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Research Article

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Intravenously Administered Fentanyl is Not Detectable in Exhaled Breath

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Abstract

Background: Relapse rates amongst anesthesia residents and CRNAs who were previously addicted to fentanyl, rehabilitated, and considered to be in stable recovery, are reported to be extremely high upon return to the operating room environment. Previous studies have proposed that there is a small amount of fentanyl in the exhalation limb of the anesthesia circuit when patients are given intravenous fentanyl, leading to a novel source of exposure for anesthesia providers and possible sensitization in predisposed individuals. However, prior studies have been limited by their small sample size and questionable study methodology. This study aimed to determine the quantity of fentanyl exhaled after intravenous fentanyl administration.

Methods: Five patients were given 10 μg/kg of fentanyl at the induction of general anesthesia. Two Humid-Vents were connected to the endotracheal tube for the duration of surgery. Humid-Vent contents were extracted with a protocol designed to capture fentanyl and then the extract was analyzed for fentanyl using isotope-dilution liquid chromatography/mass spectrometry (LC/MS/MS) as well as an enzyme immuno-assay (ELISA).

Results: Fentanyl was undetectable in the Humid-Vents for all five patients, whether analyzed by LC/MS/MS (lower limit of quantification = 5 pg) or ELISA (lower limit of quantification = 1 pg). Validation studies using nebulized fentanyl reveal that Humid-Vents capture 5.9-12.0% of nebulized fentanyl (at 6 L/min O_2) from 5 μg/mL and 50 μg/mL solutions, respectively.

Conclusions: We were unable to detect fentanyl in the exhaled air of five patients who had received intravenous fentanyl 10 μg/kg, using either isotope-dilution LC/MS/MS or ELISA. We conclude that exhaled fentanyl is not a significant exposure source for anesthesia providers.

Keywords

Fentanyl; Addiction; Anesthesiology

Introduction

Anesthesiologists are disproportionally affected by addiction when compared to other medical specialties [1]. Fentanyl and sufentanil are the most frequently abused drugs [2-5]. The relapse rate amongst anesthesia residents and CRNAs who had previously abused fentanyl, and were then rehabilitated and considered to be in stable recovery, is extremely high upon return of these individuals to the operating room environment [6,7]. As a possible explanation for the high relapse rate, other studies have reported measurable amounts of fentanyl in the air in the operating room, as well as in the expiratory limb of the anesthesia circuit in patients given intravenous fentanyl [1,8,9], leading to a novel source of exposure for anesthesia providers and possible sensitization in predisposed individuals. However, the methodologies employed in these initial studies did not exclude the possibility of exogenous contamination and utilized very large doses of intravenous fentanyl (20-30 μg/kg). As the movement of fentanyl from the lungs would depend upon its presence in the water vapor of the gas carrier, we measured the amount of fentanyl in end-tidal vapor by sampling from Humid-Vents that were placed in the expired gas line. We developed a method for the detection of water-vapor mediated-fentanyl from Humid-Vents, by two differing analytical protocols, an ELISA (more sensitive but less specific) and isotope-dilution liquid chromatography ion-trap mass spectrometry (LC/MS/MS). We then measured exhaled fentanyl in five patients administered via a bolus of 10 μg/kg of intravenous fentanyl.

Methods

To verify that the standard Humid-Vent 1 (Gibeck, Inc) captures fentanyl from vapor phase water, we nebulized (AirLife™, CareFusion, Yorba Linda, CA) 5 mL of fentanyl at two concentrations, 5 μg/mL and 50 μg/mL, with 6 L/min of O_2 for 5 minutes. The nebulization was performed 5 times for each concentration of the fentanyl fluid with new Humid-Vents and a new 5 mL lot of fentanyl fluid. The Humid-Vents (10 total) were then analyzed for fentanyl by isotope dilution LC/MS/MS, in the same manner as described below for the Humid-Vents used in patients.

After IRB approval, five non-pregnant, adult ASA I-III patients who were undergoing lengthy (greater than 4 hours) procedures with a general anesthetic and endotracheal tube at the University of California, San Diego Medical Center gave written consent for participation in this study. Prior to any fentanyl administration, standard ASA monitors were placed and the patient was pre-oxygenated for 3-5 minutes. General anesthesia was induced intravenously with 10 μg/kg of Fentanyl, Propofol 2 mg/kg and a non-depolarizing muscle relaxant. The patient underwent direct laryngoscopy and intubation with a standard endotracheal tube. Following successful endotracheal tube insertion, two standard Humid-Vent 1 (Gibeck, Inc) were attached, in series, directly to the endotracheal tube and the Y-connector. The two Humid-Vents remained in place in that sequence for the duration of the surgical procedure. The patients were ventilated with tidal volumes of 6-8 mL/kg of ideal body weight with fresh oxygen flow rates of 2 L/minute. Anesthesia was maintained with 1.0-1.5 MAC Sevoflurane. Additional fentanyl was administered as deemed necessary by the anesthesiologist. At the completion of the surgical case, the Humid-Vents were removed by a separate gloved provider, who had not handled any fentanyl throughout the day, covered with parafilm and stored at -70° until analysis.

In a limited series of studies, two male beagle dogs (11-13 kg) were sedated with xylazine (1.5 mg/kg, IM), according to the UCSD-

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IACUC approved protocol, induced via mask ventilation with isoflurane, intubated, mechanically ventilated (6-8 mL/kg), and maintained with isoflurane/oxygen/air. Atropine 0.25 mg i.v. was given. Expired gases were passed through the Humid-Vent circuit outlined above. Routine monitoring included end-tidal gases and SpO_2. After stabilization, fentanyl citrate was infused at the rate of 1.0 µg/kg/min for 30 min. The two Humid-Vents were removed from the ventilation circuit after two hours of mechanical ventilation, after which time the animals were recovered.

To initiate analysis, Humid-Vents were passively brought to room temperature. Each Humid-Vent was then "spiked" with 10 ng d5-fentanyl internal standard (Catalog #N-030, Cerriliant Corporation, Round Rock, TX) in sterile saline, delivered interstitially via five X 2 µL injections. Humid-Vents were then dried for 30 min at 37°C, prior to being extracted 3 times in succession with 30 mL n-hexane under sonication at room temperature for 30 minutes for each extraction. Hexane extracts were pooled and then evaporated to dryness under a stream of purified anhydrous nitrogen at 37°C. Dried extracts were reconstituted in 40 µL methanol, and then analyzed by either LC/MS/MS (20 µL injection) or immunoassay (ELISA-2X10 µL). For LC/MS/MS, fentanyl was isolated from other extract constituents by reverse-phase chromatography on a C-18 column utilizing a methanol: 0.1% formic acid in water gradient. The positive mode electrospray mass transitions monitored were; 337.5>188.2 and 342.4>188.2 for fentanyl and the d5-fentanyl internal standard, respectively. Fentanyl ELISA reagents (Catalog #131519) were obtained from Neogen Corporation, Lexington, KY. ELISA calibration curves were constructed from fentanyl reference standard (Cerriliant Corporation, Round Rock, TX, Catalog #F-013, 1mg/mL stock).

Results

Table 1 shows the results of the two-point *in-vitro* Humid-Vent capture of nebulized fentanyl study. 6 L/min of O_2 for 5 minutes nebulized an average of 1.7 mL (range 1.5-2.0 mL) of the 5 µg/mL fentanyl fluid. 1.7 mL of 5 µg/mL nebulized fentanyl fluid contains 8.5 µg of fentanyl. From the 8.5 µg of nebulized fentanyl (from the 5 µg/mL concentration) the Humid-Vents captured an average of 0.5 µg (range 0.4-0.6 µg) for a 5.9% efficiency (top row Table 1). 6 L/min of O_2 for 5 minutes nebulized an average of 1.4 mL (range 1.4-1.5 mL) of the 50 µg/mL fentanyl fluid. 1.4 mL of 50 µg/mL nebulized fentanyl fluid contains 70.0 µg of fentanyl. From the 70 µg of nebulized fentanyl (from the 50 µg/mL concentration) the Humid-Vents captured an average of 8.2 µg (range 7.0-11.1 µg) for a 12.0% efficiency (bottom row Table 1).

Table 2 shows the important demographic and administered fentanyl patient data.

As seen in Figure 1, isotope-dilution LC/MS/MS analysis failed to detect any fentanyl (retention time = 5 minutes), despite the presence of the d5-fentanyl recovery marker control at the same retention time, in any of the five patients. The isotope-dilution LC/MS/MS method has a lower limit of quantification of 5 pg/Humid-Vent. Similarly, the ELISA had strong positive response with the d5-fentanyl control but failed to detect any fentanyl signal in our five patients. The ELISA has a lower limit of quantification of 1 pg/Humid-Vent. All five patients had uncomplicated and uneventful anesthetic courses.

In the two follow-up isoflurane anesthetized dogs, who were infused with an effectively much larger dose of fentanyl than the operating room patients (1.0 µg/kg/min of fentanyl for 30 min.), no fentanyl could be detected from the two Humid-Vents exposed to exhaled gas for two hours by either LC/MS/MS or ELISA analysis.

Conclusion

We found that none of our five patients exhibited any fentanyl in exhaled breath, to a sensitivity of 1-5 pg/Humid-Vent, after intravenous bolus administration of 10 µg/kg of fentanyl. Our exhaled fentanyl detection method depended on extracting fentanyl from Humid-Vents and analyzing the extracts with ELISA or by LC/MS/MS. The interpretation of the results of these studies is predicated on several key issues.

The fentanyl is carried with the water vapor

Fentanyl is not a volatile substance. It is soluble in blood, tissue and the body water. If fentanyl is exhaled, then it should be in the exhaled body water. Our *in-vitro* nebulization of fentanyl study strongly supports this contention. We recognize that there may

Table 1: Efficiency of Humid-Vent Capture of Fentanyl Nebulized with 6 L/min O_2 for 5 minutes.

Concentration of Fentanyl µg/mL	mL of Fentanyl in Nebulizer Chamber	mL of Fentanyl Nebulized	Amount of Fentanyl Nebulized, µg	Amount of Fentanyl Captured on Humid-Vent, µg	Efficiency of Humid-Vent Capture of Fentanyl, %
5	5	1.7	8.5	0.5	5.9
50	5	1.4	70.0	8.2	12.0

Table 2: Demographic and Administered Fentanyl Patient Data.

Patient	Age	Weight (kg)	Fentanyl µg/kg			Length of Surgery (min)
			Induction	[Subsequent]	[Total]	
1	59	56.7	10	1.76	11.5	285
2	76	63.5	10	1.81	11.8	248
3	75	55	10	0.91	10.9	279
4	62	75	10	1.3	11.3	300
5	58	95	10	0.53	10.5	449
Average ± sd	66 ± 8.8	69 ± 16.5	10	1.26 ± 0.55	11.2 ± 0.5	312.2 ± 78.8

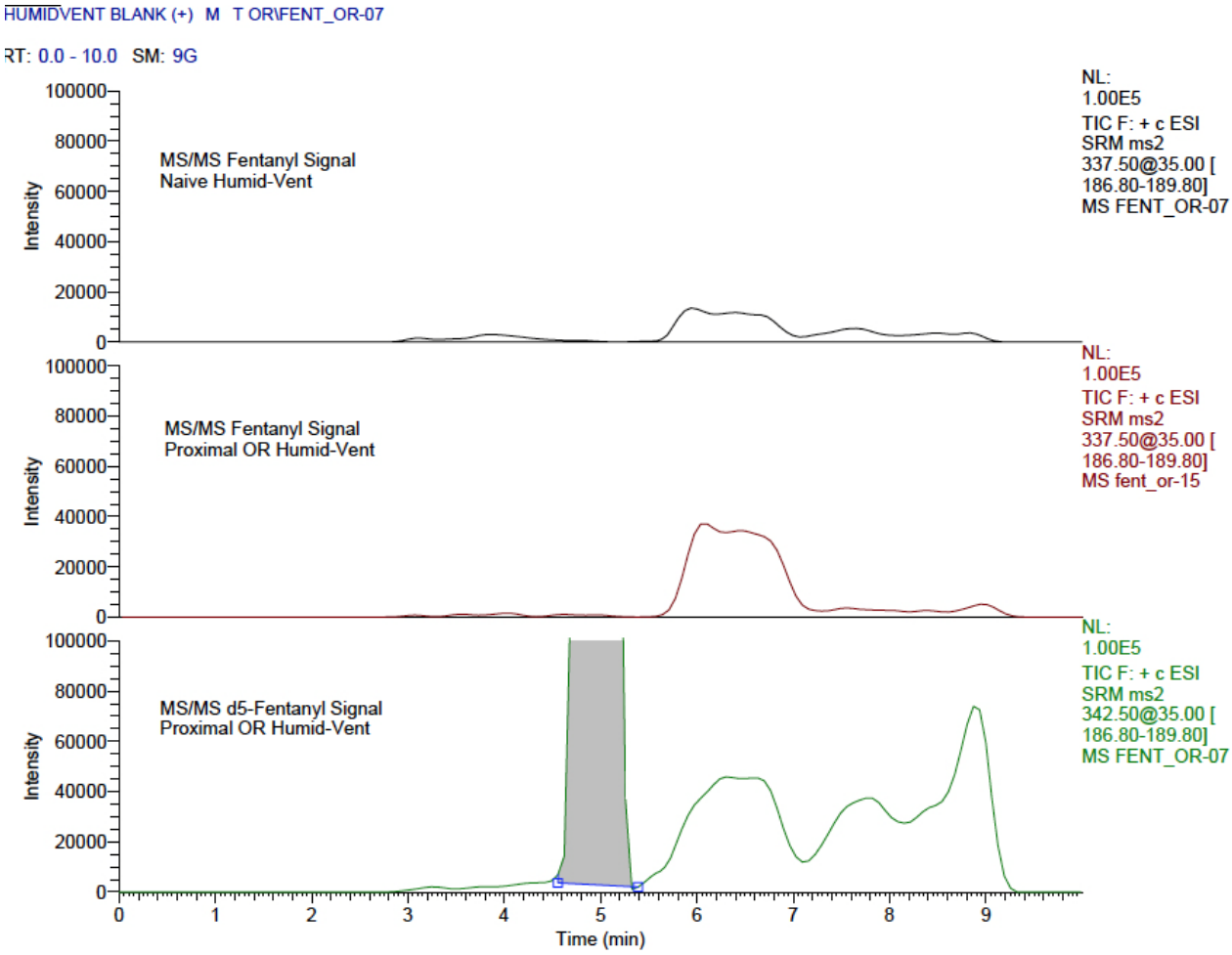

Figure 1: LC/MS/MS ion chromatograms illustrating the response of a naïve (blank) Humid-Vent (top), Humid-Vent Patient Sample (middle), and ISTD control (bottom). The Humid-Vent Patient Sample (middle) lacks the characteristic fentanyl spike (detector response) at 5 minutes, marked by gray shading in the ISTD control panel (bottom).

be a modest likelihood that the fentanyl could be dissolved in the anesthetics gas(es). However, the percentage of volatile anesthetic vapor (ordinarily 7 mm Hg) to water vapor (ordinarily 47 mm Hg) is small, with a 6.7 times greater amount of water vapor to volatile anesthetic vapor. As such, the large majority of the fentanyl would travel with the water vapor and be collected by the Humid-Vent.

The expired water vapor is collected in the Humid-Vent

The principle of humidification of the mechanically ventilated airways employed in the commercially available heat-moisture exchangers is absorption of the water vapor onto the matrix preventing loss of end-tidal water vapor in the gas distal to the Humid-Vent. Our *in-vitro* nebulization of fentanyl study strongly supports this contention. The total capacity for water vapor of a Humid-Vent is unknown by either the authors of this study or the manufacturer. However, the manufacturer states that the humidification process is maximized when tidal volumes between 50-600 mL are utilized. We followed this recommendation in all our patients. In addition, we placed two Humid-Vents in series in the patients to potentially capture any residual water vapor that may not have been captured by the first Humid-Vent.

Fentanyl in the Humid-Vents can be quantitatively recovered

To validate the recovery techniques, Humid-Vents were exposed to nebulized fentanyl. The Humid-Vents were then dried and measurable amounts of fentanyl were extracted and measured via LC/MS/MS. The *in-vitro* nebulization of fentanyl fluid studies showed that our recovery methodology has a 5.9-12.0% efficiency (see Results and Table 1 for efficiency calculation). Even if the nebulization process removes more saline than fentanyl (thereby concentrating the fentanyl in the remaining unnebulized saline), the results still show the Humid-Vents capture/retain fentanyl.

In short, based on the above comments, we believe that if fentanyl were in the expired gas that our methodology would have captured and detected this fentanyl. Based on the calibration of our measuring system, if there were fentanyl in the expired air, the concentration of expired fentanyl would have been less than 1 pg/Humid-Vent. These Humid-Vents remained in place for the duration of the surgical procedure, rather than sampling exhaled vapor at predetermined time points. Thus, the summation of all the time points in previous

studies [8,9] should correlate with the amount of fentanyl found on the Humid-Vent in our study.

We also believe that our sampling methods result in a limit of quantification similar to previous studies [8,9]. Those studies utilized a solid phase microextraction method with a stated lower limit of quantification of 0.05 pg/mL. In our study we employed two different analytic techniques, LC/MS/MS and ELISA assay. The lower limit of detection for each of these two tests is equivalent to 0.13 pg/mL and 0.03 pg/mL, respectively. Thus, the limit of detection of our analytic techniques straddles the lower limit of detection of the previous studies and should be able to detect fentanyl, as reported in previous studies.

Our results differ from previous studies. In one study [8], expired fentanyl levels of 6-21 pg/mL was captured/recovered on a solid phase microextraction fiber, which based on their data, translates to 0.240 to 0.647 pg/mL of fentanyl for every 1 µg/kg of fentanyl administered intravenously. We tried to duplicate their [8,9] methodology using solid phase microextraction fiber methodology. Despite using clinically excessive doses of 0.5-1.0 µg/kg/min in two dogs (clinically relevant dosage is 1-3 µg/kg/hr), and adhering to their [8,9] methodology, fentanyl was not detectable in the exhalation limb of the anesthesia circuit. We do not know why they [8,9] found expired fentanyl using high dose fentanyl in patients, yet we found no expired fentanyl using identical methodology and very high doses in dogs.

Differences in our results in patients, compared to their results in patients may involve several more issues. First, the previous studies induced their patients with clinically large doses (20-30 µg/kg) of fentanyl whereas we used 10 µg/kg of fentanyl. Second, it is unclear how the maintenance phase of anesthesia was carried out with the previous studies. We utilized a volatile anesthetic, which may have carried some of the water vapor fentanyl. Third, we chose to define a positive result as having a fentanyl peak-to-noise ratio of greater than 3 times the baseline, a ratio widely used in the clinical assay literature. When reviewing the ion chromatograms in these previous studies [9], the positive chromatograms do not meet this 3:1 peak-to-noise definition. Our interpretation of these previous studies would be that there is an undetectable amount of fentanyl in the exhaled air. Finally, the previous studies included cardiac patients with lesions likely resulting in left-to-right shunts (three ventricular septal defects, two atrial septal defects, two patent ductus arteriosus). Each of these lesions would lead to some degree of hyperperfusion of the pulmonary circulation. Intravenously administered fentanyl is known to rapidly reach its peak plasma level and be quickly metabolized, with less than 10% of fentanyl present ten minutes after the initial bolus. The rapid decrease in plasma levels of fentanyl is thought to be secondary to extensive hepatic metabolism, as well as, active uptake by the pulmonary endothelium [10,11]. If indeed there is active uptake of fentanyl from the pulmonary circulation by the lung, pulmonary hyperperfusion could lead to a larger percentage of uptake and, as such, a larger amount of fentanyl in the expired air.

In conclusion, these data argue that if fentanyl, administered as a 10 µg/kg intravenous bolus in patients, is present in the expired gas that these levels are below 1-5 pg/Humid-Vent. Therefore, on the basis of these results it is premature to suggest that anesthesia providers who were previously addicted to fentanyl and successfully rehabilitated, not be allowed to return to the operating room environment, based solely on the hypothesis that they can be sensitized by exhaled fentanyl from patients.

Summary Statement

We were unable to detect fentanyl in the exhaled breath of patients who were administered a 10 µg/kg bolus of intravenous fentanyl.

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