http://dx.doi.org/10.5392/IJoC.2015.11.2.069

Effect-site Concentration of Alfentanil or Remifentanil for the Relief of Postoperative Pain in the Intensive Care Unit Patients

Hae-Lan Jang
Department of Nursing, Joongbu University, Geumsan, Korea

Hoon Kang*
Department of Anesthesiology and Pain Medicine College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju, Korea

ABSTRACT

This study was performed to determine the optimal doses of alfentanil or remifentanil (effect-site concentrations) required to prevent pain and other suffering after abdominal general surgery in ICU patients. A total of 52 general abdominal surgical patients (ASA II-III) requiring artificial ventilatory care in the ICU were provided with either alfentanil (24 patients) or remifentanil (28 patients) through target controlled infusion (TCI). Alfentanil and remifentanil concentrations were titrated up and down until the pain score became less than 3 (VAS; Visual Analogue Score < 3). The effect-site concentrations (ng/ml) of alfentanil or remifentanil required to adequately control postoperative pain in the ICU were 64 +/- 12 and 1.9 +/- 0.5 for intubation with artificial ventilation, 57 +/- 9 and 1.7 +/- 0.7 for intubation with spontaneous ventilation, and 41 +/- 10 and 1.2 +/- 0.5 after extubation, respectively. Pain scores and the corresponding opioid concentrations were independent from respiratory condition. The three effect-site concentrations of alfentanil and remifentanil obtained from this clinical trial using the TCI technique can be a guideline in the administration of the same opioids to relieve the discomfort of ICU patients who have undergone abdominal general surgery.

Key words: *Alfentanil, Remifentanil, Effect-site Concentrations, Target Controlled Infusion.*

1. INTRODUCTION

Alfentanil and remifentanil are potent analgesics and anesthetics with a rapid onset and offset of action suggesting a very short half-life, and quickly achieving steady state. They have also been shown to provide analgesic protection against hemodynamic responses to surgical stress and rapid recovery by low to moderate doses in short-stay surgical procedures or major operations such as abdominal and thoracic surgeries. Alfentanil is a synthetic tetrazole derivative of fentanyl. Analgesic potency of alfentanil is one fourth to that of fentanyl. When compared with fentanyl, it has a higher degree of protein binding, a low degree of lipid solubility. These physical characteristics of alfentanil helps to explain its relatively low volume of distribution and shorter duration of action (one third) compared with fentanyl. The liver is a main site of biotransformation of alfentanil.

As the first compound of a new class of esterase metabolized opioid (EMO) drugs, remifentanil is also a potent, selective μ-opioid receptor agonist, with a rapid onset and offset of action suggesting a very short half-life, and quickly achieving steady state. It has also been shown to provide high quality analgesia after major operation such as abdominal and thoracic surgery. One of the most outstanding pharmacokinetic (PK) profile of remifentanil is that, unlike other opioids, it is quickly metabolized by non-specific blood and tissue esterases to a clinically inactive metabolite [1]. So normally elimination half-life of less than 10 min of remifentanil is resulted from the unique metabolic characteristics which is independent of the duration of infusion [2].

The target controlled infusion (TCI) using a computer controlled pump incorporated with a three compartment PK model has been shown to maintain plasma concentration of intravenous anesthetic agents with a short onset and offset of action constant (Fig. 1). The concept of TCI use in anesthesia was thus only developed in the 1980's and refined in the 1990's, but is now a part of the routine practice of many anesthetists around the world. A TCI is an infusion administered by a system capable of automatically delivering a user-defined concentration of drug. The processes of drug distribution between the different tissues of the body, and ongoing processes of metabolism and elimination, can be described in mathematical terms using a two- or three-compartment model.

Adequate analgesia and sedation are required for most critically-ill patients suffering from postoperative pain and other discomforts in the intensive care unit (ICU). Analgesia-

* *Corresponding author, Email: hkang118@chungbuk.ac.kr*
Manuscript received May. 28, 2015; revised Jun. 03, 2015; accepted Jun. 10, 2015

based sedation with alfentanil or remifentanil can be a useful option for those patients in the ICU. A number of clinical trials have compared the use of analgesia-based sedation with alfentanil or remifentanil with that of other opioids such as morphine, fentanyl or sufentanil in critically ill patients who were being mechanically ventilated in the ICU. However, the dosages of those studies were usually determined in "μg/kg/min" and "μg/kg/h" bases using conventional infusion pumps. This cannot take advantage of the TCI that enables individualized infusion of remifentanil in real time in "ng/ml" basis. The purpose of this study was to determine the optimal doses (effect-site concentrations) of alfentanil or remifentanil at the three different stages (intubation with artificial ventilation, intubation with spontaneous ventilation and extubation) required to prevent patients' pain and other sufferings after abdominal general surgery in the ICU.

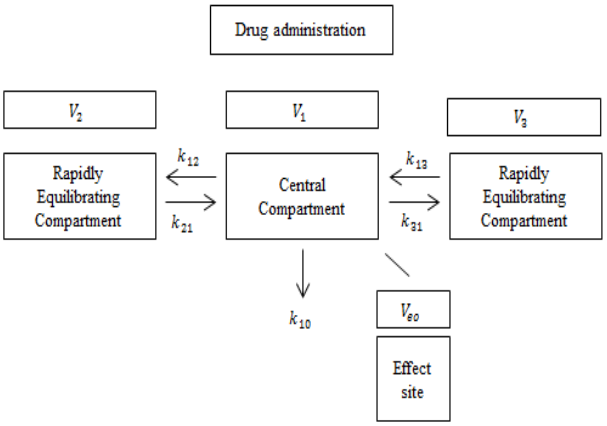

Fig. 1. Three compartment model illustrating the basic pharmacokinetic processes that occur after intravenous drug administration. I, dosing scheme as a function of time; $k_{10,}$ elimination rate constant reflecting all processes acting to remove drug irreversibly from the central compartment; $k_{eo,}$ elimination rate constant from the effect site; $k_{12,}$ $k_{21,}$ k_{13} and $k_{31,}$ inter-compartmental distribution rate constants; $V_{1,}$ volume (L or L/kg) of central compartment.

2. PATIENTS AND METHODS

After IRB approval and written informed consent, 52 general abdominal surgical patients (ASA II-III) requiring artificial ventilatory care in the ICU were recruited for the study. Patients were kept intubated (paralyzed and unconscious) while they were transported to the ICU. On arrival in the ICU ventilatory care was started, if needed. Study drug (alfentanil (24 patients) or remifentanil (28 patients) was infused throughout the study periods. Alfentanil or remifentanil was commenced to be infused at the initial target concentration of 30 ng/ml and 0.5 ng/ml and slowly increased up to 90 ng/ml and 3.0 ng/ml by increments of 5 ng/ml and 0.5 ng/ml every five minutes, respectively, depending on systolic and diastolic arterial pressure and heart rate for the first 30 minutes after being transferred to the ICU, and then titrated up and down. Neuromuscular blockade was not antagonized. When patients recovered consciousness opioid concentrations were titrated up and down, depending on systolic arterial pressure (hypotension), heart rate (bradycardia), oxygen saturation (respiratory depression) or pain score (VAS; Visual or Verbal Analogue Score < 3), and those parameters were recorded every hour throughout the study period. If the pain score was greater than 5 on the VAS of 0 to 10 in which 0 is no pain and 10 is the worst pain ever experiences, alfentanil or remifentanil was increased. If cardiorespiratory adverse effects were found while opioid concentrations were being titrated up, the concentrations were decreased to the previous ones given right before the events. Also in the case of request from the patients while they were on ventilatory support, suggesting intolerable pain, alfentanil or remifentanil was titrated up. After patients were weaned from the artificial ventilator and extubated, opioid infusion was also continued until pain was tolerable. Alfentanil or remifentanil infusion was continued while patients were intubated and pain score was more than 5 if requested by patients after weaning from the ventilator and extubation. All the data were recorded for 48 hrs, and if patients were not extubated for 48 hours after being transferred to the ICU, the data were recorded only for 48 hours, and the data after 48 hours were excluded.

The patients with medical history of long term therapy on antidepressants, psychiatric diseases or severe neurological deficit and alleged general allergy were excluded. A standard anesthetic technic using desflurane, remifentanil and neuromuscular blocking agent (vecuronium) was used for anesthetic induction and maintenance.

Patients were closely monitored until the targeted effect-site concentrations were reached. Alfentanil or remifentanil was provided using a commercially available TCI pump incorporated with PK model for each opioid. The alfentanil preparation was based on Alfenil^{TM} inj., 1.13 mg vial (DAEWON, Korea) diluted with 20 ml of normal saline (app. 50 μg ml^{-1}solution). The remifentanil preparation was based on Ultiva^{TM} inj., 1 mg vial (GlaxoSmithKline, Belgium) diluted with 50 ml of normal saline (20 μg ml^{-1}solution).

3. RESULTS

Fifty-four who were sent to the ICU after major abdominal surgery were recruited for the study (Table 1). Analysis of postoperative analgesia with TCI system showed that pain scores (VAS) and opioid concentrations were scattered broadly regardless of respiratory condition (Fig. 2 and Fig. 3). In spite of this variability VAS and opioid concentrations gradually decreased over time, suggesting good quality of pain relief. The TCI systems for the infusion of alfentanil or remifentanil were used for a mean time of 15 and 22 hours in the ICU, respectively. Pain was controlled rapidly by increasing the target concentrations of alfentanil or remifentanil. The frequent changes in plasma target concentrations were made mainly in the initial stages of postoperative period.

Table 1.Demographic data (Mean +/- SD, Range)

	Alfentanil	Remifentanil
Age (Years,Range)	60 +/- 13, 40-85	62 +/- 15, 48-89
ASA	II-III	II-III
Gender (N, M/F)	24, 15/9	28, 17/11
Weight(Kg, Range)	46 +/- 17, 36-79	44 +/- 14, 39-81
ICU stay (Mean Hours, Range)	20 +/- 14, 10-48	31 +/- 11, 8-48

Table 2. Mean effect-site concentrations (Ce) of alfentanil and remifentanil at the three different stages during the ICU stay

	Alfentanil	Remifentanil
Intubation with artificial ventilation	64+/-12, 45-75	1.9+/-0.5, 1.0 - 3.0
Intubation with spontaneous ventilation	57+/- 9, 40-60	1.7+/-0.7, 1.0 - 2.5
Extubation	41+/-10, 20-60	1.2+/-0.5, 0.5 - 2.5

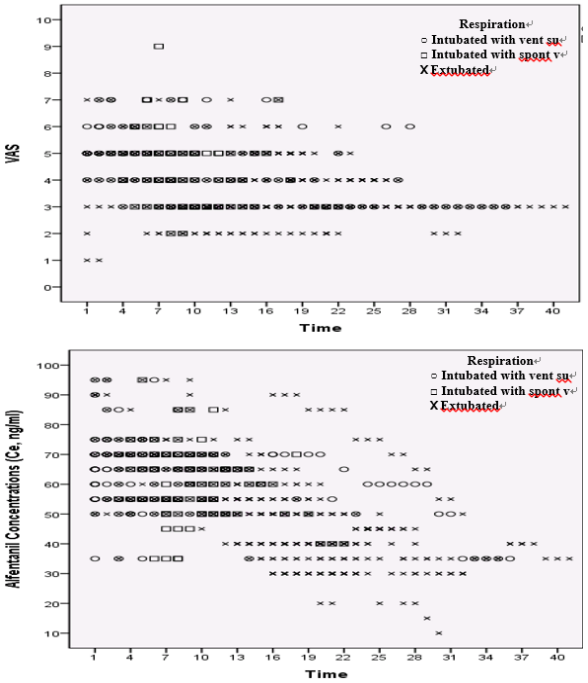

Fig. 2. Scattered plots of VAS (Visual or Verbal Analogue Scale) and alfentanil concentrations

This investigation has shown relatively good control of postoperative pain in the ICU with TCI of alfentanil or remifentanil demonstrated by the three different mean effect-site concentrations (Ce, ng/m1): 64+/-12 and 1.9+/-0.5 for intubation with artificial ventilation, 57+/-9 and 1.7+/-0.7 for intubation with spontaneous ventilation, and 41+/-10 and 1.2+/-0.5 after extubation, respectively (Table 2). Severe cardiorespiratory adverse effects were not found while opioids were being administered.

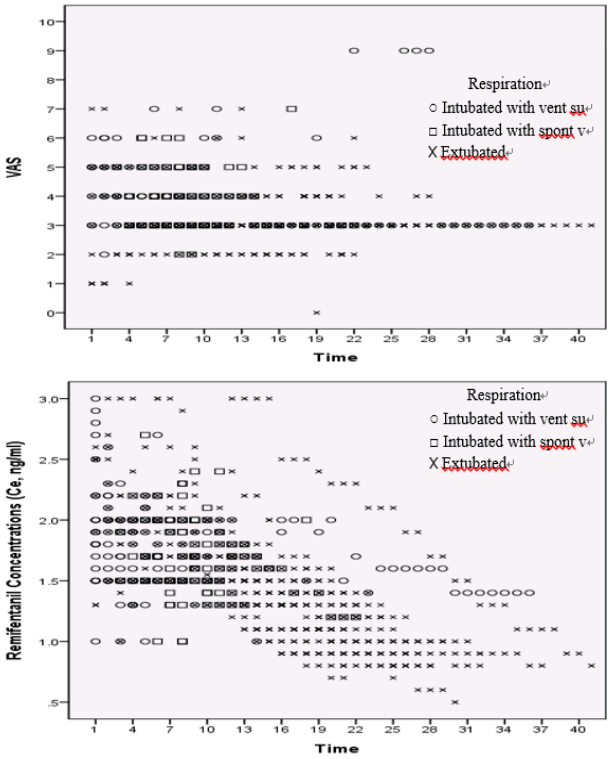

Fig. 3. Scattered plots of VAS (Visual or Verbal Analogue Scale) and remifentanil concentrations

4. DISCUSSION

This study was based on a simple clinical protocol to monitor the effect-site concentrations of alfentanil of remifentanil administered for the relief of postoperative pain and discomforts in patients during the ICU stay. The appearance of opioids such as alfentanil and remifentanil with unique pharmacokinetic (PK) and pharmacodynamic (PD) properties as suitable analgesic agents for postoperative patients, coupled with technological advances in more reliable and accurate intravenous pumps, and in our understanding of pharmacokinetic processes has enabled the development of the technique of TCI. The rapid increase in the processing power of modern computers has also enabled the development of TCI. The technique makes the titration of opioids with a short half-life very easy, allowing infusion at higher doses than are normally administered with traditional opioids and minimizing cardiorespiratory depression or delayed recovery resulted from accumulation. In recent times opioids with a long half-life such as morphine or fentanyl have not been broadly used in the ICU, because, when administered over several days, they can result in adverse effects due to delayed elimination. In this study a commercially available TCI pump incorporated with PK model for opioids (based on "ng/ml") was used instead of a conventional infusion pump ("μg/kg/min and μg/kg/h") to minimize the dose of alfentanil and remifentanil administered, and, eventually, the incidence of adverse effects.

Patients requiring intensive or critical care need effective analgesia and sedation to reduce pain, various discomforts and anxiety originated from tracheal intubation, mechanical

ventilation and other clinical procedures. A number of clinical studies have compared the use of analgesia-based sedation with alfentanil or remifentanil with that of morphine or fentanyl in the critically-ill who were being mechanically ventilated in the ICUs. Both drugs has been shown to provide effective analgesia-based sedation in those patients in the ICU. TCI of Alfentanil has been used and studied in many institutions for both intraoperative and postoperative analgesia [3]-[6]. When used for postoperative analgesia following cardiac surgery TCI alfentanil produced excellent analgesia, with patients experiencing little or no pain 96% of the time [7]. Remifentanil is similar to other traditional opioids (fentanyl or morphine) in terms of the duration of sedation and the degree pain control. Furthermore, with remifentanil, the need for additional sedation generally appeared less than that of fentanyl and morphine because of synergistic interaction with sedative agents [8], [9]. Remifentanil is well-applied to TCI by virtue of its rapid onset of action, short elimination half-life and, therefore, lack of accumulation. The context-sensitive half time is approximately three minutes and as this value does not change as the infusion duration increases the duration of effect of remifentanil is context-insensitive [10]. TCI fentanyl has been used for intraoperative analgesia in combination with isoflurane [11], sevoflurane [12] and propofol [13]. However, when used by infusion prolonged recovery can be a problem. After an infusion of more than sixty minutes the context-sensitive half time [14] and decrement time increased rapidly [15].

Attempts to improve opioid dosage regimens have been based on PK and PD characteristics of the drugs to be used. Previously a continuous relationship between opioid agonist blood concentrations and response was proposed. Minimum blood drug concentration with effective analgesia (MEAC: Minimum Effective Analgesic Concentration) was also proposed in designing dosage regimens to achieve the target blood drug concentrations. However, because of limitations of the unpredictable variability in both the dose–blood concentration and the blood concentration–effect relationship, more reasonable measures of pain control was tried such as patient-controlled analgesia (PCA). PCA has been an improvement on traditional intermittent intramuscular injection techniques and used in preference to other modalities because, but it may not be always superior, requiring the medical staffs to control administration rate of pain killer appropriately. As a matter of fact, there are still limitations in PCA for some possible reasons mentioned above. Each MEAC may differ by 30% from the mean value [16], and systematically change by 5-11% an hour [6]. Moreover, variation in MEAC between patients after intra-abdominal surgery were also reported about 50% [17]. These mean MEAC determined under specific conditions varies, and more individually titrated approach precisely reflecting opioid drug blood concentration should be used in pain control.

The postoperative pain control in the country is currently dependent on continuous infusion of opioids, but there is still a remarkable difference from complete pain relief because of above reasons. Daily experience in the ICU suggests that postoperative pain control using continuous infusion based on syringe pump has been less than expected, but how inadequate has not been well known. This investigation has shown relatively good control of postoperative pain in CBNUH ICU with TCI of alfentanil and remifentanil, demonstrated by the three mean effect-site concentrations (Ce, ng ml^{-1}): 64+/-12 and 1.9+/-0.5 for intubation with artificial ventilation, 57+/-9 and 1.7+/-0.7 for intubation with spontaneous ventilation, and 41+/-10 and 1.2+/-0.5 after extubation, respectively. Consequently it is believed that for most surgical areas including ICU pain control after surgery can be well managed using TCI. In spite of this outcome patients have pain mainly in the early postoperative period, suggesting pain control should be focused more on the initial postoperative stage than later period.

ACKNOWLEDGEMENT

This work was supported by the research grant of the Chungbuk National University in 2011.

REFERENCES

[1] C. L. Westmoreland, J. F. Hoke, P. S. Sebel, C. C. Hug Jr., and K. T. Muir, “Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GR90291) in patients undergoing elective surgery,” Anesthesiology, vol. 79, no. 5, 1993, pp. 893-903.

[2] A. Kapila, P. S. Glass, Jacobs Jr., K. T. Muir, D. J. Hermann, M. Shiraishi, S. Howell, and R. L. Smith, “Measured context-sensitive half-times of remifentanil and alfentanil,” Anesthesiology, vol. 83, no. 5, 1995, pp. 968-975.

[3] J. Vuyk, T. Lim, F. H. Engbers, A. G. Burm, A. A. Vletter, and J. G. Bovill, “Pharmacodynamics of alfentanil as a supplement to propofol of nitrous oxide for lower abdominal surgery in female patients,” Anaesthesiology, vol. 78, 1993, pp.1036-1045.

[4] J. Vuyk, T. Lim, F. H. Engbers, A. G. Burm, A. A. Vletter, and J. G. Bovill, “The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women,” Anaesthesiology, vol 83, 1995, pp. 8-22.

[5] D. P. Crankshaw, D. J. Morgan, G. H. Beemer, and F. Karrasawa, “Pre-programmed infusion of alfentanil to constant arterial plasma concentration,” Anesthesia and Analgesia, vol. 76, no. 3, Mar. 1993, pp. 556-561.

[6] C. L. Westmoreland, P. S. Sebel, and A. Gropper, “Fentanil or alfentanil decreases the minimal alveolar anaesthetic concentration of isoflurane in surgical patients,” Anesthesia and Analgesia, vol. 78, no. 1, Jan. 1994, pp. 23-28.

[7] F. W. Davies, M. White, and G. N. Kenny, “Postoperative analgesia using a computerised infusion of alfentanil following aeortic bifurcation graphed surgery,” Int J Clin Mon Comp, vol. 9, no. 4, Dec. 1992, pp. 207-212.

[8] E. Lang, A. Kapila, D. Shlugman, J. F. Hoke, P. S. Sebel, and P. S. Glass, “Reduction of isoflurane minimal alveolar concentration by remifentanil,” Anesthesiology, vol. 85, no. 4, 1996, pp. 721-728.

[9] R. J. Fragen, G. I. Randel, E. S. Librojo, M. Y. Clarke, and B. D. Jamerson, “The interaction of remifentanil and propofol to prevent response to tracheal intubation and the

start of surgery for outpatient knee arthroscopy [abstract]," Anesthesiology, vol. 81, 1994, p.A376.
[10] A. Kapila, P. S. Glass, Jacobs JR, D. J. Hermann, M. Shiraishi, S. Howell, and R. L. Smith, "Measured context-sensitive half-times of remifentanil and alfentanil," Anesthesiology, vol. 83, no. 5, 1995, pp. 968-975.
[11] A. I. McEwan, C. Smith, O. Dyar, D. Goodman, L. R. Smith, and P. S. Glass, "Isoflurane minimal alveolar concentration reduced by Fentanyl," Anesthesiology, vol. 78, no. 5, 1993, pp. 864-869.
[12] T. Katoh, T. Uchiyama, and K. Ikeda, " Effect of fentanyl on awakening concentration of Sevoflurane," British Journal of Anaesthesia, vol. 73, 1994, pp. 322-325.
[13] C. Smith, A. I. McEwan, Jhaveri R. et al., "The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision," Anesthesiology, vol. 81, 1994, pp. 820-828.
[14] M. A. Hughes, P. S. Glass, and Jacobs JR, "Context-sensitive half-time in the multicompartment pharmaco-kinetic models for intravenous anaesthetic drugs," Anesthesiology, vol. 76, 1992, pp. 334-341.
[15] Jm. Bailey, "Pharmacodynamics as a research tool," Journal Clin Anaesth, vol. 8, 1996, pp. 42S-52S.
[16] L. E. Mather, W. B. Runciaman, A. H. Ilsley, R. J. Carapetis, and R. N. Upto, "A ship preparation for studying interactions between bloods flow and drug disposition. V. The effects of general anesthesia and subarachnoid anaesthesia on blood flow and pethidine disposition," British J Anaesth, vol. 58, 1986, pp. 888-896.
[17] A. Tamsen, P. Hartvig, C. Fagerlund, and B. Dahlstrom, "Patient-controlled analgesic therapy. Part II: individual analgesic demand and analgesic concentrations of pethidine in post-operative Pain," Clin Pharmacokinetics, vol. 7, 1985, pp. 164-175.

Hae-Lan Jang
She graduated from Seoul National University in 1985 with a BS in Nursing and received a PhD with Chungbuk National University in 2012. The research she conducted for her PhD was an investigation into medical administration and informatics. She is currently an associated professor in the Department of Nursing, Joongbu University. Her main research interests are fundermental nursing and research trend analysis, and she is currently involved in MeSH Indexing.

Hoon Kang
He grew up and completed all of his education in Korea. Having completed five years of training (internship and residency in anesthesiology) and three years of national service, he joined the Chungbuk National University Department of Anesthesiology and Pain Medicine as an instructor in 1993, and he is still working as a faculty member in the same institute. He took a sabbatical in Glasgow to further specialize in intravenous anesthesia and monitoring depth of anesthesia in 1999-2001 period. His research interests include intravenous anesthesia, acute and chronic pain control (cancer pain and neuropathic pain). Other research interests also include anesthetic management of geriatric patients and intraoperative nociception monitoring.