A new system to target the effect-site during propofol sedation

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Background: We evaluated a new, integrated, covariate-adjusted, target-controlled infusion system during sedation with propofol combined with 50% nitrous oxide (N2O) and with propofol only (Air).

Methods: The protocol consisted of sequential 15-minute cycles in 20 volunteers. After a 15-minute control period, propofol was infused to an initial target effect-site concentration of 0.25 μg ml⁻¹ (N2O) or 1.5 μg ml⁻¹ (Air). Subsequently, the target effect-site concentration was increased by 0.25 (N2O) or 0.5 μg ml⁻¹ (Air) for 15 min This sequence was continued until the volunteers lost consciousness as defined by an Observer’s Assessment Alertness/Sedation (OAA/S) score = 2.

Results: Venous plasma propofol concentrations at the beginning (9 elapsed minutes) and end (15 elapsed minutes) of the pseudo-steady state period differed by only 0.00 ± 0.16 μg ml⁻¹ (P = 0.78) during the N2O and 0.00 ± 0.25 μg ml⁻¹ (P = 0.91) during the Air trial. OAA/S scores and bispectral index values, as surrogate measures of pharmacodynamic effect, were not different during this time in either trial. The median (25th, 75th percentiles) of the median performance error (%) was −13 (−24, −1) during the N2O and −18 (−26, −9) during the Air trial. The median absolute performance error (%) was 17 (10, 28) in the N2O and 22 (12, 28) in Air trial. The divergence (%/h) was −10 (−26, 4) in the N2O and 14 (−21, 26) in Air trial. The wobble was 7 (5, 10) in the N2O and 6 (4, 8) in the Air trial.

Conclusions: When tested with venous blood samples, our TCI system for propofol, using a covariate-adjusted, integrated pharmacokinetic model to target effect-site concentrations, demonstrated a clinically acceptable accuracy and stability during mild to moderate sedation.

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Key words: Effect-site; nitrous oxide, propofol; proportional-integral-derivative (PID); sedation; target-controlled infusion.

The rationale for infusion of drugs with short apparent half-lives is the reduction of fluctuating drug concentrations and drug effects. Variability similar to that observed when using inhalation agents must be achieved by choosing an appropriate pharmacokinetic model. The use of a target-controlled infusion (TCI) system, delivering proportional changes based on pharmacokinetic principles, allows titration of the concentration against the clinical effect in individual patients (1) and potentially increases the safety and efficacy of sedation with rapid-onset, short-acting drugs such as propofol (2–4). Targeting effect-site rather than plasma propofol concentration shortens the time to drug effect, without triggering any adverse hemodynamic or respiratory physiology (5, 6). Target-controlled infusion systems speed recovery from general anesthesia and are associated with few postoperative side-effects (7), while they allow the anesthesiologist more time to monitor the patient by decreasing the number of necessary interventions (8).

Although studies have evaluated the accuracy of various TCI devices (9–12), only a few of them have assessed the performance and utility of these devices when they are used to maintain constant plasma concentrations while testing the pharmacodynamic effect (13, 14), and no study has ever tested the performance of a TCI system under steady-state conditions, when an integrated pharmacokinetic model is implemented to target the effect-site.

We have developed a sedation system that uses patient feedback in an open-loop fashion to help adjust a TCI for propofol. The system uses an automated responsiveness test to indicate the sedation level and provide an indication along with other physiologic parameters about the appropriateness of a given target effect-site concentration set by the physician (15). The TCI algorithm implements a
three-compartment single-elimination model (16) with an additional effect-site compartment (17).

We evaluated the performance of our TCI system to target and maintain effect-site concentrations, using proposed kinetic indices (18), as well as recurring steady-state assessments of sedation and bispectral index of the EEG (BIS). We hypothesized that the TCI would maintain a constant plasma propofol concentration and effect at different effect-site targets relevant to the clinical practice of mild to moderate sedation.

Methods

With approval of the University Human Studies Committees and written informed consent, we evaluated 20 healthy volunteers of either sex. Age was restricted to 18–50 years. The volunteers simultaneously participated in a study of responsiveness during sedation with propofol and propofol combined with N2O (15).

Target-controlled drug delivery

The drug delivery system consisted of a Harvard 2 (Harvard Clinical Technology, South Natick, MA) electronic syringe pump, which can be commanded by a host system through an RS232 serial communication port. For the host system we used a Pentium II 450 MHz microprocessor-based system.

We used a three-compartment mamillary model for propofol, which includes age, weight, height, lean body mass, and gender as covariates (16). An effect-site compartment was implemented according to the method described by Shafer and Gregg (19) with a rate governing the migration of the drug from the effect-site back to the central compartment, \( k_{12} = 0.456 \text{ min}^{-1} \) (17). The differential equations that describe the distribution of the infused drug over time to the four compartments and the drug mass eliminated from the body were solved by Euler’s numerical method using a time step of 1.2 s (50 steps min\(^{-1}\)). We verified that Euler’s method was implemented correctly by implementation of the equations in an Excel spreadsheet and comparing the calculated values for drug concentration that result from a constant infusion rate simulation with results from Matlab (The MathWorks, version 5.0, Natick, MA) and Stanpump implementation.

The infusion algorithm was implemented using a proportional-integral-derivative (PID) technique (20) to control the output of the system. The controller commands infusion rates to the pump based on the current error (difference between target concentration and current predicted concentration), the time derivative of that error, and the integral of that error over time. The PID controller implementation was simulated using Matlab and compared with the controller implemented with Excel system equations in order to qualify the Excel system equations in order to qualify the Excel spreadsheet output. Subsequently, the PID controller was tested over a range of subject characteristics (gender, age, weight, and height) that impact the pharmacokinetic (PK) model parameters and hence the controller.

Our PK model simulations indicated that pseudo steady-state effect-site concentrations would be obtained within 4 min. Finally, the actual PID controller implementation within our system was validated against the Excel implementation to assure that the TCI algorithm contained no errors. In addition, a posteriori calculation of the effect-site and plasma propofol concentrations using the Rugloop simulation software (Rugloop \( ^{\text{R}} \) Propofol calculations validation, Revision 1.01, Bvba Demed, Belgium), with the drug amount dispensed to target specific concentrations in two different volunteers, showed virtually identical results. Rugloop uses an integrated effect-site PK set (16, 17) and calculates the \( k_{12} \) in order to reach a time to peak effect of 1.6 min after bolus infusion. For the above-mentioned simulation we set to \( k_{12} = 0.456 \text{ min}^{-1} \).

In summary, all the alternative calculations and comparisons verified the proper functionality of our system’s PK model and PID controller. In addition, it was proven that the PID controller is operational across a wide range of different subject conditions.

Protocol

The sedation system monitors were applied to the participating volunteers, as were other standard anesthesia monitors, including the BIS of the electroencephalogram (A-2000, BIS 3.3 algorithm, system revision 1.07, Aspect Medical Systems, Inc., Newton, MA). An 18-G catheter for blood sampling was inserted at the antecubital fossa on the dominant arm. A 20-G venous catheter was inserted into the contralateral arm for drug infusion. Lactated Ringer’s solution (200 ml) was infused as a bolus; subsequently, fluid was infused at a rate of 100 ml h\(^{-1}\). Tympanic membrane temperature was maintained between 37 and 37.5°C.

Volunteers were initially studied during administration of propofol (Diprivan 1%, Zeneca Inc., Wilmington, DE) and 50% N2O in O2 (N2O trial). After a 1-h recovery period they were re-evaluated with propofol only (Air trial). The protocol consisted of sequential 15-min cycles. In both trials, after a 15-min control period, propofol was infused to an
initial target concentration of 0.25 μg ml\(^{-1}\) (N\(_2\)O) or 1.5 μg ml\(^{-1}\) (Air). In the N\(_2\)O trial, we also included 15 min of N\(_2\)O alone. The propofol infusion was maintained throughout each 15-min cycle. Subsequently, the target was increased by 0.25 μg ml\(^{-1}\) (N\(_2\)O) or 0.5 μg ml\(^{-1}\) (air); the process was repeated until loss of consciousness as defined by an Observer’s Assessment of Alertness/Sedation (OAA/S) score of 2 (Table 1). The N\(_2\)O always preceded the Air trial, in order to avoid accumulation of propofol in the plasma before we began the N\(_2\)O component. We considered the period from 9 to 15 min within each cycle to be at pseudo steady-state.

**Measurements**

Demographic and morphometric characteristics of the volunteers were recorded. The sedation period for each trial separately was also recorded. The level of sedation was regularly evaluated at the 9th and 15th minutes of each concentration cycle using the OAA/S score (21) after recording of the BIS value and before a blood sample was obtained. The BIS data were gathered with two sensors arranged in a fronto-temporal montage after mild abrasion of the skin. Impedance of the BIS sensors was evaluated at 15-min intervals; the sensors were regularly checked to maintain impedance <5 kΩ. Bispectral index values were transmitted to a data-acquisition system every 5 s and then averaged over sequential 1-min periods. Volunteers were frequently advised to keep their eyes closed, especially during each pseudo steady-state recording period. The investigator, who assigned the OAA/S score, was blinded to the BIS recordings.

After 9 min of propofol administration at each target concentration, a venous blood sample for propofol concentration was obtained. Six minutes later, an additional sample was obtained to confirm the pseudo steady-state. The samples were analyzed using a high-performance liquid chromatography assay modified from the method of Plummer (22). This method has a coefficient variation of 4.1% at a propofol plasma level of 2 μg ml\(^{-1}\).

**Data analysis**

Differences in plasma propofol concentration between the beginning (9th minute) and the end (15th minute) of each pseudo steady-state period were averaged across the same volunteer and then across all the volunteers for each trial separately. Plasma propofol concentrations and BIS values at the 9th and 15th minutes of each concentration cycle were compared using paired \(t\)-tests to evaluate the validity of our pseudo steady-state assumption for each trial separately. For the same purpose, the OAA/S scores were compared between the above-mentioned time points using Wilcoxon’s signed-rank tests.

The performance of the TCI system was characterized for the N\(_2\)O and Air trial separately by calculating the median performance error, median absolute performance error, divergence, and wobble as suggested by Varvel et al. (18). First, for each blood sample the performance error (PE) was calculated as:

\[
PE = \frac{C_m - C_p}{C_p} \times 100
\]

where \(C_m\) and \(C_p\) are the measured and predicted plasma propofol concentrations, respectively. Subsequently, the median (MDPE) and the median absolute (MDAPE) performance errors were calculated for each subject and each trial (N\(_2\)O and Air) separately. Median absolute performance error is a signed value and thus represents the direction (over- or under-prediction) of the performance errors rather than the size of the errors, which is indicated by MDAPE.

Divergence is a time-related parameter that indicates how the inaccuracy of the infusion device changes as a function of time. A positive value indicates a widening gap while a negative value indicates a narrowing gap between measured plasma and predicted concentrations; a zero value means that performance accuracy does change over time. Divergence is obtained by linear regression of PE values against time for each subject and is the slope of that regression line expressed as percent change per hour (%/h).

Wobble, is a time-related index of changes in performance accuracy and measures the intrasubject

<table>
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<td><strong>Responsiveness component of the Observer’s Assessment of Alertness/Sedation (OAA/S) Scale.</strong></td>
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<tr>
<td>Score</td>
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<td>5</td>
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<td>4</td>
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variability in performance errors. Wobble is thus the median absolute deviation of the PEs of individual samples from the MDPE, where MDPE is the median performance error for each subject.

Comparison analysis of the various performance indices between the N2O and Air trials was performed using Wilcoxon’s signed-rank test. All data were presented as means ± standard deviations unless otherwise noted. P-values < 0.05 were considered statistically significant.

Results

The volunteers were 26 (19–39) years old, weighed 64 (50–85) kg, and were 168 (158–185) cm tall (median [range]). Seven of the 20 were male. The sedation period lasted 114 ± 46 min during the N2O trial and 58 ± 22 min during the Air trial. One hundred and thirteen blood samples were obtained during the Air trial and 205 during the N2O trial. Plasma propofol concentrations at the beginning (9th minute) and end (15th minute) of the pseudo steady-state period differed by only 0.00 ± 0.16 µg ml⁻¹ (P = 0.78) during N2O, and by 0.00 ± 0.25 µg ml⁻¹ (P = 0.91) during the Air trial. The relation between measured and predicted plasma propofol concentrations as a function of time for each individual blood sample and each trial is presented in Fig. 1.

Sedation level, as defined by OAA/S scores at the beginning and end of the pseudo steady-state period during the N2O (P = 0.73) or Air (P = 0.31) trials did not show any difference. Bispectral index values also did not differ at the above-mentioned time points during the N2O (P = 0.43) or Air (P = 0.15) trials. The time course of the BIS values during the 9th to 15th-min steady-state period at three different target concentrations is graphically presented for each individual subject and each trial separately in Fig. 2.

The estimated performance measures are presented in Table 2 for each trial and in Fig. 3 for each trial.

<table>
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<tr>
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<th>N2O</th>
<th>Air</th>
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<tr>
<td>MDPE (%)</td>
<td>−13 (−24, −1)</td>
<td>−18 (−26, −9)</td>
</tr>
<tr>
<td>MDAPE (%)</td>
<td>17 (10, 24)</td>
<td>22 (12, 28)</td>
</tr>
<tr>
<td>Divergence (%)</td>
<td>−10 (−26, 4)</td>
<td>14 (−21, 26)</td>
</tr>
<tr>
<td>Wobble (%)</td>
<td>7 (5, 10)</td>
<td>6 (4, 8)</td>
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MDPE = median performance error; MDAPE = median absolute performance error.
All values are reported as medians (25th, 75th percentiles).

Fig. 1. Predicted (●) and measured (○) plasma propofol concentrations at the 9th and 15th minutes of each pseudo steady-state period in N2O and Air trials. Measured propofol in individual blood samples (small ○) and the mean ± SD (large ○: vertical bars) across the volunteers at the above-detailed time points are indicated separately.

Fig. 2. Time course of bispectral index in individual subjects during the pseudo steady-state period for three different target concentrations in N2O (lower graphs) and Air (upper graphs) trials. For the N2O trial, 0.25, 0.5, and 1.0 µg ml⁻¹ target effect-site propofol concentration steps are presented; for the Air trial the targets are 1.5, 2.0, and 2.5 µg ml⁻¹.
individual subject separately. Comparison analysis of the TCI performance between the two trials did not show any significant difference.

**Discussion**

Virtually identical plasma propofol concentrations, OAA/S scores, and BIS values at the 9th and 15th minutes of each target effect-site concentration confirmed our pseudo steady-state assumption. Our TCI system generally over-estimated the plasma propofol concentrations at pseudo steady-state, while its bias (MDPE) and inaccuracy (MDAPE) were similar to those reported previously (3, 23) when venous concentrations were used. Several investigators (9, 18, 23–25) report an inevitable variation of the achieved concentrations in plasma around the targeted concentration. The use of covariates by Schnider et al. reduced the inaccuracy of their model from 23% to 17%; both values being considered reasonably accurate for clinical use.

We used Schnider’s pharmacokinetic (PK) model (16), which was originally derived from arterial propofol concentrations. Coetzee et al. tested three different PK parameter sets for propofol TCI and found that the venous concentrations were significantly less than the arterial concentrations (23). Linear regression demonstrated a positive association between the arterio-venous difference and the measured arterial concentrations and a negative association with the time of sampling. They conclude that results differ when using venous or arterial samples to evaluate the bias and precision of a TCI system. For example, whereas the arterial values indicated negligible bias with the Marsh (11) and Tackley (25) systems, negative venous performance errors suggested that each model tends to overpredict concentrations in the blood, leading to under-dosing. But according to the same authors (23), venous concentrations can be used, bearing in mind that propofol venous concentrations are generally lower than arterial values by approximately 0.5–1.0 μg·ml⁻¹ and that sampling should be performed several minutes after adjustment to the targeted concentration.

Negative bias is therefore considered typical of venous samples (23, 26) and would be expected since Schnider’s data (16) was based on arterial propofol concentrations. As others (14, 23, 26) have shown, use of targets less than 2 μg·ml⁻¹, long duration of the infusion, and sampling after a pseudo steady-state has been achieved minimize arterio-venous differences. It is therefore possible that the difference between the arterial and venous propofol concentrations is insufficient to explain the observed negative bias. Nonetheless, taking into account the stability of the pharmacodynamic effect at the different concentration targets, we conclude that the inaccuracy of our system is within the clinically acceptable range of 20–30%.

A novelty of our system is the use of a proportional-integral-derivative (PID) controller to implement an integrated PK model for targeting the effect-site. The simplicity and flexibility of PID control, provided that its different terms are ‘well-tuned’ (20), enabled us to achieve, change, and operate close to our setpoints for a clinically relevant period of time. Stanpump and Rugloop simulations of the trials showed that PID control might perform equally acceptably with a model-based or even patient-adaptive solution. Recently, PID has been applied in a closed-loop control system of sedation (27) and anesthesia (28) using BIS as the controlled variable and has demonstrated similar clinical performance with a model-based adaptive controller (29), despite the fact that the system targeted plasma rather than the effect-site propofol concentration.

According to Gentry et al. (30) the value of $k_{e0}$ is highly influenced by the PK model; therefore, as Struys et al. (6) have demonstrated, it is unwise to mix the $k_{e0}$ from one study with pharmacokinetics from another. We therefore implemented the

![Fig. 3. Target-controlled infusion system performance evaluation in individual subjects during the N₂O (○) and Air (●) trials. MDPE = median performance error; MDAPE = median absolute performance error.](image-url)
effect-site compartment using a $k_{e0}$ calculated from a covariate-adjusted, three-compartment model by the same investigators in the same series of studies (16, 17). Using this $k_{e0}$, the corresponding time to peak effect was 1.69 min. In our simulation trials using Stanpump, none of the extreme cases tested (e.g. male, aged 18 years, height 135 cm, weight 41 kg) had an equilibration time between plasma and effect-site more than 4 min. Rugloop simulation of two of our targeted infusions in two volunteers indicated that the equilibration time was between 4 and 6 min. We therefore believe that the period between the 9th and 15th minute of each concentration cycle represented a pseudo steady-state, as the sedation and BIS assessment has shown. The time course of the effect-site concentration during steady state, as this may be indicated by the BIS, showed remarkable stability (Fig. 2). However, the increased BIS variability at higher propofol concentrations during the Air trial might have been caused by the stimulation of the repeated OAA/S assessments after the volunteers no longer responded to the automated responsiveness test (15).

Divergence values indicate that there was not any systematic time-related trend of the measured concentrations away (or towards) the targeted concentrations. Divergence is not only an inherent performance characteristic of a certain TCI system, but also relates to the infusion design (stepped or constant target concentrations) that is used to drive the system (24). However according to Varvel et al. (18), wobble is the most appropriate performance index to denote failure to achieve stable plasma concentrations since it represents the variability of performance error in the individual subject. Although some performance inaccuracy was observed, our TCI system was able to maintain constant plasma concentrations well during each pseudo steady-state period. The various performance indices did not differ significantly between the two trials. However, accuracy and positive divergence were slightly worse with Air than N2O, which might be associated with the greater concentration steps in the Air trial (24).

We conclude that our TCI system for propofol, using a covariate-adjusted integrated PK model to target the effect-site concentration, demonstrated a clinically acceptable performance during mild-to-moderate sedation.

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