Estimation of the plasma effect site equilibration rate constant of sufentanil in children using the time to peak effect of heart rate and blood pressure

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ABSTRACT

Objectives: Although targeting the effect site concentration may offer advantages over the traditional forms of administering intravenous anesthetics, it is not applicable for sufentanil in children because its plasma effect site equilibration rate constant \( k_{e0} \) is not known yet. We estimated \( k_{e0} \) of sufentanil in children using the time to peak effect \( t_{\text{peak}} \) method.

Materials and Methods: Under general anesthesia, sufentanil \( t_{\text{peak}} \) was measured after administration of a submaximal bolus dose by means of the decrease in heart rate, blood pressure and calculated approximate entropy (ApEn) of electroencephalogram in 105 children (age range: 3–11 years). \( k_{e0} \) was estimated using \( t_{\text{peak}} \) and known sufentanil pharmacokinetic parameters in normal children.

Results: The mean \( t_{\text{peaks}} \) were measured as 44 ± 22 s and 227 ± 91 s by heart rate and by mean blood pressure respectively. The estimated \( k_{e0} \) were 5.16/min and 0.49/min by heart rate and blood pressure respectively. \( t_{\text{peak}} \) could not be measured using the ApEn, thus \( k_{e0} \) could not be calculated by ApEn in children.

Conclusions: Shorter measured sufentanil \( t_{\text{peak}} \) by heart rate compared to blood pressure indicate that the heart rate decrease faster than decreasing of blood pressure. Moreover, the calculated sufentanil \( k_{e0} \) in children depends on the pharmacodynamics parameters.

KEY WORDS: Children, plasma effect site equilibration rate constant, sufentanil

Introduction

Target controlled infusion (TCI) is one of the standard routes of drug administration in clinical practice. Although pharmacokinetic (PK) parameters and TCI let us predict and control the plasma concentrations, nonsteady state conditions create delayed effect in plasma concentration.\(^{[1,2]}\) Hypothetic effect compartment accounts for the delay between these two concentrations that is linked to the plasma compartment by a first-order transfer function with a plasma effect site equilibration rate constant \( k_{e0} \). Therefore, \( k_{e0} \) is an essential parameter for the effect-site TCI. The traditional approaches to calculate the \( k_{e0} \)\(^{[3,4]}\) have disadvantages such as a wide range of drug effect, starting at baseline, achieving a maximal effect and then returning to the base state. Therefore, an alternative and simple method is used that measures the time to peak effect \( t_{\text{peak}} \) after administration of a bolus dose that causes a submaximal effect.\(^{[5,6]}\) Minto et al. have shown that \( t_{\text{peak}} \) is a model-independent pharmacodynamics (PD) parameter that can be used with the appropriate PK parameter sets to calculate the value of \( k_{e0} \) that accurately predicts \( t_{\text{peak}} \).\(^{[7]}\)

Sufentanil is a potent opioid with rapid onset and short duration of action. It is a commonly used opioid for anesthesia,\(^{[7]}\) prevention of emergence agitation,\(^{[8,9]}\) and postoperative pain control.\(^{[10,11]}\) Furthermore, it has some benefits such as larger margin of safety and cheap price. Over the relatively long history of its use in anesthetic fields, several PK parameters have been introduced, but the effect of drug measurement had not been reported in children.\(^{[12-14]}\) Therefore, sufentanil cannot be used in children in effect site TCI mode because the value of \( k_{e0} \) is unknown although the previous studies have proven that sufentanil TCI provided stable analgesia, better hemodynamic control, and anticipated recovery from anesthesia.\(^{[15]}\) To use sufentanil in effect-site TCI mode, the value of \( k_{e0} \) is essential.

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Received: 06-10-2014
Revised: 17-01-2015
Accepted: 10-04-2015

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Conventionally electroencephalogram (EEG) metrics,[16] miosis[17] or blood pressure[18] have been used to characterize the effect of intravenous opioids as surrogate measurements. Therefore, these several clinical measurements could represent the effect of the opioid. In addition, miosis or blood pressure might be more useful than EEG electrodes during anesthesia because of practical application.

The purpose of this study was to determine \( k_o \) by measuring the \( t_{\text{peak}} \) of sufentanil in children using heart rate (conversion from RR interval of electrocardiograph [ECG]), blood pressure or approximate entropy (ApEn) of EEG, as surrogate measurements of opioid effect. We also aimed to investigate the effect of age on time to peak and \( k_o \) in children.

Materials and Methods

This prospective study was approved by the Institutional Review Board of Seoul National University Hospital (H-1302-038-463, Seoul, Korea). It is registered at cris.nih.go.kr (KT0008887).

After obtaining an informed consent from the parents or guardians of children who were scheduled to undergo more than 2 h of general anesthesia, we recruited 105 children (2–12 years old; 10 patients in each age with equal number of boys and girls). They were classified as American society of anesthesiologists physical status I or II.

The exclusion criteria were an abnormality of EEG, previous history of hypersensitivity to opioids, postoperative nausea and vomiting, history of the administration of neurologic or other medications that interfere with opioids.

Anesthetic Technique

Children were admitted for anesthesia after appropriate fasting and without being on premedication. At the operating room, lead II ECG, heart rate, 1-min noninvasive blood pressure (NIBP) and pulse oximetry (SpO\(_2\)) were monitored (Solar 3000, GE Medical, Milwaukee, WI).

A standard anesthesia method was followed. Anesthesia was induced via administration of 6 mg/kg of thiopental intravenously, and manual ventilation was started in shallow respiration with 6–8 vol% of sevoflurane in 100% of oxygen. After full relaxation with 0.6 mg/kg of rocuronium confirmed by nerve stimulator, intubation was performed with the appropriate endotracheal tube. General anesthesia was maintained with the fresh gas flow of 1.5 L/min mixed with medical air, oxygen and 2–3 vol% of sevoflurane and concentration of sevoflurane was adjusted by blood pressure and heart rate. Submaximal single bolus of sufentanil (0.8 mcg/kg) was administered intravenously 30 min before surgery at the same minimum alveolar concentration (MAC) of sevoflurane for prevention of emergence agitation[19] and postoperative pain control.[20]

Following the conclusion of surgery and dressing, the patients were fully awakened and transferred to the post anesthetic care unit.

Data Collection

Electrocardiograph, heart rate, NIBP SpO\(_2\) and sevoflurane concentration data were transferred from the patient monitoring system to the computer via analog-to-digital (AD) converter (DI-149, Dataq Instruments, Arkon, Ohio) with a frequency of 1000 Hz during the study period. The study period was 1-min before administration to 5 min after sufentanil injection.

Collected ECG data were analyzed using a LABCHART software (Version 7; AD Instruments, Colorado Springs, CO, USA) and RR interval was measured to determine the heart rate. The time of peak effect of sufentanil on RR interval was calculated as the time from the administration of sufentanil to largest RR interval (lowest heart rate).

Noninvasive blood pressure interval data were also obtained to determine the maximum decrease of blood pressure and calculating the time of peak effect.

An electroencephalogram was monitored with MP-100 (MP-100, Biopac, Santa Barbara, CA, USA) and stored into the computer. It was recorded continuously with parietal montage (P4). The EEG data were sampled with the frequency of 500 Hz. For the calculation of ApEn, the length of the epoch (N) was 2,056. No smoothing technique was applied for the calculation of ApEn. The number of previous values (m) used to predict the subsequent values was 2, and the filtering level (r) was 10% of the SD of the amplitude values.[20]

\( m \)

Plasma Effect Site Equilibration Rate Constant Estimation

Based on the Minto’s method, when the heart rate, blood pressure or ApEn are in maximum decrease (i.e., the maximal effect of sufentanil), the maximal effect site concentration \((C_e)\) of sufentanil is reached. \( C_e \) equals to the plasma concentration \((C_i)\) after injection of a submaximal dose of sufentanil at this \( t_{\text{peak}} \). Therefore, we could calculate \( C_i \) and \( C_e \) with the administration dose and Unit Disposition Function of the effect site at \( t_{\text{peak}} \).

\[
C_p(t_{\text{peak}}) = \text{Dose} (mg) \times \sum_{i=1}^{n} A_i e^{-\lambda_i t_{\text{peak}}} = C_e \cdot q(t_{\text{peak}}) \tag{1}
\]

where \( A \) and \( \lambda \) are PK parameters. With \( C_e(t_{\text{peak}}) \), the value of \( k_o \) is calculated using this equation.

\[
C_e(t_{\text{peak}}) = \text{Dose} (mg) \times \sum_{i=1}^{n} \frac{k_i A_i}{k_i^2 \rho - \lambda_0} e^{-\lambda_i t_{\text{peak}}} - k_o e^{-k_o t_{\text{peak}}} \tag{2}
\]

This equation was solved for \( k_o \) for each patient with the Solver function of Excel using the PK parameters for sufentanil that are reported by Guay et al.[14] The constants of Guay’s model are \( k_{10} = 0.042, k_{12} = 0.089, k_{21} = 0.029, V_1 = 0.74 \) and \( V_2 = 3.88 \).

Statistical analysis

Correlation analysis between \( t_{\text{peak}} \) and age was tested using Pearson analysis \( P < 0.05 \) was considered as significant.

Results

Demographic data are shown in Table 1. There was a large variability in the baseline heart rate or RR interval because of the wide age range of enrolled children. Time to a maximal decrease of heart rate (largest RR interval) was 44 ± 22 s after administration of the submaximal dose of sufentanil. Calculated \( k_o \) was 5.16/min. There were different patterns of changes of heart rate or RR intervals after reaching the peak effect. The most common pattern was reaching the lowest heart rate, followed by the slow increase in heart rate to reach a steady value [Figure 1a]. Another pattern was a plateau of the lowest
heart rate without an increase in heart rate (Figure 1b). However, both patterns had the similar $t_{\text{peak}}$ and differed only after the peak effect (44 vs. 39 s). A third pattern in 10 children showed a continuous decrease in heart rate without reaching the lowest heart rate over the study period. There was no correlation with common characteristics such as age or gender in the third pattern and these data were excluded for calculating the $k_{e0}$.

Figure 2 shows the changes in mean blood pressure. Blood pressure was measured at 1-min intervals. The average time to maximal decreased blood pressure was 3 min and 47 s. The estimated $k_{e0}$ was 0.49/min [Table 2]. This is later than heart rate measurements.

Approximate entropy showed more variability and we could not distinguish a pattern for ApEn changes in the enrolled children. In some cases, ApEn showed an increasing trend whereas in other children it had an evident decreasing pattern. Therefore, we could not measure the $t_{\text{peak}}$ using ApEn.

There was no correlation between the age and $t_{\text{peak}}$ in heart rate or blood pressure.

Figure 3 shows the simulation of estimated plasma or $C_e$ of sufentanil in two children along with changes of heart rate and blood pressure after the submaximal dose of sufentanil administration. It demonstrates that the calculated $k_{e0}$ was well matched with the measured time to peak.

Discussion

In this study, we found that the $t_{\text{peak}}$ of sufentanil on heart rate or RR interval was 44 s and $k_{e0}$ was calculated as 5.16/min using $t_{\text{peak}}$. We also found this effect on blood pressure at 3 min and 47 s to estimate $k_{e0}$ as 0.49/min.

In the past, several PK studies had been conducted for sufentanil in children in various clinical situations. Therefore to date the pediatric anesthesiologists could only use TCI which is based on the classic multi-compartment PK model although TCI is already one of the standard infusion methods in adults. These TCI devices calculated and maintained the plasma concentration. However, plasma concentration of sufentanil does not reflect the effect-site concentration, and surrogate measurement of effects of sufentanil such as heart rate, blood pressure of EEG-derived variables should lag behind plasma concentration. The $k_{e0}$ is an essential and critical factor, which links between plasma and $C_e$ if there is a PK model. If we can obtain the $k_{e0}$ of sufentanil in children, the pediatric anesthesiologists will be able to use the effect-site TCI devices with PD model in daily practice in the future. Also TCI findings in normal children in the age range of 2–8 years\textsuperscript{[14]} showed that PK parameters are different from adults. These differences were predictable.

Table 1:

| General data       |
|--------------------|
| Children (n=105)   |
| M/F (n/n)          | 53/52       |
| Age (year)         | 7±4         |
| Height (cm)        | 124.4±21.7  |
| Weight (kg)        | 29.4±15.6   |
| Baseline heart rate (bpm) | 118.5±23.3 |
| Baseline blood pressure (mmHg) | 67.2±13.4 |
| Baseline ApEn      | 0.40±0.21   |

Table 2:

| Time to peak and estimated $k_{e0}$ |
|-------------------------------------|
| Heart rate                         |
| Blood pressure                      |
| Time to peak (sec)                 | 44±22      | 227±91     |
| $k_{e0}$ (min$^{-1}$)              | 5.16       | 0.49       |
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Figure 3: Simulation of plasma concentration of sufentanil ($C_p$) and effect site concentration of sufentanil ($C_e$). The time to peak effect of heart rate or mean blood pressure was well-matched when $C_p$ equals $C_e$.

using the allometric size modeling. In this study, we adopted the PK parameter of the previous study, despite the difference in the age range, because no other PK parameters for sufentanil were available in children matching the same age range. Other estimated PK parameters in children with chronic renal failure or heart defects show a wider range in the variability of these parameters.

Sufentanil is strongly binding to plasma proteins such as a1-acid glycoprotein (AAG), thus the free fraction of the drug might be accountable for its analgesic and respiratory effects. Protein binding varies significantly with age, but laboratory findings of our study were all in the normal ranges, which makes the difference in the protein bindings less likely in the studied age range. This makes the possible effect of AAG negligible in our study population.

An earlier study compared the PD of sufentanil with those of fentanyl using EEG to measure opioid effects of the drug in adults. The authors estimated the $t_{1/2}$ ($6.2$ min) and $k_{0.0}$ ($0.112$/min) with a $t_{peak}$ of $5.8$ min. This is evidently different from our findings. This difference might stem from different measurement parameters. That is to say, that EEG was a measure of opioid effect in adults, whereas, in our study, heart rate (RR interval) and blood pressure were the measures of sufentanil effect in children. We collected EEG data in our study, but we could not measure the $t_{peak}$ with ApEn (derived from EEG) because of no definite pattern changes. EEG records were obtained $1$-min before sufentanil administration to $5$ min after its administration. We reviewed the EEG data and tried to calculate the ApEn. However, the changes in ApEn were widely varied and we could not find a constant trend in ApEn changes over time.

Time to peak effect of sufentanil was $5.8$ min in adults and the collected data might be too short to measure the peak effect of blood pressure in our study. The setting and the enrolled population might also partially explain this difference. In volunteering people, it is possible to evaluate the opioid effect only, and the previous data were obtained in the setting of administration of an opioid without co-administration of other drugs. In children, administration of an opioid without another drug is not ethical, and such a situation rarely happens in clinical settings. This makes it impossible to measure the opioid effect by EEG without co-administration of other drugs. In addition, inhalational or intravenous anesthetics affect the EEG and it is hard to distinguish the EEG changes induced by opioids from those induced by anesthetics. Furthermore, in the operating room, there are different sources for noises and artifacts that can easily affect the EEG. The above-mentioned obstacles had hindered reliable calculation of sufentanil $k_{0.0}$ in children.

We obtained the EEG and ECG data with the same sevoflurane concentration MAC during the surgery. Thus, we can assume that any differences in changes such as heart rate, blood pressure or ApEn are sufentanil effects. Clinically, cardiovascular responses of an opioid such as heart rate or blood pressure are more conveniently measurable to monitor the drug effects. Another study evaluated the cardiovascular effect of remifentanil on blood pressure as a measurement of opioid effects in infants, but no EEG was recorded. We usually use the opioid not only for analgesia but also for hemodynamics during the surgery. Therefore, it might be reasonable to adapt the blood pressure or heart rate as the surrogate measurement of the opioid effect although the EEG metrics were a surrogate measurement of the analgesic effect of the opioid.

In our study, under the conventional general anesthesia with sevoflurane, we measured the changes of heart rate (converted from RR interval in ECG) and blood pressure as drug effects instead of EEG recordings. We collected the ECG data to measure the heart rate because the commercial patient’s monitors show the heart rate in fixed intervals. The shortest interval to report the heart rate is $15$ s, which is not accurate to calculate the $k_{0.0}$. Using the ECG data, RR interval was measured and converted into the heart rate. Therefore, we could find the very point where the peak effect of sufentanil was exerted. To the contrary, we obtained blood pressure data in $1$-min intervals. This is because invasive arterial blood pressure monitoring is required to record continuous blood pressure data. Further studies should be conducted if a more accurate blood pressure recording is warranted to precisely calculate the $k_{0.0}$.

Normal cardiovascular physiology such as heart rate or blood pressure in children meets the value of adults around $12$ years of age. Therefore, we concerned that the cardiovascular system in the recruited children was still under maturation, which might have partially contributed to the wide range of time to peak in this study. However, there was no effect of age on $t_{peak}$ and $k_{0.0}$ of sufentanil. Furthermore, the previous study has reported that there was no age effect on $t_{peak}$ or $k_{0.0}$ of propofol in children.

There are several limitations in our study. Firstly, as mentioned above, we could not calculate the $t_{peak}$ using EEG, which might be the genuine indicator of an opioid. There is
an ethical problem to collect the changes of EEG after sole administration of an opioid in children and we do not know of any solution to this obstacle. Second was 1-min interval measurement of blood pressure relatively long interval comparing to heart rate or ECG.

**Conclusion**

The $t_{peak}$ of sufentanil was 44 s using the heart rate or RR interval and calculated $k_e$ using this $t_{peak}$ was 5.16/min in children. Using the blood pressure, $t_{peak}$ was 3 min and 47 s with $k_e$ being 0.49/min in children. This might provide useful information to use effect-site TCI of sufentanil in the future in the pediatric population.

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Cite this article as: Song IK, Lee JH, Jung S, Kim JT, Kim HS. Estimation of the plasma effect site equilibration rate constant of sufentanil in children using the time to peak effect of heart rate and blood pressure. Indian J Pharmacol 2015;47:360-4.

Source of Support: Nil. Conflict of Interest: No.