

The Fentanyl Story

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Abstract: Fentanyl, introduced more than 50 years ago, has become the most often used opioid for intraoperative analgesia. Since the early 1990s the fentanyl patch has been available for management of chronic pain of all forms of cancer as well as the persistent, intense pain from many noncancerous maladies. More than a half dozen rapid-onset transmucosal fentanyl preparations have been developed, approved, launched, and popularized for “breakthrough” pain syndromes in the past 20 years. The purpose of this article is to describe why this opioid has become so important in the treatment of pain in modern clinical practice. The data indicate that fentanyl’s popularity has occurred because it has minimal cardiovascular effects, does not result in increases in plasma histamine, is relatively short in onset of action and duration of effect, is easy and inexpensive to synthesize and prepare for the marketplace, and is now familiar to clinicians working in pain and perioperative medicine throughout the world.

Perspective: *Fentanyl has become one of the most important opioids in the management of pain because it is available for administration intravenously, transdermally, and transmucosally. Its flexibility, potency, familiarity, and physical characteristics explain why it has become so valuable to clinicians managing pain throughout the world.*

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Key words: Fentanyl, rapid-acting opioids, sublingual, patch, nasal, oral transmucosal.

Fentanyl (Fig 1), a potent synthetic μ receptor–stimulating opioid, was first synthesized by Dr. Paul Janssen and the Janssen Company of Beerse, Belgium, in December 1960.^{45,46} The drug was first used as an intravenous analgesic clinically in Europe in 1963 and in the United States (as a component of Innovar) in 1968 and since then has become one of the world’s most important and frequently used opioid analgesics. Today, fentanyl is the opioid most often used intravenously for intraoperative analgesia in the United States, the rest of North America, Central and South America, throughout Europe, the Middle East, and most of developed Asia

and Africa. In some of the world, the fentanyl patch is often used for the chronic pain of all forms of cancer as well as the persistent, intense pain from many noncancerous maladies.^{45,46} In the last 20 years, more than a half dozen rapid-onset transmucosal fentanyl preparations have been developed, approved, launched, and popularized for “breakthrough” pain syndromes.⁴⁶ Few physicians practicing anesthesia or managing all sorts of patients with chronic pain with the many fentanyl preparations now available appreciate how and why this compound has become so widely used in anesthesiology and is so valuable in the management of pain throughout much of the world.

The author received no financial support related to the creation and/or production of this manuscript. The author was the inventor and developer of oral transmucosal fentanyl citrate, including Actiq and Oralet, but has no relationship with TEVA or any of the generic companies that currently market these products. The author also has no relationship to any of the companies that are developing or have developed and/or market or sell any of the other rapid-acting fentanyl products or the fentanyl patches currently being sold today except he is a director of the Board of a public company Insys Therapeutics. Insys developed and currently markets and sells Subsys, a rapid-onset sublingual fentanyl spray that is approved for breakthrough cancer pain in opioid-tolerant patients.

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The Pre-Fentanyl Years (1953–1960)

One of the interests of Dr. Paul Janssen, who founded his company Janssen Pharmaceutica in 1953, was creating potent, effective, rapid-acting analgesics to treat the many pain problems of the time.⁴⁵ In 1953, both morphine and meperidine were known and available. Dr. Janssen and his colleagues in his company believed that the piperidine ring (Fig 2), present in both morphine and meperidine, was the most important chemical structure that produced analgesia in these molecules. They began working with meperidine, rather than morphine, as the parent molecule in the production

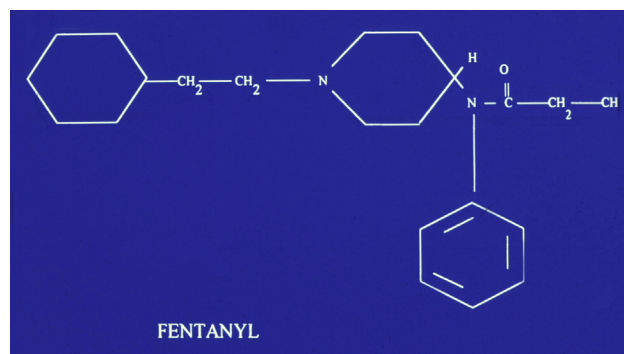


Figure 1. The chemical structure of fentanyl.

of newer and better compounds because it was much less complex a molecule and thus easier to manipulate. Their strategy was to find new molecules that were more powerful and specific analgesics than either morphine or meperidine. They hoped these newer molecules would have fewer unwanted side effects and have higher safety margins (therapeutic indices). The Janssen

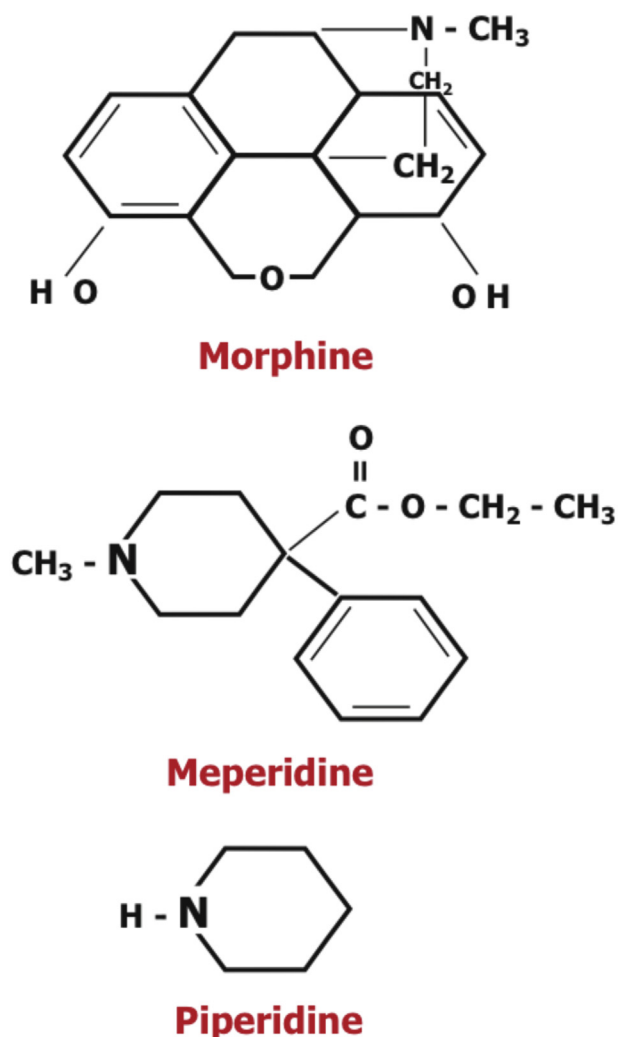


Figure 2. The chemical structures of morphine, meperidine, and piperidine.

research team realized that both morphine and meperidine were poor and slow-onset analgesics because they could not easily penetrate into the central nervous system. Therefore, they concluded that they needed to synthesize more fat-soluble derivatives. In order to do this, they began adding to and/or replacing numerous chemical entities (N, benzene rings, methyl or ethyl groups, etc) to the meperidine molecule and thus created many new, more lipid-soluble drugs, most with greater potency and faster onset of analgesic action, presumably because of better penetration through the blood-brain barrier. The chemists knew that more than increased fat solubility was required for greater analgesic potency. The compounds would also have to bind with a receptor (at that time, the μ receptor had not yet been identified, but the concept of a pain receptor was well known). Thus, other chemical entities that they believed would enhance binding of the new compounds with the pain receptor were added, positioned properly, and the new compounds then tested.⁴⁵

Between 1953 and 1957, dozens of new, more potent, lipid-soluble analgesics were created by the Janssen team until in August 1957 phenoperidine was synthesized (Fig 3).⁴⁵ Phenoperidine was 25 times more potent than morphine and more than 50 times more potent than meperidine in most animals in which it was tested. It was also, at the time it was first synthesized, the most potent opioid in the world. Phenoperidine was introduced into many European countries, but not the United States (because the Janssen Company did not have a U.S. organization at that time), as a potent, fast onset of action, short-lasting analgesic for anesthetic use. It is still available in many of the countries into which it was introduced.

The Janssen research team continued to create new molecules related to phenoperidine in the late 1950s and first synthesized fentanyl in 1960.⁴⁵ Fentanyl was more than 10 times more potent than phenoperidine and 100 to 200 times more potent than morphine in most animal models. It was also the most lipid-soluble (octanol/water partition coefficient = 813) and most potent opioid in the world when it was first created and had the fastest onset of action and highest therapeutic index (277 vs 4.7, 71, and 39.1 for meperidine, morphine, and phenoperidine respectively) ever measured in an opioid. The Janssen team only considered fentanyl useful as an intravenous analgesic when it was first synthesized because approximately 60 to 70% of

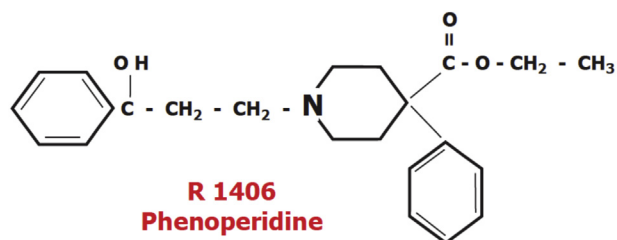


Figure 3. The chemical structure of phenoperidine, a precursor of fentanyl.

the compound was destroyed (only 30–40% bioavailable) after oral administration in their studies in the early 1960s (J. de Castro, 1961, unpublished data from Janssen Pharmaceutica).

Fentanyl Pharmacology

Fentanyl is a completely synthetic μ receptor-stimulating opioid.⁷ It was the first of the fentanyl family of opioids that somewhat later included sufentanil, alfentanil, and remifentanyl for human patients and carfentanyl and thiofentanyl approved for wild animals.^{7,46} Fentanyl's onset of action and its peak plasma concentrations are dependent on the dosage used and the method of delivery.^{4,8,35-38,40,41} Analgesia may occur as soon as 1 to 2 minutes after intravenous administration of fentanyl, whereas most buccal transmucosal delivery systems produce analgesia in 10 to 15 minutes.^{4,8,35-38,40,41} In contrast, sublingual and intranasal sprays of fentanyl may produce analgesia in 5 to 10 minutes or sooner (see Fig 4).^{35,38} Fentanyl plasma concentrations do not peak or plateau until 8 to 16 hours after application of a fentanyl transdermal patch.^{2,7,11,17,32}

Significant analgesia may occur with fentanyl plasma concentrations as low as .2 to 1.2 ng/mL in opioid-naïve patients and often at concentrations only slightly higher in some opioid-tolerant patients. However, plasma concentrations of fentanyl may need to be

much higher in some other opioid tolerant patients. Fentanyl's duration of action usually lasts 2 to 4 hours after intravenous or transmucosal delivery, but fentanyl blood levels fall quite slowly after transdermal patch removal because absorption of drug deposited on the skin continues for some time. The half-life for the decline in fentanyl plasma levels after patch removal is high (17 ± 2.3 h).⁷

Fentanyl, like morphine, meperidine, oxycodone, and others, produces the usual μ opioid central nervous system actions such as fatigue, sedation, nausea, vomiting, dizziness, respiratory depression (leading to apnea in higher doses), bradycardia (secondary to a central vagal stimulating action), and unconsciousness/anesthesia in higher doses irrespective of the mode of administration.⁷ Chest wall rigidity can be seen after intravenous administration and is related to the dose and speed of delivery and has occasionally been encountered with as little as 50 μ g given intravenously.⁷ The author is unaware of chest wall rigidity being reported after buccal, sublingual, intranasal, or transdermal fentanyl administration at any dose. Although constipation does occur after fentanyl irrespective of how the drug is given, it is reported to be less frequent than after morphine, as is pruritus.³¹ Some have suggested that these advantages may be due to the fact that fentanyl does not cause increases in plasma histamine, in contrast to morphine, meperidine, and most of the nonfentanyl μ receptor-stimulating opioids.⁷

STORY OF FENTANYL: Rapid Onset Opioids (ROOs)







Formulation	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Compressed Powder	FENTANYL CITRATE Nasal Solution	FREE FENTANYL Oral Solution
Route of Administration	 Buccal Lozenge	 Buccal Tablet	 Buccal Film	 Sublingual Tablet	 Intranasal Spray	 Sublingual Spray
Administration Time Requirements	Consumed over 15 min	Disintegration takes 14–25 min	Dissolves within 15–30 min	1–5 min	Seconds	Seconds
Bioavailability	50%	65%	71%	54%	Est 60%	76%
Onset of Action (mins)	10–15	15 minutes	15 minutes	10 minutes	10 minutes	5 minutes
Dosage Strengths (mcgs)	6 strengths	5 strengths	5 strengths	6 strengths	4 strengths	7 strengths

Figure 4. Some properties and characteristics of the rapid-onset opioid products currently available and being developed.

Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system, and as a result, potential drug interactions may occur when fentanyl is given concurrently with other drugs that affect CYP3A4 activity.¹⁹ When these interactions occur in patients in the operating room or intensive care unit, the potential increase in fentanyl plasma concentrations can rise or prolong the opioid's activity but are often not dangerous and usually are easily managed by clinicians in attendance. In contrast, concomitant use of transmucosal immediate-release fentanyl (TIRF) preparations (see section "Morbidity, Mortality, and Misuse of Fentanyl and the TIRF REMS Access Program") with CYP3A4 inhibitors (such as certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, and verapamil) may result in an increase in fentanyl plasma concentration sufficient to cause potentially fatal respiratory depression.^{19,22,25} Thus, these patients need to be carefully monitored for signs of opioid overdose.

The Fentanyl Early Years (1960–1975)

After its introduction as an intravenous analgesic in 1963 in numerous Western European countries, fentanyl was often used in combination with a number of intravenous sedatives, hypnotics, and amnestics in a variety of mixtures in attempts to create a type of total intravenous anesthesia in the 1960s and 1970s.^{12,34,45,46} Fentanyl was more potent than any other opioid analgesic available at that time, which meant that only small amounts of it was necessary in most of the mixtures evaluated. A combination that achieved a reasonable degree of popularity was fentanyl given with a new (at that time) butyrophenone called droperidol. The technique of giving the 2 drugs together was called neuroleptanalgesia, and when nitrous oxide was added to the mixture, it was labeled neuroleptanesthesia.^{12,18,34,45,46} Neuroleptanalgesia and neuroleptanesthesia were described, studied, and used throughout Western and Eastern Europe for more than 25 years as an alternative to the potent inhaled anesthetics of the time. The technique is still sometimes used (where droperidol is still available) in some Eastern European countries, and a few South American countries.

In Belgium in the late 1960s and early 1970s, an anesthesiologist, Gorge de Castro, became interested in what he called "stress-free anesthesia."^{14,15,46} Stress-free anesthesia was the use of a drug or combination of drugs that provided deep anesthesia with minimal or no alteration of cardiovascular dynamics and also blocked the increase in the stress-responding hormones that normally occurred with surgical stimulation. After some studies that de Castro was able to accomplish with the assistance of the Janssen team in animals and then later in patients, he announced that large doses of intravenous fentanyl could provide stress-free anesthesia. He called the technique analgesic-anesthesia and first reported on this experience at the World Congress of Anesthesia in 1976 in Mexico City.¹⁵ Dr. de Castro gave analgesic-anesthesia using doses of fentanyl up to 50 µg/kg plus oxygen to patients having cholecystectomy,

gastric resection, bowel surgery, and similar operations. He believed the technique was simple (it required no other drugs), was easy to master, blocked stress hormonal changes both during and after surgery, produced minimal cardiovascular changes, and resulted in minimal side effects. His patients did not report awareness but did often need to be ventilated for up to 3 hours after surgery before extubation could be accomplished. He was unable to publish his results in a major anesthesia journal but did publish them in a regional European journal.¹⁴ Because his work remained unknown to most anesthesiologists, it had little impact on the world anesthesia community.

Though fentanyl, when used alone and also when used in combination with other intravenous drugs, including droperidol, was achieving success and enjoying popularity in Europe in the early and mid-1960s, the same did not occur at first in the United States.^{45,46} Unfortunately, the Janssen Company had difficulty getting fentanyl through the Food and Drug Administration (FDA) approval process in the United States. One strong opponent to the approval of fentanyl was Dr. Robert Dripps, the distinguished professor of anesthesiology at the University of Pennsylvania, in Philadelphia. Dr. Dripps felt that fentanyl was too potent and caused rigidity. This, he thought, would result in many patients needing to be tracheally intubated and would lead to many abuse problems.⁴⁵ After a good deal of time, Dr. Janssen, the CEO of Janssen Pharmaceutical, managed to meet Dr. Dripps and begin a dialog and negotiation with him. Eventually, a compromise was reached that allowed Dr. Dripps to lessen his opposition to fentanyl's approval. The agreement was that fentanyl would only be approved in combination with droperidol. As a result, when fentanyl was approved by the FDA in 1968, clinicians could only get it in combination with droperidol in a ratio of 50:1 droperidol to fentanyl. The combination was called Innovar in the United States and Thalamonal in other countries.

The 50:1 ratio came about after Dr. Janssen consulted with his friend and advisor Dr. Gorge de Castro. Dr. de Castro often used fentanyl in combination with droperidol in patients in the neuroleptanalgesia technique he helped develop and make popular in Europe. Dr. de Castro calculated what his usual mixture of fentanyl to droperidol was in his clinical practice. It turned out to be approximately 50:1 droperidol to fentanyl. The ratio was suggested by Dr. Janssen to Dr. Dripps. Both of them knew that droperidol produced a "bad high" if taken as a recreational drug, and both believed that the mixture of droperidol and fentanyl would likely minimize its abuse potential. The FDA agreed, and Innovar was approved for use in the United States. Four years later, fentanyl became available alone, but for the next 6 years only as a 1-mL vial containing 50 µg.^{45,46}

Neurolept-analgesia/anesthesia, but not fentanyl, began to lose its popularity in Europe in the late 1980s and early 1990s. Some historians believe that numerous variations in the technique used and unclear indications for and contradictions to its use were the most important

reasons for the lost interest. In the United States, neither neuroleptanalgesia nor neuroleptanesthesia achieved any popularity because of all of the above, plus a high incidence of associated dysphoria and the paucity of clinicians who were comfortable with droperidol, fentanyl, and some of the other intravenous agents that were often employed with the techniques.⁴⁶

High-Dose Opioid Anesthesia

In the early to mid-1960s, cardiac surgery was still in its infancy, and patients with end-stage mitral and aortic valvular disease were a particular problem because the severity of their cardiopulmonary dysfunction made them huge anesthetic risks for the anesthetic techniques then available.^{7,9,46} An induction of anesthesia, even carefully performed with thiopental and succinylcholine followed by N₂O, halothane, or any other inhaled agent and then curare, frequently resulted in severe hypotension and arrhythmias and often cardiac arrest. Death during or soon after surgery was common. However, in December 1969, the cardiac anesthesia group at the Massachusetts General Hospital published an important study in the *New England Journal of Medicine*.²⁹ The study demonstrated that large doses of morphine slowly administered intravenously could produce unconsciousness and extremely stable cardiovascular dynamics before, during, and after open heart surgical procedures in severely ill patients with valvular heart disease. As a result, large-dose morphine anesthesia became popular as an anesthetic technique in very sick patients having heart surgery within a year or so after the publication of the Massachusetts General Hospital paper.^{9,24,46} However, in a couple of years, problems with awareness, severe hypertension during surgery, and other issues called into question the wisdom of using large doses of morphine for anesthesia, especially in more physically fit patients, such as those undergoing the new coronary artery bypass operation.^{46,47} This led to many studies in animals evaluating large-dose fentanyl as an alternative opioid anesthetic and later in patients having cardiac surgery.^{21,28,46,48,49} At first, cardiac anesthesiologists were skeptical of the advantages of large doses of fentanyl versus large doses of morphine, especially when some patients experienced truncal rigidity during induction of anesthesia with fentanyl.^{7,47} However, with a little experience, these minor problems were solved, and within a year or two, high-dose fentanyl essentially replaced high-dose morphine as the technique of choice for patients having valvular and, a little later, coronary artery surgery in the early to mid-1980s.^{7,46,47} Fentanyl's advantages over morphine were its greater potency and ease of use (it could be safely administered rapidly in a minute or less), its shorter onset and duration of action, and its absence of histamine release and lack of venodilation. As a result, inductions of anesthesia were faster. There was less hypo- and hypertension during induction throughout the entire surgical procedure and postoperatively; blood and crystalloid volume

requirements were not increased, as occurred with morphine; and extubation and postoperative recovery occurred sooner.⁴⁶

The clinical successes of large doses of fentanyl in cardiac and then vascular surgery in the late 1970s and early 1980s resulted in a dramatic increase in the sales of fentanyl as the branded product lost marketing exclusivity. Indeed, the sales of fentanyl in the United States increased 10-fold the first year (1981) the drug was off patent.⁴⁶ Rarely does this kind of an increase in sales occur with any drug going off patent, much less an opioid that was, at least at that time, only used in the perioperative period by anesthesiologists and their associates. Why did this happen? One reason was that fentanyl is easy and inexpensive to produce for the marketplace. In addition, before the reports of high-dose fentanyl anesthesia, fentanyl was rarely used in doses exceeding 50 µg for an entire operation. However, after the reports, fentanyl doses increased in cardiac operations to 50 to 100 µg/kg.

The marked increase in fentanyl usage throughout the world in the 1980s resulted in a number of events that would further improve the popularity of fentanyl, lead to other fentanyl-like compounds, increase the use of other opioids, and begin an entire new field of novel opioid drug delivery development.⁴⁶ The Janssen Company began the evolution by beginning to develop sufentanil and alfentanil. They also invited the author and then numerous other research anesthesiologists interested in opioids to study their new opioids in patients and also wild animals. De Lange, Stanley, Stanski, and many others began a series of studies in January of 1980 with alfentanil and sufentanil at the University of Leiden in The Netherlands that spread to many other medical centers in the United States and Europe for almost 2 decades, changing the way clinicians viewed and used fentanyl, the other fentanyls, and virtually all opioids.⁴⁶ It also resulted in the development of the "super fentanyls" as wild animal immobilization drugs and antiterrorist agents^{6,33} and stimulated Glaxo to study other new opioids (that resulted in remifentanyl) and Anaquest (of the British Oxygen Company) to develop its own series of opioids that are now available for wild animal immobilization.^{26,46} In the 1980s, fentanyl began to be used intrathecally as part of some spinal anesthetics or epidurally for epidural anesthesia and analgesia.⁷ It has become popular in these applications because its high lipid solubility appears to localize its effects better than morphine. Finally, Alza and Anesta (young drug delivery companies in the mid-1980s) began experiments with fentanyl in transdermal patches and oral transmucosal lozenges (lollipops).^{17,43,50,51} The Alza researchers believed that transdermal fentanyl could be useful for acute pain after surgery and for patients with chronic pain who needed steady, sustained blood levels of a strong opioid. Oral transmucosal fentanyl was first developed to provide sedation, analgesia, and anxiolysis prior to surgery and later for breakthrough pain (BTP) episodes in patients who were opioid tolerant.

The New Fentanyl Drug Delivery Technologies

In the past 30 years, the cost of inventing, developing, getting approval for, and then marketing new drugs in the United States and throughout the world has markedly increased. In the early 1980s, the cost of this process was less than \$75 million for the average drug. Today, it is more than \$1 billion.⁴⁶ As a result, most large pharmaceutical companies can only afford to invest in new drugs that have the potential of being “blockbusters” (having possible sales of more than \$1 billion per year). New drugs with potential sales of \$200 million or lower are far less attractive for the largest pharmaceutical companies. In contrast, smaller pharmaceutical companies often focus on patenting and developing older, well-known drugs in newer drug delivery systems if those novel systems can provide advantages to patients and/or caregivers. The smaller companies do this because the cost of developing the older drugs in newer drug delivery systems today is much less expensive, sometimes only \$30 to \$50 million per drug.⁴⁶ In the second decade of the 21st century, the problem of developing new pain drugs or drug delivery concepts is becoming even more difficult as costs of development continue to escalate and the intense focus on cost containment by clinicians and hospitals and the difficulty for industry in getting sales personnel in front of clinicians are breaking apart many useful relationships that used to exist between industry and the clinical community.

Transdermal Fentanyl

The success in the early 1980s of one of the first transdermal drug delivery patches ever studied, scopolamine, convinced a then-small company, Alza Corporation, in northern California, to consider in the mid-1980s developing a fentanyl patch for patients with pain.^{17,43,46} Alza was successful in creating a patch containing fentanyl (later called Duragesic) and getting it through the FDA approval process. It was first studied in opioid-naïve patients with acute postoperative pain but produced too much respiratory depression.^{11,17} When later evaluated in opioid-tolerant patients having cancer-induced chronic pain in the late 1980s and early 1990s, it proved useful and was approved by the FDA and European regulatory authorities.⁴⁶

The next step for Alza was getting the product in the hands of oncologists and pain physicians. Because at that time they did not have a sales force, they tried to get the Janssen Company (by then a successful division of Johnson & Johnson, the huge conglomerate of health-care companies) to sell their new product. Although the marketing and sales groups of Janssen were excited about the possibility of selling Duragesic, the first transdermal opioid approved for patients with cancer, Dr. Janssen was not convinced this new way of giving pharmaceutical products was not just a “gimmick.” It was only after months of negotiation and an extensive market analysis that suggested Duragesic could be a

very successful pain medicine that he consented and the product was launched. By the mid- to late 1990s, it became clear that transdermal fentanyl was a preferred way for many patients to get analgesia for the intense chronic pain of cancer and numerous other conditions. Duragesic proved to be one of the most successful analgesic pharmaceutical products ever developed, with sales in 2004 (its last year of patent life) exceeding \$2.4 billion. The success of the fentanyl patch caused many generic companies to produce equivalents once it went off patent.⁴⁶

Duragesic was successful in the management of chronic pain because it produced a steady-state blood level of fentanyl that lasted for 2 to 3 days with a single patch. It was much less useful for acute pain because it took 14 to 18 hours to get to a steady-state concentration,⁴⁶ and it could produce severe respiratory depression in opioid-naïve patients even at the lowest doses available at that time. This prompted a number of investigators and later companies to study methods that would speed opioid passage across the skin, such as iontophoresis, which augments drug passage through the skin with a small electric current applied to salts such as morphine HCl and fentanyl citrate^{5,46} and a number of mucosal surfaces. (Although a number of iontophoretic devices have been developed and shown to be effective in moving sufficient amounts of fentanyl across the skin to produce analgesia, none have so far been successful in achieving regulatory approval.)

Fentanyl Transmucosal Delivery

The idea of evaluating fentanyl for transmucosal delivery came about by chance, approximately 4 years following the recommendation of Dr. Paul Janssen to the author that he consider studying carfentanil (an ultrapotent cousin of fentanyl, also developed by Janssen) in some of the wild animals in the state of Utah. The author's studies, started in 1980, demonstrated that carfentanil was an ideal immobilizing drug when used in a dart delivery system for the rapid and safe immobilization of wild elk, moose, and numerous other ungulates.^{6,33} Some years later, carfentanil was approved for this indication by the FDA and regulatory agencies of numerous other countries. These approvals and a number of publications by the author and other researchers studying carfentanil and other potent opioids stimulated U.S. government authorities to consider some of these compounds as potential antiterrorist agents.^{6,26,33,46} (T.H. Stanley, 1992, unpublished data provided by the author to numerous U.S. government agencies). The latter resulted in the author's receiving a number of U.S. government contracts to study carfentanil and other potent opioids for their immobilizing potential in numerous animal models. First rats, then dogs, and later ferrets were studied using all sorts of delivery techniques. A final evaluation was planned in Rhesus monkeys using an aerosol delivery system. During the studies in monkeys, a veterinarian colleague one day wondered whether

carfentanil could be injected into the sugar cubes that some of the study team were using that day in their coffee. He knew that monkeys love to suck on sugar cubes. He was also aware of the fear and anxiety monkeys experience when they are placed in a squeeze cage so that they can be safely given an intramuscular injection of drugs for induction of anesthesia. He wondered if a sugar cube loaded with carfentanil could be used as a safe and powerful sedative, allowing an intravenous infusion to be started or an intramuscular injection to be administered without the need of a squeeze cage and the huge associated emotional stress. An hour later, 2 monkeys were given sugar cubes filled with 2 different doses of carfentanil. The monkeys sucked on the sugar cubes until they were completely dissolved in their mouths over a period of 3 to 4 minutes. The monkey with the large dose of carfentanil became deeply narcotized. An awake endotracheal intubation was possible without the need for another medication. The monkey with the smaller dose of carfentanil became moderately sedated, but could still walk across a room (hand in hand) with his veterinarian keeper.

On an airplane flight later that day, the author wondered if something similar to carfentanil in sugar cubes could be developed for human patients, especially children, experiencing severe stress and anxiety prior to surgery. Some days later, the idea of fentanyl in a lozenge on a stick (a lollipop) was born as a premedication before surgery. (The idea of a lozenge on a stick or lollipop was important because it allowed patients or clinicians to titrate fentanyl noninvasively to a clinical end point—sedation or analgesia—and it also allowed a new patent to be obtained for this new method of use.) In 1984, Oralet, a “child friendly” sweetened, red lollipop-like product (Fig 5) was developed and presented to the Janssen Company as a product they should license, get through the FDA approval process, and sell. Janssen was in the process of getting alfentanil and sufentanil through the regulatory process in Europe and the United States and declined to become involved, although they assisted in getting an investigational new drug status for Oralet approved by the FDA. The author and his

colleagues believed that the delivery of oral transmucosal fentanyl citrate (OTFC) was important and valuable. They reasoned it was simple, noninvasive, and easily titratable, and the unit could be quickly and easily removed by the patient or clinician when the desired effect (sedation or analgesia) was evident. They felt all the above was unique and useful, especially because the onset was rapid (5–15 minutes) and the duration of effect relatively short (1–2 hours). As a result, a small, new company, Anesta, was formed in the summer of 1985 in order to develop and get OTFC approved and into the marketplace.

Oralet achieved regulatory approval in 1993 for use as a premedication before surgery and painful procedures in children and adults.^{4,46,50,51} It was introduced to clinicians later in 1993 but was never a commercial success. During clinical studies with Oralet in the late 1980s, a couple of clinicians at the University of Utah (Drs. Perry Fine and Michael Ashburn) raised the question of whether OTFC might be useful in patients with cancer being treated for moderate to severe pain with chronic opioid therapy who were experiencing episodes of BTP. Portenoy and colleagues had begun describing “breakthrough pain” and discussing its prevalence, impact on patients, and potential therapies for its treatment at approximately the same time.³⁹ Drs. Fine and Ashburn found that Oralet units used by patients with BTP could result in effective analgesia in 10 to 15 minutes, much faster than with any other opioid product available at that time.^{3,20} They also found that when the patients rubbed OTFC units on their buccal mucosa until analgesia occurred, the patients usually did not need to consume the entire unit. Thus, the patients were able to titrate just the right amount of fentanyl for the analgesia they required at the moment the OTFC unit was used. These results were exciting and stimulated Anesta to seek a new indication for OTFC. After approximately 9 additional years and many studies, a different-looking OTFC unit, called Actiq (Fig 6), was approved by the FDA in 1998 for opioid-tolerant patients having breakthrough cancer pain. (Actiq was made to look different [more medicinal and less like a candy lollipop] because it was intended for

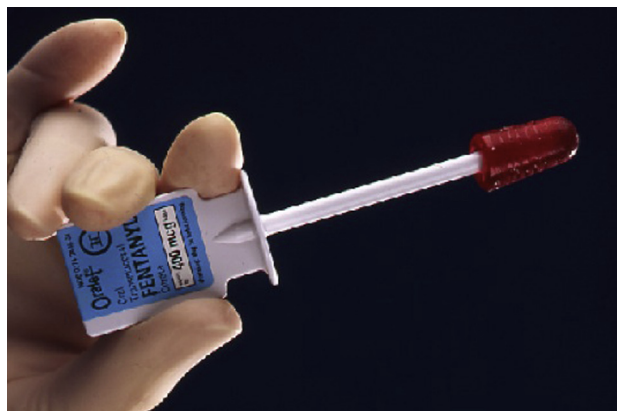


Figure 5. The Oralet buccal transmucosal delivery system of fentanyl.



Figure 6. The Actiq buccal transmucosal delivery system of fentanyl.

out-of-hospital use, whereas Oralet was approved for use within a hospital or outpatient facility where control of the units was assumed to be better and misuse less likely.)

In the fall of 2000, Anesta was purchased by a larger pharmaceutical company, Cephalon, which was effective in making Actiq a significant commercial success. In its last year of patent life (2006), Cephalon sold more than \$625 million of Actiq units. This success stimulated Cephalon, and other companies, to look at other methods of delivering fentanyl through the oral mucosa and, also, how they might minimize some of the limitations of Actiq, that is, its sugar content and potential cause of dental cavities and problems in diabetes, its slow dissolution, and the potential of shortening its onset of action to more effectively cover the BTP episode (Fig 7).

The Newer Rapid-Onset Opioid Delivery Systems

Actiq's commercial success convinced numerous companies to develop other rapid-onset opioid delivery systems⁴⁶ (Fig 8). Cephalon purchased a technology called OraVescent drug delivery and developed, got FDA approval for, and marketed an oral transmucosal buccal tablet that contained no sugar, called Fentora, in 2006.

The OraVescent drug delivery technology generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. Transient pH changes accompanying this reaction optimize dissolution of the tablet (at a lower pH) as carbon dioxide is being released and, moments later when the tablet is dissolved and carbon dioxide is gone, optimize membrane permeation (at a higher pH).¹⁶ The upshot of all of the above was that the OraVescent buccal tablet produced faster and higher blood levels of fentanyl that appeared to more effectively cover the BTP episode than equivalent does of Actiq.^{16,37} Fentora was also a successful rapid-onset opioid product for Cephalon for the treatment of BTP and further stimulated the search for still better fentanyl rapid-onset delivery systems.

In the last 6 to 7 years, numerous companies have begun developing and selling generic forms of Actiq, as well as other fentanyl nasal, buccal, and sublingual transmucosal products for providing rapid-onset analgesia (Fig 4).⁴⁶ They include a sublingual tablet, a buccal soluble film, nasal and sublingual sprays, and others.^{13,38,40,41} Most of these newer products use the citrated salt of fentanyl, and some may have an earlier onset and better bioavailability than Oralet and Actiq (Fig 4). One of these new products, the sublingual fentanyl spray, uses un-ionized (free) fentanyl, has an onset of action that is 5 minutes or less, has a bioavailability of

STORY OF FENTANYL:

Rapid Onset Opioids (ROOs)

- All ROO manufacturers desire earlier onset to promote better overall coverage of a median duration BTP episode

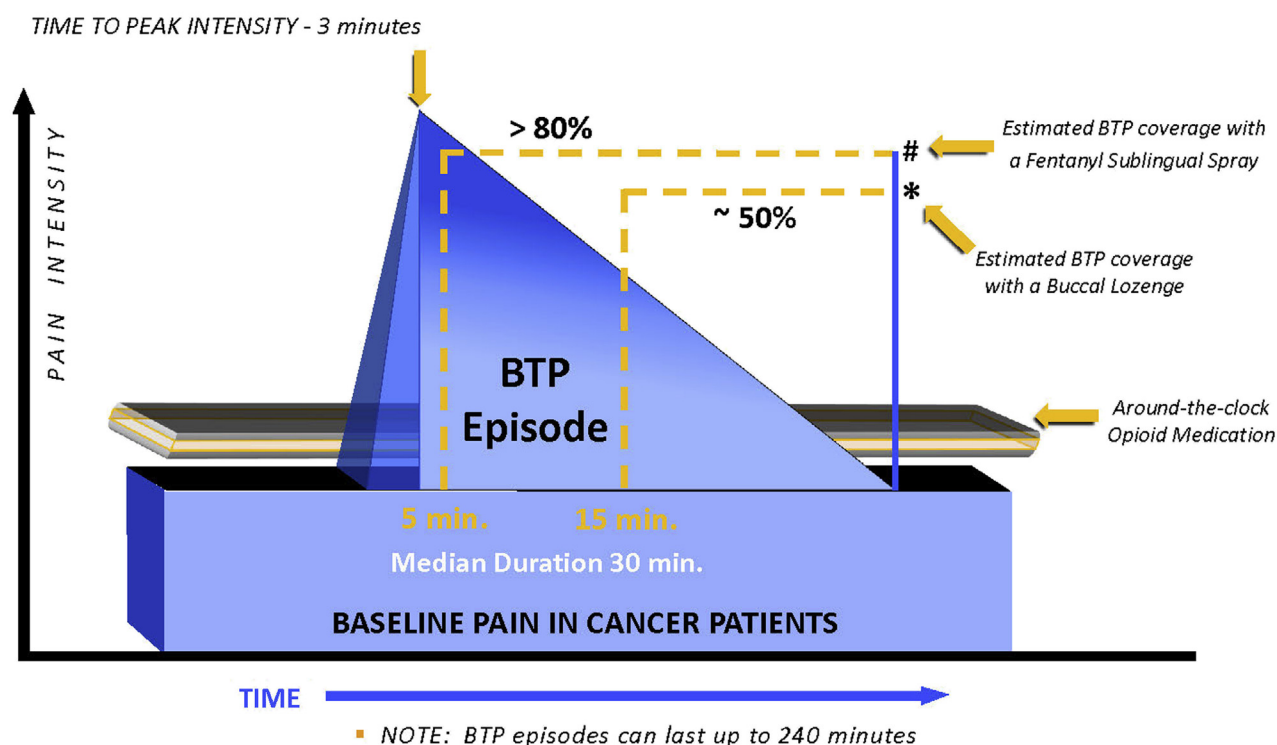


Figure 7. The estimated coverage of a median-duration BTP episode with OTFC buccal lozenge and a new sublingual fentanyl spray technology.

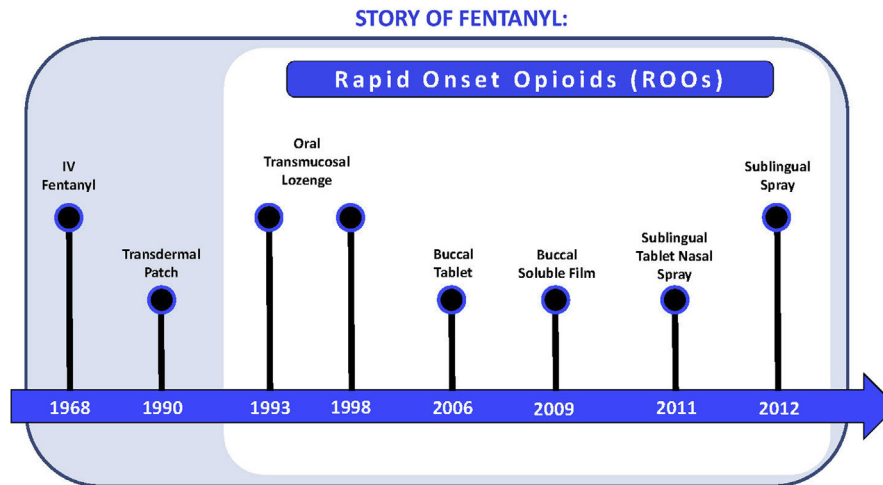


Figure 8. The history of the fentanyl rapid-onset opioids.

76%, and appears to cover approximately 80% or more of most BTP episodes (Figs 4 and 7).^{35,40} It will be interesting to see the impact of this and the other new technologies and devices on patients with pain in the next few years. The early results are impressive.

Morbidity, Mortality, and Misuse of Fentanyl and the TIRF REMS Access Program

Overdoses of fentanyl with resulting severe respiratory depression, apnea, and death first appeared in the United States a few years after its approval in 1972 for use during anesthesia and the perioperative period.^{1,8,23,34,44,52} Both misuse and illicit use by clinicians were reported. As more ways of administering the drug became available over the last 2 to 3 decades, more fentanyl-related deaths have occurred.^{2,10,11,19,22,25,27,30,32,42} The increase in fatal fentanyl overdose has been due to misuse by patients, inappropriate prescriptions by clinicians, and increased illicit use and abuse of prescriptions of fentanyl as often occurs with the increased medical use of any opioid.^{22,25,27,30}

The approval of the first oral transmucosal (rapid/immediate release) fentanyl product (Oralet), which was only approved for hospital use, was held up for some months in 1993 because of concerns about the possibility of unintentional overdoses of fentanyl. Although the incidence of respiratory depression after use of Oralet was rare, the FDA required that the company (Anesta) put in place a risk mitigation strategy prior to approval of the second OTFC product, Actiq, because this drug would be used by patients outside the hospital. In spite of that strategy, unintentional respiratory depression after use of Actiq has occurred. Because of this and continued problems with fentanyl overdosage with other TIRF products in the first decade of this century, on December 11, 2011, the FDA developed and put in place a single, shared system (shared by all companies, patients, providers, and pharmacists dealing with TIRF

products) of risk evaluation and mitigation strategy (REMS) for the entire class of TIRF prescription medicine.⁵³ This “TIRF REMS Access Program” was developed to ensure safe use and access of the TIRF drugs for patients who need them and attempts to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors. The program attempts to accomplish the above by

1. Prescribing and dispensing TIRF medicines only to appropriate (opioid tolerant) patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom TIRF medicines were not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose with TIRF medicines

All currently available TIRF medicines have either an individual or shared TIRF REMS system in place.

Unfortunately, deaths secondary to fentanyl and its analogs synthesized in clandestine laboratories and sold as heroin substitutes will not likely be reduced by the TIRF REMS program. Since 1979, a number of these illegal laboratories have been producing and selling fentanyl and its analogs to consumers involved in the illicit sale of the drug. An increasing number and percentile of the fentanyl overdose deaths in the United States in the last few years have been attributed to illicit versions of fentanyl produced by these clandestine laboratories.^{22,27,30}

The Alternate Delivery Systems—Why Fentanyl?

A logical question any modern clinician could ask is, Why was fentanyl, rather than other potent lipid-soluble opioids such as sufentanil and carfentanil, chosen as the opioid first used for transdermal, oral (buccal and sublingual), and nasal transmucosal drug delivery when these systems were first evaluated in patients

with pain? Most of the other fentanyl had been synthesized and under development by the mid-1980s when the fentanyl patch and the first buccal lozenge (Oralet) were conceived. In addition, all the new fentanyls eventually approved for human patients, including sufentanil, alfentanil, and remifentanyl, were available and on the market before the beginning of the 21st century, after which most of the rest of the transmucosal delivery systems began to be developed. This question becomes even more important when one considers that fentanyl is less potent, is less lipid soluble, and has a lower safety margin than sufentanil and carfentanyl, issues that are considered pivotal in developing an alternative drug delivery system. The simple answer is that although fentanyl was less ideal than some of the newer fentanyl opioids, it was "good enough" and, even more important, it was well known, studied, and understood and thus far less of an investment risk than any of the newer opioids.

The Future

It is instructive to recognize that all of the newer delivery systems for administering fentanyl, from the first fentanyl transdermal patch, Duragesic, and the buccal transmucosal systems that began their development in the 1980s to all the TIRF products begun in the late 1990s and early 2000s, were initiated by entrepreneurs starting small, new companies. These entrepreneurs believed that their new way(s) of giving fentanyl would be useful for patients principally because it would be easier for the patient to be compliant (the patch), be less threatening (Oralet), or have a faster onset of action and/or be more pleasant to consume (Actiq and the rest of the TIRF products). Potency, lipid solubility, acid strength (pKa), the uniqueness of the formulation and delivery device, as well as the cost of the finished product, were believed to be the most important issues in each product's eventual success or failure. The entrepreneurs had to convince their investors that their devices

were better than what was currently available and would be a significant commercial success and result in a good to great return on their investment. So far, the results are mixed. Oralet was a commercial failure whereas Duragesic, Actiq, and Fentora have been good to great successes. It is too soon to say much about the newer TIRF products. The continuing increases in the cost to develop these products and administrative regulations to get them FDA approved and into the marketplace raise serious questions of whether future entrepreneurs and their investors will be willing to take on the risks of going down that pathway with fentanyl or any other opioid. Of course, if one of the newer TIRF products or any other potent opioid (sufentanil) is a significant commercial success, that would likely stimulate others to try again.

Conclusion

Fentanyl, a potent rapid-acting synthetic opioid first synthesized more than 50 years ago, has become the opioid most commonly used intravenously for intraoperative analgesia throughout the world. This has occurred because the drug has minimal cardiovascular effects, does not result in increases in plasma histamine, is relatively short acting, is easy and inexpensive to synthesize and prepare for the marketplace, and is now familiar to clinicians working in perioperative medicine all over the planet. In the last 20 to 30 years, the development of novel, noninvasive drug delivery systems has enabled fentanyl, because of its physical characteristics and familiarity, to become extremely useful to pain physicians for around-the-clock opioid analgesia via transdermal patches and rapid-onset analgesia through nasal, buccal, and sublingual transmucosal drug delivery technologies. The early results of the impact of these new technologies and devices on patients with pain is encouraging, although the increase in morbidity, mortality, misuse, and abuse of fentanyl is concerning.

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