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# Postmortem Fentanyl Concentrations: A Review

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## Abstract

Fentanyl is a potent synthetic narcotic analgesic available through the prescription of various formulations; intravenous injection, transmucosal lollipops and lozenges, as well as transdermal patches. Over the years, fentanyl has been a steadily increasing topic of discussion in the literature with pharmacokinetic studies, postmortem case studies, antemortem case studies, comparison of postmortem specimens for cause of death interpretation, comparison of specimens in regards to postmortem redistribution, as well as many others. The objective of this paper was to review the fentanyl literature, assemble some key concepts into a single publication, and introduce additional scientific data through retrospective studies from the Los Angeles County Department of Coroner and the San Diego Medical Examiner's Office that support, as well as refute, some concepts previously published. Our paper is organized into sections by history, dosing, pharmacology and pharmacokinetics, toxicity, biological concentrations, postmortem concentrations, and postmortem redistribution that include discussion and data relating central to peripheral blood ratios, and liver to peripheral blood ratios. Overall, this paper "Postmortem Fentanyl Concentrations: A Review" examines over 85 different literary sources, independently interprets scientific data, and draws conclusions with support from retrospective laboratory studies.

**Keywords:** Fentanyl; Schedule II; Review; Postmortem redistribution; Blood; Liver

## History

Fentanyl (Actiq, Duragesic, Fentora, Ionsys, Matrifen, Sublimaze, Innovar) is a high potency synthetic narcotic analgesic with a rapid onset (2-3 minutes) [1] and short duration of action (30-60 minutes) [2]. Synthesized in Belgium by Janssen Pharmaceuticals in the late 1950s, fentanyl was first approved for use in Europe in the 1960s and the United States in 1972. Clinically, given intravenously, it has become a mainstay as an adjunct to surgical anesthesia and for conscious sedation [3]. Structurally, it is closely related to methylfentanyl (a street drug; china white), and to alfentanil and sufentanil, which are also marketed as adjuncts to surgical anesthesia [4]. Over the last few decades, fentanyl has enjoyed increasingly widespread popularity in the relief of postoperative pain and, more recently, in the management of chronic pain.

On a weight-for-weight basis, fentanyl is 80 to 100 times more potent than morphine [1,5], and consequently has been demonstrated to have substantial potential for abuse [6,7]. Fentanyl, classified as a schedule II drug, has been reportedly diverted from medical resources; being abused by anesthesiologists [8], and produced by clandestine laboratories [9]. It has been implicated in outbreaks of illicit drug deaths, often mixed with heroin or cocaine [10-12], resulting in over 1000 non-pharmaceutical fentanyl related deaths from April 2005 to March 2007 in six states [9].

Due its low molecular weight, lipophilic nature, high potency and short duration of action, fentanyl has been developed with several unique methods of delivery including transmucosal and transdermal. Development of the transdermal delivery system (introduced into the United States in 1991) was considered the primary reason for the 1100% increase in fentanyl prescription rate noted from 1990 to 1996 [13]. The Federal Drug Administration (FDA) approved a generic version in 2005. Expanded utilization led to the total number of prescriptions written for generic and brand name transdermal fentanyl to 4.3 million by 2005 [14]. As the availability and popularity of this form of fentanyl delivery system increased, so did the reports of overuse, misuse, abuse, and deaths. From 1998 to 2005, fentanyl was reported as the second ranked drug in the United States in most frequent suspect drugs in death and serious nonfatal outcomes [15], despite the fact that it was not in the top 200 prescribed drugs. Consequently, in 2005, the FDA issued its first public health advisory (a second was issued in 2007) listing very specific warnings concerning the use of transdermal fentanyl. This advisory included cautions against using the patch together with any heat exposure including environmental (sauna, hot tub, sunbathing), external applications such as an electric blanket, or heating pad, or in the case of fever. Also mentioned was that the patch must be placed on intact skin, and the patch itself should not be damaged. In addition, the co-administration of medications with central nervous (CNS) depressant activity including alcohol, as well as drugs that inhibit cytochrome P450 3A4 activity (thereby reducing fentanyl metabolism) was to be avoided. The advisory continued with a caution for patients with significant respiratory disease; the danger of decreased respiration leading to death from overdose [14].

Never the less, deaths due to transdermal fentanyl have continued to rise. There have been reports of excessive patch application [16,17], and others of misuse by cutting, injecting, rectally administering, inhalation following volatilization, or eating/sucking the patch [18-27]. Additionally, in some cases, the patch has been reported as being defective [28] and deaths have been reported after just a single patch application [14,29].

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## Dosing

Fentanyl is available as the citrate salt in an injectable solution containing 50 μg/mL; single doses of 25 to 100 μg are administered intravenously or intramuscularly as needed. Oral transmucosal dosage forms containing 100 to 1600 μg are provided for breakthrough cancer pain; they are placed in the mouth for about 15 minutes at the rate of 4 doses or less per day [4]. The transdermal therapeutic system was designed for the rate-controlled delivery of fentanyl. Transdermal patches are available that contain about 1.2 to 10 mg fentanyl, and provide a dose of 12.5 to 100 μg/hr for 72 hours for the management of chronic pain. Dosing is recommended only for patients considered opioid-tolerant (taking at least 60 mg morphine daily, or an equianalgesic dose of another opioid, for a week or longer). Individualized dosing is recommended to be based upon the daily oral morphine dose. Evaluation of the maximum analgesic effect cannot be made before 24 hours of wearing, and 50% of patients are likely to require a dose increase after initial application. Doses may be increased after three days [30].

The original Duragesic® patch (Janssen Pharmaceutica, Inc.) consists of four layers. The outermost layer is made of a polyester film. The drug reservoir contains the fentanyl and an alcohol gel with hydroxyethyl cellulose, which enhances the drug delivery rate through the copolymer ultimately increasing the permeability of the skin. The release membrane consists of an ethylene vinyl acetate copolymer membrane, which controls the rate of fentanyl delivery. The final layer, closest to the skin, is the adhesive material, which is a fentanyl-containing silicone adhesive material [17,30]. A generic fentanyl transdermal system manufactured by Mylan® Pharmaceuticals, Inc., is a translucent rectangular patch with rounded corners comprising a protective liner and two functional layers. Proceeding from the outer surface towards the surface adhering to the skin, these layers are a backing layer of polyolefin film, and a fentanyl containing silicone adhesive layer [31]. This particular patch design has been espoused as being safer due to the fact that the fentanyl is contained in the adhesive rather than in a reservoir, and is also more commonly known as a 'matrix based' patch. On the other hand, this particular patch design does not provide a rate limiting membrane to control the fentanyl release into the skin. Following direct application of these patches to the skin, fentanyl is rapidly absorbed forming a depot of the drug in the upper layers of the skin [30]. It accumulates in the skeletal muscle and fat and is then gradually released into the systemic circulatory system [31].

## Mode of Action, Pharmacology and Pharmacokinetics

Fentanyl is an opioid analgesic. It interacts primarily with the opioid mu-receptors, which are distributed throughout the body; brain, spinal cord, and other tissues. Clinically, fentanyl exerts its principal pharmacological effects on the central nervous system (CNS) [30]. In addition to analgesia, like most opioids, fentanyl affects mood; euphoria, dysphoria, and causes drowsiness. One of the main concerns following administration is respiratory depression, which can be a problem even among the clinical population receiving fentanyl under medical supervision [25]. Like all mu-receptor agonists, fentanyl decreases respiratory rate and tidal volume and reduces the sensitivity of the respiratory center to carbon dioxide [32]. Other significant effects include depression of the cough reflex (which can present a risk of aspiration), constriction of the pupils, sweating, nausea and vomiting. An increase in tone and decrease in propulsive contractions of the smooth muscle of the gastrointestinal tract result in prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Although at therapeutic dosages fentanyl does not usually exert major effects on the cardiovascular system, some patients may exhibit orthostatic hypotension and fainting [31]. As opioids can cause serious or life threatening respiratory depression and hypoventilation, fentanyl should be administered with caution to patients with pre-existing medical conditions such as chronic obstructive pulmonary disease and conditions predisposing them to hypoventilation.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 μg (2 mL). Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is one to two hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect [30]. Following intravenous administration (100 μg doses), fentanyl has a terminal half life of elimination of 7 (range 3 to 12) hours, but this may increase to as much as 16 hours in neonates [33] or the elderly [34]. It does not appear to be significantly influenced by either hepatic or renal disease [35,36].

The oral formulation (OTFC) (available in 200, 400, 600, 800, 1200, & 1600 μg dosage strengths) is designed to dissolve slowly in the mouth to facilitate transmucosal absorption. However, bioavailability depends on the fraction of the dose that is absorbed through the oral mucosa (~25%) and the fraction that is swallowed (~75%; but swallowed dose is only partially bioavailable). Absolute bioavailability was reported to be 50% compared to intravenous fentanyl [30]. OTFC can produce a rapid onset of analgesia, even during unit consumption (fentanyl begins to cross the blood-brain barrier in as little as 3 to 5 minutes), with peak effect at 20 to 40 minutes after the start of administration; total duration of activity is 2 to 3 hours. The terminal elimination half life after OTFC is about 7 hours [30]. The amount of fentanyl absorbed from each single dose remains stable over multiple administrations. This fact, combined with fentanyl's short half-life, reduces the risk of a cumulative increase in serum level with repetitive doses.

With the transdermal administration of fentanyl, the drug is designed to be released at a nearly constant amount per unit time; the concentration gradient between the patch and the skin driving drug release [30]. Fentanyl moves in the direction of the lower concentration at a rate determined by the patch release through the skin layers. The actual rate of fentanyl delivery to the skin varies over the 72 hour application but each patch is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin. The nominal flux for the 12.5, 25, 70, 75 and 100 μg/hr patches is sufficiently accurate as to allow individual titration of dosage [30]. Alterations in pH may also affect distribution between plasma and the central nervous system [30]. After removal of the patch, serum fentanyl concentrations decline gradually, with a half life of elimination of 17 (range 13 to 22) hours. Continued absorption from the skin accounts for a slower disappearance of the drug from the serum than is seen after intravenous infusion.

After absorption, fentanyl is rapidly distributed to the brain, heart lungs, kidneys and spleen. This is followed by a slower redistribution

to muscle and adipose tissue [30], and is then slowly released into blood [37]. Fentanyl, a lipophilic compound with an n-octanol/ water coefficient of 860:1 [38], has 80 to 86% protein binding, and a moderate volume of distribution (Vd) of 3-8 L/kg [39,40], and a pKa of 8.4.

Fentanyl is metabolized primarily via the human cytochrome P450 3A4 isoenzyme system. In humans, the drug is metabolized by oxidative N-dealkylation to norfentanyl and other inactive metabolites. Within 72 hours of intravenous administration approximately 75% of the dose is excreted in urine. This is increased to 85% over a 3 to 4 day period, with 0.4 to 6% eliminated as unchanged drug; 26 to 55% excreted as nor fentanyl, together with unknown amounts of hydroxyfentanyl and hydroxynorfentanyl [41-43]. About 9% of the dose is recovered in the feces, primarily as inactive metabolites. Norfentanyl and despropionylfentanyl have been found in human plasma at concentrations similar to the parent drug [44]. Norfentanyl was detectable for up to 72 hours in the urine after 50-100 µg intravenous doses, fentanyl was detectable for 24 hours in only 3 of 7 patients, and despropionylfentanyl was not found in any of the subjects [45]. Chronic pain patients given 25 to 100 µg/hr transdermal patches had random urine concentrations of fentanyl and norfentanyl that generally increased in parallel with the increasing strength of the patch [46]. The skin does not appear to metabolize fentanyl delivered transdermally [30].

The concomitant use of fentanyl and cytochrome P450 3A4 isoenzyme inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amprenavir, aprepitant, diltiazem, verapamil, fluconazole, fosamprenavir and erythromycin) may result in an increase in fentanyl plasma concentrations which, in turn, could increase or prolong adverse drug effects and may cause fatal respiratory depression. Although not specifically demonstrated with transdermal patch administration, ritonavir decreased fentanyl clearance by 67%, resulting in an average of 174% increase in area under the curve following intravenous use [30]. Grapefruit juice can decrease cytochrome P450 3A4 isoenzyme activity and should also be avoided. Drugs that induce cytochrome P450 3A4 isoenzyme activity, on the other hand, may have the opposite effect. Additionally, the use of concomitant CNS active drugs requires care and observation. Other opioids, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, muscle relaxants, and alcohol may cause respiratory depression, hypotension, sedation and even coma. A reduction of dose for one or both agents is recommended [30]. Fentanyl is not recommended in patients using monoamine oxidase inhibitors (MAOI) because severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics.

## Toxicity

As noted earlier, fentanyl is capable of producing severe respiratory depression. It has also been reported to cause nausea, vomiting, dizziness, muscle rigidity, seizures, hypotension, coma, and death. Occasionally, patients exhibit delayed CNS and respiratory depression several hours after apparent recovery from surgical anesthesia [47]. Plasma concentrations were reported to rebound at about an hour after an intravenous dose in some patients [44,48]. Several patients treated with 75 and 100 µg/hr transdermal patches developed obtundedness, pinpoint pupils and respiratory depression attributed to the use of heating pads or increased physical activity [49-51]. Fentanyl is not recommended for patients who are not opioid tolerant and, due to the serious risk of hypotension and respiratory depression, patients should be monitored clinically within the initial 24 to 72 hours and following increases in dosage.

## Biological Concentrations

### Clinical concentrations

Healthy young patients given 75 µg doses of fentanyl reached peak plasma concentrations of 0.7 µg/L (or ng/mL) after 11 minutes following intranasal application, and 0.9 ng/mL after 5 minutes of receiving an intravenous injection [52]. Serum concentrations after a single 2 µg/kg intravenous dose to healthy young adults were initially as high as 11 ng/mL, but declined to about 1 ng/mL after one hour [53]. An increased dose (6.4 µg/kg intravenously) produced initial plasma concentrations of 18 ng/mL which fell to less and 1 ng/mL by 1.5 hours [42]. A higher 60 µg/kg intravenous injection in older cardiac surgery patients resulted in plasma concentrations greater than 100 ng/mL which declined to about 10 ng/mL after one hour [54]. Patients were noted to lose consciousness at average plasma concentrations of 34 ng/mL after 75 µg/kg [55].

Following 800 µg oral transmucosal doses to healthy adults, peak plasma concentrations averaged 2.1 (range 1.4 to 3.0) ng/mL at 0.4 hours [56]. Healthy adults given 400 µg buccal tablets every 6 hours for 6 days showed average peak plasma concentrations of 0.9 ng/mL at 0.9 hrs after the first dose and 1.8 ng/mL at 0.8 hrs after the last dose [57].

Mean (± standard deviation) serum fentanyl concentrations have been reported to range from 0.3 (± 0.2), 0.6 (± 0.3), 1.4 (± 0.5), 1.7 (± 0.7) to 2.5 (± 1.2) ng/mL within 24 hours of the administration of 12.5, 25, 50, 75 and 100 µg/hr transdermal patches, respectively [30]. It is considered a "dose dump" if a fentanyl patch causes blood levels to exceed 5 ng/mL [58]. An early report of administration of 75 µg/hr transdermal patches found mean serum fentanyl concentrations of 1.9 (± 0.9) ng/mL after 24 hours [59]. Another report found no detectable fentanyl concentration in three patients with 25 and 50 µg/hr patches; however the limit of detection for the analytical method was only 2.0 ng/mL [60]. In one example of extreme tolerance to fentanyl, a patient with a history of multiple malignancies was admitted to hospital with 34, 100 µg/hr patches (total dose 3,400 µg/hr) all over the anterior and posterior parts of her body. The fentanyl plasma concentration was measured at 178 ng/mL [61].

### Postmortem blood concentrations

As mentioned earlier, reports of fentanyl abuse are not uncommon. Individuals injecting fentanyl have reported with postmortem blood concentrations of 4.9 to 27 ng/mL [62,63], and as high as 240 ng/mL in heart blood [12]. Fatalities associated with chewing fentanyl patches have been reported with concentrations of 8.6 ng/mL [27] and ranging from 7 to 96 ng/mL (in seven cases) [26]. In other reports, concentrations reported in fatalities due to fentanyl have ranged from 5 to 152 ng/mL in mixed drug overdoses, and from 3 to 120 ng/mL in cases of fentanyl alone [2,25,60]. Because there is considerable overlap between fentanyl related deaths and the effective concentrations reported in patients [64], authors have concluded that in postmortem cases, the concentrations must be interpreted in the context of the deceased's past medical history and autopsy findings [60]. However, Anderson and Muto [17] came to the conclusion that in cases of therapeutic administration of fentanyl patches, postmortem blood concentrations can range up to 7 ng/mL, although blood concentrations could not be correlated directly with the number of patches or patch strength.

## Postmortem Redistribution (PMR)

For some drugs, the postmortem blood concentrations may not always reflect antemortem concentrations due to the movement of the drugs after death. The mechanisms involved in this postmortem redistribution are both complicated and poorly understood. However, postmortem drug concentrations in blood may follow some generally accepted trends that aid with interpretation. Generally speaking, the characteristics of the drug itself can be used to predict if a drug is subject to PMR; large changes in blood drug concentrations are predicted for basic, lipophilic drugs with a high volume of distribution (>3 L/kg). When PMR occurs, blood specimens drawn from the central body cavity and heart generally will have higher drug concentrations postmortem than specimens drawn from peripheral areas, most commonly the femoral vein. The diffusion of drugs from organ tissue into the blood may explain the observed phenomenon [65].

It appeared that a partial answer to the understanding of difficulties associated with interpretation of postmortem drug concentrations was provided by two papers published in the 1990s. The first provided detailed information about blood drug concentrations attained from different sites for over fifty drugs [66]. The second, by Dalpe-Scott and coworkers [67], provided a tabular list of the drug concentrations from both cardiac and peripheral blood samples expressed as a ratio of cardiac to peripheral blood (C/P) for over one hundred drugs. The C/P ratio became the accepted benchmark with the accepted guideline that "high ratios" were associated with "potential for redistribution" [67]. This guideline was repeated in a review published a few years later that republished the C/P ratios for many of the drugs included in the Dalpe-Scott and coworker's paper [68].

## Fentanyl Central Blood and Peripheral Blood Ratio

With average published C/P ratios for fentanyl reported as ranging from 1.1 to 2.8 [12,17,25,69], it would appear at first thought, that there may be some potential for PMR. The fact that fentanyl is a basic, lipophilic drug with a moderate volume of distribution (3 to 8 L/kg) further supports the contention.

However, erroneous C/P ratios may be obtained in cases of acute overdose where the drug has not undergone complete distribution. While extensive case data is not available, Dalpe-Scott and colleagues [67] reported a C/P ratio of 1.1 in a therapeutic amitriptyline case, and 2.5 in a fatal amitriptyline case. Similarly, Prouty and Anderson [66] reported a single case of metoprolol overdose with a C/P ratio of 3.8, while ratios of 0.9 and 1.0 were observed in two other cases [67]. The variable C/P ratios observed for fentanyl, therefore, may be reflective of the inclusion of data from both drug abuse (incomplete drug distribution) and non-drug abuse related fatalities.

Fentanyl being a highly potent CNS depressant is likely to cause a rapid death following abuse; un-prescribed or unintended use. With death occurring so quickly, most likely there will be incomplete distribution of fentanyl throughout the body tissues and fluids. This concept has been previously considered in a number of fentanyl related fatalities [12,26]. Consequently, the C/P ratio may be expected to be considerably higher than in cases of prescribed fentanyl administration. The average C/P ratio of 2.8 (range 0.29 to 12) reported in illicit fentanyl drug deaths when mixed with heroin or cocaine [12], therefore, will not be representative of the expected C/P ratio following therapeutic patch use. Evaluation of the Anderson and Muto [17] report further supports this conclusion. These data showed a mean C/P ratio of 1.62 and median of 1.16 (range 0.70 to 4.58). However, the two highest ratios were found in cases of very high concentrations and both apparent cases of abuse; one with a hypodermic needle at his side, the other reportedly wearing six patches on the morning prior to his death. Removal of these two cases from the assessment, gives a mean C/P ratio of 1.21 and median 1.13 (range 0.70 to 1.96), consistent with the other reports for fentanyl [25,69].

A retrospective study from the Los Angeles County Department of Coroner further supports this finding. Postmortem specimens were evaluated for fentanyl concentrations specifically measured in central blood (CB) and femoral (peripheral) blood (PB). In approximately a nine-year period (2000 to 2008), there were a total of 397 cases that were confirmed positive for fentanyl. However, only 179 cases could be included in this study because quantitative measurements were available in both blood specimens. The positive cases in this study were chosen regardless of the fentanyl route of administration and the postmortem interval of the blood samples varied, but was no greater than 72 hours. Blood samples were collected by the pathologist during the autopsy and maintained at a refrigeration temperature prior to and after the analysis. Central blood (heart, chest, or jugular) was collected in a glass jar (200 mL maximum) and preserved with 2% sodium fluoride; whereas the peripheral blood was collected in 10 mL Kendall Monoject Vacutainer® (Seneca, SC) glass tubes containing sodium fluoride (25 mg) and potassium oxalate (20 mg). Central blood specimens were screened by ELISA and the presumptive positives were confirmed in both blood specimens for fentanyl utilizing gas chromatography (GC) coupled with a mass spectrometer (MS). Briefly, the analysis included calibrators (1.67, 5.0, 10, 25, 100 ng/mL), case blood samples, positive control, and negative control that were subjected to a basic liquid/liquid chlorobutane extraction procedure and introduced to the GC/MS [17]. Linearity was achieved by either applying a quadratic or least squares curve ($r^2 \geq 0.99$). The fentanyl blood concentrations along with the ratio of C/P from the 179 cases are summarized in Table 1. The fentanyl concentration ranged from 1.8 to 176 ng/mL in central blood with a mean of 20.61 ng/mL and a median concentration of 13 ng/mL. The peripheral blood had concentrations of 1.7 to 373 ng/mL with a mean of 20.46 ng/mL and a median concentration of 11 ng/mL. The mean C/P fentanyl ratio was 1.55 and the median value was 1.09. The median C/P value being considerably lower than the mean, together with a large standard deviation (1.78), suggests a skewing or oddities in the fentanyl concentrations between the specimens of the casework. To further examine this, fentanyl C/P ratios were categorized into increments of 0.50 (Table 2), and plotted in a histogram (Figure 1). From this evaluation, it can be seen that the vast majority (93%) of the

| | Fentanyl Concentrations (ng/mL) | | |
|---|---|---|---|
| | CB | PB | C/P Ratio |
| N | 179 | 179 | 179 |
| Min | 1.8 | 1.7 | 0.03 |
| Max | 176 | 373 | 15.19 |
| Mean | 20.61 | 20.46 | 1.55 |
| Median | 13 | 11 | 1.09 |
| | | Standard Deviation | 1.78 |

CB = Central Blood, PB = Peripheral Blood, C/P = Central/Peripheral Blood

**Table 1:** Summary of 179 fentanyl positive cases from the Los Angeles County Department of Coroner.

casework had C/P ratios less than 2.5. If one would consider that the remaining 7% of casework with C/P ratios greater than 2.5 be askew, removal of those 13 cases from the data set may be justified, thus leaving 166 cases for investigation. Table 3 details the fentanyl blood concentrations that were removed (C/P ratios of greater than 2.5) from the population size. Blood fentanyl concentrations along with the ratio of C/P from the 166 cases are summarized in Table 4. Although the central and peripheral blood concentration ranges did not change and their mean and median values did not change substantially, the mean C/P values demonstrated more homogeny; 1.23 in comparison to 1.55 previously with the standard deviation decreased to 0.57 in comparison to 1.78 prior. The median C/P values remained essentially unchanged; 1.09 to 1.03. Figure 2, a histogram that represents a plot of the frequency versus fentanyl C/P ratios for the 166 cases, confirms a more normal distribution or gaussian like shape to the data. Furthermore, in addition to 93% of cases showing a C/P ratio less than 2.5, 45% of the cases had a C/P ratio less than 1.0. This demonstrates that the peripheral fentanyl concentration was greater than that of the central blood in almost half the cases. In conclusion, this retrospective analysis of fentanyl positive cases from the Los Angeles County Department of Coroner confirms that the fentanyl C/P concentration ratio averages about 1.2; suggestive of only a minimal difference between central and peripheral fentanyl blood concentrations.

Previously unpublished data collected from the San Diego County Medical Examiner's Office revealed a similar C/P ratio to this retrospective investigation from Los Angeles, and to that of the majority of the literature. Blood samples were collected by the pathologist during the autopsy and maintained at a refrigeration temperature prior to and after the analysis. Peripheral blood was drawn from the iliac veins and stored in 10 mL BD Vacutainer® (Franklin Lakes, NJ) glass tubes containing sodium fluoride (25 mg) and potassium oxalate (20 mg). Central blood was collected from the heart or adjacent great vessels and collected in identical tubes. Central blood specimens were screened by ELISA and the presumptive positives were confirmed in both blood specimens for fentanyl utilizing gas chromatography (GC) coupled with a mass spectrometer (MS). Briefly, the analysis included calibrators (1.0, 2.0, 5.0, 10, 20, 50 ng/mL), case blood samples, positive control, and negative control that were subjected to an alkaline liquid/liquid extraction procedure with n-butyl chloride, back extracted with hydrochloric acid, re-extracted with n-butyl chloride and finally introduced to the GC/MS following solvent evaporation and reconstitution with ethyl acetate. Linearity was achieved by applying a linear least squares calibration curve ($r^2 \geq 0.99$). The limit of quantitation (LOQ) was 0.50 ng/mL. Inter-assay precision was assessed over a 12 month period: mean=8.99, S.D.=0.34, CV%=3.9 (10 ng/mL; N=12); mean=1.88, S.D.=0.106, CV%=5.6% (2 ng/mL; N=12). Although a smaller number of cases were studied, a mean C/P ratio of 0.95 ± 0.26 (mean ± standard deviation; range 0.49 to 1.60) was found in 18 sequential fentanyl cases evaluated in 2002 to 2003 (Table 5).

| C/P Ranges | No. of Cases | % of Cases | Accumalative% |
|---|---|---|---|
| 0-0.50 | 13 | 7.26 | 7.26 |
| 0.51-1.0 | 68 | 37.99 | 45.25 |
| 1.01-1.5 | 46 | 25.70 | 70.95 |
| 1.51-2.0 | 24 | 13.41 | 84.36 |
| 2.01-2.5 | 15 | 8.38 | 92.74 |
| 2.51-3.0 | 3 | 1.68 | 94.41 |
| 3.01-3.5 | 1 | 0.56 | 94.97 |
| 3.51-4.0 | 1 | 0.56 | 95.53 |
| 4.01-4.5 | 1 | 0.56 | 96.09 |
| 4.51-5.0 | 0 | 0.00 | 96.09 |
| >5.01 | 7 | 3.91 | 100.00 |
| | 179 | 100.00 | |

**Table 2:** Number of cases in incremental ranges of 0.50 for fentanyl C/P ratios.

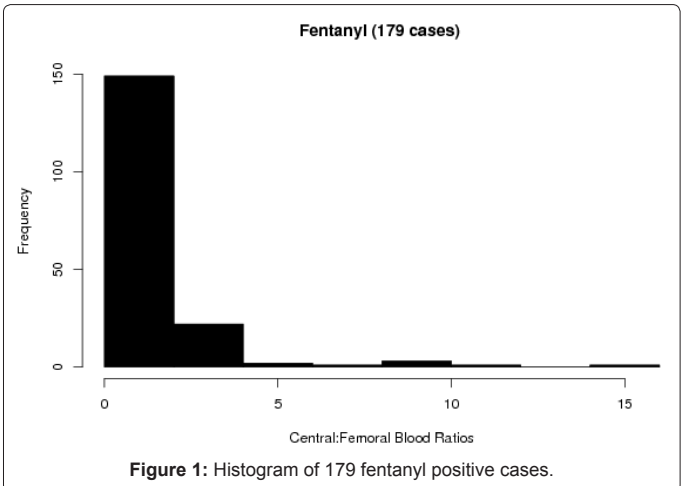


**Figure 1:** Histogram of 179 fentanyl positive cases.

| Concentrations (ng/mL) | | |
|---|---|---|
| CB | PB | C/P Ratio |
| 12 | 4.4 | 2.73 |
| 42 | 14 | 3.00 |
| 42 | 14 | 3.00 |
| 115 | 36 | 3.19 |
| 49 | 13 | 3.77 |
| 10 | 2.4 | 4.17 |
| 21 | 4.0 | 5.25 |
| 20 | 3.0 | 6.67 |
| 17 | 2.0 | 8.50 |
| 28 | 3.0 | 9.33 |
| 74 | 7.5 | 9.87 |
| 18 | 1.8 | 10.00 |
| 41 | 2.7 | 15.19 |

CB = Central Blood, PB = Peripheral Blood, C/P = Central/Peripheral Blood

**Table 3:** 13 'Outlier/Oddity' cases (C/P ranges >2.5) removed from population size of 179.

| | Fentanyl Concentrations (ng/mL) | | |
|---|---|---|---|
| | CB | PB | C:P Ratio |
| N | 166 | 166 | 166 |
| Min | 1.8 | 1.7 | 0.03 |
| Max | 176 | 373 | 2.43 |
| Mean | 20.18 | 21.16 | 1.23 |
| Median | 12.00 | 11.00 | 1.03 |
| | | Standard Deviation | 0.57 |

CB = Central Blood, PB = Peripheral Blood, C/P = Central/Peripheral Blood

**Table 4:** Summary of 166 fentanyl positive cases (13 cases removed).

Overall, consideration of C/P ratio data supports the view that in cases of therapeutic use, fentanyl (with a ratio of about 0.95 to 1.2) is indicative of a compound with only minimal potential for PMR.

## Other Postmortem Investigations

A couple of recent reports, however, have concluded that fentanyl is indeed prone to PMR. The first examined seven postmortem cases [70]. Femoral blood was collected at two postmortem intervals; shortly after death (FB1) (between 2.5 and 6 hours), and at autopsy (FB2) (between 7 and 53 hours). Fentanyl concentrations in FB1 ranged from not detected to 14.6 ng/mL (mean 4.6 ng/mL) and in FB2 from 2.0 to 52.5 ng/mL (mean 17.3 ng/mL). The authors' explanation was that fentanyl is prone to PMR within first few hours of death. A more thorough re-evaluation of these seven cases on the other hand, seriously questions this conclusion. One of the seven cases showed no change in fentanyl concentration (5.0 to 5.1 ng/mL) following a therapeutic 50 µg/h patch administration, and two cases showed a dubious increase from not detected to 2.0 and 2.2 ng/mL. (The limit of fentanyl detection utilized in this study was 2.0 ng/mL.) The remaining four cases each demonstrated a substantial increase between FB1 and FB2. However, three of these four were cases of obvious fentanyl abuse; one was a case of intravenous injection, one involved a 75 µg/h patch found in the mouth, and one involved multiple patch administration (5 patches found on the body). Considering our previous discussion concerning incomplete distribution, it is more likely that these three cases of abuse reveal incomplete fentanyl distribution between the two blood specimens, rather than actual PMR. The fourth and final of these cases (a subject with terminal metastatic cancer) was more difficult to interpret because of the longer postmortem interval between the collection of FB1 and FB2 (53 hours); the concentration increased from not detected to 5.5 ng/mL.

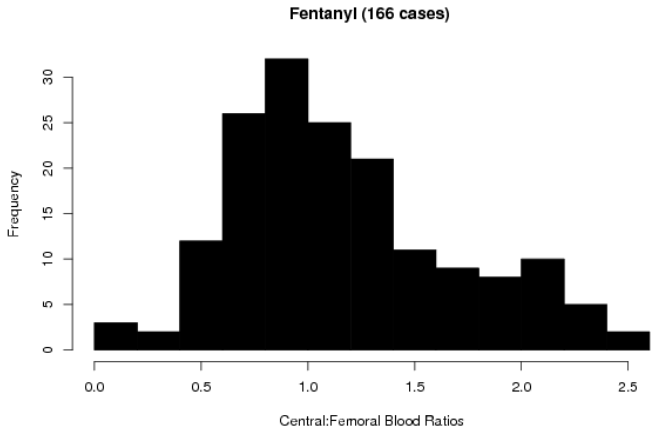


**Figure 2:** Histogram of 166 fentanyl positive cases.

| | Fentanyl Concentrations (ng/mL) | | |
|---|---|---|---|
| | **CB** | **PB** | **C/P Ratio** |
| N | 18 | 18 | 18 |
| Min | 0.8 | 0.5 | 0.49 |
| Max | 84 | 73 | 1.60 |
| Mean | 9.60 | 10.10 | 0.95 |
| Median | 4.6 | 5.9 | 0.94 |
| | | Standard Deviation | 0.26 |

CB = Central Blood, PB = Peripheral Blood, C/P = Central/Peripheral Blood

**Table 5:** Summary of 18 fentanyl cases from the San Diego Medical Examiner's Office (C/P ratios).

Postmortem blood concentrations were also recently reported in a study of 118 cases with therapeutic use of fentanyl compared to serum levels of 27 living persons receiving therapeutic administration of fentanyl patches [71]. These authors concluded that blood concentrations in postmortem specimens cannot be directly compared with *in vivo* serum levels; postmortem fentanyl blood concentrations were up to nine times higher than *in vivo* serum concentrations at the same dose. However, final interpretation of the data presented should be more cautiously considered in light of substantial problems with the study design. The study included only cases where the cause of death was unrelated to fentanyl. As a consequence, cases where fentanyl was found to be a cause of death at similar blood concentrations were excluded. None of the cases studied had a forensic autopsy. The lack of forensic autopsy greatly reduces the level of certainty about the actual cause of death. It also reduces the level of certainty of additional sources of fentanyl; it is unknown if there was evidence of illicit patch use such as patches in the mouth (or the stomach) or additional patches on the body. Furthermore, it is not clear if the bodies were externally examined to assess and confirm that the actual prescribed fentanyl dose was being used at the time of death. Additionally, possible treatment with other drugs was not evaluated to assess pharmacokinetic interaction, as have been postulated with inhibitors of isoenzyme CYP 3A4 [72]. The subjects included were very old and many cachectic; the average age was 78 (median 81). A significant increase in the terminal half life of fentanyl elimination and a greatly decreased clearance has been described in the elderly [30,34]. As a consequence, the expected concentrations for each transdermal patch size may not apply in the extremely old [31]. Moreover, many of the patients were critically and terminally ill (most of them with cancer), and a modified organ function may be conceivable [71]. It is perhaps not surprising therefore that in this group of extremely elderly, cachectic and sick patients, that postmortem fentanyl concentrations were elevated in some individuals. Analytically, the limit of fentanyl detection was 0.9 ng/mL. As the mean maximal concentration expected for the 25 µg/h patch is 0.6 ng/mL and concentrations less than 0.9 ng/mL are within the reported lower range for 50 and 75 µg/h patches, the study may be reporting concentrations that are skewed higher by the exclusion of such data. Also, in most cases, there was an exceptionally long time between death and postmortem tissue sampling; postmortem interval averaged 10 days and was as long as 41 days. Although the authors concluded that postmortem concentrations were not inevitably higher, there is a possibility of higher blood concentrations as a result of these unusual and extended periods [70,73]. Finally, there was no attempt to assess and compare fentanyl concentrations within the same individual over time; i.e. before death (or immediately following death) compared to the autopsy sample. As a result, it is premature to conclude that the concentrations determined postmortem are a result of an actual increase after death, but rather a consequence of the issues examined above.

## Animal Model

In an attempt to investigate fentanyl PMR, rabbits were assessed after the application 50 µg/h Duragesic® patches [74]. In a study sponsored by the Johnson & Johnson Pharmaceutical company, two cycles of patch administration were applied and plasma fentanyl concentrations were determined following animal termination with

patch removal and compared to animals that were not terminated with patch removal. A 4- to 6-fold increase was reported in the femoral blood (plasma). The authors concluded that this was evidence of postmortem redistribution of fentanyl relative to antemortem blood concentrations. However, the validity of this particular animal model for any assessment of fentanyl PMR in humans following transdermal patch application is critically flawed. Firstly, rapid hair re-growth in rabbits has been proposed as a complicating factor that may impede dermal absorption of fentanyl, particularly when the animals' fur is clipped prior to patch application [75]. Additionally, the actual delivery rate of fentanyl is often substantially less than the theoretical rate of delivery in animals than in humans, and species-specific skin characteristics also play a role in percutaneous drug adsorption [75]. Secondly, rabbits have been demonstrated to have a 3-fold faster metabolism than man [74], which would acutely affect fentanyl blood concentrations during the patch treatment period. These considerable pharmacokinetic differences compared to humans most likely account for the need to apply such a large 50 µg/h dose (to 7.5 pound animals) to achieve what was considered "therapeutic concentrations of fentanyl in the rabbits", and thereby make direct comparison to human subjects imprudent. Thirdly, a substantial weight loss in the treated animals was recorded over the dosing period. This was attributed to an inconvenient patch application by the authors, but alternatively it may represent a symptom of drug toxicity. Although care was taken to minimize trauma to the application site during the fur clipping process, there may have been disruption to the external skin layers which could significantly affect drug absorption from the patch. Finally, the possibility of incomplete fentanyl distribution following a comparatively massive fentanyl 50 µg/h dose to small, opioid naive animals is a legitimate possibility. The consequences of incomplete fentanyl distribution with misinterpretation of both the C/P model of PMR, and collection of blood samples at two postmortem intervals have been discussed earlier.

## Fentanyl Liver and Peripheral Blood (L/P) Ratio

While drug properties such as volume of distribution, protein binding, and pKa are thought to contribute to PMR, a relationship between C/P and drug properties has not been established [76]. Data does not always support the speculation that basic drugs with a large volume of distribution tend to have larger C/P ratios [77]. Some basic drugs and some acidic drugs with large C/P ratios have small volumes of distribution [67]. Also, there has been little agreement as to what ratio actually defines that a compound is prone to PMR, or not [78]. Additionally, limitations of the C/P model have been noted. Reports of a C/P ratio greater than 1.0 have been published for some drugs (carisoprodol, tramadol) which are not prone to redistribution [78,79]. Arterio-venous differences, anatomic variability within individuals, and statistical chance may result in a C/P ratio greater than 1.0 in drugs that do not redistribute. Furthermore, resuscitation attempts may result in a C/P ratio less than 1.0 [80]. Inaccurate ratios may also be obtained as an artifact of sampling when the cardiac blood volume is depleted by the collection of blood from connected blood vessels, or in cases of acute overdose where the drug has not undergone complete distribution (as discussed earlier).

The liver to peripheral blood (L/P) ratio has been recently proposed as an alternative marker for PMR, with ratios exceeding 20 indicative of a propensity for significant PMR and ratios less than 5 indicating no propensity towards PMR [78,81]. The magnitude of the liver concentrations compared to the blood concentrations appears to provide an additional advantage over the conventional C/P model by demonstrating a wider range of values for interpretation [82]. Several scientists have already obtained and published liver data for fentanyl casework [14,17,62,70,77,83- 87]. Some authors have actually suggested measuring postmortem liver concentrations in preference to blood in order to differentiate therapeutic from toxic or fatal concentrations [88]. Liver concentrations are unlikely to be substantially influenced by PMR [70]. Anderson and Muto [17] proposed liver fentanyl concentrations for this purpose, although they principally relied upon blood concentrations for the initial interpretation. An evaluation of the published liver data in which blood concentrations were also reported, suggests a fentanyl L/P ratio of 5.0 ± 3.7 (mean ± standard deviation) (Table 6). (Peripheral blood concentrations were evaluated when available; however some studies reported alternative blood collection sites such as subclavian, iliac or heart, or were unstated.)

A retrospective study from the Los Angeles County Department of Coroner revealed a similar L/P ratio to that of the of these literature data. In approximately a five and a half year period (2007 to 2012) there were a total of 87 cases that could be included in this study because quantitative measurements were available in both liver and peripheral blood specimens. The positive cases in this study were chosen regardless of the fentanyl route of administration and the postmortem interval (details of the analytical procedure were described earlier). In the 87 cases studied, a mean L/P ratio of 6.5 ± 5.1 (mean ± standard deviation; range 1.0 to 42.3) was found (Table 7).

Previously unpublished data from the San Diego Medical Examiner's Office revealed an analogous L/P ratio (details of the analytical procedure were described earlier). In the 16 cases studied,

| Author/Publication (Reference) | No. of Cases Reported | L/P Ratio |
|---|---|---|
| Pare et al. 1987 [83] | 1 | 3.7 |
| Matejczyk 1998 [84] | 1 | 2.4 |
| Levine et al. 1990 [62] | 1 | 1.2 |
| Chaturvedi et al. 1990 [85] | 1 | 4.3 |
| Anderson & Muto 2000 [17] | 10 | 5.5 ± 2.9* |
| Ropero-Miller 2004 [86] | 1 | 5.0 |
| Coopman et al. 2007 [87] | 1 | 1.3 |
| Luckenbill et al. 2008 [77] | 9 | 9.5 ± 11.2* |
| Jumbelic 2010 [14] | 8 | 5.0 ± 2.1* |
| Olson et al. 2010 (FB2) [70] | 18 | 12.2 ± 15.7* |
| | Overall Mean | 5.0 |
| | Standard Deviation | 3.7 |

L = Liver, P = Peripheral Blood
*Mean ± standard deviation

**Table 6:** Evaluation of Literature Fentanyl L/P Ratios.

| | Fentanyl Concentrations | | |
|---|---|---|---|
| | **Liver (µg/kg)** | **PB (ng/mL)** | **L/P Ratio** |
| N | 87 | 87 | 87 |
| Min | 6.9 | 2.6 | 1.00 |
| Max | 689 | 246 | 42.30 |
| Mean | 93.33 | 17.93 | 6.50 |
| Median | 66 | 12 | 5.36 |
| | | Standard Deviation | 5.10 |

L = Liver, PB = Peripheral Blood, L/P = Liver/Peripheral Blood

**Table 7:** Summary of 87 fentanyl positive cases from the Los Angeles County Department of Coroner (L/P Ratios).

| | Fentanyl Concentrations | | |
|---|---|---|---|
| | Liver (µg/kg) | PB (ng/mL) | L/P Ratio |
| N | 16 | 16 | 16 |
| Min | 3.8 | 0.65 | 2.30 |
| Max | 270 | 66 | 19.50 |
| Mean | 74.10 | 14.70 | 6.90 |
| Median | 43.5 | 9 | 5.90 |
| | | Standard Deviation | 4.50 |

L = Liver, PB = Peripheral Blood, L/P = Liver/Peripheral Blood

**Table 8:** Summary of 16 fentanyl cases from the San Diego Medical Examiner's Office (L/P Ratios).

a mean L/P ratio of 6.9 ± 4.5 (mean ± standard deviation; range 2.3 to 19.5) was found in sequential fentanyl cases evaluated in 2009 to 2010 (Table 8).

In view of the hypothesis that drugs with an L/P ratio less than 5 have no propensity towards PMR [78,81], overall consideration of L/P ratio data supports the judgment that (with an average literature ratio of 5; together with larger studies from Los Angeles and San Diego that averaged 6.5 and 6.9, respectively) fentanyl is indicative of a compound with only minimal potential for PMR. This determination clearly substantiates the conclusion reached for the fentanyl C/P ratio data presented previously.

## Conclusion

Fentanyl is a potent opioid widely prescribed for the relief of pain and is subject to abuse, whether intended or not. The drug is highly litigated because of its association with death, either as the sole cause or as a contributing factor, of many opioid users. Although fentanyl has a Vd of 3 to 8 and is a basic compound, in postmortem cases when it has undergone complete distribution, the drug exhibits minimal PMR. Central to peripheral blood fentanyl ratios of about one demonstrate minimal tendency towards PMR. This fentanyl ratio was confirmed with a nine year study from the Los Angeles County Coroner (166 cases; average C/P ratio 1.2), as well as a smaller study from the San Diego Medical Examiner (18 cases; average C/P ratio 0.95). Moreover, consideration of the fentanyl liver to peripheral blood ratio corroborates the lack of fentanyl distribution or PMR. The Los Angeles County Coroner and the San Diego Medical Examiner data (combined total of 103 cases) revealed L/P ratios that averaged 6.5 and 6.9, respectively; thus supporting the average literature L/P ratio of 5. In view of the premise that drugs with an L/P ratio less than 5 have no propensity towards PMR, these new data sustain the conclusion that fentanyl is indicative of a compound with only minimal potential for PMR. Overall, many literary sources have been independently evaluated, and additional laboratory scientific data has been presented, all in context with concepts of PMR.

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