Correction of target-controlled infusion following wrong selection of emulsion concentrations of propofol

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**Background:** We investigated the correction methods following wrong-settings of emulsion concentrations of propofol as a countermeasure against erroneous target-controlled infusions (TCI).

**Methods:** TCIs were started with targeting 4.0 μg/ml of effect-site concentration \( C_{\text{eff}} \) of propofol, and the emulsion concentrations were selected for 2.0% instead of 1.0% (FALSE\(_{1-2}\), \( n = 24 \)), or 1.0% instead of 2.0% (FALSE\(_{2-1}\), \( n = 24 \)). These wrong TCIs were corrected at 3 min after infusion start. During FALSE\(_{1-2}\), the deficit was filled up while injecting after equilibrium (\( n = 12 \)), or while overriding (\( n = 12 \)). During FALSE\(_{2-1}\), the overdose was evacuated while targeting \( C_{\text{eff}} \) (\( n = 12 \)) or targeting plasma concentration \( C_{\text{p}} \) (\( n = 12 \)). The gravimetrical measurements of TCI reproduced the \( C_{\text{p}} \) and \( C_{\text{eff}} \) using simulations. The reproduced \( C_{\text{eff}} \) at 3 min (\( C_{\text{eff-3min}} \)) and the time to be normalized within ± 5% of target \( C_{\text{eff}} \) (\( T_{\pm 5\%} \)), were compared between the correction methods.

**Results:** During the wrong TCI, \( C_{\text{eff-3min}} \) was 1.98 ± 0.01 μg/ml in FALSE\(_{1-2}\), and 7.99 ± 0.05 μg/ml in FALSE\(_{2-1}\). In FALSE\(_{1-2}\), \( T_{\pm 5\%} \) was significantly shorter when corrected while overriding (3.9 ± 0.25 min), than corrected after equilibrium (6.9 ± 0.05 min) (\( P < 0.001 \)). In FALSE\(_{2-1}\), \( T_{\pm 5\%} \) was significantly shorter during targeting \( C_{\text{p}} \) (3.6 ± 0.04 min) than targeting \( C_{\text{eff}} \) (6.7 ± 0.15 min) (\( P < 0.001 \)).

**Conclusions:** The correction methods, based on the pharmacokinetic and pharmacodynamic characteristics, could effectively and rapidly normalize the wrong TCI following erroneously selections of the emulsion concentration of propofol. (Korean J Anesthesiol 2014; 66: 377-382)

**Key Words:** Drug delivery systems, Infusion pumps, Intravenous infusion, Propofol.
Introduction

There are various kinds of errors possible while starting the target-controlled infusion (TCI) of anesthetics, resulting from mechanical causes or the wrong selection of TCI settings. A mechanical error of the infusion assembly of a TCI device was reported as a start-up delay that prolonged the stable state of infusion [1,2]. However, this kind of inaccuracy could be normalized as time passed, while the infusion system established stability. On the other hand, when settings of TCI variables are mistaken, such as patient-covariates, syringe brand compatibility [3], and drug name or diluent concentration, an estimation of the consequences will still be difficult.

The Diprifusor® for propofol with an automatic security tag system using a radio-frequency technology [4] can prevent the possibility to select the wrong emulsion concentration. However, all TCI machines are not equipped with automatic drug-recognizing systems. Accordingly, sometimes, if various emulsions of propofol were concomitantly prepared in the same anesthetic units, or if the TCI were prepared using various drug-infusion protocols saved in the TCI workstation, this kind of error-setting could be encountered. In our institute, such an error setting was found after the initiation of TCI and the wrong TCI was to be given up and switched to a zero-order continuous infusion pattern.

Therefore, in the present study we established the methods of correction for the TCI of propofol following wrong selection of emulsion concentration during the induction of anesthesia and we pharmacokinetically investigated the validity of the correction methods for each potential error situation.

Materials and Methods

In this study bench experiments were conducted, using sterile distilled water as a virtual solution for 1.0 and 2.0% propofol-TCIs targeting 4.0 μg/ml of effect site concentration (Ceff). Three TCI workstations (Orchestra®, Fresenius Vial, Le Grand Che-
Table 1. Time Courses of the Procedures of Fill-up Corrections at the Time (Time) from the Start of Correction during Wrong Target-controlled Infusion of 1.0% Propofol Following False-setting to 2.0% Propofol

| Time (min) | After equilibrium | Procedures |
|-----------|------------------|------------|
|           | 0.0              | 0.0        |
|           | Over-riding      | Test-increase of target to 6.0 μg/ml. |
|           |                  | Calculate a fill-up amount. |
|           |                  | Decrease target to 4.0 μg/ml. |
| 6.0       | 0.33             | Turn stopcock and Evacuation. |
|           |                  | Inject fill-up bolus manually. |
| 7.5       | 0.66             | Replace 1% with 2% propofol. |
|           |                  | Purge the syringe. |
| 8.5       | 1.66             | Turn stopcock to main stream. |
|           |                  | Start infusion. |

Values indicate mean ± SD. C_{eff-3min} indicates the effect-site concentration of propofol at 3 min after the start of infusion, and T_{eqi} (min) indicates the time to normalize within ± 5% of target concentration.

Table 2. Time Course of the Procedures of Evacuation Corrections at the Time (Time) from the Start of Correction during Wrong Target-controlled Infusion of 2.0% Propofol Following False-setting to 1.0% Propofol

| Time (min) | Targeting effect-site | Procedures |
|-----------|-----------------------|------------|
| 0.0       | 0.0                   | Turn stopcock to evacuation line. |
| 3.85      | 2.88                  | Replace 2% with 1% propofol. |
| 4.85      | 3.88                  | Start infusion. |

The corrections were performed during targeting effect-site or after switching to targeting plasma concentration of propofol.

Table 3. The Fill-up Corrections for the False-setting of 1.0% to 2.0% Propofol were Performed after the Equilibrium (FILL_{eqi}), or While Overriding (FILL_{over}). The Evacuation Corrections for False-setting of 2.0% to 1.0% Propofol were Performed during Targeting Effect-site Concentration (EVAC_{eff}), or after Switching to Targeting Plasma Concentration (EVAC_{pl}). All Corrections were Made at 3 min after the Start of Infusions

| Fill-up correction | P value | Evacuation correction | P value |
|--------------------|---------|-----------------------|---------|
| FILL_{eqi} (n = 12) | FILL_{over} (n = 12) | EVAC_{eff} (n = 12) | EVAC_{pl} (n = 12) |
| C_{eff-3min} (μg/ml) | 1.98 ± 0.016 | 1.99 ± 0.007 | 7.99 ± 0.036 | 7.98 ± 0.070 |
| T_{eqi} (min) | 6.9 ± 0.05 | 3.9 ± 0.25 | < 0.001 | 6.7 ± 0.15 | 3.6 ± 0.04 | < 0.001 |
| Fill-up bolus (mg) | 62.4 ± 14.0 | 62.5 ± 13.8 | 1.000 | – | – | – |

Values indicate mean ± SD. C_{eff-3min} indicates the effect-site concentration of propofol at 3 min after the start of infusion, and T_{eqi} indicates the time to normalize within ± 5% of target concentration.

Results

The C_{eff-3min} after the start of TCI were not significantly different between the sub-groups of each wrong TCI (P = 1.000) (Table 3). Time courses of the reproduced actual concentration of propofol are illustrated in Fig. 2 and 3. Data were expressed until 30 min after the start of infusion. Gray bands indicate the range of ± 5% of the target concentration.

In FALSE_{1.2}, the test-increase of target to 6.0 μg/ml led to C_{eff} increase to 2.98 ± 0.03 μg/ml during the fill-up corrections of FILL_{eqi}, and the calculated fill-up amount was 62.4 ± 14.0 mg. Therefore, 3.1 ± 0.7 ml of virtual infusate was manually injected, which increased C_{eq} to 4.24 ± 0.33 μg/ml (Fig. 2A). During the fill-up corrections of FILL_{over}, the calculated fill-up amount was 62.5 ± 13.8 mg which override the test-increase and led C_{eff} to be

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overshot to 5.4 ± 0.02 μg/ml (Fig. 2B). T_{5\%} of FILL_{eq} was significantly shorter than that of FILL_{eq} (P < 0.001) (Table 3).

During the evacuation corrections, EVAC_{eff} led C_{eff} to 4.0 ± 0.02 μg/ml after 3.85 min of evacuation, then C_{eff} decreased to 3.2 ± 0.02 μg/ml and C_p also decreased to 2.7 ± 0.03 μg/ml during the drug replacement (Fig. 3A). EVAC_{pl} led C_p to 4.0 ± 0.03 μg/ml after 2.88 min of evacuation, then C_{eff} decreased to 3.9 ± 0.04 μg/ml and C_p decreased to 3.3 ± 0.08 μg/ml during the drug replacement (Fig. 3B). T_{5\%} of EVAC_{pl} was significantly shorter than that of EVAC_{eff} (P < 0.001) (Table 3).

**Discussion**

The wrong TCI following false-setting to higher emulsion concentration of propofol could be effectively corrected using the fill-up method during targeting C_{eff} and the false setting to lower concentration could be corrected using the evacuation method after switching to targeting C_p of propofol.

Propofol is known to have a linear pharmacokinetic [5]. Therefore, TCI with wrong settings between 1.0 and 2.0% emulsion concentrations have shown double or half of the target concentration like the results of this study. These wrong selections could be easily detected or possibly neglected during the early phase of anesthesia induction. When the emulsion concentration is falsely selected to higher concentration, the loss of consciousness (LOC) will be delayed or hardly induced. When a lower concentration is falsely selected, the patient will show a faster LOC or more hemodynamic depressions. Therefore, the
simulation scenario of correction at 3 min after the start of infusion was chosen.

During preliminary experiments before this study, we tried to correct the wrong TCI due to a simple replacement to the correct emulsion concentration which was identical to a starting concentration. But, in order to normalize \( C_{\text{eff}} \) to be within ± 5% of the target, it took 19.5 min for the false setting of 1.0 to 2.0% propofol and 54.4 min for the false setting of 2.0 to 1.0% (Fig. 4). In addition, the TCI could not provide accurate information on the predicted concentrations during the period of normalization. Moreover, it might become more confused if we alter the target concentration during this normalization period. Therefore, we investigated the correction methods based on the pharmacokinetic and pharmacodynamic of propofol in order to normalize rapidly and effectively. The sequences of each correction were as followings; (1) estimation of the amount to fill-up or the duration to evacuate (2) correction (3) emulsion replacement to the correct concentration.

For the fill-up corrections, we anticipated that the amount of propofol needed to increase 2.0 μg/ml to 4.0 μg/ml might be the same as that needed to increase 4.0 μg/ml to 6.0 μg/ml. After estimating the amount for fill-up using a test increase of 4.0 μg/ml to 6.0 μg/ml, we waited until the pseudo-steady state of equilibrium in order to validate the correction method. Then the fill-up bolus led \( C_{\text{eff}} \) to 4.24 μg/ml, which was about 6% higher than expected. However, in clinical settings, it is not a short period to wait until the pseudo-steady state of equilibrium. Therefore, the method of overriding correction could more rapidly normalize the wrong TCI. The overshot of \( C_{\text{eff}} \) might be anticipated, but the maximum \( C_{\text{eff}} \) after the fill-up bolus was 5.41 μg/ml.

The TCI workstation used in this study shows Csdt for \( C_{\text{eff}} \) rounding off below the decimal point. For example, it displays Csdt between 1.45 min to 2.44 min as 2.0 min. Therefore, we used a simulation software (PKPD Tools for Excel) to calculate accurate durations of evacuation for \( C_{\text{p}} \) and \( C_{\text{eff}} \). The evacuation correction was performed based on the time point where the time required to decrease \( C_{\text{p}} \) and \( C_{\text{eff}} \) to a certain degree would be identical and irrelevant to maintaining concentrations, but relevant to the duration of infusion [7]. Csdt of 8.0 μg/ml to 4.0 μg/ml at 3 min of TCI would be identical to that of 4.0 μg/ml to 2.0 μg/ml. Eventually, \( C_{\text{p}} \) and \( C_{\text{eff}} \) decreased to 4.0 μg/ml after Csdt-\( C_{\text{p}} \) and Csdt-\( C_{\text{eff}} \). But the \( C_{\text{p}} \) decreases faster than the \( C_{\text{eff}} \) after cessation of infusion [8,9]. Therefore, during EVAC\( C_{\text{eff}} \), \( C_{\text{p}} \) would be lower than \( C_{\text{eff}} \) after Csdt-\( C_{\text{eff}} \), but the wrong TCI would regard this status as a pseudo-equilibrium state. Accordingly, the \( C_{\text{p}} \) could be over-predicted around the emulsion replacement. However during EVAC\( C_{\text{p}} \) the TCI system would not miss the time course of \( C_{\text{p}} \) and more accurately infuse the deficit during the drug replacement.

However, there were some limitations in our experiment. First, as discussed earlier in our previous report [3], the corrections were performed on the basis of the concentration of central compartment (\( C_{\text{p}} \)) and \( C_{\text{eff}} \). But the pharmacokinetic model of this study was not a one compartment model but a three compartment model. Therefore, the correction methods were not perfect, even though they were rapid. Simulations of the concentration of three compartments using PK/PD software showed that the TCI following falsely selected to higher concentration setting and predicted the concentrations of the peripheral compartments to be higher as well as \( C_{\text{p}} \) (Fig. 5).

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**Fig. 4.** The reproduced actual plasma (solid lines) and effect-site (dotted lines) concentration during targeting 4.0 μg/ml of effect-site concentration using 1.0% virtual emulsion with false setting to 2.0% propofol (black lines), or using 1.0% virtual emulsion with false setting to 2.0% (gray lines). The simple corrections were performed at 3 min after the start of infusion. Gray bands indicate the range of ± 5% of the target concentration.

**Fig. 5.** The nominal (dotted lines) and reproduced actual (solid lines) predicted plasma concentrations at the central compartment, C1 (upper), and at two peripheral compartments, C2 (middle), and C3 (lower) targeting 4.0 μg/ml of effect-site concentration, and the false setting of 1.0% virtual emulsion to 2.0% was corrected after achieving the equilibrium state. Gray bands indicate the range of ± 5% of the target concentration.
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These differences at the peripheral compartments are considered to be the cause of the small amount of over-correction after the manual bolus during the fill-up correction and led to a slight decrease of $C_{\text{eff-rep}}$ after the drug replacement. On the contrary, TCI following falsely selected to lower concentration predicted the concentration of the peripheral compartments to be lower as well as $C_p$. Therefore, the $C_{\text{eff-rep}}$ after the drug replacement slightly increased, then approached to the target. However, the mean deviations from the target were within the range of ± 5.0%. Second, some clinicians might consider the correction methods of this study to be more complicated than just imaging the predicted concentrations to be double or half of the concentrations displayed on the TCI workstation. And this method could be useful for a short duration of infusion but might be not suitable for a long duration of anesthesia. Third, in this study, we used distilled water as virtual emulsion. Therefore, we did not replace the emulsion to correct concentrations, and waited just 1 min to simulate the syringe replacement time in clinical circumstances. Also, the gravimetrically measured amount was converted into the correct concentration of propofol during the simulation.

The purpose of this study was to investigate the risk management for an erroneous situation during TCI. There is no doubt that it is essential to pay attention to the preparation of TCI. Also the wrong selection of the drug emulsion concentration may not be frequent in clinical settings. However, if we know how to handle possible error situations in advance we will be able to effectively deal with those issues.

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