

## Review Article

# Sufentanil: Pharmacology and Current Applications in Clinical Practice

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**Abstract**

Sufentanil is the most potent opioid use today in clinical practice, yet there is scarcity in the literature addressing this novel drug. The purpose of this article is to review sufentanil's pharmacologic characteristics, the historical reasons for its development, and its current and future clinical applications after a recently developed sublingual formulation.

**ABBREVIATIONS**

FDA: Food and Drug Administration; AAG:  $\alpha_1$ -acid glycoprotein; EEG: Electroencephalographic;  $CSt^{1/2}$ : Context-sensitive half-time;  $t^{1/2}ke0$ : blood-effect-site equilibration half-life; CNS: Central Nervous System; SSEP: Somatosensory Evoked Potentials; LD 50: lethal dose in 50% of animals; ED 50: Effective dose in 50% of animals; ICP: Intracranial Pressure; PCA: Patient Controlled Analgesia; MEPs: Motor Evoked Potentials; IAs: Inhalation Anesthetics; NSAIDs: Non-steroidal Anti-inflammatory Agents.

**INTRODUCTION**

Sufentanil, a synthetic analogue of the opioid fentanyl, was synthesized in the 1970s and approved for clinical use by the United States Food and Drug Administration (FDA) in 1984 [1,2]. A highly selective  $\mu$ -opioid receptor agonist, intravenous sufentanil has been used extensively in anesthesia practice and especially in the context of cardiac surgery [1]. In addition to its most common routes of administration, intravenous, intrathecal and epidural, more recently, there has been increased interest in a sublingual formulation for the management of acute and chronic pain. In our article we will discuss the pharmacokinetic and pharmacodynamic profiles of sufentanil, the clinical reasons for its development and its current obstetric and perioperative applications.

**DISCUSSION & CONCLUSION****Chemical Structure**

Sufentanil is a thienyl derivative of fentanyl, a 4-anilidopiperidine [3] (Figure 1).

**Mechanism of Action**

Similar to the other members of this class, sufentanil produces physiologic effects through  $\mu$ -receptor agonist activity. Indeed, sufentanil has 100 times more affinity for the  $\mu$ -opioid receptor than the  $\delta$ -receptor [4]. In addition when compared to fentanyl and morphine it has shown to be more selective too for the  $\mu$ -opioid receptor, this explains the fact that sufentanil is 10 times more potent than fentanyl [1,5,6].

**Pharmacokinetics**

Sufentanil is a highly lipid soluble molecule. This pharmacokinetic characteristic allows the drug to cross freely the blood-brain barrier and achieve a fast onset of action [5]. Sufentanil's pKa is 8.1, and this means that at physiologic pH it is highly ionized [6,7]. To further understand sufentanil's pKa effect on its bioavailability, one should compare sufentanil to alfentanil. Alfentanil has a pKa of 6.5 and at physiologic pH exists

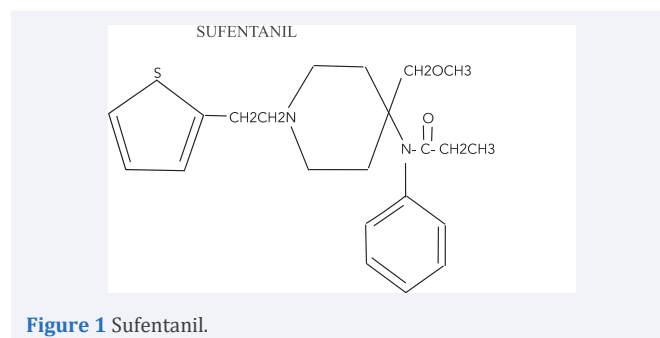


Figure 1 Sufentanil.

in a non-ionized form, this makes it readily available at site specific receptors achieving peak brain effect site concentration after 1.4 min of intravenous administration [7,8], Whereas sufentanil instead takes, 6.2 +/- 2.8 min, similar to fentanyl, 6.6 +/- 2.8 min [7]. Yet, another sufentanil pharmacokinetic property is that is heavily protein-bound, 90%, predominantly to  $\alpha_1$ -acid glycoprotein (AAG) [1,6,7]. This is an important pharmacokinetic characteristic to consider if used in neonates and infants. In these age groups AAG plasma levels are low as reported by Meistelman C. et al., therefore avoiding or decreasing the dose is recommended, this subject will be addressed again in this article [9].

### Clearance

Several studies have shown that the pharmacokinetic profile of intravenous sufentanil follows a three-compartment model [6,10,11]. In the adolescent population, the elimination of sufentanil goes through 3 phases and averages about 164 minutes in total [12]. There is an initial distribution phase, a redistribution phase, and then a terminal elimination phase. The first two phases are the shortest, while the terminal phase takes up the majority of the half-life plasma time. In children, the elimination half-life is around 97 minutes, but in neonates, that time actually increases to 434 minutes [12]. This difference is due to the changes in volume of distribution that correlate with age and degree of liver and kidney function. Another determining factor for rate of elimination and clearance is hepatic blood flow. The greater the hepatic blood flow, the higher the hepatic extraction ratio, which results in a faster clearance rate [13].

Following intravenous administration, peak plasma concentration is achieved after 3 minutes, whereas the average onset of action, as defined by evidence of electroencephalographic (EEG) slowing, is approximately two minutes following injection [8,11].

Compared to fentanyl, sufentanil has a smaller volume of distribution [1,5,6]. In keeping with its lipophilic nature, sufentanil's volume of distribution is approximately three times that of total body water, with the peripheral tissue compartment acting as a reservoir for the drug [6]. Following a bolus injection, sufentanil is rapidly redistributed from the plasma, with an initial fast distribution half-time of 1.4 minutes, followed by a redistribution half-life of 18 minutes [1,10,14]. The terminal half-life has been found to be 2.5 hours [8].

Several studies have found that the volume of distribution of sufentanil is affected by the arterial partial pressure of carbon dioxide and by the acid-base status [5,9,10]. Demonstrated that reductions in pH secondary to respiratory or metabolic acidosis results in an increased ionization of sufentanil, reducing its protein binding, metabolism and clearance and therefore prolonging its duration of action [9]. Conversely, hyperventilation has been shown to produce the opposite effect, increasing the drug's volume of distribution and its elimination half-life, possibly due to an increase of its non-ionized form [5,15].

Context-sensitive half-time ( $CSt^{1/2}$ ) is the time needed for the plasma concentration of the drug to decrease by 50% from a steady state [3]. The ideal  $CSt^{1/2}$  of an analgesic drug should be

neither too short allowing an early return of pain in the immediate postoperative period nor too long which may produce protracted side effects including, postoperative sedation, and respiratory failure requiring re-intubation. The  $CSt^{1/2}$  of sufentanil is about 1 hour after an i.v. infusion lasting for 6 hours, which is much faster than the  $CSt^{1/2}$  of fentanyl > 6 hours [4]. This is the reason why intraoperative sufentanil infusions are discontinued 45 minutes to 1 hour prior to patient awakening from general anesthesia.

Sufentanil is a highly lipophilic drug, hence readily crosses the blood-brain barrier [7]. Scott et al., estimated the blood-effect-site equilibration half-life ( $t^{1/2}ke0$ ), by measuring the lag time between changes in plasma sufentanil concentration and changes in spectral edge frequency of the electroencephalogram. The  $t^{1/2}ke0$  for sufentanil is 6.2 min, which is very close to that of fentanyl (6.6 min), however the  $t^{1/2}ke0$  of morphine is 3 hours and its active metabolite morphine-6-glucuronide is 6 hours [5,9,10]. This explains why the concentration of morphine in the central nervous system lags significantly behind its plasma concentration. In contrast, the effect-site concentration of sufentanil closely follows its plasma concentration with minimal lag. This pharmacokinetic profile makes sufentanil more titratable than morphine [14].

### Dosing

Sufentanil dosing should be calculated using the patient's lean body weight instead of total body weight. This fact is especially important when administering the drug to obese or morbidly obese patients. The infusion dose recommended in adults is 0.3 to 1.5 mcg/kg/hr [14,16,17].

Freye E. et al comparing the potency of sufentanil vs fentanyl showed that a bolus of sufentanil 1mcg/kg blunts the sympathetic response to laryngoscopy, while to achieve the same effect, a bolus of 5 mcg/kg of fentanyl is required [18].

### Metabolism

Sufentanil is characterized by a high hepatic extraction ratio of 0.8 and is metabolized extensively in the liver by the CYP3A4 enzyme [6,8,10]. To a lesser degree, the drug is also metabolized in the small intestine [12,14]. There are two major metabolites, norsufentanil and n-phenylpropanamide, that are excreted in the urine inactive and one metabolite demethylsufentanil that keeps approximately 10% of sufentanil's potency but is produced in very small quantities [12,14].

Following oral administration, sufentanil undergoes extensive first pass metabolism, thus reducing its oral bioavailability [10]. This is the reason why new sufentanil formulations have been developed for sublingual administration.

### Pharmacodynamics

Sufentanil is a potent synthetic opioid that produces analgesia and sedation. It was developed to produce physiologic effects through mu receptor agonist activity in the central nervous system (CNS). In addition sufentanil also exerts effects on the cardiovascular, respiratory, and gastrointestinal systems. Sufentanil can cause hypotension and bradycardia, likely secondary to inhibition of sympathetic outflow from the central nervous system [19,20]. Therefore, effort should be made pre- and

intra-operatively to ensure our patients are euvoletic and their vitals signs closely monitored while receiving this drug. Other medications that could worsen this hypotension and bradycardia seen with the administration of sufentanil are antihypertensive drugs, for example beta blockers.

Dose related respiratory depression is also an effect of sufentanil secondary to inhibition of central respiratory centers in the medulla [21]. Given the high potency and lipophilicity of the drug, the respiratory status of patient's given sufentanil should be continuously monitored.

Similar to other opiates, sufentanil also affects the mu-receptors in the gastrointestinal tract. It will increase smooth muscle tone which can lead to decreased peristalsis and constipation. This is likely secondary to the increased efferent motor neuron traffic that also leads to chest wall rigidity and glottic closure [22].

Comparable to other opiates, sufentanil does not appreciably affect intracranial pressure. In comparison to fentanyl, sufentanil is 7-12 times as potent with quicker initiation and recovery of clinical effects, as well as, a shorter elimination half-life [4,6,23,24]. Sufentanil's greater potency may be the reason it is able to provide near complete anesthesia as shown by the dose-response reduction in the minimum alveolar concentration of halothane and isoflurane [25,26]. When sufentanil sedation is titrated to limit changes in mean arterial pressure, there does not appear to be an associated increase in intracranial pressure [27]. Sufentanil would appear advantageous in neurosurgery secondary to its short context-sensitive half-life. A study in patients undergoing craniotomies, however, showed no difference in emergence time and ability to perform a post-operative neurological exam when compared with alfentanil and fentanyl [28]. Sufentanil does have a small, but significant effect on somatosensory evoked potentials (SSEP); however, the clinical impact of this finding appears to be minimal [29].

While sufentanil affects several systems in the body, it has been postulated that age-related changes in plasma protein content, volume of distribution, and metabolism can lead to changes in the intensity of sufentanil's effect. This may be the reason for an increased effect in neonates. They have a significantly lower level of  $\alpha_1$  acid glycoprotein, this causes a greater concentration of sufentanil in its unbound form. In a trial looking at free fraction plasma concentrations of sufentanil, neonates had an elevated level in comparison to older children and adults [9]. The increased free fraction leads to a greater volume of distribution and availability of the drug to penetrate the blood brain barrier.

Therapeutic index or therapeutic ratio is the margin of safety that exists between the dose of a drug that produces the desired effect and the dose that produces unwanted side effects. This is measured as the lethal dose in 50% of animals divided by the effective dose in 50% (LD50/ED50) [6]. Compared with the therapeutic index of fentanyl, 280, morphine, 70 and pethidine, 5, sufentanil has a much greater margin of safety, with its therapeutic index around 26,700.

A study looking at pharmacokinetics of sufentanil between middle aged and elderly individuals found no significant difference in elimination half-life, total volume of distribution,

and plasma clearance. The only significant difference was initial volume of distribution which was decreased in the elderly. This trial controlled for albumin between the groups to decrease likelihood of protein binding influencing results [22]. Similar findings were seen in comparison of cirrhotic patients to controls [30]. As such, significant decreases in hepatic blood flow or hepatic enzymatic function would be necessary to alter sufentanil pharmacokinetics and subsequently pharmacodynamics. These results suggest that sufentanil's effect on elderly patients may be related to the drug's interaction at its specific sites of action rather than its pharmacokinetic distribution or metabolism.

In neurosurgery, when sufentanil sedation is titrated to limit changes in MAP, there does not appear to be an associated increase in intracranial pressure (ICP) [31]. If MAP is affected the maintenance of autoregulation determines an increase or decrease ICP. If autoregulation is maintained then there is an inverse relationship between MAP and ICP. There is a direct relationship if it is not maintained. While sufentanil appears advantageous secondary to the low context-sensitive half-life, a second study in patients undergoing craniotomies showed no difference in emergence time and ability to perform a post-operative neurological exam when compared with alfentanil and fentanyl [32]. Sufentanil does have small, but significant effect on somatosensory evoked potentials (SSEP); the practical effect appears to be minimal [27].

### Adverse Effects

Sufentanil has increased selectivity for the opioid receptors in the CNS, which explains its improved side effect profile [1]. Opioids are known to cause various side effects including sedation, nausea, vomiting, pruritis, respiratory depression, urinary retention, bradycardia, hypotension, dependence and tolerance. Gastrointestinal effects of opioids include inhibition of intestinal and pancreatic secretion, increased bowel tone and decreased intestinal propulsive activity, these effects manifest clinically as delayed gastric emptying, constipation, abdominal cramps and paralytic ileus [14].

Side effect profile of sufentanil was compared to morphine, meperidine and fentanyl in a prospective double blinded study during general and orthopedic surgeries. After induction with equipotent doses of sufentanil (that is up to 1.5 microgram/kg), no side effects were reported while hypotension, laryngeal spasm, chest wall rigidity, tachycardia, marked flushing, elevated plasma histamine level were observed in patients who received meperidine and morphine. Heart rate, blood pressure and plasma catecholamine (norepinephrine and epinephrine) values were lowest during induction, intubation, incision and throughout the entire length of the surgery in patients who received sufentanil, while all these parameters were elevated in patients who received morphine and meperidine. Intraoperative hemodynamic stability was observed consistently in all patients in the sufentanil group, while 30% of the patients who received morphine, meperidine or fentanyl had tachycardia and hypertension which required supplementation with potent inhalational anesthetic. However hemodynamic stimulation was observed during emergence and extubation in all groups. Postoperative respiratory depression was the least common in sufentanil group and this was short-lasting due to the shorter elimination half-life of sufentanil.

Pre-induction administration of nalbuphine was found to cause a significant reduction in the incidence and intensity of sufentanil-induced cough [2]. Pre-treatment with various other agents including tramadol, remifentanil, ketorolac and dexmedetomidine have been shown to reduce sufentanil-induced cough [3-6].

Intrathecal sufentanil for labor analgesia was associated with hypotension in 11-14% of cases, perineal pruritis in 95% of patients and mild sedation in all cases. FHR changes occurred in 15% of the parturient, however this was not associated with adverse neonatal outcomes [7]. Sufentanil use in combined spinal epidural for labor analgesia was associated with a much higher incidence of pruritis (80%) as compared to fentanyl (47.4%), although no significant difference in incidence of nausea, vomiting and hypotension was observed [9]. Although sufentanil (5 µg) was associated with significantly less hypotension as compared to equianalgesic dose of clonidine (75 µg) when administered for labor epidural analgesia, the former had a much higher incidence of pruritis.<sup>10</sup> Addition of epinephrine to epidural sufentanil for labor epidural analgesia led to significant reduction in sedation and lightheadedness, implying that systemic uptake of the drug rather than cephalad migration in the CSF is the primary mechanism for respiratory depression and sedation [11].

Addition of dexmedetomidine to postoperative sufentanil patient controlled analgesia (PCA) was associated with lower incidence of postoperative nausea, vomiting and pruritis [8]. Retrospective review comparing hydromorphone, sufentanil and oxycodone in intravenous PCA for advanced cancer pain management revealed common side effects including constipation (11.8%), nausea (8.2%), and sedation (5.9%), although there was no significant difference noted amongst the different opioids [15].

Transient muscle rigidity in the lower limbs have been described in patients who received intrathecal sufentanil [12,13]. A recent study revealed that sufentanil increases monocyte-endothelial adherence which led to a decrease in release of ATP from Cx43 channels in monocytes [33]. This effect of sufentanil could have clinical implications on the pathophysiology of vascular inflammatory states.

## Clinical Uses

To have a better understanding of the clinical use of sufentanil, it is important to make a historical review for the reasons of its development. Perhaps the most relevant reasons were the less than ideal pharmacodynamic and pharmacokinetic properties of morphine. These include its prolonged half-life, consistent with a high incidence of postoperative respiratory depression, histamine release leading to hemodynamic instability as well as bronchoconstriction, etc. This led to the study and development of new synthetic opiates with greater receptor specificity, greater potency and less side effects in the 1950's [34]. Dr. Paul Janssen after a decade studying the chemical structures of morphine and meperidine focused on developing a new drug with greater lipid solubility to increase the molecule bioavailability at receptor site and to improve its onset of action as well as to make it more specific in its binding to the mu receptor.<sup>2</sup> On December 1960 he discovered fentanyl. The 1960 decade was also the start of the

coronary artery bypass graft. In May 1967 Dr. Rene Favaloro performed the first coronary artery bypass graft at the Cleveland Clinic, starting a new era in cardiac surgery [35]. This led to further development of new anesthetic drugs and techniques focused on achieving a greater hemodynamic stability. In those years neuroleptanalgesia / anesthesia techniques were widely used in all anesthetic subspecialties. This technique was first reported in France in 1954 by Campan and Lazothés [36]. It consisted on the combined administration of a neuroleptic agent such as haloperidol, later changed for droperidol, a potent synthetic opiate, such as phenoperidine, later changed for fentanyl and sufentanil and a long acting, non-depolarizing muscle relaxant, pancuronium [37]. Neuroleptanesthesia/analgesia proved not to be the ideal pharmacokinetic and pharmacodynamic drug combination for reliable amnesia and optimal muscle relaxation during induction of anesthesia. The mild sedative properties of droperidol in conjunction to the delayed onset of action of pancuronium, generally required higher doses of opiate administration, producing unreliable hypnosis and frequently chest rigidity, making hand ventilation difficult. The discovery of the benzodiazepine receptor and the development of short and intermediate acting benzodiazepines in the 50's, 60's and 70's, in addition to the discovery of other induction agents such as propofol and etomidate, made the use of neuroleptanesthesia obsolete, and led to the development of the balanced anesthesia techniques, well known today [37-40].

Besides its current use in cardiac anesthesia, sufentanil has been successfully used in spine surgery [41,42]. Not only for its analgesic properties, but also due to its limited interference with somato sensory and motor evoked potentials (SSEPs and MEPs) when these neurologic monitoring techniques are indicated [43]. It is important to note that sufentanil, as many other opiates, potentiate the effect of inhalation anesthetics (IAs) as described by Murtua M et al., with the use of remifentanil [44]. This potentiation allows the anesthesiologist to reduce the dose of IAs delivered and therefore decrease even further the interference in SSEPs and MEPs signals [43,44]. In the authors clinical practice, sufentanil is being used in patients undergoing extensive spine surgery, including multiple level cervico, thoracic and lumbar spine fusion that very often includes the intraoperative use of MEPs. In these cases, sufentanil is delivered as a continuous infusion, ranging from 0.3 to 0.7 mcg/kg per hour, dosed at patient's lean body weight in combination with a hypnotic agent [45]. The continuous infusion is discontinued 60 to 45 minutes prior to emergence from anesthesia. This technique has proved to provide a better pain control and transition to oral analgesics in the immediate postoperative period when compared to remifentanil, an opiate with a much shorter context sensitive half-life. It is important to note that in complex spine surgery, the implementation of multimodal analgesia has led to a decrease in the need for postoperative opiate use. These non-opiate analgesics include gabapentin, pregabalin, ketamine, extended action local anesthetics, non-steroidal anti-inflammatory agents (NSAIDs) including acetaminophen etc [46-48].

In the obstetric field, sufentanil has been used successfully in epidural and spinal anesthesia and analgesia. One important pharmacokinetic characteristic of this opiate is its high lipid solubility, this feature allows for a faster onset of action and also

leads to a short duration of action when compared to the less lipid soluble opioids such as morphine. Therefore, the use of sufentanil might be better suited as a continuous infusion through an epidural catheter. This characteristic makes it a drug suitable in the treatment of postoperative pain in the modality of patient controlled epidural analgesia [48,49]. Another use in obstetric anesthesia is its intrathecal administration in the combined spinal epidural technique, generally practiced in patients who are in the latest stages of labor and require an opioid with a fast onset of action [50].

In orthopedic surgery, Hassani V. et al., found that when administered in the intrathecal space in patients undergoing lower extremity surgery, the combination sufentanil/bupivacaine (sufentanil 2.5 to 3 mcg / isobaric bupivacaine 0.5% 15 mg) when compared to fentanyl/ bupivacaine and placebo/ bupivacaine, produced less hypotension, a decreased incidence in nausea and vomiting, a greater mean SPO<sub>2</sub>, and a longer duration of analgesia. In terms of length of motor block there was no difference among the 3 groups, however, there was a higher incidence of pruritus in the sufentanil group [51].

In 2018 the FDA approved the use of a new sufentanil formulation, a sublingual tablet system. These tablets come with a single dose applicator that contain a 30 mcg sufentanil tablet. The FDA approved its hospital use for the treatment of postoperative pain and it should be administered by a health care provider hourly only. When compared to intravenous PCA morphine, the sublingual administration of sufentanil showed a faster onset of analgesia and greater patient and nurse satisfaction scores. In addition to its use in the immediate postoperative period, this sufentanil formulation has also found an important application in the battle fields, where IV access might be limited. Despite all its advantages and ease of use, it is important to remind ourselves that sufentanil is one of the most potent opiates in current medical use and that its side effects, especially respiratory depression is still a concern. This is the reason why the healthcare professional community is rising awareness of the potential for its abuse. Should this happen it would produce a devastating step back in our current battle against opiate addiction in the US and in the world [52,53].

## REFERENCES

1. Monk JP, Beresford R, Ward A. Sufentanil. A review of its pharmacological properties and therapeutic use. *Drugs*. 1988; 36: 286-313.
2. Stanley TH. The history and development of the fentanyl series. *J Pain Symptom Manage*. 1992; 7: S3-7.
3. Pasternak GW, Pan YX. Mu opioids and their receptors: evolution of a concept. *Pharmacol Rev*. 2013; 65: 1257-1317.
4. Leysen JE, Gommeren W, Niemegeers CJ. [3H]Sufentanil, a superior ligand for mu-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. *Eur J Pharmacol*. 1983; 87: 209-225.
5. Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. *Clin Pharmacokinet*. 1996; 31: 275-292.
6. Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. *Anesthesiology*. 1984; 61: 502-506.
7. Metz C, Göbel L, Gruber M, Hoerauf KH, Taeger K. Pharmacokinetics of human cerebral opioid extraction: a comparative study on sufentanil, fentanyl, and alfentanil in a patient after severe head injury. *Anesthesiology*. 2000; 92: 1559-1567.
8. Hudson RJ, Bergstrom RG, Thomson IR, Sabourin MA, Rosenbloom M, Strunin L. Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology*. 1989; 70: 426-431.
9. Meistelman C, Benhamou D, Barre J, Levron JC, Mahe V, Mazoit X, et al. Effects of age on plasma protein binding of sufentanil. *Anesthesiology*. 1990; 72: 470-473.
10. Zhao Y, Duan JL, Wu XM, Jiang JY, Lu W, Zhang LP, et al. Two-stage analysis of pharmacokinetics of sufentanil administered by target-controlled infusion in Chinese patients. *Chin Med J (Engl)*. 2009; 122: 1979-1984.
11. van de Donk T, Ward S, Langford R, Dahan A. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. *Anaesthesia*. 2018; 73: 231-237.
12. Lundeberg S, Roelofse JA. Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. *Paediatr Anaesth*. 2011; 21: 274-279.
13. Schwartz AE, Matteo RS, Ornstein E, Young WL, Thornhill M. Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. *Br J Anaesth*. 1989; 63: 385-388.
14. Maciejewski D. Sufentanil in anaesthesiology and intensive therapy. *Anaesthesiol Intensive Ther*. 2012; 44: 35-41.
15. Bowdle TA, Ward RJ. Induction of anesthesia with small doses of sufentanil or fentanyl: dose versus EEG response, speed of onset, and thiopental requirement. *Anesthesiology*. 1989; 70: 26-30.
16. Schwartz AE, Matteo RS, Ornstein E, Young WL, Myers KJ. Pharmacokinetics of sufentanil in obese patients. *Anesth Analg*. 1991; 73: 790-793.
17. Priya Shinde LD. Perioperative Care for Bariatric Surgery. *World Federation of Societies of Anaesthesiologists*. 2020.
18. Freye E, Dehnen-Seipel H, Latasch L, Behler M, Wilder-Smith OH. Slow EEG-power spectra correlate with haemodynamic changes during laryngoscopy and intubation following induction with fentanyl or sufentanil. *Acta Anaesthesiol Belg*. 1999; 50: 71-76.
19. Flacke JW, Bloor BC, Kripke BJ, Flacke WE, Etten APV, Wong DH, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. *Anesth Analg*. 1985; 64: 897-910.
20. Flacke JW, Davis LJ, Flacke WE, Bloor BC, Van Etten AP. Effects of fentanyl and diazepam in dogs deprived of autonomic tone. *Anesth Analg*. 1985; 64: 1053-1059.
21. Arkoosh VA, Cooper M, Norris MC, Boxer L, Ferouz F, Silverman NS, et al. Intrathecal sufentanil dose response in nulliparous patients. *Anesthesiology*. 1998; 89: 364-370.
22. Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. *Anesthesiology*. 1997; 87: 1070-1074.
23. Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiology*. 1991; 74: 34-42.
24. Sanford TJ, Jr., Smith NT, Dec-Silver H, Harrison WK. A comparison

- of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: induction, emergence, and extubation. *Anesth Analg*. 1986; 65: 259-266.
25. Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS. The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. *Anesth Analg*. 1983; 62: 987-990.
  26. Brunner MD, Braithwaite P, Jhaveri R, McEwan AI, Goodman DK, Smith LR, et al. MAC reduction of isoflurane by sufentanil. *Br J Anaesth*. 1994; 72: 42-46.
  27. Lauer KK, Connolly LA, Schmeling WT. Opioid sedation does not alter intracranial pressure in head injured patients. *Can J Anaesth*. 1997; 44: 929-933.
  28. From RP, Warner DS, Todd MM, Sokoll MD. Anesthesia for craniotomy: a double-blind comparison of alfentanil, fentanyl, and sufentanil. *Anesthesiology*. 1990; 73: 896-904.
  29. Kimovec MA, Koht A, Sloan TB. Effects of sufentanil on median nerve somatosensory evoked potentials. *Br J Anaesth*. 1990; 65: 169-172.
  30. Guay J, Gaudreault P, Tang A, Goulet B, Varin F. Pharmacokinetics of sufentanil in normal children. *Can J Anaesth*. 1992; 39: 14-20.
  31. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology*. 1983; 58: 438-440.
  32. Thomson IR, MacAdams CL, Hudson RJ, Rosenbloom M. Drug interactions with sufentanil. Hemodynamic effects of premedication and muscle relaxants. *Anesthesiology*. 1992; 76: 922-929.
  33. Wilde M, Pichini S, Pacifici R, Tagliabracci A, Busardo FP, Auwarter V, et al. Metabolic Pathways and Potencies of New Fentanyl Analogs. *Front Pharmacol*. 2019; 10: 238.
  34. Yang Y, Wu J, Li H, Ye S, Xu X, Cheng L, et al. Prospective investigation of intravenous patient-controlled analgesia with hydromorphone or sufentanil: impact on mood, opioid adverse effects, and recovery. *BMC Anesthesiol*. 2018; 18: 37.
  35. Oh SK, Lee IO, Lim BG, Jeong H, Kim YS, Ji SG, et al. Comparison of the Analgesic Effect of Sufentanil versus Fentanyl in Intravenous Patient-Controlled Analgesia after Total Laparoscopic Hysterectomy: A Randomized, Double-blind, Prospective Study. *Int J Med Sci*. 2019; 16: 1439-1446.
  36. Stanley TH. The fentanyl story. *J Pain*. 2014; 15: 1215-1226.
  37. Melly L, Torregrossa G, Lee T, Jansens JL, Puskas JD. Fifty years of coronary artery bypass grafting. *J Thorac Dis*. 2018; 10: 1960-1967.
  38. Bissonnette B, Swan H, Ravussin P, Un V. Neuroleptanesthesia: current status. *Can J Anaesth*. 1999; 46: 154-168.
  39. Raza SM, Masters RW, Zsigmond EK. Comparison of the hemodynamic effects of midazolam and diazepam in patients with coronary occlusion. *Int J Clin Pharmacol Ther Toxicol*. 1989; 27: 1-6.
  40. Zakhary WZA, Turton EW, Flo Forner A, von Aspern K, Borger MA, Ender JK. A comparison of sufentanil vs. remifentanil in fast-track cardiac surgery patients. *Anaesthesia*. 2019; 74: 602-608.
  41. Hobbs WR RT, Verdoorn TA. Hypnotics and Sedatives; Ethanol. Goodman & Gilman's the pharmacological basis of therapeutics. 1996: 361-397.
  42. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med*. 1997; 15: 221-230.
  43. Hudson RJ, Thomson IR, Jassal R. Effects of cardiopulmonary bypass on sufentanil pharmacokinetics in patients undergoing coronary artery bypass surgery. *Anesthesiology*. 2004; 101: 862-871.
  44. Andrianopoulou A, Triandaphillidis A, Bakatselou V, Leventis A, Michailidis D. Evaluation of sufentanil as a supplement to anaesthesia in lengthy spinal surgery. *J Int Med Res*. 1994; 22: 40-46.
  45. Bithal P. Anaesthetic considerations for evoked potentials monitoring. *J Neuroanaesthesiol Critical Care*. 2014; 1: 2.
  46. Maurtua MA, Deogaonkar A, Bakri MH, Mascha E, Na J, Foss F, et al. Dosing of remifentanil to prevent movement during craniotomy in the absence of neuromuscular blockade. *J Neurosurg Anesthesiol*. 2008; 20: 221-225.
  47. Ethuin F, Boudaoud S, Leblanc I, Troje C, Marie O, Levron JC, et al. Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med*. 2003; 29: 1916-1920.
  48. Dunn LK, Durieux ME, Nemergut EC. Non-opioid analgesics: Novel approaches to perioperative analgesia for major spine surgery. *Best Pract Res Clin Anaesthesiol*. 2016; 30: 79-89.
  49. Minoshima R, Kosugi S, Nishimura D, Ihara N, Seki H, Yamada T, et al. Intra- and postoperative low-dose ketamine for adolescent idiopathic scoliosis surgery: a randomized controlled trial. *Acta Anaesthesiol Scand*. 2015; 59: 1260-1268.
  50. Kurd MF, Kreitz T, Schroeder G, Vaccaro AR. The Role of Multimodal Analgesia in Spine Surgery. *J Am Acad Orthop Surg*. 2017; 25: 260-268.
  51. Väänänen A, Kuukasjärvi M, Tekay A, Ahonen J. Spinal and epidural sufentanil and fentanyl in early labour. *Acta Anaesthesiol Scand*. 2019; 63: 1413-1418.
  52. Grass JA. Sufentanil: clinical use as postoperative analgesic--epidural/intrathecal route. *J Pain Symptom Manage*. 1992; 7: 271-286.
  53. Hassani V, Movassaghi G, Safaian R, Safari S, Zamani MH, Hajjashrafi M, et al. Bupivacaine-sufentanil versus bupivacaine-fentanyl in spinal anesthesia of patients undergoing lower extremity surgery. *Anesth Pain Med*. 2014; 4: e12091.