

In Vitro Variability in Fentanyl Absorption by Different Membrane Oxygenators

David A. Rosen, MD, Kathleen R. Rosen, MD, and Daniel L. Silvasi, MD

The membrane oxygenator has replaced the bubble oxygenator in a wide variety of clinical settings. The membrane oxygenators now manufactured can be grouped into three categories based on composition and design: (1) silicone with a true membrane structure; (2) polypropylene with a microporous sheet; and (3) polypropylene with a microtubular structure. The capacity for fentanyl uptake by membrane oxygenators from these three categories was studied in vitro. Representative membrane samples were incubated in solutions containing tritiated fentanyl in Normosol-R (Abbott, North Chicago, IL) with pH adjusted to 7.4 at 37°C. Fentanyl analysis was performed using liquid scintillation and radioimmunoassay techniques. The uptake of fentanyl at various concentrations (340 to 10 ng/mL) was studied. The SciMed (type 1; SciMed, Minneapolis, MN) membrane showed the greatest capacity for fentanyl uptake at all concentrations. The SciMed oxygenator

was capable of binding 130 ng fentanyl/cm² membrane. When presented with a smaller concentration (≤ 20 ng/mL) of fentanyl, the membrane was able to extract all available fentanyl from solution. All of the microporous polypropylene oxygenators (types 2 and 3) absorbed significantly less fentanyl than did the SciMed brand. When exposed to 10 or 20 ng/mL, the Shiley and Omnis brands (type 2) absorbed 0.1 and 0.4 ng/cm², respectively. Using the higher fentanyl concentrations (≥ 200 ng/mL) uptake by the Omnis membrane was 11 ng/cm² compared with only 2 ng/cm² by the Shiley. The Bentley BCM 7 and Terumo Capiox II 08 microtubular microporous membranes (type 3) did not show absorption of fentanyl using isolated or intact membrane models. It is concluded that oxygenators of different design and/or composition have different capacities for fentanyl uptake.

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ALTERATIONS IN plasma fentanyl levels with the initiation of cardiopulmonary bypass (CPB) have been appreciated for the past decade.¹ Previous clinical studies describe decreases in plasma fentanyl concentrations ranging from 20% to 75% during CPB.¹⁻⁷ Many early reports explain the change in fentanyl concentration as a result of hemodilution.¹⁻³ However, other investigators have reported a decrease in fentanyl concentration in excess of that expected by dilution alone.⁴⁻⁶ Furthermore, laboratory studies report a loss of fentanyl from the isolated circulating CPB circuit used in vitro.^{5,7,8}

Despite widespread recognition of the alteration of fentanyl pharmacokinetics by CPB, there is a great quantitative variation in the data available from previous clinical reports. Many important physiological variables were not controlled in these clinical studies, including temper-

ature, pH, protein content, fentanyl dose, and delivery regimen, all of which have the potential to modify fentanyl pharmacokinetics. The types of CPB circuits in these reports were, likewise, not uniform. In many studies, the type and brand of CPB equipment was not stated.^{2,3,6,9} A bubble oxygenator was used in three clinical studies^{1,4,10} and in one in vitro study⁷; however, the oxygenator manufacturer was the same in only two of these reports.^{7,10} Koren et al⁵ used a membrane oxygenator in both the in vivo and in vitro phases of their study. The oxygenator has been noted to be the major site of fentanyl uptake by the CPB circuit^{5,7,8,11} for both membrane and bubble oxygenators. Differences in CPB circuitry, specifically the oxygenator, may be responsible for a large portion of the variability in previous clinical studies. The purpose of this study was to compare five different membrane oxygenators in vitro under controlled conditions for fentanyl uptake using a previously validated technique.

From the Department of Anesthesiology, University of Michigan Medical Center, C.S. Mott Children's Hospital, Ann Arbor.

Supported by a grant from Janssen Pharmaceutica, Inc, Piscataway, NJ.

Address reprint requests to David A. Rosen, MD, Dept of Anesthesiology, C.S. Mott Children's Hospital, University of Michigan Medical Center, Ann Arbor, MI 48109.

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MATERIALS AND METHODS

Five different membranes were studied: SciMed 3500-2A, Shiley M-2000 (Irvine, CA), Omnis LPM 50 (Deerfield, IL), Bentley BCM 7 (Irvine, CA), and Terumo Capiox II 08 (Tokyo, Japan). The SciMed, Shiley, and Omnis all have a sheet structure, whereas the Bentley and Terumo have a microtubular structure (Table 1). Fentanyl analysis in the isolated membrane studies was performed by liquid scintillation counting in the manner previously described.⁸ Radioim-

Table 1. Structure and Composition of Membranes Studied

Model	Structure	Composition
SciMed 3500-2A	True Membrane	Silicone rubber Dacron-impregnated
Shiley M-2000	Microporous sheet Single ply	Polypropylene
Omnis LPM-50	Microporous sheet Double ply	Polypropylene
Terumo Capiox II	Microporous Microtubular	Polypropylene
Bentley BCM-7	Microporous Microtubular	Polypropylene

munoassay (RIA) performed by Analytical Technologies (Tempe, AZ) was performed to follow fentanyl concentrations in the intact circuit studies. In prior studies of a sheet membrane oxygenator,⁸ the characteristics of fentanyl uptake in the isolated circuit have been shown to correlate with uptake in the intact circuit. Therefore, only the microtubular membranes were studied in the intact circuit in the present study. All experiments were performed at 22°C.

Isolated Sheet Membrane Studies

The intact sheet structure membranes were dissected to expose the membrane material. Thirty-two 1 × 1-cm squares of the membrane were randomly obtained from the three oxygenators with a sheet structure. Each membrane sample was weighed before exposure to fentanyl. Using the membrane density supplied by the manufacturer, the surface area was calculated. A balanced salt solution (Normosol-R, Abbott Laboratories, North Chicago, IL) containing tritiated fentanyl was prepared, with the pH adjusted to 7.4, at 37°C; the solution had a total fentanyl concentration of 340 ng/mL. For the three oxygenators with a sheet structure, 1 mL of the fentanyl solution was then placed in each of 96 test tubes. A single membrane square was added to each test tube. Two membrane samples of each oxygenator brand were removed from the solution at each sample time. A sample pair was removed immediately after immersion, and then every 15 minutes for 3.5 hours. After removal from the solution, the membrane squares were rinsed with distilled water and dried. The experiment was performed at a room temperature of 22°C. The experiment was then performed with decreasing fentanyl concentrations of 255, 200, 20, and 10 ng/mL.

Intact Circuit Microtubular Membrane Studies

A circuit was assembled for each oxygenator using a bubble trap, polyvinyl chloride (PVC) tubing, and the membrane oxygenator. The CPB circuit was primed with Normosol-R, with pH adjusted to 7.4, at 37°C. The priming volume in the Terumo Capiox II 08 CPB circuit was 225 mL. Flow was maintained at 0.8 L/min. The Bentley BCM 7 CPB circuit circulating volume was 315 mL, and flow was maintained at 2 L/min. A control sample was obtained, and then 1

mg of fentanyl was added to the circulating prime. Samples for fentanyl analysis were then obtained at 5, 10, 20, 30, 40, 50, and 60 minutes after fentanyl exposure.

Isolated Microtubular Membrane Studies

One membrane of each brand was dissected to expose the membrane material. Two random samples of microtubules, approximating 1 cm² of surface area, were obtained from each membrane. Three milliliters of tritiated fentanyl in Normosol-R solution, adjusted to pH 7.4, at 37°C, was placed into each of 4 tubes. The starting fentanyl concentration was 200 ng/mL. Control samples were obtained before the addition of the membrane material. The microtubules were then added, and the tubes were agitated. Ten-microliter aliquots of solution were removed for fentanyl analysis every 15 minutes for 2.5 hours. This experiment was performed at 22°C.

RESULTS

The five membranes tested showed a remarkably different capacity for fentanyl uptake. The fentanyl concentrations greater than 200 ng/mL were all adequate to produce saturation of all 5 brands. There was no difference in fentanyl uptake by any of the membranes as a function of fentanyl concentration in this range (200 to 340 ng/mL). The ratio of fentanyl uptake for the membranes with a sheet structure was approximately 100:10:1 for the SciMed, Omnis, and Shiley membranes, respectively (Table 2). As in previous studies,¹⁰ the SciMed membrane became saturated at 130 ng/cm². The Shiley membrane showed the least affinity for fentanyl; less than 1% of the fentanyl in solution was absorbed by this brand. The degree of fentanyl uptake by the Omnis membrane was between those of the other two models but much closer to that of the Shiley membrane.

Using fentanyl concentrations more like those achieved in clinical practice (10 and 20 ng/mL), the SciMed membrane was able to extract all the fentanyl available from the solution. The Shiley membrane absorbed only 0.1 ng/cm² in either the 10 or 20 ng/mL solutions. Fentanyl uptake by the Omnis membrane was also reduced to only 0.4 ng/cm².

Table 2. Fentanyl Uptake for Different Membranes

Fentanyl Concentration (ng/mL)	Maximum Fentanyl Uptake (ng/cm ²)				
	SciMed	Shiley	Omnis	Bentley	Terumo
10	10	0.1	0.4	—	—
20	20	0.1	0.4	—	—
≥200	130	2	11	0	0

For the membranes with the microtubular structure (Bentley and Terumo), no uptake of fentanyl by the membrane could be shown in either the intact or isolated membrane at any concentration.

DISCUSSION

The present data show a marked variability in the capacity for fentanyl uptake by five different membrane oxygenators in vitro. In the absence of hemodilution and other clinically variable parameters such as pH, protein content, duration of prebypass, hematocrit, drug interactions, fentanyl dose, patient pharmacokinetics, surgery and anesthesia, the affinity of different apparatuses alone for fentanyl can be compared. The tremendous capacity for fentanyl uptake by the SciMed brand was again shown to be 130 ng/cm² as in a previous study.⁸ Although the two polypropylene microporous membrane oxygenators showed much less affinity for this opiate, the microtubular membranes did not bind any fentanyl under the experimental conditions. Clinically, this could be extrapolated to adult membranes: SciMed model 3500-2A, with a surface area of 3.5 m², would bind 4.55 mg; the Omnis, with a surface area of 3 m², would bind 0.33 mg; and the Shiley, with a surface area of 2 m², would bind 0.04 mg.

Fentanyl pharmacokinetics are modified by CPB. Early reports explained the precipitous decrease in plasma fentanyl concentrations by hemodilution or sequestration in the lung.¹⁻³ More recently, several studies have documented the concept of direct fentanyl uptake by the oxygenator of the cardiopulmonary bypass circuit.^{5,7,11} Most early studies of fentanyl uptake and CPB equipment used bubble oxygenators or did not state circuit composition. Application of fentanyl pharmacokinetic data derived from bubble oxygenators to these new CPB membrane systems may not be valid. The newer membrane oxygenators are becoming more popular in clinical practice for a variety of reasons: efficiency of gas exchange; less damage to blood components; size; integration of heat exchangers; and durability. Clinical studies suggest that membrane oxygenators can produce a much greater alteration (75% reduction in circulating fentanyl^{5,6}) in plasma level than the bubble oxygenator (30% to

50% reduction in circulating fentanyl).^{1,2,4,10} One study using a membrane oxygenator noted fentanyl levels below the level associated with awakening.⁶

This report suggests that the differences in fentanyl uptake may be explained by variations in CPB circuit and oxygenator structure and composition. The membranes studied are representative of the three major designs in modern membrane oxygenators. The SciMed membrane oxygenator is a solid membrane sheet without pores. Membranes in the other four oxygenators have a microporous structure in the form of either a sheet or microtubules. Membrane materials also vary. The SciMed oxygenator is made of a silicone rubber sheet impregnated with Dacron fibers. The Shiley, Omnis, Bentley, and Terumo membrane oxygenators are made of polypropylene. The Omnis membrane has a double layer of polypropylene, whereas the Shiley membrane has a single layer. This may account for the differences in absorptive capacities between the two. The microtubular design has recently become available from Bentley and Terumo. The advantage of the microtubular design is the improved efficiency of gas exchange and small priming volumes compared with the other microporous oxygenators.

In vitro, both siliconized tubing and silicone-containing oxygenators have been shown to bind fentanyl.^{5,8} Even the SciMed oxygenator's silicone watertight wrapper (which has no role in gas exchange) can bind fentanyl.⁸ It is hypothesized that the silicone is responsible for greater fentanyl affinity in the SciMed oxygenator and that the silicone products may have a large affinity for other lipophilic anesthetics. Silicone is also frequently used in the defoamer and may be the major site of fentanyl uptake in bubble oxygenators. One in vitro study using a bubble oxygenator described a larger decrease in fentanyl concentration than previous reports of bubble oxygenators,⁷ but the circuit was assembled using silicone tubing. PVC tubing has been shown to be inert to fentanyl.^{5,6}

The SciMed's tremendous uptake capacity for fentanyl poses the greatest potential for the development of subtherapeutic (<20 ng/mL) fentanyl concentrations. Despite a 10- to 100-fold increase in fentanyl-absorptive capacities

compared with the polypropylene designs, there are advantages to the silicone sheet design. Only the SciMed membrane oxygenator has been approved for such long-term use as extracorporeal membrane oxygenation. The microporous designs are frequently associated with decreased efficiency (leaking or plugging) after prolonged usage. The SciMed membrane oxygenator is also available in a greater variety of sizes so that the patient's oxygen requirement may be more closely matched with the membrane surface area and circuit size, thereby allowing the use of a minimal priming volume.

In summary, this study has shown the differential capacity for absorption of fentanyl by five different membrane oxygenators. The absorptive capacity seems to be related to its composition and structural design. The silicone SciMed has a much larger affinity for fentanyl both at clinical concentrations and at concentrations above that required for membrane saturation. The capacity for fentanyl uptake by the polypropylene membranes was minimal (0.5% to 4%) at clinical fentanyl concentrations. At very high fentanyl levels (200 to 340 mg/mL), the Omnis

showed a larger capacity for fentanyl uptake than the Shiley. However, the fentanyl uptake was still only 11 ng/cm². The two microporous microtubular membranes seem to be practically inert to fentanyl. Any decrease in fentanyl levels when these oxygenators are placed in a nonsilicone circuit should be explainable on the basis of dilution alone.

Further investigation is necessary to examine the interactions of the oxygenators with other anesthetic agents. There is a potential for any lipophilic drug to be taken up by silicone-containing oxygenators. Following clarification of the *in vitro* characteristics, further studies must be performed to determine any modification by clinically relevant variables in the fentanyl-membrane interaction.

In conclusion, there is a need for greater awareness about CPB circuit composition. This study has identified one variable, fentanyl uptake, that is significantly altered as a function of the apparatus alone. Most important, CPB circuits must be individually examined for drug interactions.

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