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ORIGINAL RESEARCH EXPERIMENTAL ANESTHESIA

Good correlation between necessary remifentanil concentrations in individual patients determined from sedative-analgesic interactions using pharmacokinetic simulations and the remifentanil concentrations used at anesthesiologists' discretion

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ABSTRACT

Background: Analgesic and sedative agents interact with each other, and their relationship is explained in a curve convex below. In the automated control anesthesia system based on this relationship that we developed, the dose of analgesic is adjusted with the necessary remifentanil concentration, determined with propofol-remifentanil interactions, as an estimated maximal individual concentration (esMIC). With the system, a study in patients under anesthesia management by an anesthesiologist was conducted to compare the effect-site concentration (ESC) of remifentanil administered at the anesthesiologist's discretion and the esMIC calculated with drug-drug interactions for their relationship and to assess whether the analgesic dose administered based on esMIC is appropriate.

Methodology: In the present study involving 20 patients, anesthesiologists changed the propofol (P) infusion rate and remifentanil (R) infusion rate to maintain BIS value of 45. The estimated target-effect-site concentration of propofol for maintaining BIS 45 and the ESC of remifentanil (ESC_R) based on the model by Minto et al. were calculated. Moreover, with these data sets, the isodynamic curve of ESC of propofol (ESC_P) for maintaining BIS 45 (Y) and ESC_R (X) was determined to be an equilateral hyperbola (Y = c/(X-a) + b). With the ESC_R at which even raising ESC_R would result in small decreases in ESC_P considered the esMIC, the ESC_R at the point at which the slope of this curve is apos;1 (neutral point) and at the point of the curve where the y-component deviation of the asymptote (y = b) is 20% ($esMIC_{20}$) calculated every 6 sec. The ESC_R at the time point of an adequate analgesic state as deemed by the anesthesiologist after anesthesia had been started for 15 min was compared with the $esMIC_{20}$ determined by objective calculations.

Results: The ESC_R and esMIC were 11.9 ± 2.4 and 11.6 ± 2.0 ng/ml, respectively. Moreover, the median ESC_R and esMIC in the patients showed a very good correlation (correlation coefficient $R^2 = 0.88$, $p < 0.01$).

Conclusion: The necessary analgesic concentrations estimated with drug-drug interactions did not contradict those determined at anesthesiologists' discretion and are considered to assure a reasonable analgesic state.

Key words: Analgesia; Sedation; Remifentanil; Effect-Site Concentrations

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1. INTRODUCTION

Bispectral Index™ (BIS™) monitors are commonly used to measure sedative effects. However, since there are no monitors that measure analgesic effects at present, we anesthesiologists have been assessing analgesic effects comprehensively based on blood pressure and heart rate, among other parameters. Currently, monitors that have been reported to measure analgesic effects include the Analgesia Nociception Index (ANI) and the Nociception Level (NoL) index,[1,2] but they are not in widespread use clinically. For the adjustment of sedative effect, the dose-effect relationship between the effect-site concentration (ESC) of propofol (ESC_P) and the BIS value is approximated by a sigmoid curve to determine the estimated target-effect-site concentration (esTEC) of propofol that provides the target BIS value, which has facilitated objective and real-time calculation of the propofol concentration necessary to maintain the desired level of sedation.[3] Meanwhile, due to the presence of analgesic-sedative interactions and the presence of interactions between esTEC and opioid concentration, as shown in the curve convex below, it may be possible to use this relationship to estimate the opioid concentrations that provide an adequate analgesic effect in a particular patient at individual time points and to measure analgesic effects objectively.[4] However, there has never been an examination of whether the objectively determined reasonable opioid concentration that provides analgesic effects is the same as the opioid concentration administered at anesthesiologists' discretion.

The present study investigated the relationship between $esMIC_{20}$, which is the objective ESC of remifentanil (ESC_R) determined based on drug-drug interactions, and the ESC_R at the time point of an adequate analgesic state as deemed by the anesthesiologist and whether $esMIC_{20}$ can explain the analgesic adjustments by anesthesiologists.

2. METHODOLOGY

This study was conducted with the approval of the ethics committee at the University of Fukui (approval number 20170084) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants and/or their legal guardian(s).

The study involved 20 patients under 75 y of age, who underwent scheduled gynecological surgery between October 2017 and March 2018. To enable assessment of the analgesic effect of remifentanil, no other analgesic treatment (i.e., epidural anesthesia, nerve block, or intravenous fentanyl administration) was administered concomitantly during surgery. The patients were placed under total intravenous anesthesia (TIVA) with propofol, remifentanil, and rocuronium. With the BIS value maintained at 45 by adjusting the propofol infusion rate, the real-time propofol and remifentanil concentrations in the body were calculated based on the model by Marsh et al. [5] and the model by Minto et al.,[6] respectively. The remifentanil concentration was changed depending on operative stress by the attending anesthesiologist by adjusting the infusion rate within the range of 0.2 to 1.0 μg/kg/min. The estimated target-effect-site concentration for maintaining BIS 45 ($esTEC\text{-}P_{45}$) was determined from a regression curve (sigmoid function) of the BIS value and ESC_P every 6 sec, and the isodynamic curve of $esTEC_{45}$ and ESC_R was determined to be an equilateral hyperbola ($Y = c/(X-a) + b$) every 6 sec. Based on this isodynamic curve, even if ESC_R is raised, the decreases in the estimated target-effect-site concentration of propofol necessary for maintaining BIS 45 (esTEC-P45) would be less; that is, with regard to the remifentanil concentration at the point where the absolute value of the slope becomes smaller, even if the analgesic effect is increased further, the decreases in the necessary dose of sedative in the individual patient would be slight; in other words, it suggests that the analgesic effect would level off. As such, this concentration is given the term "estimated maximal individual concentration (esMIC)", since it is the estimated maximum concentration for achieving a realistic analgesic effect in an individual patient.[4] Such a

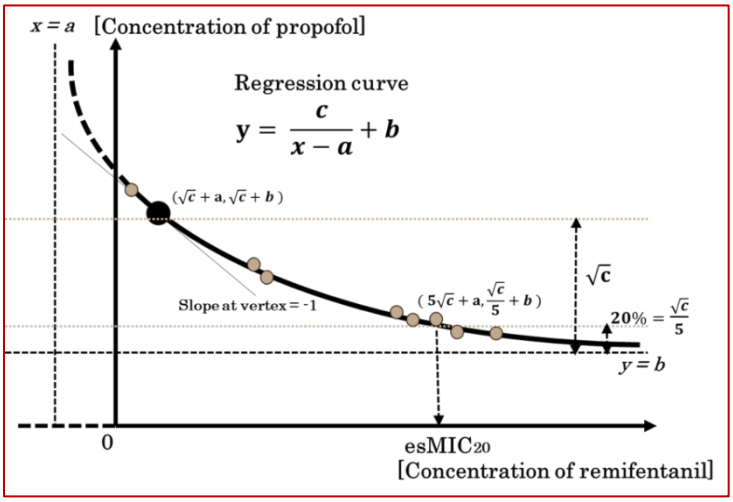

Figure 1: Equation for estimating esMIC value

Estimated maximal individual concentration (esMIC) is the effect-site concentration with an increase in analgesic effect of at least 20% from the asymptote to the vertex even if the concentration of remifentanil is raised above this concentration. Gray dots represent data at each time. See reference 4 for details.

coordinate can be determined by assigning a percentage of residual value (δ [%]) for the difference between the vertex and asymptote, in addition to the vertex (a+√ c, b+√ c) and asymptote (y = b) obtained from the regression curve (isodynamic curve) at a slope of −1 (Figure 1). In the present study, the esMIC of remifentanil was calculated at a percentage of residual value (δ) of 20% ($esMIC_{20}$).

Meanwhile, the relationship between the ESC_R at 15 min after surgery has begun when the anesthesiologist deemed an adequate analgesic state had been achieved and maintained an infusion rate (the necessary remifentanil concentration as estimated by the anesthesiologist) and the $esMIC_{20}$ (the necessary remifentanil concentration objectively determined with analgesic-sedative interactions) during that time period was examined. The results are expressed as mean ± SD values to compare ESC_R and $esMIC_{20}$ by correlation analysis.

3. RESULTS

A total of 20 patients with a mean age of 49 ± 17 y and body mass index (BMI) of 21 ± 2 kg/m^2 were included (Table 1).

Table 1: Characteristics of the patients (n = 20)

Characteristics	Value
Age (y)	49 ±17
Gender, female (%)	100%
Height (cm)	157 ± 6
Weight (kg)	53 ± 7
BMI (kg/m^2)	21 ± 2
Operation time (min)	168 ± 54
Anesthesia time (min)	247 ± 56
ASA-PS 1 / 2 / 3	9 / 10 / 1

Data presented as mean ± standard deviation
BMI; body mass index

At about 15 min after the necessary remifentanil concentration as estimated by the anesthesiologist was maintained following the initiation of surgery, the mean ESC_R and $esMIC_{20}$ (±SD) of all patients were 11.9 ± 2.4 and 11.6 ± 2.0 ng/ml, respectively, showing that $esMIC_{20}$ was distributed within the range of ±15.7% of ESC_R. Furthermore, $esMIC_{20}$ ranged from as low as 8.9 µg/ml to as high as 16.6 µg/ml, showing an inter-individual variation of approximately 1.9-fold. In addition, the median ESC_R and $esMIC_{20}$ in patients showed a very good correlation (y = 0.78x + 2.26; correlation coefficient $R^2 = 0.88$, $p < 0.01$) (Figure 2).

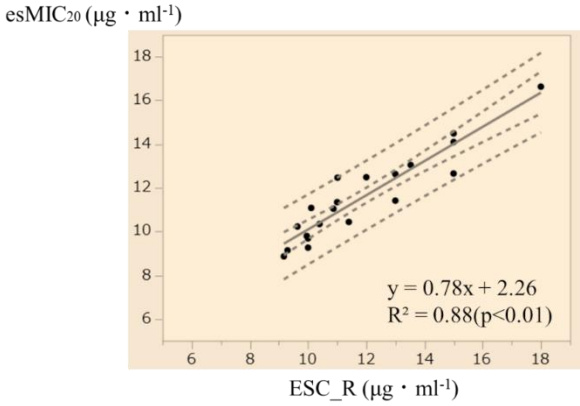

Figure 2: Correlation between ESC_R and esMIC20. The correlation between ESC_R and esMIC20 is significant (R2 = 0.88, P < 0.01)

4. DISCUSSION

In the present study, $esMIC_{20}$ values varied among individual patients despite similar levels of operative stress; however, ESC_R and $esMIC_{20}$ correlated well in each patient, and $esMIC_{20}$ behaved similarly to the ESC_R determined by the anesthesiologists. We previously reported that, compared with young patients, elderly patients require about 61% less of an analgesic dose, and that some differences among individuals were also noted.[7]

Most remifentanil concentrations delivered by the anesthesiologists are achieved with infusion rate adjustments at the anesthesiologists' discretion within a narrow range and may differ slightly from $esMIC_{20}$, which is an objective value. Given such a reason, the objectively calculated esMIC can be used as an analgesic index that is practically equivalent to the "adequate analgesic state" determined subjectively by the anesthesiologists.

Using the real-time $esMIC_{20}$, calculated with propofol-remifentanil interactions makes available at all times the remifentanil concentration needed to establish an adequate analgesic state, regardless of not only differences among individuals (inter-individual variability), but also intra-individual variabilities such as changes in operative stress. In fact, the system we developed allowed changes in the analgesic infusion rate based on this algorithm to ensure a stable analgesic state.[4] This also shows that the necessary analgesic concentrations estimated with drug-drug interactions do not contradict those determined at the anesthesiologists' discretion and can be considered a practical approach for ensuring a reasonable analgesic state.

5. CONCLUSIONS

The remifentanil concentrations necessary for achieving analgesia in individual patients as determined from sedative-analgesic interactions showed a good correlation with the remifentanil concentrations determined at the discretion of the anesthesiologists. The necessary analgesic concentration estimated using drug-drug interactions was equivalent to the necessary analgesic concentration determined at the anesthesiologists' discretion.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

9. Authors' contribution

All authors took part in concept, conduct the study, data collection, data analysis. manuscript writing, editing and correction, final approval of the manuscript.

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