively after TCI (up to 8 hours).

Conclusions The TCI system programmed for sufentanil at 4 or 6 ng/ml was considered acceptable for clinical use in low risk Chinese surgical patients. But the relatively larger MDPE and MDAPE after TCI suggest improvements of the pharmacokinetic model are needed.

Chin Med J 2009;122(20):2503-2508

Target-controlled infusion (TCI) is a significant step forward in the administration of drugs by intravenous infusion and has been successfully implemented in clinical practice.[1,2] TCI can attain desired plasma or effect-site concentrations of an intravenous anesthetic drug using a computer-controlled infusion pump driven by the published pharmacokinetics of the drug. Sufentanil is a new synthetic μ-opioid analgesic characterized by good potency and minimal cardiovascular effects.[3,4] Sufentanil TCI provides stable analgesia, better hemodynamic control than a bolus injection of intravenous anesthetics, anticipated recovery and improved quality of anesthesia during perioperative period.[5,6] However, the predictive accuracy of TCI system for sufentanil when administered in high concentrations and using the pharmacokinetic parameters described by Bovill et al[7] in combined intravenous-inhalational general anesthesia, has not been previously investigated. The aim of this study was to evaluate the predictive accuracy and feasibility of the TCI system (using the population pharmacokinetic variables of sufentanil introduced by Bovill et al) for sufentanil in Chinese surgical patients.

METHODS

Patients

After approval by the medical ethics committee of Peking University and written informed consent was obtained from all patients, twelve patients with American Society of Anesthesiologists (ASA) physical status I or II (healthy or with only mild systemic disease except the local sickness needing surgery), aged 23–76 years, undergoing

DOI: 10.3760/cma.j.issn.0366-6999.2009.20.019
Department of Anesthesiology, Peking University Third Hospital, Beijing 100191, China (Zhao Y, Zhang LP, Jiang JY, Li M, Ni C, Xu M and Guo XY)
Department of Anesthesiology, Peking University First Hospital, Beijing 100034, China (Wu XM)
Department of Pharmacy, Peking University Third Hospital, Beijing 100191, China (Duan JL, Hu YF, Liu W and Sheng XY)
Correspondence to: Dr. JIANG Jian-yu, Department of Anesthesiology, Peking University Third Hospital, Beijing 100191, China (Tel: 86-10-82267271. Email: jiang_jianyu@yahoo.com.cn)
This study was supported by grants from the Anesthesiology Scientific Research Foundation of B. Braun Medical (Shanghai) International Trading Co., Ltd (No. BL09-6-14) and Seed Foundation of Peking University Third Hospital (No. YZZ07-7-11).

elective surgery of anticipated duration more than 3 hours under combined intravenous-inhalational general anesthesia, were prospectively studied. Patients with ASA≥III, aged<18 years, with a history of psychiatric, neurological, cardiac, respiratory, hepatic or renal dysfunction, with uncontrolled hypertension, regular use of opioids or hypnotics, with use of monoamine oxidase inhibitor within 2 weeks before surgery or expected intraoperative blood loss greater than 500 ml, were excluded. Each patient had fasted for at least eight hours before anesthesia and surgery.

Anesthesia and monitoring

After arrival in the operating room, an 18-gauge intravenous cannula was inserted in a forearm vein, and Ringer's lactate solution was infused at a rate of 8–10 $ml \cdot kg^{-1} \cdot h^{-1}$. A radial artery catheter was placed for both continuous arterial blood pressure monitoring and arterial blood sampling. Arterial blood pressure, electrocardiography, heart rate and blood oxygen saturation measured by pulse oximetry were monitored continuously during anesthesia and surgery. Scopolamine 0.3 mg was administered intravenously before anesthesia. General anesthesia was induced by intravenous injection of propofol 1.5–2 mg/kg (at a rate of 1 ml/3–5 seconds) and rocuronium 0.6 mg/kg after onset of unconsciousness to facilitate tracheal intubation, followed by activating a TCI system incorporating the population pharmacokinetic parameters of sufentanil determined by Bovill et al[7-9] (Silugao Science & Technology Co, Beijing, China) to administer sufentanil (Impfstoffwerk Dessau-Tornau, Germany). Depending on the expected duration of surgery, each patient received a sufentanil dosage regimen (target effect-site concentration) of either 4 ng/ml (Group A) or 6 ng/ml (Group B).

After tracheal intubation, the lungs were mechanically ventilated with oxygen-enriched air to maintain an end-tidal partial pressure of carbon dioxide ranging between 30 and 35 mmHg. After induction of anesthesia, a double lumen central venous catheter was inserted into the right internal jugular vein for central venous pressure monitoring and fluid administration. Anesthesia was maintained with sufentanil TCI, inhalation of isoflurane and intermittent intravenous injection of atracurium as needed to keep muscle relaxation. Warm blanket was used to keep nasopharyngeal temperature at 36–37°C.

During anesthesia, hypotension (mean arterial blood pressure, MAP<65 mmHg in patient aged<65 years, or MAP<70 mmHg in patient aged≥65 years, and lasting more than 1 minute) was treated by stepwise reduction in inhaled isoflurane concentration. Additional intravenous fluids were given as deemed appropriate. If this method did not work, further a bolus dose of ephedrine (10 mg) was administered. A bolus dose of atropine (0.25–0.50 mg) was given as necessary to treat bradycardia (heart rate (HR)<50 beats/min). Naloxone (0.1–0.2 mg) was used intravenously by cautious and slow administration if respiratory rate < 10 breaths/min in the recovery room.

Sampling time and processing of blood samples

Arterial blood samples (1.5 ml) were taken before the start of anesthesia and at 1, 3, 5, 10, 15, 20, 25, 30 minutes during sufentanil TCI, then at 1, 2, 4, 6, 8, 10, 15, 30, 45 minutes, and 1, 2, 4, 6, 8, 10, 12, 24 hours after sufentanil TCI. Blood samples were collected in heparinized tubes, centrifuged (4000 r/min for 10 minutes), and the plasma obtained frozen (–40°C) for storage until time of analysis.

Assay of plasma sufentanil concentration

Plasma sufentanil concentrations were determined by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS).[10,11] LC-MS/MS analysis was performed with an Agilent 1100 high performance liquid chromatography system (Agilent Technology, USA) and an API 3000 triple quadrupole mass spectrometer equipped with a TurboIon Spray source (Applied Biosystems, USA), run by Analyst software (Version 1.4). A linear gradient elution system was applied. The mobile phase consisted of 10 mmol/L ammonium acetate (pH=3.0) and acetonitrile with flow rate of 300 μl/min. Ratios of analyte peak area and internal standard peak area (y-axis) were plotted against concentration (x-axis), then standard curve and regression equation were calculated ($y=1.27x+0.0132$, coefficient correlation $r=0.9976$, weighting coefficient was $1/x^2$, the linear range of the plasma sufentanil concentration was 0.005 ng/ml to 40 ng/ml), and sufentanil concentration of each blood sample was calculated thereafter. The limit of quantitation was 0.005 ng/ml (5 pg/ml).

Other clinical observations

Systolic and diastolic arterial blood pressure (SAP and DAP), and HR values were recorded at baseline (after each patient having ten minutes resting time before drug administration), then at 1, 5, 10, 30 minutes during TCI and the end of surgery. Duration of surgery, time to eye-opening and extubation from the end of surgery, total sufentanil dose, the use of ephedrine, atropine or naloxone and adverse effects (agitation, muscle rigidity, postoperative nausea, vomiting and intraoperative awareness) were recorded.

Statistical analysis

The statistical analysis was performed with SPSS 11.5 (SPSS Inc., Chicago, IL, USA). Predictive accuracy of the sufentanil TCI system was evaluated by examining the performance error (PE), median performance error (MDPE), median absolute performance error (MDAPE) and wobble[12-15] in the present study. For each blood sample, the PE was calculated as follows: PE_{ij} $(\%)=(Cm_{ij}-Cp_{ij})/Cp_{ij}\times 100$, where Cm_{ij} is the measured plasma sufentanil concentration in sample j from patient i, and Cp_{ij} is the predicted plasma sufentanil concentration in the same sample. Subsequently, the intrasubject bias and precision of the TCI device were assessed by

determination of the MDPEi and MDAPEi. Wobble measures the intrasubject variability of performance error. They were calculated as follows: $MDPE_i(\%)$=median $\{PE_{ij}, j=1, \ldots, N_i\}$; $MDAPE_i(\%)$=median$\{|PE|_{ij}, j=1, \ldots, N_i\}$; $wobble_i$ (%)=median$\{|PE_{ij}-MDPE_i|, j=1, \ldots, N_i\}$, where N_i is the number of PE values obtained from patient i. The pooled MDPE, MDAPE, and wobble of the sufentanil TCI system were estimated by examing them over 261 blood samples (during and up to 8 hours after sufentanil TCI).

The quantitative data were expressed as mean±standard deviation (SD) unless stated otherwise or median for data that were not normally distributed (PE, |PE| and |PE–MDPE|). The one-way analysis of variance (ANOVA) followed by LSD post hoc test for repeated measurements was used to compare multiple-time consecutive variables (cardiovascular data). The comparisons of measured and predicted sufentanil concentrations for the same blood sample were done using the paired-samples *t* test. The independent-samples *t* test was used to compare measured sufentanil concentrations between the two groups at the same time. Statistical significance was defined by two-tailed $P<0.05$.

RESULTS

General and perioperative characteristics

Demographics and perioperative characteristics of the 12 patients are summarized in Table 1. One patient was transferred to intensive care unit (ICU) with continued tracheal intubation after operation because of complex and long-lasting surgery (12.7 hours). Naloxone was administered in another patient because of a notably shorter duration of surgery than expected. The types of operations included abdominal cystectomy, right hemicolectomy, radical colectomy, thoracic cystectomy, pancreatoduodenectomy, pancreatic cystectomy, total gastrectomy and radical rectectomy. There was no episode of agitation, muscle rigidity or intraoperative awareness in any patient.

Table 1. Patient demographics and perioperative characteristics

Items	Mean±SD (Range) or number
Age (years)	56±17 (23–76)
Gender (male/female)	5/7
Body mass index (kg/m^2)	20±3 (17–27)
Total sufentanil dose (μg/kg)	7.2±1.5 (5.7–8.8)
Duration of surgery (hours)	6.7±2.6 (3.5–12.7)
Time to eye opening (minutes)	5.6±1.7 (1–7)
Time to extubation (minutes)	7.2±2.3 (3–10)
Using of ephedrine	3
Using of atropine	4
Using of naloxone	1
Postoperative nausea and vomiting	2

Cardiovascular changes during anesthesia and surgery

All patients had comparable and stable cardiovascular variables during induction and maintenance of anesthesia. The changes of arterial blood pressure and heart rate are listed in Table 2.

Table 2. Cardiovascular changes at the different time (*n*=12, mean±SD)

Variables	Baseline	During TCI (minutes)			End of surgery
		1	5	10	30	
SAP (mmHg)	133±14	116±12†	110±11†	114±11†	121±10*	127±12
DAP (mmHg)	80±9	69±8†	66±7†	67±8†	69±7†	75±7
HR (beats/min)	81±14	70±12*	68±11†	67±12†	65±10†	77±11

Baseline: baseline values before drug administration. TCI: target-controlled infusion. SAP: systolic arterial blood pressure. DAP: diastolic arterial blood pressure. HR: heart rate. $^{*}P<0.05$, $^{\dagger}P<0.01$ vs baseline values.

Measured and predicted plasma sufentanil concentrations

The changes of measured and predicted plasma sufentanil concentrations of the sufentanil TCI system (during and up to 24 hours after sufentanil TCI) are shown in Table 3. The correlations between the measured and predicted plasma sufentanil concentrations during and after sufentanil TCI (up to 8 hours) are displayed in Figures 1 and 2.

Table 3. Changes of measured and predicted plasma sufentanil concentrations in the two groups (ng/ml, *n*=6)

Time	Group A		Group B	
	Cp	Cm	Cp	Cm
During TCI				
1 minute	16.2	20.1±6.5	22.3	31.0±3.2†‡
3 minutes	7.3	6.6±1.0	12.1	15.6±8.5§
5 minutes	4.5	4.2±0.5	7.1	8.1±3.0§
10 minutes	4.0	4.0±0.6	6.0	6.6±1.9§
15 minutes	4.0	4.0±0.6	6.0	5.7±1.5§
20 minutes	4.0	3.8±1.3	6.0	5.6±1.9
25 minutes	4.0	3.7±0.9	6.0	5.1±1.0§
30 minutes	4.0	3.7±1.4	6.0	5.6±1.3§
After TCI				
1 minute	3.50	3.11±1.02	5.40	4.85±0.70‡
2 minutes	3.25	2.66±1.17	4.92	4.53±1.16§
4 minutes	2.92	2.35±0.86	4.40	3.74±1.03§
6 minutes	2.70	2.19±0.86	4.02	3.37±0.82§
8 minutes	2.53	1.45±0.47†	3.80	2.89±0.70*‡
10 minutes	2.38	1.55±0.50*	3.61	2.51±0.47†‡
15 minutes	2.06	1.35±0.56*	3.12	2.17±0.51†§
30 minutes	1.42	0.94±0.38*	2.10	1.41±0.50*
45 minutes	1.07	0.72±0.37	1.57	1.08±0.43*
1 hour	0.87	0.60±0.25*	1.27	0.85±0.40*
2 hours	0.55	0.38±0.20	0.80	0.58±0.29
4 hours	0.305	0.210±0.062*	0.442	0.358±0.199 (*n*=5)
6 hours	0.164	0.138±0.036	0.230	0.226±0.128
8 hours	0.090	0.115±0.037 (*n*=4)	0.131	0.191±0.153
10 hours	0.062	0.093±0.026*	0.078	0.183±0.181
12 hours	0.029	0.079±0.020†	0.042	0.148±0.122
24 hours	0.0005	0.046±0.013 (*n*=4)†	0.001	0.054±0.040 (*n*=5)*

TCI: target-controlled infusion. Group A: target sufentanil concentration was 4 ng/ml. Group B: target sufentanil concentration was 6 ng/ml. Cp: predicted plasma sufentanil concentrations of TCI system. Cm: measured plasma sufentanil concentrations. $^{*}P<0.05$, $^{\dagger}P<0.01$ vs Cp in the same group. $^{\S}P<0.05$, $^{\ddagger}P<0.01$ vs Cm in the Group A.

Predictive accuracy of the sufentanil TCI system

MDPE (bias), MDAPE (precision) and wobble for appraising predictive accuracy of the TCI system (during and up to 8 hours after sufentanil TCI) are shown in Table 4.

DISCUSSION

The present study is the first clinical experience with the

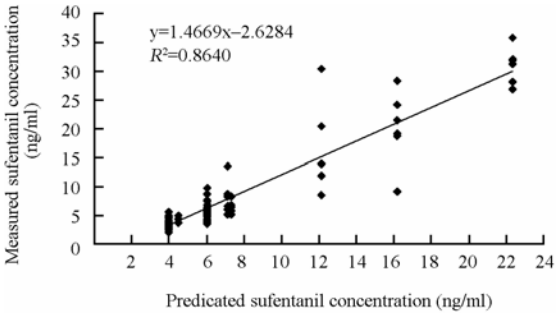

Figure 1. Correlation between the measured and predicted plasma sufentanil concentrations during target-controlled infusion.

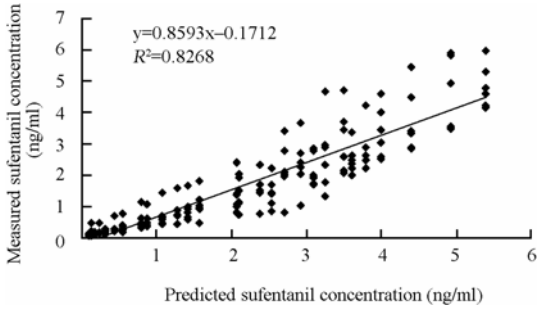

Figure 2. Correlation between the measured and predicted plasma sufentanil concentrations after target-controlled infusion (1 minute–8 hours).

Table 4. Accuracy of the sufentanil TCI system (during and up to 8 hours after sufentanil TCI)

Time	Number of samples	MDPE (%)	MDAPE (%)	Wobble (%)
During TCI (1–30 minutes)	96	–3.7	18.9	19.6
After TCI (1 minute–8 hours)	165	–29.1	31.7	15.0

TCI: target-controlled infusion. MDPE: median performance error. MDAPE: median absolute performance error.

TCI system incorporating the pharmacokinetic parameters of high-dose sufentanil as reported by Bovill et al[7] for sufentanil. The results demonstrated that all patients had stable cardiovascular variables during anesthesia. There was no obvious adverse effect. The MDPE, MDAPE and wobble were –3.7%, 18.9% and 19.6% respectively during TCI, and they were –29.1%, 31.7% and 15.0% respectively after TCI (up to 8 hours), showing that the TCI system was considered acceptable for clinical use in Chinese surgical patients. But the relatively larger MDPE and MDAPE after TCI suggest improvements of the pharmacokinetic model are needed.

TCI has revolutionised the administration of intravenous anesthetics.[16-21] A stable blood drug concentration is achieved rapidly and maintained with TCI, allowing the anesthetist to monitor therapeutic effect and adjust the drug concentration according to clinical requirements. However, pharmacokinetic variation between patients will result in difference in actual concentration of the drug. Information on the predictive accuracy of any TCI system is important to allow comparison with other systems and to provide a baseline for possible future modifications.

Some studies have examined the predictive accuracy or performance of sufentanil TCI system, using the population pharmacokinetic parameters of sufentanil introduced by Gepts[22] or Hudson et al.[23,24] In our previous study, we assessed a sufentanil TCI system (during TCI) incorporating the pharmacokinetic parameters of sufentanil described by Bovill et al[7] in low or medium target concentrations (0.4–0.8 ng/ml) of sufentanil, but neither in high target concentrations of sufentanil nor including the period after TCI.[8] In the present study we confirmed the pharmacokinetic accuracy of Bovill et al′s TCI program parameters for sufentanil at high target concentrations of sufentanil during prolonged surgery in Chinese patients.

In order to evaluate the predictive accuracy or variation of a TCI system, bias (MDPE), precision (MDAPE) and wobble are commonly used.[12-15,24-26] Bias represents the direction of performance error, the positive value indicates a tendency for measured blood concentrations of sufentanil to be higher than predicted concentrations. Negative values express a tendency for measured concentrations to be lower than predicted concentrations. Precision reflects the size of performance error and wobble measures the variability in performance error. Other investigators have suggested criteria for satisfactory performance of a TCI system. Generally, a about mean 20%–30% variation of measured blood concentrations above or below target (predicted) drug concentrations, with a maximum of 50%–60%, can be considered clinically acceptable.[26]

Variability in a TCI device may result from a variety of different possible sources. Particularly, patients receiving TCI do not necessarily belong to the same population as that to determine the original pharmacokinetic model. Furthermore, the blood sample method, assay variability and other factors (including factors affecting the pharmacokinetics, such as the patient age, function of the liver or kidney, plasma protein content, cardiovascular stability, fluid balance, acid-base status and body temperature during the operation）may have influences on the evaluation of a TCI system.

Our previous results showed that age has no significant effect on the measured plasma sufentanil concentrations and accuracy of sufentanil TCI system.[8] The reason might be: TCI was related with pharmacokinetics. With advanced age, although sufentanil pharmacokinetics changes may play a minor role, pharmacodynamics differences are primarily responsible for the decreased sufentanil dose requirement in the elderly.[27] In this study, in order to reduce other influencing factors, we chose the patients with good physical status (ASA I or II, the hepatic or renal function and plasma albumin were normal). We kept the patient cardiovascular stable, fluid balance (Ringer's lactate solution was infused at a rate of 8–10 $ml \cdot kg^{-1} \cdot h^{-1}$ and the intraoperative blood loss was less than 500 ml), while acid-base status and body

temperature were normal (warm blanket was used to keep nasopharyngeal temperature at 36–37°C) during the prolonged surgery.

Pandin et al[15] observed the predicted accuracy of a sufentanil TCI system using the pharmacokinetic parameter set developed by Gepts et al[22] in 10 patients. The TCI system, with acceptable MDPE, MDAPE and wobble (–10.0%, 20.7% and 22.3% respectively), proved to be accurate for predicting plasma sufentanil concentration at low concentrations.

Similarly, selecting the same pharmacokinetic parameter, Slepchenko et al[26] evaluated the accuracy of a sufentanil TCI system in 11 obese patients, and found the MDPE and MDAPE were –13% and 26% respectively also using low concentrations. Therefore, they reported that the pharmacokinetic parameter set derived from a normal-weight population accurately predicted plasma sufentanil concentrations in obese patients. In addition, Hudson et al[24] determined a pharmacokinetic model for sufentanil that can be used to maintain desired target concentrations of sufentanil before cardiopulmonary bypass, with virtually no bias (MDPE was –0.4%) and good precision (MDAPE was 18.4%).

Compared with sufentanil TCI systems used above, Mertens et al[14] explored the predictive performance of remifentanil TCI system using five parameter sets of remifentanil, and found that pooled MDPE and MDAPE of the remifentanil device were –15% and 20% for the parameter set of Minto et al,[28] 1% and 21%, –6% and 21%, and –6% and 19% for the three parameter sets described by Egan et al,[29] and –24% and 30% for the parameter set defined by Drover and Lemmens.[30] Thus, they concluded that remifantanil can be administered by TCI with acceptable bias and inaccuracy. The three pharmacokinetic parameter sets described by Egan et al[29] resulted in the least bias and best accuracy.

In present study, the pooled MDPE, MDAPE and wobble of the sufentanil TCI system were –3.7%, 18.9% and 19.6% during TCI (smaller bias, good precision and acceptable variability), and –29.1%, 31.7% and 15.0% after TCI (approximation of the borderline for acceptable range and lower variability). Our results inferred that the measured plasma concentration of sufentanil is about 3.7% (during TCI) and 29.1% (up to 8 hours after TCI) lower than the predicted plasma concentration. Moreover, our study demonstrated that all patients had stable cardiovascular variables during anesthesia. The time to eye opening and extubation would be not delayed with TCI system for sufentanil administration in high target concentration matching prolonged surgery.

The sufentanil TCI system, using the pharmacokinetic model described by Bovill et al,[7] proved to be accurate (especially during TCI) and feasible (considering overall profile of anesthesia and calculated index) in clinical use. However, the relatively larger MDPE and MDAPE after TCI indicated that the pharmacokinetic model could use minor corrections for use in Chinese surgical patients. We assessed the accuracy of the sufentanil TCI system during and after TCI (up to 8 hours). The data from 10–24 hours after TCI completion were not included. There are two reasons for this. Firstly, Bovill et al[7] sampled blood and measured plasma sufentanil concentrations only for 8 hours after a bolus intravenous injection of sufentanil for determining its pharmacokinetics. Secondly, the majority of the measured and predicted sufentanil concentrations were too low to have significant clinical meanings (effect on circulatory, respiratory function or analgesia) in this period.

We also compared the measured and predicted plasma sufentanil concentrations during and up to 24 hours after sufentanil TCI within group and the measured sufentanil concentrations between the two groups. Over the entire duration of sufentanil TCI, the Bovill model[7] predicted plasma sufentanil concentrations well (P >0.05, compared with measured sufentanil concentrations) in each group (Table 3, except for 1 minutes during TCI in the group B because that sufentanil concentrations between plasma and effect-site did not reach the steady-state). Afterwards, from 8 minutes after TCI, the differences between the measured and predicted sufentanil concentrations in each group became statistically significant in some time-points. These results were consistent with the changes of the MDPE, MDAPE and wobble (smaller during TCI, then, larger after TCI).

Despite distinctions in the measured sufentanil concentrations between the two groups (Table 3, P <0.05) during TCI and until 15 minutes after TCI (resulting from the different chosen target concentrations of sufentanil), the measured sufentanil concentrations in the two groups decreased to the similar levels (P >0.05) from 30 minutes after TCI, reflecting the feature of sufentanil pharmacokinetics when administered by TCI (rapid elimination and little accumulation).[6,27]

The limitations of our study are the smaller number of patients and shorter TCI duration because of considering administration for sufentanil in high concentrations and avoiding delayed postoperative recovery. Further studies are required to evaluate the predictive accuracy of sufentanil TCI systems incorporating the pharmacokinetic parameters of sufentanil developed by other investigators (for example, Gepts et al[22] or Hudson et al[23]) in large scale randomized controlled trials, with low or medium target sufentanil concentrations commonly used in various Chinese surgical patients.

In summary, the TCI system for sufentanil administered in high concentrations was considered acceptable for clinical use in Chinese surgical patients (ASA I or II). But the relatively larger MDPE and MDAPE after TCI suggest requiring improvements of the pharmacokinetic model.

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(Received March 11, 2009)
Edited by GUO Li-shao