Review

Current Concepts of Phenylpiperidine Derivatives Use in the Treatment of Acute and Chronic Pain

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Phenylpiperidines are a chemical class of drugs with a phenyl moiety directly attached to piperidine. These agents have an important role in many aspects of medicine including anesthesia and pain medicine. After the development of meperidine, fentanyl, which is a second generation synthetic phenylpiperidine series opioid, was synthesized and introduced into clinical anesthesia practice as fentanyl citrate in 1968. Fentanyl-mediated or modulated responses involve action at the mu-opioid receptor as an agonist at the dorsal horn inhibiting ascending pain pathways in the rostral ventral medulla, increasing pain threshold, and producing both analgesic and sedative effects. Since fentanyl is metabolized mainly via CYP3A4, potential adverse effects can occur with concomitant use of any drug which affects CYP3A4 activity. Discontinuation of CYP3A4 inducers can also result in an increase in fentanyl plasma concentration. Fentanyl-based formulations can be administered via intravenous, intramuscular, transdermal, transmucosal, and neuraxial routes. We describe the clinical utility of remifentanil, an ultra short-acting analgesic and newer formulations of sufentanil currently being evaluated for acute pain management. We examine the routes of administration and clinical considerations, including the role of opioids such as fentanyl as a natural killer cell suppressive agent. Fentanyl and other opioids have been shown to potentiate propagation of infection and cancer. In recent years, fentanyl and other phenylpiperidine formulations have been developed and successfully marketed for chronic pain management. Because all opioids have complex physiological responses and potential drug-drug interactions, the clinician should appreciate all aspects of this drug class and consider all available options in appropriate clinical settings.

Key words: Fentanyl, remifentanil, sufentanil, opioids, analgesics, pain, perioperative formulations, management

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Phenylpiperidines (Table 1) are a chemical class of drugs with a phenyl moiety directly attached to piperidine. Pharmacological effects associated with phenylpiperidines are vastly different, yet similar; they include morphine-like activity in some derivatives, while in others they exert potent central nervous system effects (Table 1). A drug synthesized by a German chemist, Otto Eisleb, pethidine (Europe) e.g., meperidine (US) was marketed initially as one of the first synthetic anticholinergic agents. It was later discovered to have analgesic, as well as local anesthetic properties. Fentanyl was synthesized via assaying pethidine opioidergic properties in the 1960s by a team lead by Dr. Paul Janssen, a Belgian physician (founder of Janssen Pharmaceuticals). From there, additional fentanyl series opioids were derived: alfentanil, sufentanil, remifentanil, and many others used in human and veterinary medicine (1).

The purpose of this review is to highlight phenylpiperidine derivatives and their use in current anesthesia and perioperative medicine practice.

US Food and Drug Administration

Intravenous (IV) fentanyl and sufentanil formulations are approved by the US Food and Drug Administration (FDA) for use in children. However, fentanyl

Table 1. *Phenylpiperidines*.

Compound	N	4-position	3-position	4'-position	Type of Pharmacology
MPPP	Me	Ph	H	-OCOEt	opioid analgesic
Prodine	Me	Ph	Me	-OCOEt	opioid analgesic
PEPAP	CH_2CH_2Ph	Ph	H	-OCOMe	opioid analgesic
Pethidine	Me	Ph	H	$-CO_2Et$	μ-agonist with SRI properties
Budipine	t-Bu	Ph	H	Ph	Anti-Parkinson disease agent
Ketobemidone	Me	3-HO-Ph	H	-COEt	opioid + NMDA antagonist
Paroxetine	H	4-F-Ph	$-CH_2OAr$	H	SSRI (+ NET)
Femoxetine	Me	Ph	$-CH_2O(4\text{-}MeOPh)$	H	(S)SRI

SRI – Selective Reuptake Inhibitors, NMDA – N-Methyl-d-Aspartate, SSRI – Selective Serotonin Reuptake Inhibitor, NET – Norepinephrine Transporter.
Modified from Janssen, PA. A Review of the Chemical Features Associated with Strong Morphine-Like Activity. *B J Anaesth* 1962; 34:260–268.

and sufentanil are not officially approved for all ages, and would be used off label for children less than 1 year old (fentanyl) and less than 2 years old (sufentanil). FDA approves use for Duragesic in children older than 2, Actiq older than 16 and Abstral, Fentora, Onlisis, Subsys older then 18 years of age (2).

Fentanyl Pharmacology

Marketing Information: Fentanyl formulations are marketed in the United States as fentanyl citrate, Duragesic, Actiq, Abstral, Fentora, Sublimize, Subsys, Ionsys, Onsolis and Lazanda.

Fentanyl, like other potent opioids, acts primarily as a mu-opioid receptor agonist at the dorsal horn to inhibit ascending pain pathways in the rostral ventral medulla. Its major effect is to increase a patient's pain threshold and to produce an analgesic and sedative effect (3). There are 3 major types of opioid receptors coupled to G-protein receptors that modulate synaptic transmission, and there is considerable overlap in receptor location throughout the body and function. In general, the various classes of opioids, including fentanyl, have varying ratios of receptor affinities or potency which result in differences in analgesic effects. In this regard, some fentanyl derivatives have also been shown to act on the delta- and kappa-opioid receptors (4). There are multiple factors, including a patient's age, body weight, kidney and liver function, as well as cardiac factors which affect the pharmacokinetic and pharmacodynamic properties of all opioids. Fentanyl is considered to be 80–100 times as potent as morphine. It is highly lipid soluble and the first pass effect on fentanyl is mediated by the lungs. After contact with a patient's blood, approximately 80% of the injected dose is bound to plasma proteins, while significant amounts are taken up by red blood cells. The duration of action of fentanyl is largely related to its redistribution to highly vascular structures. Liver metabolizes fentanyl by dealkylation and hydroxylation into norfentanyl. It is detectable in urine up to 48 hours after fentanyl has been in contact with the blood. As with other opioid analgesic agonists, fentanyl administration is associated with dose-dependent respiratory depression and sedation.

Interaction, Adverse Effects, and Warnings

Since fentanyl is metabolized mainly via CYP3A4, potential adverse effects can occur with concomitant use of any drug which affects CYP3A4 activity. Strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) and weak CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may increase plasma concentrations if coadministered (5). The discontinuation of a concomitant CYP3A4 inducer can also result in an elevated fentanyl plasma concentration.

It is not recommended to use fentanyl concurrently or within 14 days of discontinuation of monoamine oxidase inhibitors (MAOIs). Adverse reactions such as respiratory depression, hyperpyrexia, convulsions, coma, and death have been reported with opioid analgesic use following treatment with MAOIs (6).

Breakthrough Cancer Pain Treatment

A careful titration regimen should consist of initial dosing, adjustment, re-dosing, maintenance, dose adjustment and down titration. As a corollary, because

of the differences in pharmacokinetic properties, age, bioavailability, individual variability, and other factors, patients should not be routinely switched from one fentanyl preparation to another without thoroughly understanding pharmacodynamic and pharmacokinetic drug properties.

Pregnancy

Fentanyl, which is a pregnancy category C drug, can readily pass across the placenta, and caution should be taken when used during labor and delivery since the fetus is at risk of respiratory depression (7). Similar to other opioids, fentanyl is not recommended for use in breastfeeding women because it may be transferred in breast milk and lead to respiratory depression or sedation in infants (5).

Routes of Administration of Fentanyl

Intravenous

The greatest clinical use of fentanyl is for premedication, general anesthesia for minor and major surgery, and as an adjunct to general anesthesia for its role as an analgesic agent. The benefit of intravenous (IV) administration is rapid onset of action, with peak effect observed in 5 to 10 minutes and duration of 30 to 60 minutes after a single dose. Fentanyl can still be detected in plasma after 6 hours of administration and the elimination half-life is 2 to 4 hours.

Elderly patients are twice as sensitive to fentanyl than younger patients, and it is important to take into account weight and physical status of each patient at the time of administration. For surgical premedication, 50–100 µg of fentanyl should be administered via slow IV 30 to 60 minutes prior to surgery. For use during general anesthesia, dosage depends on the length of the surgical procedure. During minor procedures, 0.25–1 µg/kg may be administered, whereas during a major surgery an initial dose of 1–3 (or more) µg/kg may be followed with 1–2 µg/kg/hour of maintenance IV infusion. Historically, much larger doses have been administered for cardiac surgery and for patients with significant cardiac disease because there are minimal cardiovascular depressive effects associated with opioid administration (including fentanyl). However, over the past 2 decades this technique has lost considerable popularity because of significant improvements in recovery and less unfavorable cardiovascular effects of newer inhalational agents. To account for context-sensitive half-time, an infusion should be stopped 30 to 60 minutes prior to the end of surgery. In the management of postoperative pain, 50–100 µg should be administered intravenously and repeated as necessary, titrated to effect (8).

Intramuscular

Intramuscular (IM) fentanyl is not commonly administered, and can be used for surgical premedication and postoperative analgesia when there is no intravenous access available. As such, IM injections can be administered to the deltoid, quadriceps or gluteus muscles. The IM route of administration is associated with a slower onset of action than IV and is successful because of the high lipid solubility of fentanyl. Following IM administration of fentanyl, the onset of analgesic effect occurs within 7 to 15 minutes and lasts up to 2 hours. For surgical premedication, 50–100 µg of fentanyl should be administered intramuscularly 30 to 60 minutes prior to incision. Similarly, severe acute pain can be treated via the IM route; a 50–100 µg aliquot and can be administered every 1–2 hours or until IV access becomes available (8).

Transdermal

The fentanyl transdermal patch is used in chronic non-cancer pain and cancer pain management in patients who are opioid tolerant or have significant gastrointestinal side effects, a side effect lessened with transdermal delivery (9). The lipophilicity and low molecular weight of fentanyl makes the transdermal system a favorable mode of administration and bioavailability of close to 98%. There are 2 types of transdermal patches: the reservoir and the matrix system. The reservoir patch contains a fentanyl-based gel with hydroxyethyl cellulose; the delivery is determined by a rate-controlling membrane between the drug reservoir and the skin. The matrix patch contains fentanyl in the polyacrylate adhesive matrix itself and the drug is released continuously into the skin (10). The rate of delivery is dependent on the surface area of the patch. The reservoir patch is currently being phased out in favor of the matrix system because the matrix formulation decreases the risk of accidental overdose and drug leakage and is also smaller and thinner (11).

It is recommended that initial doses be underestimated to minimize adverse effects (5); dosing should be based on the prior opioid dosage requirement. Fentanyl 25 mcg/hr patch is approximately equal to 60–90 mg/d of oral morphine.

Patches contain 2.5, 5, 7.5, and 10 mg fentanyl and are designed to release 12.5, 25, 50, 75, and 100 mcg/hr,

respectively over a period of 72 hours. After discarding the old patch, each new patch should be applied to a different area. Multiple patches can be used simultaneously if dosages above 100 mcg/hr are required.

After initial application, there is a gradual increase in fentanyl absorption due to the large concentration gradient between the patch and the skin. A depot of fentanyl also forms in the stratum corneum before it permeates through the skin, and is taken up into the circulation. The rate of absorption is affected by body temperature, body fat, and patch placement to name a few, while recognizing variability between patients (11). Serum fentanyl concentrations do not peak until 12 to 24 hours after the first application and steady-state concentration is typically reached after 24 hours. While waiting for the analgesic effect, faster-acting rescue medications should be made available in the first 12 hours of fentanyl patch application and between dose increases. The elimination half-life after removal is 20 to 27 hours; therefore, careful monitoring is essential to avoid untoward effects of drug withdrawal and undertreatment of pain (12). Approximately 30% of fentanyl remains in the depot formed in the skin, so serum fentanyl concentrations decline quite slowly as absorption continues to occur even after patch removal. End-of-dose failure is commonly observed as therapeutic levels of sustained-release opioids fall. At maximal doses, opioid rotation is commonly used to prevent this effect in opioid tolerant patients. Various strategies such as multimodal analgesia, opioid rotation and interventional techniques can be utilized to avert this effect.

Iontophoresis

The fentanyl iontophoretic transdermal system (ITS) system is a needle-free, patient-controlled, preprogrammed fentanyl delivery system for the management of postoperative pain in hospitalized adult patients. The ITS is about the size of a credit card and is applied to the chest or upper arm. Ionsys (fentanyl iontophoretic transdermal system) is a patient-controlled analgesia (PCA) system which administers a fixed bolus of 40 µg each time the electronic controller is activated. It relies on an active electric current rather than passive diffusion to deliver fentanyl hydrochloride across the skin. In order to avoid overdose, the system has a safety lockout interval of 10 minutes and also displays the total number of administered doses. Treatment is limited to a maximum of 3 days and a new system should be applied to a different site on the chest or upper arm every 24 hours or every 80 doses (10,13).

Iontophoresis holds several advantages over other fentanyl formulations. Unlike the transdermal matrix patch which has a slow elimination half-life after removal, ITS does not form a drug depot in the skin and serum concentrations of fentanyl decrease rapidly following each patient-controlled dose. Fentanyl delivery is proportional to the amount of current applied; iontophoresis overcomes skin resistance compared to passive diffusion, which enhances the rate of delivery (13,14). ITS is less cumbersome than IV administration and can be used in patients with nausea, vomiting, or dysphagia who are unable to use transmucosal analgesics.

Transmucosal

Lozenge

The fentanyl buccal lozenge is a solidified form of fentanyl citrate on a stick that allows for direct absorption through the oral mucosa. Lozenges are effective in providing fast-acting relief for breakthrough cancer pain in opioid-tolerant individuals (15). Approximately 25% of the drug is absorbed in the mouth and another 25% swallowed and absorbed in the small intestine, for a total bioavailability of approximately 50% (16). Oral absorption results in relatively rapid onset of action and analgesic effect occurs in 10 to 15 minutes. Lozenges are available in 200 µg, 400 µg, 600 mcg, 800 µg, and 1.6 mg doses. Initial dose should start at 200 µg and ideally be consumed within 15 minutes. Doses can be titrated as necessary, though no more than 4 lozenges should be consumed daily once an effective dose has been determined. The elimination half-life of a buccal lozenge is around 7 hours (17).

Tablet

Oral transmucosal tablets increase the bioavailability of fentanyl across the oral mucosa by utilizing a pH-dependent system that improves the absorption across the oral mucosa (18). Tablet disintegration takes 15 to 25 minutes and bioavailability is approximately 65%, with 50% being absorbed through the mouth. Tablets are available in 100 µg, 200 µg, 400 µg, 600 µg, 800 µg doses. An initial dose of 100 µg should be given for breakthrough pain, followed by doses no less than 2–4 hours for subsequent episodes of breakthrough pain (19).

Buccal

Fentanyl buccal soluble film contains fentanyl

citrate in a polyvinylpyrrolidone film which dissolves in the mouth and delivers the drug through the oral mucosa in a pH-dependent manner similar to the oral transmucosal tablet (10). The film typically dissolves within 15–30 minutes and has a bioavailability of 71%, which is greater than for the buccal lozenge. Like the buccal lozenge, the buccal film has a rapid onset of action and is also used in analgesia for breakthrough pain. Buccal films are available in doses of 200 µg, 400 µg, 800 µg, and 1.6 mg. Initial dosing should start at 200 µg and films should be administered at least 4 hours apart. Dosing can be titrated as necessary. Elimination half-life is approximately 14 hours (20). A major advantage of the buccal film is that it cannot be abused through crushing or inhaling, as a major concern for fentanyl is its potential for abuse outside the clinical setting (21).

While these transmucosal fentanyl formulations have a much faster onset of action than fentanyl transdermal patches, they are not fast enough for the treatment of acute and postoperative pain. Transmucosal delivery has been shown to be optimal for managing breakthrough pain in opioid-tolerant patients with cancer. It is critical to note, however, that each transmucosal formulation cannot be substituted for one another due the significant differences in bioavailability. Fatalities and serious adverse effects have resulted from inappropriate substitution and misunderstanding of dosing instructions (22).

Sublingual

Spray

The spray has a bioavailability of 76% and produces an analgesic effect in 5 to 10 minutes. The sublingual spray is made available in 100 µg, 200 µg, 400 µg, 600 µg, 800 µg, 1.2 mg, and 1.6 mg dosages. The initial dose should start at 100 µg sprayed under the tongue. Up to 2 doses can be administered per episode of breakthrough pain and at least 4 hours should pass before treating another breakthrough pain episode. A maximum of 4 doses should be used in a 24-hour span (18).

Intranasal spray

Intranasal fentanyl has been demonstrated to be safe and effective for management of breakthrough cancer pain in opioid-tolerant patients. The nasal mucosa has a small surface area, but it is highly vascularized and thus fentanyl can be rapidly absorbed into the bloodstream. Intranasal spray has approximately 89% bioavailability, which is higher than that of transmucosal fentanyl. Mean peak plasma time is 15 to 21 minutes.

The indication for intranasal spray is to treat cancer pain in opioid-tolerant patients. Intranasal fentanyl is available in 2 formulations: 100 µg/µL (8 sprays/bottle) and 400 µg/100 µL (8 sprays/bottle). The initial dose is defined as 100 µg spray in one nostril or 100 µg/µL into each nostril (200 µg), followed by careful titration not sooner than every 2 hours; maximal daily dose should be capped at 4 doses per 24-hour period (800 µg/d). If pain is not controlled, another rescue medication may be used in the interim.

Intranasal-administered fentanyl has also been used for the management of acute and procedural pain in pediatric patients (currently not FDA approved for use in children less than 18 years of age). The intranasal route of delivery is favorable in children as it does not require intravenous line placement or injection, and avoids the variability in onset and duration of transmucosal delivery, as this is affected by oral intake status. Intranasal fentanyl was demonstrated to have consistently lower pain scores compared to placebo and comparable pain scores to IM and IV morphine. Moreover, the review found intranasal fentanyl to significantly reduce time to analgesia compared to morphine. Effective analgesia occurred at intranasal dosages of 1 to 2 µg/kg per dose in children (23).

Intrathecal/Epidural

Intrathecal pumps are implantable devices that can be used to deliver higher concentrations of opioids, including fentanyl, sufentanil, and other medications, into the intrathecal space. This method for pain control can be an attractive technique for patients on high-dose oral and transdermal opioids. Its use is beyond the scope of this review and will not be discussed here.

Substance Abuse

Fentanyl and its 2 metabolites (norfentanyl and despropionylfentanyl) can be detected in urine for up to 72 hours. Because of its high abuse potential, in addition to prescription misuse, analogs of fentanyl continue to be produced illicitly and sold on the black market under street names such as "China white," "white Persian," and "synthetic heroin." Those that are especially likely to be abused in recreational use include α-methylfentanyl, 3-methylfentanyl, acetyl-α-methylfentanyl, α-methylthiofentanyl, p-fluorofen-

tanyl, β-hydroxyfentanyl, β-hydroxy-3 methylfentanyl, thiofentanyl, and 3-methylthiofentanyl. Despite available technologies, these compounds are not commonly tested on urine drug toxicology reports.

All forms of fentanyl preparations, from IV preparations to transmucosal, have been reported being misused. Used transdermal patches still contain significant amounts of fentanyl and need to be discarded properly to prevent harm to others. Reports have shown that both used and unused fentanyl patches have been smoked, snorted, and injected though removal of the drug from the patch, and ingested orally as a whole patch, which has resulted in some fatalities (21).

Immunosuppressive Effects with Long-Term Opioid Administration

Opioids, including phenylpiperidine derivatives, have been shown in recent years to have potent immunosuppressive effects with long-term administration. Many opioids, including phenylpiperidine derivatives, can attenuate natural killer cells and one of the consequences is when taken chronically, they can potentiate propagation of infection or cancer. Specifically, some evidence demonstrates an opioid-mediated suppression of innate immune responses and acquired immune responses. This suppression may lead to a decreased resistance to infection and may expedite the progression of cancer in patients who take opioids, including phenylpiperidine derivatives (16,24-25). Intravenous opioids, such as phenylpiperidines, have demonstrated immunosuppressive properties, which include suppression of natural killer (NK) cells (16). NK cells are vital to the rejection of tumor cells and to the eradication of viruses. In both in vivo animal studies and in vitro human studies, intravenous opioids have been shown to decrease NK cell cytotoxicity (16,26). There is an ongoing debate whether opioids such as phenylpiperidine derivatives should be administered as part of an anesthetic technique for patients with infection or those presenting for cancer surgery. Studies evaluating patient outcomes with and without opioids will help define best practice strategies. In addition, patients with chronic pain who are suffering from infectious disease or cancer will need to balance pain needs with potential propagation of their disorders (27,28).

Remifentanil Pharmacology

Remifentanil is marketed as Ultiva. Remifentanil is the shortest-acting synthetic opioid available (29). It is approximately twice as potent as fentanyl and 100 to 200 times as potent as morphine (30). Unlike other opioids which are metabolized by the liver, remifentanil is an esterase-metabolized opioid. Its ester linkage makes it susceptible to hydrolysis by nonspecific tissue and plasma esterases, resulting in the carboxylic acid metabolite, 3-[4-methoxycarbonyl-4-[(1oxopropyl) phenylamino] -1-piperidine] propanoic acid. This carboxylic acid metabolite is essentially inactive and excreted through the urine (31). Due to a lack of drug accumulation, the duration of action at a given dose does not increase with increasing duration of administration unlike other fentanyl analogs.

Remifentanil is available as a 1, 2, and 5 mg powder, which can be reconstituted into an intravenous solution. The short onset and duration of action of remifentanil makes it useful for short outpatient surgical and diagnostic procedures. The drugs can be titrated very easily during an operation and there is a lack of accumulation during repeat injections. Remifentanil is indicated for postoperative analgesia and the induction and maintenance of general anesthesia. For immediate postoperative pain, the dose may range between 0.025–0.2 μg/kg IV. During the induction of general anesthesia, a bolus between 0.5–1 μg/kg may be administered. For maintenance of general anesthesia, the usual dose range is between 0.05-0.3 μg/kg/min. There is an emerging role of remifentanil in the PCA, in particular for patients who can receive epidurals for labor pain (32). Similar to other opioids, the adverse effects of remifentanil include respiratory depression, bradycardia, tachycardia, hypotension, and trunk rigidity. Dizziness, pruritus, nausea, and vomiting are also reported as common side effects (33,34).

Sufentanil Pharmacology

Sufentanil is marketed as Sufenta. Sufentanil (chemical name: N-[4-(methoxymethyl)-1-[2-(2-thienyl) ethyl]-4-piperidinyl]-N-phenylpropanamide) is a fentanyl analog which is 5 to 10 times as potent as fentanyl and has a high safety margin with a therapeutic index (25,000 vs. 277 for fentanyl, 71 for morphine) (35). Compared to fentanyl, sufentanil has a smaller volume of distribution and a terminal half-life between that of alfentanil and fentanyl (36). Sufentanil is unique in that it can produce complete anesthesia with minimal cardiovascular side-effects. It produces excellent cardiovascular stability and preserves cardiac output and myocardial oxygen balance with minimal changes in heart rate (37).

Table 2. *Fentanyl preparations used in acute and chronic pain medicine.*

Fentanyl	Route	Dose	Bioavailability	Onset	Peak Plasma	Elimination $t_{1/2}$
Sublimize	Intravenous (µg/kg)	1–2 Q 5 min	100%	5–10 min	30–60 min	2–4 h
Sublimize	Intramuscular (µg/kg)	1–2 Q 1 h		7–8 min	60–120 min	2–4 h
Duragesic	Transdermal Patch (µg/hr)	25, 50, 75 100 Q 72 h	90%	6–12 h	12–24 h	20–27 h
Ionsys	Iontophoretic transdermal (µg)	40 Q10 min	100%	30 min	1.37 h	11 h
Actiq	Lozenge (µg)	200, 400, 600, 800, 1200, 1600 Q 15 min	50%	10–15 min	15–20 min	7 h
Fentora	Buccal Tablet (µg)	100, 200, 400, 600, 800 Q 2 h	65%	< 5 min	46.8 min	2.6–11.7 h
Onsolis	Buccal Soluble Film (µg)	200, 400, 600, 800 1200 Q 2 h	71%	< 5 min	1 hr	14 h
Abstral	Sublingual Tablet (µg)	100, 200, 300, 400. 600, 800 Q 2 h	54%	< 1min	30–60 min	5–13.5 h
Subsys	Sublingual Spray (µg/spray)	100, 200 400, 600 800 Q 4 h		3–5-minute	0.67–1.25 h	5–12 h
Lazanda	Intranasal Spray (µg/spray)	100, 200, 400, 800 Q 6 h	20 % > transmucosal	< 3 min	15–21 minutes	

$t_{1/2}$ = half life

In the United States, sufentanil is available as a 50 µg/mL intravenous and epidural injection. Sufentanil with and without lidocaine or mepivacaine is available as a transdermal patch similar to Duragesic in Europe under trade names such as Chronogesic. The intravenous solution is indicated for the induction and maintenance of anesthesia for major surgical procedures, such as open heart surgery and neurosurgical procedures. The epidural administration is combined with low dose bupivacaine for analgesia during labor and vaginal delivery. Due to the high potency of sufentanil, it is of particular use in opioid-tolerant patients. For complete anesthesia in major surgical procedures, 8 to 30 µg can be administered intravenously with 100% oxygen and a muscle relaxant. Maintenance dosing is 0.5 to 10 µg/kg, and no more than 30 µg/kg should be used for the entire procedure. Sufentanil can also be given via epidural administration as an analgesic adjunct during labor. The typical dose is 10 to 15 µg sufentanil mixed with 0.125% bupivacaine. The onset of analgesia is approximately 10 minutes with duration of action of 1–2 hours. Up to 3 doses can be given until delivery, spaced in at least one hour intervals (38).

Sufentanil administration can cause significantly higher rates of respiratory depression and muscular rigidity compared to fentanyl. Therefor an opioid antagonist, resuscitative and intubation equipment, and oxygen should be made readily available. Other adverse effects of sufentanil include nausea, vomiting, and pruritus. Bradycardia is infrequently seen in patients administered sufentanil (38).

A novel sufentanil sublingual tablet system is cur-

rently pending approval from the FDA for the management of moderate to severe acute pain in hospitalized patients. The system possesses the advantages of the PCA while overcoming the invasive nature of IV PCA. Sublingual administration also allows for rapid absorption. The benefits of oral sufentanil when compared to many other opioids are that sufentanil lacks active metabolites and possesses a high therapeutic index, as well as a rapid equilibration half-life. The sufentanil sublingual tablet system works by using a hand-held device to administer a 15 µg bioadhesive tablet with a 20-minute lockout interval. Each system cartridge contains 40 sufentanil tablets, which can be used over a period of approximately 48 hours (39). A phase 3 clinical trial was recently conducted comparing the use of the sublingual sufentanil system to IV PCA with 1mg morphine sulfate and 6-minute lockout interval in the management of postoperative pain. In a sample of 357 patients, the results demonstrated noninferiority for the sublingual tablet system in terms of pain control, as well as more rapid patient-reported onset of analgesia and higher patient and nurse satisfaction scores (40). Other phase 3 clinical trials have also demonstrated the sufentanil sublingual tablet system to be both safe and effective for the management of postoperative pain following open abdominal surgery and major orthopedic surgery compared to placebo (41,42). The frequency of adverse effects are comparable to those of IV opioid analgesics (40).

Conclusion

Phenylpiperidine derivatives such as meperidine, sufentanil, remifentanil, and fentanyl remain versatile anesthetic-analgesic agents, and their utilization has expanded over the past five decades. New phenylpiperidine preparations such as oral sufentanil (Zalviso, AcelRx Pharmaceuticals, Redwood City, CA) are pending FDA approval, while others such as Chronogesic (DURECT Corporation, Cupertino, CA) are in the development process. This diverse group of compounds have become invaluable in the fields of anesthesia and pain management (Table 2). An appreciation of these phenylpiperidine derivatives and the various pharmacological properties will ensure the clinician the greatest ability to utilize these agents in an effective and efficient manner. Understanding side effects and the novel formulations in development, such as oral sufentanil, will be imperative as we strive to find the best medications for our patients for both perioperative and chronic pain management.

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