# INVESTIGATIONAL OPIOIDS

by

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# INTRODUCTION

Potent intravenous opioid analgesics are used frequently by anesthesiologists as a supplement to general anesthesia. Most commonly the drugs are administered in combination with anesthetic vapors and muscle relaxants as part of what has come to be known as "balanced anesthesia," wherein various pharmacologic agents are administered for specific effects, the culmination of which is the anesthetized state. During a typical balanced anesthetic, for example, opioids are administered for analgesia, along with neuromuscular blockers for relaxation, anesthetic vapors for unconsciousness and benzodiazepines for amnesia.

The fentanyl family of opioids (i.e., fentanyl, sufentanil and alfentanil) has all but replaced their predecessors for use as supplements to general anesthesia because, unlike morphine which causes hypotension and meperidine which causes tachycardia, the fentanyl derivatives have minimal hemodynamic side effects. Because of their relatively shorter duration of action, moreover, the fentanyl family of opioids is pharmacokinetically better suited for intraoperative use.

The current trio of potent opioids, however, is still far from ideal. Pharmacodynamically, the current drugs are associated with a number of very troublesome side effects including respiratory depression, nausea, vomiting, muscular rigidity and bradycardia. Pharmacokinetically, the drugs are less than optimal because, while they are superior to their predecessors in this regard, they are still relatively long acting, potentially delaying emergence from anesthesia.

# PRIORITIES IN NEW DRUG DEVELOPMENT

The development of new intravenous opioids thus focuses on improving pharmacodynamics to decrease undesirable side effects and adjusting pharmacokinetics to increase the titratability Recognizing that, with the exception of potency, the pharmacodynamic profile of the fentanyl family of opioids is not likely to change significantly when relying on the same basic molecule for opioid receptor activity, it is modifying the pharmacokinetic profile that has received the most attention. The current trend is to develop compounds with responsive, "titratable" pharmacokinetics, or pharmacokinetic properties that are somehow unique and clinically exploitable. In practical terms this essentially means developing drugs with rapid onset and offset of drug effect.

The extreme importance of pharmacokinetic factors in drug selection is somewhat unique to the clinical pharmacology of anesthesia. Most settings in clinical medicine do not require immediate onset and rapid offset of pharmacologic effect. When an internist prescribes a beta blocker for treatment of hypertension, for example, the fact that a few days may be required for the onset of a steady state level of drug effect is of little consequence. The anesthesiologist, on the contrary, must rely on drugs with rapid onset and predictable offset of effect in order to ensure maintenance of an anesthetic state intraoperatively with return of consciousness at the appropriate time. The pharmacokinetic profile of the intravenous opioids is thus of paramount importance in providing successful balanced anesthesia. In fact, it is the pharmacokinetic profile that forms the basis of rational opioid selection in anesthesia.[1] In this way, the fentanyl family of opioids can individually be considered pharmacodynamic equals with important pharmacokinetic differences. These differences become especially pronounced when the drugs are administered by infusion for long periods.

# THE CONTEXT SENSITIVE HALF-TIME CONCEPT

The pharmacokinetic profile of the fentanyl family of opioids, like all drugs whose pharmacokinetics are described by multi-comparmental models, are surprisingly complex. Pharmacokinetic parameters of drugs described by such multi-comparmental models are often not intuitively interpretable and can be clinically misleading, especially when comparing one drug to another with respect to a single pharmacokinetic parameter.[2] The terminal half-life, for example, which has traditionally been the basis for the prediction of drug effect termination by clinicians, can be particularly misleading. There is growing appreciation among anesthesia practitioners that multi-compartment pharmacokinetic parameters can only be interpreted with the aid of computer simulation. A table of parameters is confusing, whereas a graphic representation of the drug levels resulting from a given dosage regimen is intuitively comprehensible.

The concept of "context sensitive half-time," a measure of the time required for a 50% drop in drug concentration after a variable length infusion is emerging as a new standard for comparison of the pharmacokinetic profiles of opioids.[3,4] These context sensitive halt-times, where the "context" is the duration of an infusion, are determined by computer simulation and are typically represented graphically. These simulations reveal surprisingly striking differences regarding the pharmacokinetic behavior of the various opioids, differences that are not obviously apparent from inspection of the pharmacokinetic parameters. Thus, in view of the importance of an opioid's pharmacokinetic profile in terms of drug selection in anesthesia, context sensitive half-time has become an important parameter. Although more investigation is needed to define the magnitude of opioid concentration decrease required to meet various clinical endpoints, there is a general consensus that a 50% drop in concentration is a clinically important change in concentration for a typical opioid dosage regimen.

This brief monograph will focus on two new intravenous opioids currently in development and will concentrate in particular on the pharmacokinetic profile of these drugs, with special reference to the clinical relevance of their context sensitive half-times.

# REMIFENTANIL

Remifentanil, formerly known as G187084B (Glaxo), is a synthetic opioid now in late Phase III development.[5] While chemically related to the fentanyl family of short acting phenylpiperidine derivatives commonly used as supplements to general anesthesia, remifentanil is structurally unique among currently available opioids because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood and tissue nonspecific esterases, resulting in very rapid degradation to essentially inactive metabolites as shown in FIGURE 1. Remifentanil may thus constitute the first true ultra-short acting opioid for use as a supplement to general anesthesia.

Remifentanil's opioid receptor agonist properties have been demonstrated in vitro. Remifentanil inhibits electrically evoked contraction in guinea pig ileum, rat vas deferens and mouse vas deferens, three isolated animal tissues commonly used to demonstrate opioid receptor activity.[6] In these studies remifentanil exerted its pharmacologic effect at the pt subtype of opioid receptor as evidenced by the complete naloxone reversibility of the effects and the ineffectiveness of antagonists selective for non-μ receptor subtypes. Naloxone antagonism of remifentanil's effects have also been demonstrated in humans.[7]

Remifentanil's apparent opioid receptor effects have also been observed in the central nervous system of humans and dogs as demonstrated by the electroencephalogram (EEG). Remifentanil causes an increase in amplitude and a decrease in frequency in the EEG tracing of both dogs and humans.[8,9] The pronounced EEG delta wave activity observed in these studies is characteristic of opioids and can be viewed as the EEG fingerprint of this drug class.

The potency of remifentanil appears to be somewhere between fentanyl and alfentanil depending upon the methodology used to determine potency. In a dog model the analgesic efficacy of remifentanil was tested by observing the reduction in the minimal alveolar concentration (MAC) of enflurane achieved by various rates of remifentanil infusion.[10] As is typical of the fentanyl family of opioids, remifentanil caused a maximal 60% reduction in the level of enflurane required to maintain anesthesia in dogs (i.e., MAC). The concentration of remifentanil producing a 50% maximal enflurane MAC reduction ($EC_{50}$) was 7.4 ng/ml which is slightly less potent than the $EC_{50}$ of fentanyl under similar conditions. In a human volunteer EEG model, the concentration causing 50% maximal EEG brain depression was 19.9 ng/ml, which again is slightly less potent than fentanyl.[8] Similarly, in a human volunteer experimental pain model, the analgesic potency of remifentanil was approximately 22 times greater than that of alfentanil,[11] a magnitude of potency somewhat less than fentanyl. It should be noted, of course, that the remifentanil potency studies have relied on an assay of whole blood, while the other opioids have traditionally been assayed in plasma.

Remifentanil's latency to peak effect, a parameter especially important when an opioid is used intraoperatively, appears to be very rapid and is comparable to that of alfentanil. Remifentanil's $t_{1/2}k_{e0}$, a parameter used to characterize the delay between peak drug blood level and peak pharmacodynamic effect utilizing a theoretical effect compartment, is similar to that of alfentanil as reported in two human volunteer studies, one using the EEG and the other using an experimental pain method. In both studies the $t_{1/2}k_{e0}$ was 1.3 minutes.[8,11] Thus, by both an EEG and a more clinically oriented measure, remifentanil appears to have a short latency to peak effect similar to that classically associated with alfentanil.

Like its other effects, the respiratory depressant effects of remifentanil are comparable to the fentanyl family of opioids but are much shorter in duration. In a study comparing the respiratory depressive effect of remifentanil *versus* alfentanil in human volunteers, both drugs exhibited the rapid onset of respiratory depression manifested by an increase in $PaC0_2$, but the depression produced by remifentanil was much shorter lived. [11]

The hemodynamic effects of remifentanil appear to be similar to those of the other fentanyl derivatives. In dogs, remifentanil produces dose dependent decreases in heart rate, arterial blood pressure and cardiac output.[12] Similarly, in patients undergoing elective surgery, remifentanil causes decreases in heart rate and arterial blood pressure characteristic of the potent opioids.[13] Unlike morphine, the decreases in arterial blood pressure observed with remifentanil are not secondary to histamine release. [13]

Other miscellaneous effects have been observed in human volunteer and patient studies that are consistent and expected for µ agonists. For example, in many of the human volunteer studies completed to date remifentanil was associated with nausea and vomiting. [11,14] In addition, like other opioids, remifentanil was observed to cause muscular rigidity at high doses, a complication known to complicate anesthesia induction by rapid opioid administration. [14]

The evanescent nature of remifentanil's effects are of course due to the unique pharmacokinetic profile of remifentanil. Two high resolution human pharmacokinetic studies, one in volunteers, the other in patients, have confirmed the unique pharmacokinetic profile of remifentanil. [14,15] Remifentanil's pharmacokinetics are best described by a three compartment model. The clearance of remifentanil is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic hydrolysis of remifentanil by blood and tissue esterases. Recent evidence suggests that the site of remifentanil metabolism in the blood is within the red cell. [16]

Several patient covariates influence remifentanil pharmacokinetics and pharmacodynamics. For example, remifentanil central clearance and distribution volume decline with age, whereas potency increases with advanced age. [17] This implies that both bolus and infusion dosing regimens must be decreased in the elderly. Like age, body weight also impacts remifentanil's pharmacokinetic parameters. Because remifentanil's clearance and distribution correlates best with lean body weight, dosing regimens should be calculated on lean body weight and not absolute body weight. [18]

Conversely, it appears that within reasonable limits, no dosage adjustment for impaired renal clearance or hepatic function will be necessary.[5] The pharmacokinetics of remifentanil in patients awaiting liver transplantation for end stage hepatic failure *versus* healthy control subjects have been prospectively compared.[19] Remifentanil's pharmacokinetics are unaltered by severe hepatic disease at doses up to 0.025 µg/kg/min. This conclusion is supported by the observation that remifentanil metabolism continues even during the anhepatic phase of liver transplantation.[20] Similarly, the pharmacokinetics of remifentanil administered by infusion for 4 hrs in renal dialysis patients *versus* healthy volunteers has also been investigated.[21] Remifentanil clearance in healthy volunteers was 34.2 ml/min/kg *versus* 36.0 ml/min/kg in patients with renal failure, a statistically insignificant difference. Remifentanil's volume of distribution was also unaltered by renal failure. Not surprisingly, gender also has no impact on remifentanil pharmacokinetics or pharmacodynamics.[22]

A graphic representation of remifentanil's context sensitive half-time is perhaps the most intuitively meaningful method of highlighting remifentanil's unique pharmacokinetic profile. FIGURE 2 illustrates the context sensitive half-time of remifentanil *versus* the other fentanyl family of opioids (with parameters for the other opioids taken from the literature).[14] The simulation reveals that remifentanil's context sensitive half-time is independent of infusion duration. Remifentanil thus represents a new pharmacokinetic class of opioid in terms of the rapidity with which drug levels fall after termination of an infusion. The robustness of remifentanil's context sensitive half-time has been confirmed prospectively.[23] The rapid return of consciousness observed on emergence from anesthesia when remifentanil is used as part of a balanced anesthetic technique is clinical evidence of its evanescent pharmacokinetics.[24]

An issue remaining to be addressed with regard to remifentanil's pharmacokinetics is the fate of remifentanil's major metabolite, G190291. While G190291 is thought to be essentially inactive, it is possible that because it is eliminated in the urine, there could be an accumulation of the metabolite after prolonged infusion, resulting in some as yet unobserved pharmacodynamic activity or toxicity.[25] Obviously, this issue is especially relevant in renal failure patients. This remains an area of active investigation. Recent evidence from dog studies has confirmed that the metabolite is in fact at least three orders of magnitude less potent than the parent compound, suggesting that the likelihood of toxicity related to the metabolite is low.[26]

Because of its unusual metabolic degradation pathway, questions regarding remifentanil pharmacokinetics in patients who are deficient in pseudocholinesterase activity inevitably arise. *In vitro* tests indicate that remifentanil is not a good substrate for butyrylcholinesterase (pseudocholinesterase), suggesting that dose alterations for this patient group will not be necessary.[16] *In vitro* studies investigating the rate of remifentanil hydrolysis in plasma taken from volunteers homozygous for psuedocholinesterase deficiency *versus* plasma from normal volunteers demonstrate that pseudocholinesterase deficiency does not appear to alter the rate of remifentanil metabolism.[27]

Remifentanil is, of course, far from the ideal analgesic despite its unique pharmacokinetic profile. Like the other members of the 4-anilidopiperidine class, its side effect profile includes ventilatory depression, muscular rigidity, bradycardia, hypotension, nausea and vomiting, among others. An issue unique to remifentanil in terms of adverse effects is the possibility of an excessively rapid decline in analgesia that can occur if the drug is not administered carefully. An undetected infusion pump malfunction, for example, could conceivably result in a rapid dissipation of the anesthetic state with obviously undesirable consequences.[5] A related disadvantage is the fact that for sustained effect remifentanil must be administered by continuous infusion, a method of administration that many practitioners may find inconvenient and complicated.

Based on its pharmacokinetic profile and lack of unusual side effects, remifentanil is likely to be a welcome addition to the anesthesia pharmacologic arsenal. It may well be useful in a variety of settings in which profound opioid effect with rapid return of consciousness is desirable. Outpatient surgery, neurosurgery, painful diagnostic procedures and painful manipulations in the intensive care unit or emergency room are all potential areas in which the pharmacokinetic profile of remifentanil are exploitable. Ongoing research describing remifentanil's pharmacokinetics and pharmacodynamics in various patient groups and diverse clinical settings will further define its future role in anesthesia. Widespread clinical use will be required before the theoretical advantages associated with a short acting opioid can be confirmed.

# TREFENTANIL

Trefentanil, formerly known as 01-IM-3665 (Ohmeda), is a piperidine opioid derivative currently undergoing phase I evaluation in humans. The structure of trefentanil is shown in FIGURE 3. Trefentanil is thought to be a µ agonist that exhibits pharmacodynamic effects similar to the other fentanyl congeners, including analgesia, sedation and respiratory depression. While comparatively little has been published regarding its clinical pharmacology, based on a few early studies trefentanil appears to have a pharmacokinetic profile that may be clinically exploitable.

In the only published clinical study beyond the abstract stage, trefentanil was found to have an analgesic potency similar to alfentanil in a double blind, placebo controlled comparison study of trefentanil and alfentanil using an experimental pain model.[28] In this study trefentanil was much shorter acting in terms of analgesic effect and respiratory depression. The authors concluded that trefentanil's short duration of effect may be a clinically useful characteristic that deserves further investigation.

The unique pharmacokinetic profile of trefentanil was confirmed in a high resolution pharmacokineticdynamic- modeling study comparing trefentanil, alfentanil and fentanyl in volunteers.[29] These investigators compared the pharmacokinetics and EEG pharmacodynamics of these three drugs. Each of five volunteers received each of the three drugs on separate occasions. Trefentanil was noted to have a potency roughly equivalent to alfentanil (trefentanil $EC_{50}$ = 429 ng/ml, alfentanil $EC_{50}$ = 577 ng/ml) and a latency to peak effect slower than alfentanil but faster than fentanyl (trefentanil $t_{1/2}k_{e0}$ = 1.2 min, alfentanil $t_{1/2}k_{e0}$ = 0.6 min and fentanyl $t_{1/2}k_{e0}$ = 5.4 min). Most importantly, despite no intuitively obvious differences in the pharmacokinetic parameters, computer simulations using the concept of context sensitive half-time revealed an unexpected pharmacokinetic profile for trefentanil, a profile that would be potentially valuable for long duration opioid infusion intraoperatively as shown in FIGURE 2.

Thus, although trefentanil is still very early in development and comparatively little is known about its clinical pharmacology, it has promising characteristics as revealed by just a few well designed clinical studies.

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# FIGURE 1

# Remifentanil's (GI87084B) metabolic pathway

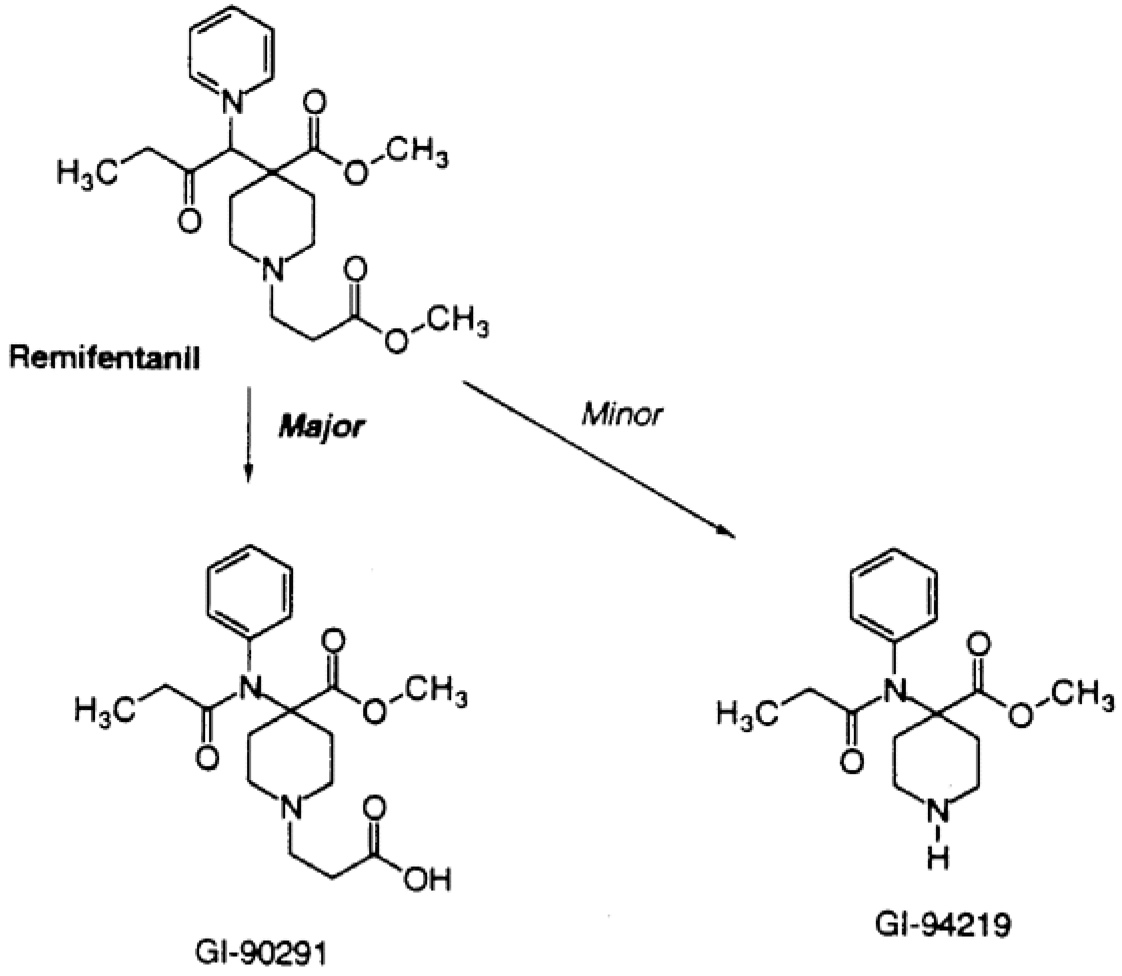


FIGURE 2
A simulation of the time necessary to achieve a 50% decrease in drug concentration in the blood (or plasma) after variable length intravenous infusions of remifentanil, fentanyl, alfentanil, sufentanil and trefentanil.

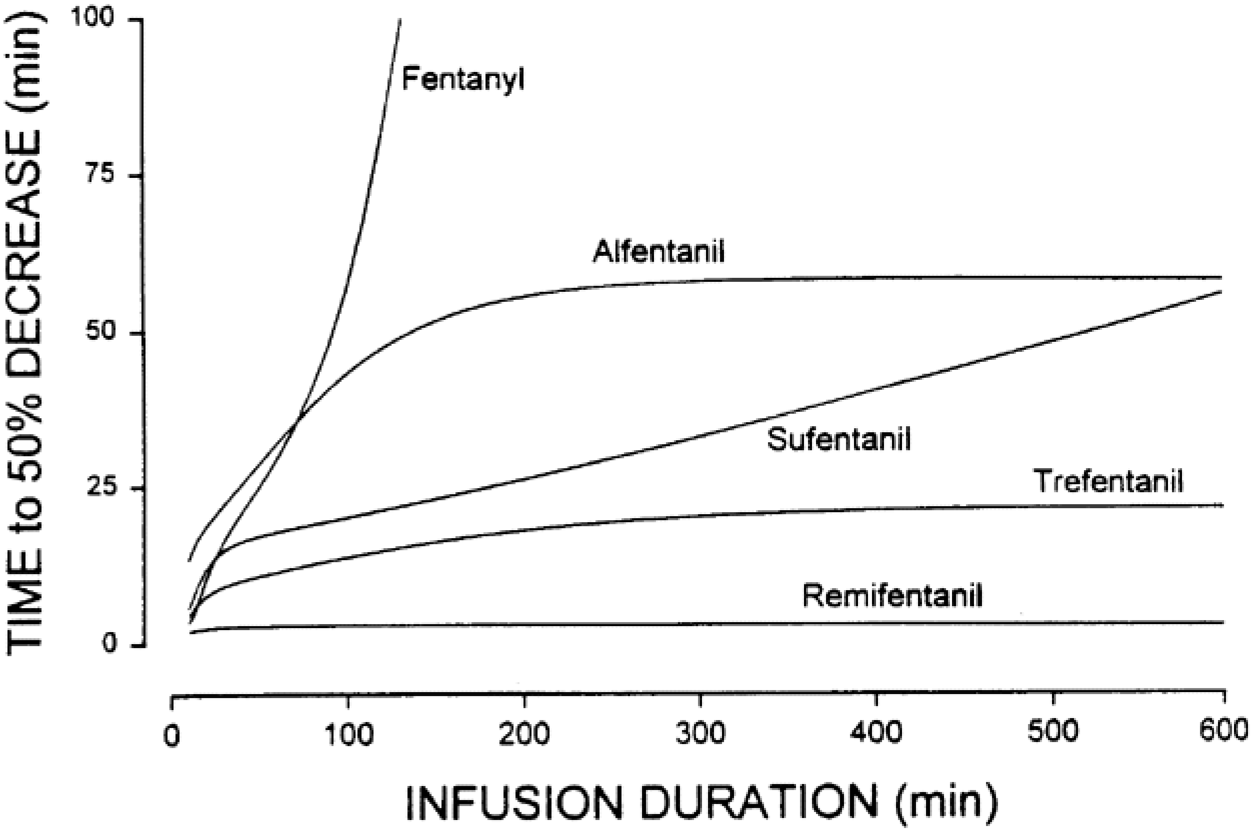
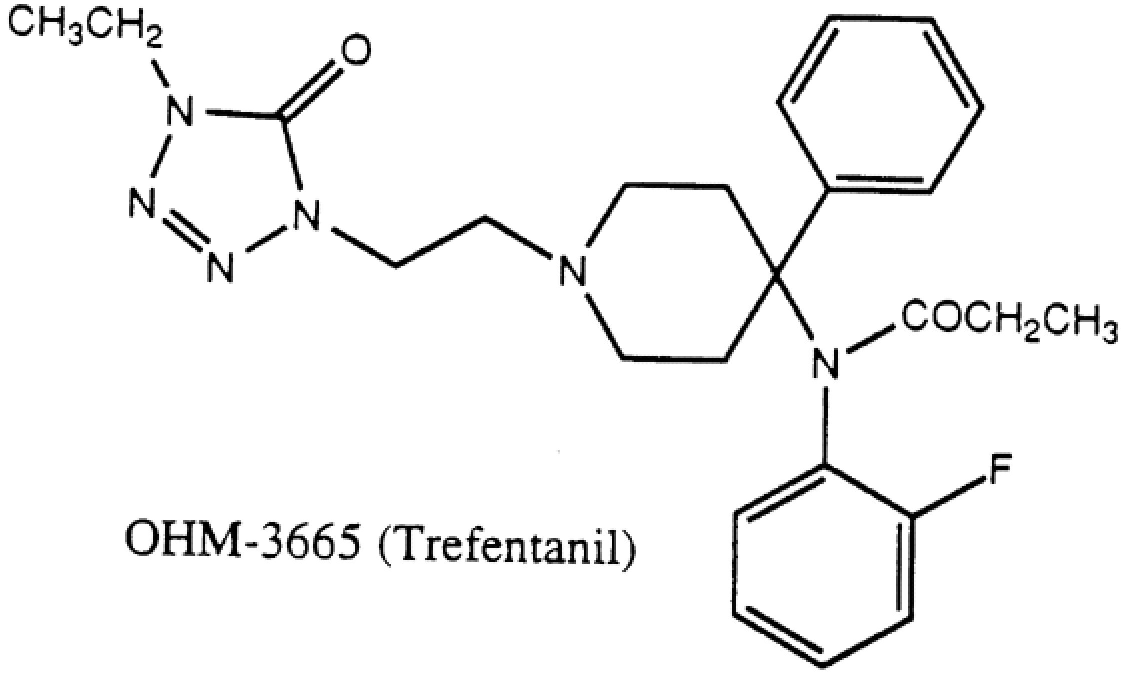


**FIGURE 3**

**The trefentanil molecule (OHM-3665).**



OHM-3665 (Trefentanil)