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Predictive performance of 'Diprifusor' TCI system in patients during upper abdominal surgery under propofol/fentanyl anesthesia*

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Abstract: Objective: To evaluate the predictive performance of 'Diprifusor' TCI (target-controlled infusion) system for its better application in clinical anesthesia. Methods: The predictive performance of a 'Diprifusor' TCI system was investigated in 27 Chinese patients (16 males and 11 females) during upper abdominal surgery under total intravenous anesthesia (TIVA) with propofol/fentanyl. Measured arterial propofol concentrations were compared with the values predicted by the TCI infusion system. Performance was determined by the median performance error (MDPE), the median absolute performance error (MDAPE), the divergence (the percentage change of the absolute PE with time), and the wobble (the median absolute deviation of each PE from the MDPE). Results: The median (range) values of 14.9% (–21.6%~42.9%) for MDPE, 23.3% (6.9%~62.5%) for MDAPE, –1.9% h^{-1} (–32.7%~23.0% h^{-1}) for divergence, and 18.9% (4.2%~59.6%) for wobble were obtained from 227 samples from all patients. For the studied population, the PE did not increase with time but with increasing target propofol concentration, particularly following induction. Conclusions: The control of depth of anaesthesia was good in all patients undergoing upper abdominal surgical operation and the predictive performance of the 'Diprifusor' target controlled infusion system was considered acceptable for clinical purposes. But the relatively bigger wobble showed that the pharmacokinetic model is not so suitable and requires improvement.

Key words: Target-controlled infusion (TCI), 'Diprifusor' TCI system, Predictive performance assessment, Wobble, Infusion
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INTRODUCTION

Target-controlled infusion (TCI) devices offer a means for producing relatively stable, controllable plasma concentrations of drugs administered intravenously (Absalom and Kenny, 2003; Mertens *et al*., 2003). Drug administration by iv boluses produce rapid fluctuations in plasma drug concentrations, whereas a constant rate infusion produces plasma concentrations that slowly rise to reach a stable concentration only after 5–7 drug elimination half-lives (in the usual clinical situation, 3–4 elimination half-lives are the accepted standard). TCI was introduced for research purposes years ago, with computer-driven infusion pumps using two- or three-compartment pharmacokinetic (pk) models (Schuttler and Ihmsen, 2000; Li and Rui, 2003). A commercial target-controlled infusion system for propofol is now available ('Diprifusor' TCI, Zeneca Pharmaceuticals, Macclesfield, UK) in China and large hospitals have begun to use it for research purposes.

TCI devices allow the anesthetist to provide anesthesia by controlling the theoretical (predicted) concentration of the drug in the central compartment. Rapid changes in the depth of anesthesia are therefore possible with similar ease to that achieved with in-

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halational anesthesia. But unlike inhalational anesthesia, where the end-tidal concentration of vapors can be monitored, on-line blood concentration monitoring is not practical at the present time. The accuracy (predicted vs measured blood concentration) is not only dependent on the pk parameters, but also on the variability of the pk parameters within the population. Pharmacokinetic parameters incorporated into 'Diprifusor' TCI systems were proposed by Gepts *et al*.(1987) and later modified by Marsh *et al*.(1991) and may be different from Chinese patients'.

The purpose of this study was to assess the predictive performance of the commercially available 'Diprifusor' TCI system in Chinese patients. Performance may vary with time and chosen target concentrations. Therefore, it was assessed by comparing measured concentrations of propofol with concentrations predicted by 'Diprifusor' system in subjects undergoing upper abdominal surgical operation at various time-points during anesthesia and for different calculated blood concentrations. In addition, the overall performance was based on its ability to accomplish its intended purpose of achieving and maintaining target concentrations of propofol, which were clinically acceptable for induction and maintenance of anesthesia in patients.

SUBJECTS AND METHODS

The study was approved by the Hospital Research Ethics Committee and written informed consent was obtained from all patients before the start of the study. Twenty-seven ASA I, II patients scheduled for elective abdominal surgery expected to last for 2–5 h under general anesthesia were recruited. Patients were not studied if they had serious impairment of respiratory, cardiovascular, hepatic, renal, hematic or endocrine function; or if they were receiving medication likely to influence the course of anesthesia.

Patients did not receive any premedication. In the operating room, one iv cannula was inserted into a large forearm vein for infusion of propofol only and the another in the contralateral arm for infusion of fluid, fentanyl and vecuronium. A radial artery catheter was inserted for both arterial blood sampling and continuous measurement of arterial blood pressure. In addition the AEP index (audio evoked potential index), BIS (Bispectral index), ECG, heart rate, end-tidal carbon dioxide partial pressure and oxyhemoglobin saturation (SpO_2) were monitored continuously throughout the study.

Before induction of anesthesia, patients received a crystalloid solution (Ringer's solution) of 20 ml/kg. Immediately before induction of anesthesia with propofol, all subjects received fentanyl 3 μg/kg for 30 s followed by a continuous infusion (Graseby 3100 pump) of fentanyl, 2 μg/(kg·h) for 30 min, 1.5 μg/(kg·h) from 31–150 min, and 1 μg/(kg·h) until 30 min before skin closure. Propofol was administered with a Graseby 3500-syringe pump (Graseby Medical, Watford, UK) integrated with 'Diprifusor' (controller and software, including the pharmacokinetic model for propofol only). The propofol blood target concentration (C_T) for induction of anesthesia was set at 4 μg/ml for the younger patients and 3 μg/ml for the elderly. If anesthesia was not induced within 5 min, the C_T was increased sufficiently to complete the induction of anesthesia. When consciousness was lost, vecuronium, 0.1 mg/kg, was given and trachea intubated; the lungs of the patients were then mechanically ventilated with oxygen, with ventilation adjusted to maintain the end-tidal carbon dioxide partial pressure between 4–4.5 kPa and arterial oxygen saturation above 95%.

During maintenance of anesthesia, the anesthetist could increase or decrease the propofol C_T at any time, titrating according to the patient's response and the degree of surgical stimulation. In the absence of signs of inadequate anesthesia, it was titrated downwards to avoid maintaining propofol concentrations higher than clinically necessary. Arterial blood samples (5 ml) for measurement of propofol concentration were drawn from the indwelling radial arterial cannula at the following intervals: before and at 2 and 5 min after the start of the infusion; two to five samples during the maintenance stage, before and 2 and 5 min after stopping the infusion. In this way, a total of 8–14 arterial blood samples were collected from each patient. All samples were collected in heparinized tubes and centrifuged within 30 min of collection. The plasma was transferred to polypropylene tubes and frozen at –20 °C until assayed. Propofol concentrations in plasma were measured within 14 weeks by

high-pressure liquid chromatography with fluorescence detection (Plummer, 1987). The propofol concentration calculated by the TCI system was recorded every time a sample was taken. In addition, the quality of induction was assessed as good (smooth induction, no problem); adequate (minor problems, but easily managed) or poor (significant problems). Maintenance of anesthesia, the overall ease of control of anesthesia and cardiovascular stability were also assessed, and the total doses of fentanyl and propofol were recorded.

The performance error (PE) data from each subject were evaluated according to the recommendations of Varvel *et al*.(1992). We proposed that the size of the error, bias, divergence, and wobble summarizes the clinically relevant characteristics of 'Diprifusor' TCI system. The median of absolute PE (MDAPE) indicates the inaccuracy of TCI while the median of PE (MDPE) reflects the bias. Divergence is a measure of how the resulting drug concentrations in a subject are affected by time. It is defined as the slope of the linear regression equation of absolute values of PE against time and is expressed in units of percentage divergence per hour. A positive value indicates progressive widening of gap between predicted and measured concentrations, whereas a negative value reveals that the measured concentrations converge on the predicted values. Wobble is another index of the time-related changes in performance and measures the intrasubject variability in performance errors.

For each blood sample the performance error (PE) of the predicted concentration in plasma was calculated according to the formula (Varvel *et al*., 1992).

$$PE=(C_m-C_p)/C_p\times 100\%$$

where C_m and C_p are the measured and calculated plasma propofol concentration respectively.

For all patients, median values for MDPE, MDAPE, divergence and wobble were calculated. All of the data analysis was performed in Microsoft Excel 2000.

RESULTS

Sixteen men and 11 women were included in the study. Demographic information is summarized in Table 1.

Table 1 Characteristics of the subjects (n=27)

Demographic characteristics	All patients
Age (years)*	17–68 (46±15.6)
Gender (M:F)	16:11
Weight (kg)*	45–86 (61±10.6)
Height (cm)*	106–175 (162±15.0)
ASA (I:II)	7:20
Induction dose of propofol (mg/kg)*	0.55–1.51(1±0.2)
Maintenance C_T (μg/ml)*	2.5–5.5 (4±0.7)
Total dose of propofol (mg)*	621–2370 (1156±405.6)
Total dose of fentanyl (μg)*	253–662 (376±94.6)
Duration of anesthesia (min)*	47–496.5 (161±87.1)

* Data are expressed as range (mean values±*SD*)

The lower limit of detection was approximately propofol 16 ng/ml in plasma. The coefficient of variation of the HPLC method did not exceed 10% in the concentration range encountered in this study.

The propofol C_T was adequate for induction in all patients. The quality of induction was assessed as good in all patients. The quality of maintenance and ease of control of anesthesia were assessed as good in all patients. Hemodynamic effects and recovery times were similar to those expected with conventional administration techniques using the same drugs.

The median values for MDPE, MPAPE, divergence, and wobble are depicted in Table 2. Regression analysis revealed that the coefficient of relation between measured and predicted concentration was 0.86 (y=0.6045x+1.077112, where y stands for measured concentration, x for calculated concentration).

Table 2 MDPE, MDAPE, divergence and wobble for all patients

	All patients
MDPE (%)*	14.9 (–21.6~42.9)
MDAPE (%)*	23.3 (6.9~62.5)
Divergence (%/h)*	–1.9 (–32.7~23.0)
Wobble (%)*	18.9 (4.2~59.6)

* Data are expressed as medians (range)

Fig.1 depicts a scatter diagram with measured propofol concentrations plotted against the predicted values displayed when all samples were collected. The 95% confidence interval for the ratio of measured to calculated concentrations extended from 0.53 to 1.67 (median 1.07). Thus, if one sample were taken, 95% of blood propofol concentrations would be ex-

pected to lie within –47%~33% of TCI system prediction. Consistent with the positive value of MDPE, measured concentrations tended to be greater than calculated concentrations.

Fig.2 shows how the errors (measured-predicted) obtained from all 227 blood samples related to predicted values and shows that the performance error was positive with higher predicted blood concentrations. Fig.3 shows performance error variation vs the time after administration of propofol. The values of errors were positive during the introduction of anaesthesia, negative during the maintenance of anaesthesia. However, when MDPE (one value per patient) was plotted against the calculated concentration for middle maintenance period, no obvious relationship was seen (Fig.4). Fig.5 depicts the patients with the best, median and worst performance (based on ranked MDAPE values).

DISCUSSION

The positive value for MDPE indicates a tendency for measured blood concentrations of propofol to be higher than calculated concentrations. The performance error tended to positive after induction but negative during maintenance of anesthesia (Fig.3). The under prediction by Diprifusor occurring immediately after start of propofol administration may results in serious side effects such as profound hypotension. Anaesthetist should pay more attention to the setting of induction C_T of propofol when using this system.

The error, however, did not increase with time after administration of propofol, which was demonstrated by the negative divergence (–1.9% h^{-1}) for all patients.

At higher calculated concentrations, the per-

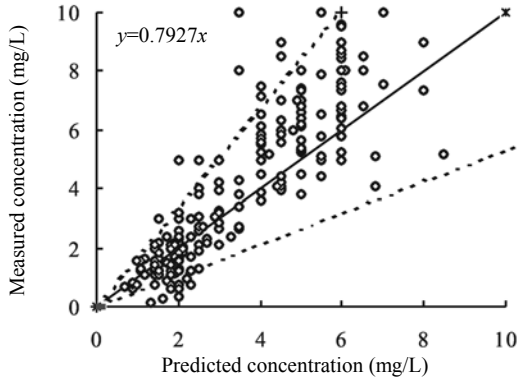

Fig.1 All measured propofol concentrations against calculated concentrations, with the line of identity (solid line) and limits of the 95% population distribution (dotted line)

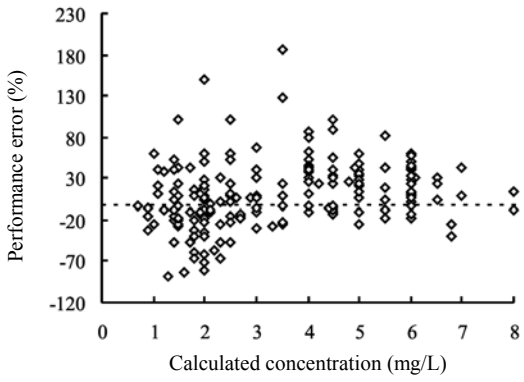

Fig.2 Performance error (%) obtained from 227 blood samples against the calculated concentrations with the horizontal, dotted line indicate *PE*=0

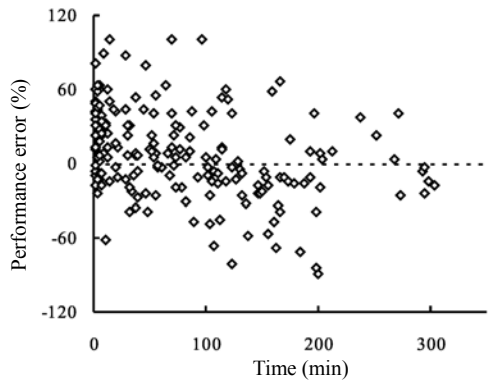

Fig.3 Performance error (%) vs time after administration of propofol with the horizontal, dotted line indicate *PE*=0

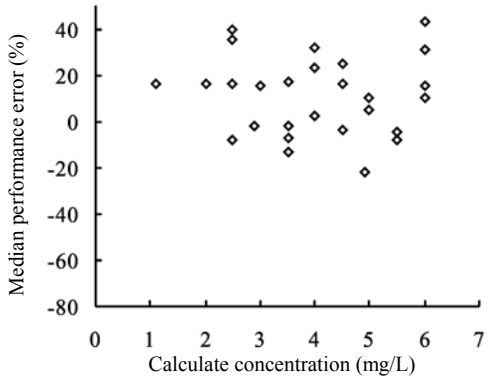

Fig.4 MDPE (%) vs calculated time-averaged middle maintenance period propofol concentration in patient

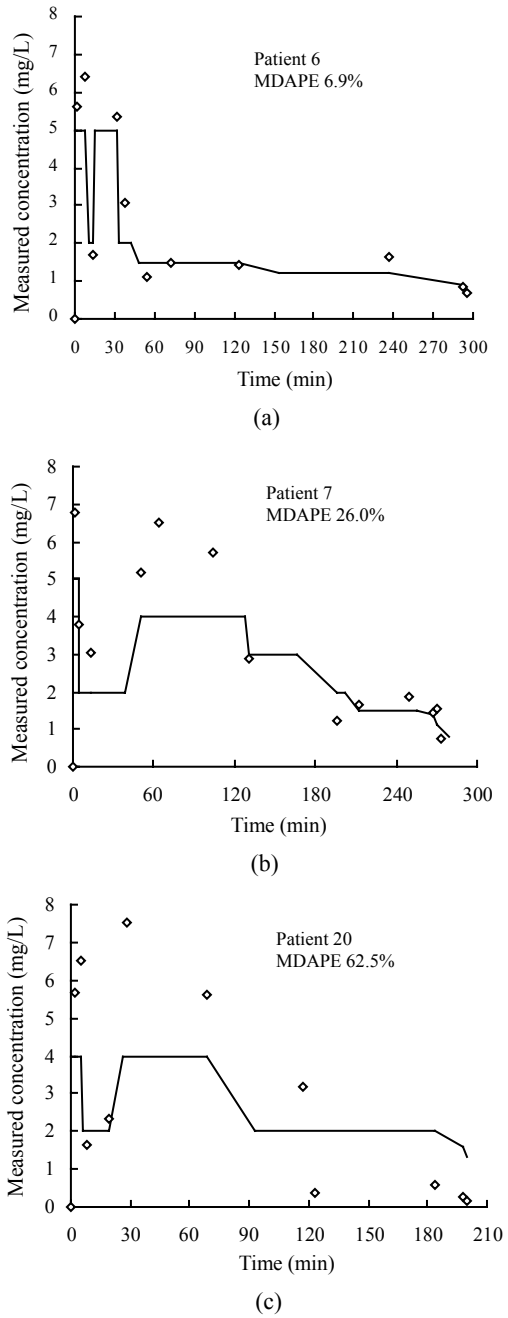

Fig.5 Plots from three individual patients of measured propofol concentrations (diamond) superimposed on calculated propofol concentrations profile (solid line) indicated by the 'Diprifusor' TCI system. (a) Best; (b) Median; (c) Worst performance

formance error values tended to increase (Fig.2). In this situation, the pump flow must be accelerated to maintain high-predicted blood concentrations of propofol. This may result in poor mixing between the blood and the central compartment as postulated by the 3-compartment pharmacokinetics model used in the system. Some lower calculated concentrations were observed as the calculated concentration fell towards a lower target at the end of the procedure. An improved predictive performance during zero pump flow was observed in another study (Swinhoe *et al*., 1998).

Fig.4 shows MDPE vs calculated time-averaged steady propofol concentration. When steady concentration is achieved, the MDPE will not change along with the time or the calculated concentration.

It is not possible to measure effector-site concentrations of propofol. These are likely to be lower than blood concentrations immediately after increases in C_T and higher immediately after decreases in it. In both cases, this would tend to reduce the bias if measured concentrations comparable to effector-site concentrations.

Other studies have examined the predictive performance of TCI system using the same pharmacokinetic parameters as those in 'Diprifusor'. Davidson *et al*.(1993) found mean values of bias and precision of 21% and 30%, respectively, while Swinhoe *et al*.(1998) found bias and precision of 16.2% and 24.1%, respectively, which are similar to those obtained in the present study. On the other hand, Mertens *et al*.(2003) found a minimal degree of bias (median MDPE −15%) when propofol administered by TCI was supplemented with remfentanyl rather than fentanyl. Clearly, further studies are required to clarify the influence of ancillary agents on the pharmacokinetics of propofol and the predictive performance of the 'Diprifusor' system.

The TCI system is used clinically in similar fashion to the vaporizer. That there is usually a difference between predicted and actual concentrations is not of great consequence, provided the actual concentrations are within the desired therapeutic window within which the clinician may make final adjustments to the targeted concentrations. Moreover, the bias with the TCI system (MDPE −10.0%) is smaller than the difference between end-tidal and arterial partial pressures of inhalational anesthetics: after 15 min of isoflurance administration. It had been observed that a mean ratio of arterial to end-tidal partial pressure is 0.78 (Frei *et al*., 1991). After 1 h of administration, the arterial concentration remained about 20% lower than the end-tidal concentration.

There is obviously greater discrepancy between inspired and arterial partial pressure (Dwyer *et al*., 1991).

Performance error with TCI systems may result from errors in the blood sampling technique, assay variability, recording inaccuracy, and so forth. The outlying results shown in Figs.2 and 3 have been included in the overall calculations. This also goes some way towards explaining the wide range of MDPE and MDAPE in Table 2, which may be partly explained by inadequate mixture at greater rates of drug delivery and the inability to measure effector site concentration of propofol as discussed earlier. The principal source of error, however, is interindividual variability of pharmacokinetics, which may be genetic or a result of hemodynamic variations during anesthesia or coadministration of other drugs. Improving the predictive accuracy of the pk model further may require population kinetics or Bayesian forecasting. We concluded that although it may be preferable to administer propofol TCI by using a pharmacokinetic parameter set derived from the population in question, it is acceptable to use a set that had been derived elsewhere. The pharmacokinetic parameter sets adopted by this TCI system proved adequate with acceptable prediction errors, divergence, and wobble. It has been suggested that the performance of a TCI system is clinically acceptable if the bias (MDPE) is no greater than 10%–20% (Glass *et al*., 1990). Assessed on these criteria and the good control of depth of anesthesia achieved in this study, the accuracy of the 'Diprifusor' TCI system can be considered clinically acceptable.

The usefulness of TCI lies in its ability to more accurately maintain stable drug concentrations and to make proportional changes to the concentrations. From a clinical point of view, information on bias and precision is of little practical value. Interpatient pharmacokinetic variability must always be expected, and titration of propofol C_T to achieve a desired effect will be essential to account for this. Such titration is facilitated by the ability to make proportional changes in blood concentration quickly to achieve the desired effect with the 'Diprifusor' TCI system. The small amount of divergence noted in this study indicates that the amount of titration required to accommodate any bias resulting from a mismatch between the patient and the model is likely to be reasonably constant over time. More important than accuracy is the desirability of standardizing the pharmacokinetic model, and hence the performance of 'Diprifusor' (Glen, 1998), so that there is a transferable learning curve for all such delivery systems for propofol.

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