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In Vitro Drug Adsorption and Plasma Free Hemoglobin Levels Associated With Hollow Fiber Oxygenators in the Extracorporeal Life Support (ECLS) Circuit

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Abstract: The purpose of this study was to identify the percentage of fentanyl or morphine sulfate lost from adhesion to either the polyvinylchloride (PVC) tubing or the surface of two different hollow fiber oxygenators used in current extracorporeal life support circuits and to identify any difference in the plasma free hemoglobin (PFH) levels generated when using these oxygenator and/or drug combinations. For each drug examined, six simple circuits were assembled; for each drug, two circuits contained tubing without an oxygenator (control), two circuits contained the Jostra Quadrox D (Maquet Cardiopulmonary, AG Hirrlingen, Germany), and two circuits contained the Terumo Baby Rx (Terumo Cardiovascular Systems Corp., Ann Arbor, MI). Fentanyl or morphine sulfate was added to yield initial circuit concentrations equal to 1430 ng/mL, respectively. Throughout the 6-hour in vitro testing, samples to evaluate the drug and PFH levels were drawn at various time intervals. Significance in this study is defined as $p < .05$. Fentanyl's initial adsorption seems to be 80% in circuits without oxygenators, 86% in the circuits containing the Quadrox D oxygenator, and 83% in the circuits with the Baby Rx oxygenator. Morphine sulfate seems to be initially adsorbed at a rate of 40% in all circuits and does not seem to be adsorbed by either of the tested oxygenators. The PFH levels were significantly ($p < .05$) elevated in the fentanyl circuits. The type of oxygenator does not seem to play a significant role in drug adsorption. During this in vitro study, the majority of both drugs were lost to the PVC tubing. The type of oxygenator did not seem to significantly affect PFH. However, fentanyl in any combination or alone was associated with increased PFH levels. **Keywords:** extracorporeal membrane oxygenation, adsorption, plasma free hemoglobin, morphine, fentanyl. *JECT. 2007;39:234–237*

The extracorporeal membrane oxygenation (ECMO) community has been using the silicone (Kolobow) oxygenator in the extracorporeal life support (ECLS) circuit for >30 years (1). The Kolobow oxygenator had been used as the oxygenator of choice because of its ability to promote gas exchange while having a limited predisposition for plasma leak over time from its true membrane design. Today, the silicone oxygenator is still available through Medtronic (Minneapolis, MN) as the 0600, 0800, and 1500 plus additional sizes of I-2500, I-3500, and I-4500, respectively, that have an internal heat exchanger. Unfortunately, the silicone polymer membrane oxygenator suffers from high pressure drops and significantly limited gas and blood flow rates, leaving the end user with a number of oxygenators to choose from based on the patient size needing support.

Centers throughout the United States and abroad have begun using hollow fiber oxygenators for ECLS because of their flow characteristics, gas exchange potential, relatively small pressure drops, and the wider patient range that they are able to cover. Unfortunately, the hollow fiber oxygenators were/are susceptible to plasma leak at various days of use, leading to either an interruption in blood flow or, at a minimum, an exposure to yet another foreign surface when they are changed to a new oxygenator (2). Maquet recently received US Food and Drug Administration (FDA) 510 (K) approval for the Jostra Quadrox D (Maquet GmbH & Co. KG, Rastatt, Germany), introducing the US market to a combination oxygenator heatexchanger that is promoted as both a hollow fiber and a true

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membrane oxygenator. This new oxygenator seems to provide acceptable gas exchange and blood flow rates without plasma leak, making it an ideal oxygenator for the ECLS circuit. However, as this new oxygenator is used more for ECLS, questions surrounding its adsorption of medication and its hemolytic properties must be evaluated as they were in the past for the silicone oxygenator (3–6). In a previous study, authors from University Hospital, Regensburg, Germany, described a significant difference between the Quadrox D and other hollow fiber oxygenators in regard to the ability of isoflurane to cross the fibers and enter the circulation. They concluded that very little isoflurane crossed the new polymethylpentene fibers compared with the standard polypropylene fibers, resulting in a decrease in circulating quantities of isoflurane (7). Evidence that drugs may react differently with hollow fiber oxygenators, both polymethylpentene and polypropylene, than with silicone membranes is intriguing, and with this in mind, we set out to quantify the amount of two common sedatives, morphine sulfate (Hospira, Lake Forest, IL) or fentanyl (Baxter, Deerfield, IL), that were lost because of adsorption in the Maquet Quadrox D oxygenator, the Terumo (Terumo Cardiovascular, Ann Arbor, MI) Baby Rx oxygenator, or simply because of the tubing. Secondarily we assessed the hemolytic nature surrounding these drugs or oxygenator or drug/oxygenator combinations (8).

MATERIALS AND METHODS

Each drug being tested had six identical circuits set up using a simple design that included an uncoated Medtronic CLASS VI ⅜ × 3⁄32-in (Medtronic) venous line 65 in (165 cm) in length, an uncoated Medtronic CLASS VI ¼ × 3⁄32-in arterial line 60 in (152 cm) in length, an uncoated Super Tygon S-65-HL ⅜ × 3⁄32-in (Saint-Gobain, Akron, OH) boot 17 in (43 cm) in length, and an injection/sampling port that was inserted after the oxygenator or in a similar location after the roller head for circuits without an oxygenator (Figure 1). Eight of the 12 circuits contained a hollow fiber oxygenator. Four contained the Quadrox D (Maquet Cardiopulmonary), four contained the Baby Rx (Terumo Cardiovascular Systems Corp.), and the final four circuits did not include an oxygenator and would serve as the control for drug lost because of its adsorption by the tubing.

Each circuit was primed with Plasma-Lyte-A (Baxter). All 12 circuits recirculated for 12 hours through two uncoated Medtronic Affinity reservoirs (Medtronic). The two reservoirs were subsequently drained air-free and filled with <2-hour-old bovine whole blood, followed by all 12 circuits being re-primed in such a manner as to displace the Plasma-Lyte-A. The bovine blood had been anticoagulated with heparin 4 IU/mL during collection; therefore, no further anticoagulation was used throughout this study.

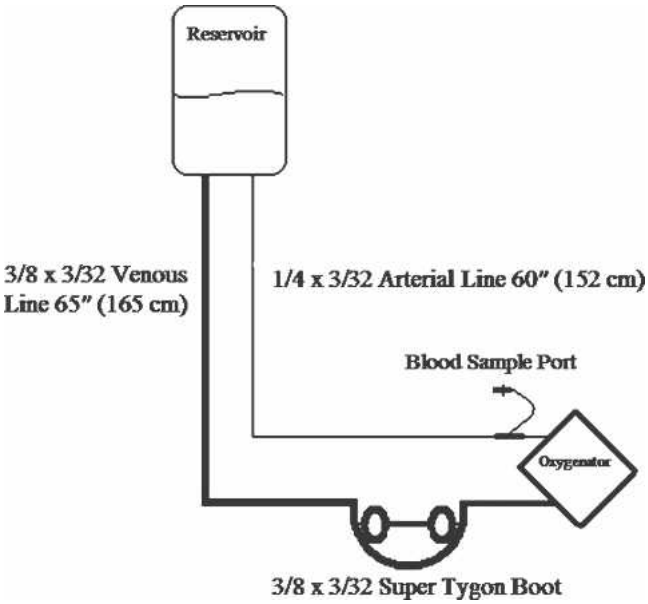

Figure 1. Schematic of circuit used in this experiment.

Once primed, the blood was recirculated continuously again through the two Affinity reservoirs, ensuring all 12 circuits contained the same physiologic blood before beginning the experiment. The blood was corrected for pH, pCO_2, and pO_2, such that all blood gas values were within the normal physiologic range. A sample of blood was withdrawn and served as the baseline for plasma free hemoglobin (PFH), morphine sulfate, and fentanyl concentrations. After the baseline sample, all circuits were separated from the two central reservoirs and connected to a 200-mL sterile autologous blood collection bag so 12 individual circuits now existed (Figure 1). Once separated, each pump and circuit had a blood flow rate of 300 mL/min, and recirculation remained constant throughout the experiment. A fentanyl [100 μg/70 mL blood; dosing for general anesthesia is 50–150 μg/kg; 2005 American Hospital Formulary Service (AHFS) drug information] bolus was added to two circuits containing the Quadrox D oxygenator, two circuits containing the Baby Rx oxygenator, and two circuits without an oxygenator. A morphine sulfate (100 μg morphine/70 mL blood; dosing is 5–20 mg every 4 hours; 2005 AHFS drug information) bolus was added to two circuits containing the Quadrox D oxygenator, two circuits containing the Baby Rx oxygenator, and two circuits without an oxygenator. Samples were drawn at 5 minutes and at 2 and 6 hours for analysis. Analysis by high-performance liquid chromatography (HPLC) was performed at NMS Labs (Willow Grove, PA) to determine the concentration of drug remaining in the samples at the various time intervals. Knowing the initial quantity, we subtracted the quantity determined by HPLC, which revealed the amount of drug lost to the circuit or circuit plus oxygenator.

PFH analysis was performed with the Plasma Low/Hb photometer (Hemocue, Lake Forest, CA) at baseline and at 2 and 6 hours.

The average drug levels at different times, for different circuits and for the two drugs, were compared using univariant analysis of variance (SPSS 15.0; Statistical Software, Chicago, IL). Specific drug levels at specific times were compared using the Bonferroni method. Significance was set at 0.05.

RESULTS

Our evaluation showed an average of an 80% loss of fentanyl to the tubing at 120 minutes, and an average loss of 40% of morphine at 5 minutes (Figures 2 and 3). These results were similar ($p < .0001$) among all three circuit configurations. Fentanyl in our study was lost at a greater rate to circuits containing oxygenators, with the greatest loss to circuits containing the Quadrox D type oxygenators (loss = 86%). However, the majority of the drug was lost to the polyvinylchloride (PVC) tubing, with an average additional 5% lost to the oxygenators.

PFH levels increased in all circuits after the sedatives were added. However, there was a significant ($p < .0001$) increase in the circuits containing fentanyl, with the most significant increase within circuits containing fentanyl and the Quadrox D oxygenator (Table 1).

DISCUSSION

To our knowledge, morphine sulfate and fentanyl adsorption rates to either the safeline-coated Quadrox D with its 1.8-m^2 polymethylpentene surface area and maximum blood flow of 7 L/min or the *X*-coated Baby Rx with its 0.5-m^2 surface area and maximum blood flow of 1.5 L/min have not been measured. We therefore conducted this experiment to determine the amount of these two common sedatives lost to the surface of an ECLS circuit, and more specifically, to determine whether the majority of the medication was lost to the PVC tubing or to one of the two oxygenator surfaces.

Prior studies have determined in similar experiments that the majority of morphine sulfate was lost to the PVC tubing; the main difference between our study and previous work was the silicone oxygenator in past studies vs. the Maquet polymethylpentene and the Terumo *X*-Coated hollow fiber oxygenators in our study (6).

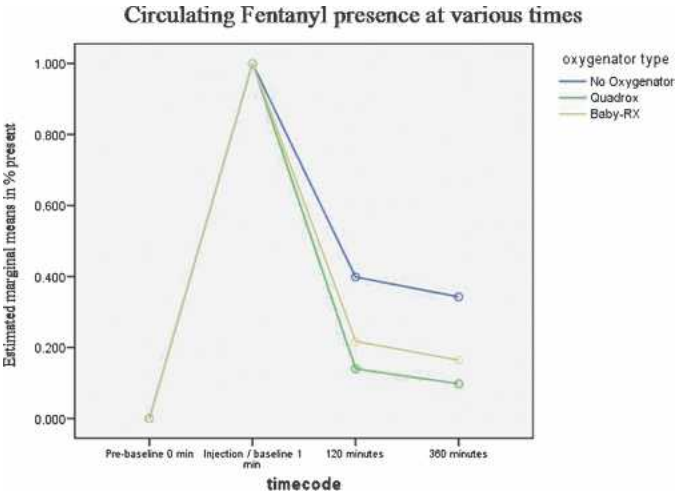

Figure 2. Fentanyl loss to the ECLS circuits.

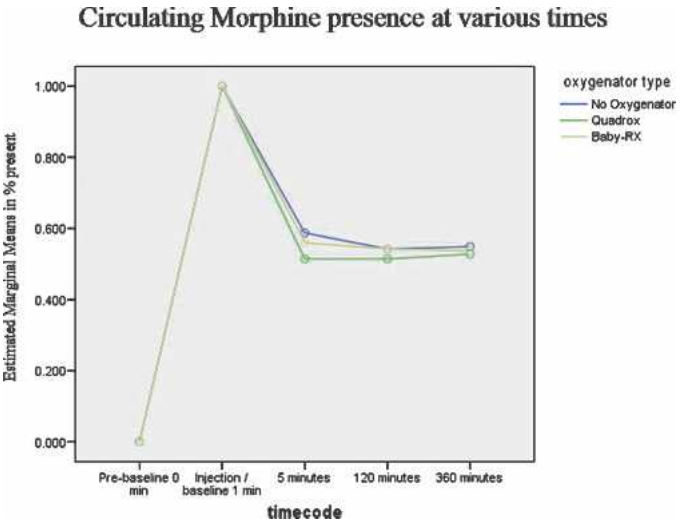

Figure 3. Morphine loss to the ECLS circuits.

Table 1. PFH levels.

Time	Drug	Oxygenator	PFH (mg/dL)
Baseline	Morphine	None	45 ± 0
		Quadrox	45 ± 0
		Baby Rx	45 ± 0
	Fentanyl	None	45 ± 0
		Quadrox	45 ± 0
		Baby Rx	45 ± 0
120 minutes	Morphine	None	73 ± 15
		Quadrox	69 ± 4
		Baby Rx	70 ± 4
	Fentanyl	None	192 ± 51
		Quadrox	261 ± 126
		Baby Rx	194 ± 34
360 minutes	Morphine	None	90 ± 15
		Quadrox	73 ± 1
		Baby Rx	77 ± 8
	Fentanyl	None	195 ± 42
		Quadrox	262 ± 125
		Baby Rx	200 ± 31

PFH is the mean ± SD.
For all oxygenator types including no oxygenator, the mean PFH levels were significantly greater for fentanyl compared with morphine ($p \leq 0.001$) at 120 and 360 minutes. At any given time, there was no significant difference between oxygenators tested, and there was no significant difference between 120 and 360 minutes for either oxygenator or drug tested.

In this in vitro experiment, we determined that the majority of morphine sulfate was indeed lost to the PVC tubing. We also could not determine a statistical difference among oxygenators, potentially because of the drug's high affinity to the PVC tubing. We additionally determined that fentanyl was lost at a greater rate than morphine within the ECLS circuit, with the greatest loss in circuits containing the Quadrox D style oxygenator.

While this experiment was lacking other contributors to drug loss one should always keep in mind the role of the patient's rate of drug excretion, and hemofiltration, if used, as they contribute to changes in circulating drug concentrations (9).

Likewise, the PFH levels associated with these drugs plus oxygenator combinations have not been reported, but in this study, it was quite evident that fentanyl generated a significantly larger amount of PFH than did morphine (Table 1). In light of fentanyl's increased affinity for PVC tubing and its apparent connection to increased PFH within the ECLS circuit, it seems that morphine may be a better sedative for use in the ECLS circuit at this time.

Further experiments with the new hollow fiber oxygenators, the variety of coated PVC tubing types, and new sedative agents need to be conducted. These experiments are difficult to accomplish because of component cost, specific HPLC testing availability for these new medications, and time needed to conduct the experiment.

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