The History and Development of the Fentanyl Series

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Abstract

In the last two decades, opioid analgesics have assumed an important place in general anesthetic practice in the United States. Part of the reason for this has been the introduction of the potent new agonists fentanyl, sufentanil, and alfentanil. Because of problems with morphine–oxygen anesthesia (incomplete amnesia, occasional histamine-related reaction, marked increases in intra- and postoperative respiratory depression), a suitable alternative was sought but not found among existing opioids. A breakthrough came in 1960, when fentanyl was synthesized, laying the foundation for a better understanding of the structure–activity relationships of narcotic analgesics and stimulating interest in developing compounds with even greater potency and safety margins. Investigators interested in opioid anesthesia began to study fentanyl in animals and then in humans. Fentanyl (50–100 μg/kg) with oxygen (100%) was evaluated as an anesthetic in patients undergoing mitral valve and coronary artery surgery. Changes in cardiovascular dynamics with induction doses ranging from 8 to 30 μg/kg consisted of small decreases in heart rate and arterial blood pressure. All other cardiovascular variables studied, including cardiac output, remained unchanged, even with additional doses up to 100 μg/kg. It was determined that fentanyl had use as a narcotic anesthetic, despite its potential for cardiovascular depression and stimulation, respiratory depression, muscle rigidity, and, occasionally, incomplete anesthesia. Since the introduction of fentanyl, two other potent synthetic opioids have been introduced into clinical practice—sufentanil and alfentanil. J Pain Symptom Manage *1992;7:S3–S7.*

Key Words

Opioids, fentanyl, sufentanil, alfentanil

Although opium derivatives have been used for thousands of years, it was not until the 1970s that morphine and its congeners began to come of age with their use as components of neurolept and balanced anesthesia and as complete anesthetics in cardiovascular surgeries. Until that time morphine was employed as a preanesthetic, postanesthesia analgesic, and anesthetic supplement. In the late 19th and early 20th centuries, morphine in combination with scopolamine had been employed as an anesthetic, but reports of increased operative morbidity and mortality led to the abandonment of this technique. It was not until the 1950s, in a search for new nonbarbiturate intravenous anesthetic agents, that researchers again turned their attention to opioids.

In 1953, Paul Janssen became interested in developing the most potent narcotic analgesic possible. His initial discovery of dextromoramide, a 3.3-di-phenylpropylamine that was more potent than currently available analgesics, stimulated his interest in synthetic narcotics. He reasoned that with increased potency and increased receptor specificity would come increased safety.

The studies that led to the synthesis of fentanyl by Janssen in 1960 laid the foundation for a better

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understanding of the structure–activity relationships of narcotic analgesics and stimulated interest in developing compounds with even greater potency and safety margins.[1-3] Structurally, narcotics are complex, three-dimensional compounds existing as two stereoisomers,[4] of which usually only one isomer is able to produce analgesia. Indeed, the presence or absence of analgesic activity is intimately related to its stereochemical structure, in keeping with the "lock-and-key" hypothesis of narcotic action.[5-10] Hence, relatively minor changes in conformation of a narcotic molecule significantly alter pharmacologic activity. This concept and dissatisfaction with available opioids, especially morphine and meperidine, as less-than-optimal molecules to reach and stimulate the opioid (μ) receptor have been two major forces in the design and development of better compounds.

Lipid solubility has long been recognized as a key factor in the passage of drugs across the blood–brain barrier. Because meperidine is almost 30–35 times more lipid soluble than morphine (octanol pH 7.4 buffer partition coefficient = 38.8 compared with 1.42), chemists began experimenting with congeners of meperidine.[11] Because benzene rings are known to enhance lipid solubility, a phenyl group replaced one hydrogen of the methyl group attached to the nitrogen in meperidine in one of the earliest compounds studied (P. Janssen, personal communication). The result was enhanced analgesic activity, although the spatial arrangements of those elements of the molecule chiefly responsible for interacting with the receptor were still less than ideal. It was subsequently found that by separating the phenyl group linking the nitrogen on meperidine by three carbons instead of one and then adding a hydroxyl group to the third carbon, a compound, later called phenoperidine, could be created. This compound was 20 times more potent than morphine and approximately 200 times more potent than meperidine.[6]

Continuing attempts to optimize molecular configuration eventuated in fentanyl, a compound with 100–300 times the potency of morphine (depending on the species evaluated).[6,7,10] Note that the distance between the peperidine nitrogen and the benzene ring is reduced from three to two carbon atoms, the ester on the right side of the molecule is reversed, and one of its oxygen molecules is replaced with a nitrogen.

In addition to increased potency, fentanyl possesses an analgesic therapeutic index approximately four times that of morphine (277 vs. 70) and more than 50 times that of meperidine (277 vs. 5). With the attachment of a small C-O-C tail, fentanyl is converted to a new variant called carfentanil. This molecule has a potency of approximately 10,000 times that of morphine and a therapeutic index of about 8500 in (nonventilated) rats.[1]

At the same time Janssen was beginning his research, attempts were being made in France to produce sedation with intense analgesia, termed twilight sleep or artificial hibernation. These techniques were popularized with the use of mixtures of tranquilizers (phenothiazines) and narcotics called lytic cocktails.[12] Early investigations in which these compounds were used focused attention on the need for more potent narcotic analgesics with fewer side effects and a higher safety margin. Among the opioids studied were the ones synthesized by Janssen—dextromoramide, phenoperidine, piritamide, and, finally, fentanyl.[3,13-16] Fentanyl was most impressive because of its greater potency (150 times that of morphine), its higher therapeutic index (LD_{50}/ED_{50}) (400 vs. 4.8 for meperidine and 70 for morphine), and the absence of side effects.

It was also during this time that DeCastro and Mundeleer[17] developed the concept of neurolept analgesia, which combines the use of a major tranquilizer, most frequently the butyrophenone droperidol, and a potent opioid analgesic, fentanyl or phenoperidine. Neurolept analgesia is characterized by analgesia, amnesia, absence of overt motor activity, suppression of autonomic reflexes, and maintenance of cardiovascular stability. The use of droperidol and fentanyl, available in the United States as a 50:1 mixture of 2.5 mg and 50 μg, respectively, gained popularity in both the United States and Europe. The combination is now used as a component of a balanced anesthetic technique with nitrous oxide (50–70%) in oxygen.

Another important development in the evolution of the opioids occurred in 1969, when Lowenstein and colleagues[18] reintroduced the concept that opioids in sufficient doses can be anesthetic. The beginnings of open-heart surgery featured importantly in this event, because clinicians were attempting to anesthetize and operate on patients with markedly impaired cardiovascular and pulmonary function in whom even small degrees of myocardial depression could be catastrophic. Thus, the discovery that morphine (1–3 mg/kg) with oxygen (100%) produced anesthesia without myocardial depression, and often with increased cardiac output, was initially widely acclaimed.[19-23]

Significant disadvantages soon became apparent, however, including incomplete amnesia, occasional histamine-related reactions (cutaneous flushing, hypotension, and bronchoconstriction), marked increases in intraoperative and postoperative blood and fluid requirements, and especially prolonged postoperative respiratory depression.[19-24] In addition, cardiovascular stability was not always complete: Bradycardia, hypotension, or hypertension occurred frequently, and the addition of nitrous oxide caused cardiovascular depression.[19,25] Difficulties with morphine anesthesia were most evident in patients undergoing coronary artery surgery, particularly those lacking a history of heart failure.[19,20,24]

Because of these problems with morphine–oxygen anesthesia, a suitable alternative was sought among existing opioids. Meperidine was the first substitute studied. After about a year, it was concluded that meperidine was not a suitable alternative to morphine as an anesthetic in patients with serious cardiovascular disease. Studies showed that it caused significant cardiovascular depression and tachycardia and, in anesthetic doses, a marked decrease in cardiac output and even cardiac arrest.[26-29] Additional studies demonstrated that alphaprodine and piritramide were not appreciably different from meperidine.[30,31]

Investigators interested in opioid anesthesia then began to study fentanyl.[32-35] In animals anesthetized with other anesthetics, fentanyl caused only minor changes in cardiovascular function, e.g., small decreases in blood pressure and minimal or no change in ventricular performance.[32,33,35] Huge doses of fentanyl, up to 3 mg/kg, given to dogs under basal anesthesia with barbiturates were found to produce a dose-dependent decrease in heart rate; only small reductions in cardiac output, peripheral resistance, and arterial pressure; and an increase in stroke volume.[34] These findings suggested that fentanyl might be a useful anesthetic in humans.

Fentanyl (50–100 μg/kg) with oxygen (100%) was then evaluated as an anesthetic in patients undergoing mitral valve and coronary artery surgery.[34,36] Changes in cardiovascular dynamics with induction doses ranging from 8 to 30 μg/kg consisted of small decreases in heart rate and arterial blood pressure. All other cardiovascular variables studied, including cardiac output, remained unchanged, even with additional doses up to 100 μg/kg.

Fentanyl currently is popular for use as a narcotic anesthetic, despite its potential for cardiovascular depression and stimulation, respiratory depression, muscle rigidity, and, occasionally, incomplete anesthesia.[37-40] Its success, particularly in higher doses, portends changes in anesthetic practice of the future, especially with newer, more potent analgesics with higher therapeutic indices and other desirable pharmacokinetic characteristics.

Sufentanil is a new synthetic opioid that is approximately 5–10 times more potent than fentanyl and has a therapeutic index (LD_{50}/ED_{50}) approximately 100 times greater than that of fentanyl (25,000 vs. 277) in rats. Sufentanil, a derivative of carfentanil, is about 5000 times more potent than morphine and has an even higher analgesic therapeutic index than carfentanil, more than 25,000.[10]

The degree of lipid solubility of sufentanil is more than 1100 times that of morphine.[10] An important concept in the search for better narcotics is the hypothesis that increased potency implies increased specificity for the opioid (μ) receptor, including greater lipid solubility. Therefore, fewer molecules are required to cross the blood–brain barrier to reach receptor sites, thus leaving fewer molecules available in the circulation to produce unwanted reactions. Data indicate that the gain in potency of sufentanil has been achieved not with increased toxicity but with increased safety.

Sufentanil was approved for clinical use by the United States Food and Drug Administration in 1984 as an anesthetic supplement and complete anesthetic.[41]

The cardiovascular actions of this opioid are similar to those of fentanyl; however, sufentanil may be more effective in blocking sympathetic activation during surgical stimulation, especially in patients prone to intraoperative hypertension.[41,42] Sufentanil also provides as much cardiovascular stability as fentanyl (or possibly greater) when employed in a balanced anesthetic technique.[43-46]

Alfentanil is another new narcotic analgesic. It is one-fourth as potent as and shorter acting than fentanyl.[47] Its therapeutic index is also high (1080) in rats.[28] These actions have indicated that the drug may be of use as an anesthetic induction agent or analgesic supplement, especially in patients undergoing short operative procedures. Studies in dogs demonstrated little change in hemodynamics with moderate doses (160 μg/kg) of alfentanil, whereas very large doses (5 mg/kg) resulted in transient cardiac stimulation (increases in left ventricle contractility, aortic blood flow velocity, and accel-

eration).[28] Heart rate, cardiac output, and pulmonary and systemic vascular resistance also increased following 5 mg/kg of alfentanil.

Transient increases in myocardial contractility; mean aortic, pulmonary artery, left- and right-atrial pressures; and increased systemic vascular resistance have been reported with lower doses (200 μg/kg) of alfentanil in dogs.[48,49]

Despite some problems (e.g., potential for cardiovascular depression and stimulation, respiratory depression, muscle rigidity, and, occasionally, incomplete anesthesia), opioids probably will remain popular as anesthetic supplements and as complete anesthetics in the future because of their minimal effect on most organ systems.[50–53]

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