Original Article

Hemofiltration: Determinants of Drug Loss and Concentration

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ABSTRACT

Ultrafiltration has proven to be an effective method of reducing post-cardiopulmonary bypass edema and the inflammatory response associated with activation of the complement cascade. Recently, a modified ultrafiltration process has been developed which allows further hemoconcentration after weaning from bypass. Both of these procedures can have an effect upon the concentrations of many of the pharmaceutical agents being used either pre- or peri-operatively. Based upon work done by other investigators in the field of dialysis, we have developed sieving coefficients for many cardiovascular drugs in order to provide an estimation of their loss during extended periods of hemofiltration. Our study utilized the pharmacological and physical characteristics for volume of distribution and protein binding to determine the movement of drugs through a hemofilter. Our results demonstrated that concentrations of certain drugs used during open heart surgery may be significantly increased or decreased with the use of hemofiltration techniques.

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INTRODUCTION

In recent years, hemofilters have become a common addition to extracorporeal circuits. While many studies have been conducted regarding the beneficial effects of ultrafiltration, studies have not been reported regarding the effects on drug transport through the membrane. Depending upon its permeability, a drug may be eliminated or concentrated during hemofiltration. We have sought to characterize these movements mathematically using the physical and distribution characteristics of drugs used during open heart surgical procedures. Although our methods were originally developed for dialysis, we applied the same principles to characterize hemofiltration techniques.

ULTRAFILTRATION

The practice of ultrafiltration was begun by Peter Kramer in 1977 as an alternative to dialysis therapy in patients with renal failure. Without the use of external pumps, the patient's own blood pressure was the driving force to push blood through a filter and generate the hydrostatic pressure necessary for the ultrafiltrate to be passed through the membrane. The driving force was enhanced by a slight negative pressure exerted by the draining ultrafiltrate (1,2). This method was found to be beneficial to some patients who could not tolerate dialysis and for whom diuretics did not work (3). Another advantage of this technique was the avoidance of hypotensive episodes which had been known to occur in systems which were pump-driven. Since the driving force is the patient's blood pressure, as the pressure drops, so does filtration (2).

Magilligan and Oyama described the use of ultrafiltration during cardiopulmonary bypass (CPB) operations in 1984 (4). They stated that, although the use of crystalloid priming solutions has its advantages, patients showed more signs of edema postoperatively. While most patients were able to tolerate this extra fluid and remove it through excretion, some suffered from organ dysfunction as a result of the fluid overload. The goal of Magilligan's study was to remove a volume of water equivalent to that of the prime solutions as well as any fluids given during CPB (4). This and further studies proved the efficacy of ultrafiltration as an anti-edemic measure during CPB, especially in the decrease of extravascular lung water (4,5,6).

In addition to the reduction of edema, other benefits of ultrafiltration have been described, including elevation of blood pressure, removal of inflammatory mediators, raised hematocrit, improved hemostasis, and improved left ventricular function in sepsis (6,7,8,9).

Further modifications to the ultrafiltration procedure were made in 1991 by Naik and colleagues (10). They found that in conventional ultrafiltration, the amount of fluid which could be removed was limited by the level in the venous reservoir. In many cases, especially with pediatric patients, there was not sufficient volume in the reservoir to bring the hematocrit up to a desired level through ultrafiltration. Their technique, known as modified ultrafiltration (MUF) was executed for approximately 10 minutes after weaning from bypass. Blood was pumped at a low rate from the aortic cannula through a hemofilter and then back to the right atrium. Volume was kept constant by replacing lost ultrafiltrate with pump blood delivered via the main pump head through the hemofilter and into the right atrium. In this manner, crystalloid could be used to flush the system, allowing it to remain primed in case of an emergency while permitting salvage of almost all the patient's blood (10,11).

Research has shown that MUF allows a hematocrit of 40% to be easily reached. This is due, in part, to the ability to concentrate not only the remaining pump blood, but also the patient's blood. As a result, more extravascular water is removed, in addition to high levels of inflammatory mediators (6,10,12). A reconfiguration of the MUF system was proposed by Groom, et al. in 1994. This took advantage of the blood cardioplegia system, thereby allowing the use of the bubble trap as a safeguard (13).

With the degree of hemoconcentration possible through MUF, the use of homologous blood products after CPB can be greatly reduced. Additionally, the potential now exists for the use of a bloodless prime solution in pediatric cases, further decreasing exposure to homologous blood.

DRUG REMOVAL THROUGH HEMOFILTRATION

While conventional dialysis removes solutes and electrolytes according to a gradient established by the composition of the dialysate solution, ultrafiltration theoretically removes plasma water and solutes in the same concentration as they are found in the blood. As a result of this, significant quantities of drugs may be removed or concentrated without the knowledge of the anesthesiologist or perfusionist. It is important to have an idea of which drugs are likely to change in concentration during extended periods of ultrafiltration; this is what we sought to characterize mathematically.

Although the main determinant of passage through a membrane is the molecular weight (size) of the drug, the majority of drugs used in CPB have molecular weights well below the pore size (55,000 - 65,000 Daltons) of the hemofilters in use today. Because of this, the most essential factor to be considered is the percentage of drug which is bound to large, non-filterable, plasma proteins. We have used the physical properties of selected drugs to determine their delivery to the hemofilter and their passage through it.

MATERIALS & METHODS

The sieving coefficients were developed by use of the pharmacokinetic principles described below.

VOLUME OF DISTRIBUTION (V_d):

When a drug is introduced into the body, the entire dose is not readily available in the plasma as a percentage of it will bind to the tissues. Since only the proportion of the drug which is free has a pharmaceutical effect, this must be taken into account when measuring plasma concentrations (14). Volume of distribution is defined as:

$$V_d = \frac{\text{Concentration of drug in the body (mg/kg)}}{\text{Concentration of drug in plasma (mg/L)}} \quad \text{(Eq. 1)}$$

Therefore, when given a value of V_d and the administered dose of the drug, the concentration of the drug which will be available in the plasma can be determined (15).

SIEVING COEFFICIENT (S):

The sieving coeficient of a drug defines its movement across a membrane. In 1975, Colton and colleagues developed a complex equation to describe this property (16). They were able to abbreviate the formula to:

$$S = \frac{2 \times \text{Drug concentration in ultrafiltrate}}{\text{Filter inlet concentration} + \text{Filter outlet concentration}} \quad \text{(Eq. 2)}$$

Golper and Saad later proved the formula could be abbreviated to:

$$S = \frac{\text{Drug concentration in ultrafiltrate}}{\text{Drug concentration at filter inlet}} \quad \text{(Eq. 3)}$$

without loss of accuracy, thus preventing the need for samples to be collected at the filter outlet (16). As the value of S approaches 1.0, its ability to diffuse through the membrane increases. An S value of 1.0 indicates a solute which will freely diffuse through a membrane at the same concentration found in the plasma (15).

PROTEIN BINDING:

Drugs are only pharmacologically active if free in the plasma. Protein binding effectively removes a percentage of the drug from therapeutic use. Additionally, protein binding prevents drugs from being passed through a hemofilter. Therefore, when considering the flux of solute through a membrane, one must take into account what percentage of the drug is bound to protein and thereby unfilterable (16). Plasma protein binding is influenced by a host of factors including pH, drug concentration, protein concentration, heparin, and free fatty acids (1). Free fatty acids have been found to displace certain drugs from proteins while enhancing the binding of others. Heparin has an indirect effect upon protein binding via activation of lipoprotein lipase which, in turn, causes an increase in the concentration of free fatty acids (15).

It is not possible to take all of these factors into account when predicting sieving coefficients based upon standard values for protein binding and volume of distribution. This is especially true since a variance can be found in protein binding values based upon the method used to determine binding and the age and/or disease state of the individual (17,18). A valid estimate can be obtained, though, by use of the method described by Golper and associates in 1985 (15). This method assumes the drug has reached a steady-state concentration and the drug has known volume of distribution and protein binding values. Thus, to predict a seiving coefficient, the following procedure was used:

1. Based upon the volume of distribution and the dose of the drug, determine the concentration of the drug in the plasma (Eq. 1).

2. Multiply the concentration of the drug in the plasma by the percentage of the drug which is not protein bound. The product is the concentration of the drug in the plasma water. This value is equivalent to the concentration of the drug at the filter inlet (denominator of Eq. 3).

3. In order to find the drug concentration in the ultrafiltrate, multiply the concentration of the drug at the filter inlet (as determined in step 2) by the percentage of the drug which is not protein bound. This product will become the numerator of Eq. 3.

4. Divide through equation 3 to obtain a prediction of the sieving coefficient.

RESULTS

Table 1 shows the results obtained for a variety of drugs which may be used either pre- or peri-operatively in patients presenting for CPB surgery. The sieving coefficients were determined by use of the previously described method, based upon standard values of protein binding, volume of distribution, and realistic drug doses for a 70kg individual.

Although the values we have found are by no means precise measures of drug movement, they do provide a general indication of what will occur during extended periods of ultrafiltration. The drugs most likely to be lost in appreciable amounts have sieving coefficients nearest to 1.0. From the values developed in Table 1, aprotinin, bretylium, digoxin, and dobutamine appear most likely to be significantly reduced in concentration during hemofiltration.

Modified ultrafiltration, as stated earlier, is conducted post-CPB and is a method of removing large amounts of ultrafiltrate in a short time period. It is during this period that many patients receive inotropic support, frequently dobutamine. Since dobutamine has a theoretical sieving coefficient of 1.0, the dosage seen by the patient could be lower than expected when it is administered during MUF.

The reverse of this would be expected with many of the

anesthetic agents used during CPB. Fentanyl, midazolam, pancuronium, and vecuronium are all highly protein bound and, as a result, have low sieving coefficients. Removal of excess water from the patient is a commonly used anti-edemic application of ultrafiltration. If volume is removed through the ultrafiltrate without subsequent replacement, the drugs which are not removed with the plasma water will become concentrated in the remaining blood volume. Therefore, it is possible to have higher, possibly harmful, concentrations of certain drugs present following a period of hemofiltration.

Table 1: Sieving coefficients for selected cardiovascular drugs

	PB (%)	V_d	PC	S
Ions:				
Ca^{++}	45	n/a	5.0 mEq/L	.55
K^{+}	0	n/a	4.4 mEq/L	1.0
Mg^{++}	0	n/a	2.0 mEq/L	1.0
Drugs:				
Aprotinin	0	---	250 KIU/ml	1.0
Bretylium	6	8	.63 mg/L	.94
Digoxin	25	5.3	.0005 mg/L	.75
Diltiazem	83	4	.215 mg/L	.17
Dobutamine	0	.20	.025 mg/L	1.0
Fentanyl	71	2.25	.016 mg/L	.28
Furosemide	95	.14	6.14 mg/L	.05
Heparin	80	.08	4821.25 U/L	.20
Lidocaine	63	1.75	1.63 mg/L	.37
Midazolam	95	1.1	.18 mg/L	.06
Pancuronium	87	.25	.20 mg/L	.13
Vecuronium	70	.21	.38 mg/L	.30
Verapamil	90	4.5	.19 mg/L	.10

PB = Percent protein bound; V_d = Volume of distribution; PC = Plasma concentration; S = Sieving coefficient. All values obtained for PB, V_d from references 29-33.

DISCUSSION

Although this method provided a reasonably accurate prediction of the sieving coefficient, many other factors which can only be controlled experimentally will influence the transport of a drug across a hemofilter (14,15,20). Golper and colleagues have mentioned a number of the determinants which also play a part in drug movement. A brief summary of these includes:

Drug/membrane interaction
Drug charge
Drug size (if large enough to approach pore size)
Protein concentration (influencing both drug binding and oncotic pressure)
Ultrafiltrate line suction
Blood flow
Viscosity of blood
Length and diameter of tubing
Venous resistance
Filter surface area and properties

Even within the class of synthetic filter materials, sieving coefficients differ based upon whether the membrane is polyacrylonitrile or polysulfone (19). Additionally, the same type of material can yield different sieving coefficients in different hemofilter models (21). Membrane properties also influence ionic movement. Small, non protein-bound ions such as sodium, chloride, and bicarbonate which are assumed to have sieving coefficients of 1.0 actually have values greater or less than 1.0 based upon their charge (19). Finally, interaction of the hemofilter with blood will cause a layer of protein to build up on the membrane surface. The degree of deposition and its effects upon filtration rate also differ with membrane composition (22).

Since the hemofilter alone is able to introduce this much variability without even taking into account the other determinants listed above, it is easy to understand why theoretical sieving coefficients do not always agree with those found in a clinical setting. Quantitatively describing these characteristics is a subject which has not been explored to great lengths, especially in the relatively new field of ultrafiltration during CPB. The majority of the available literature deals with hemodialysis and the membranes used for such procedures. Interactions of drugs with ultrafiltration membranes and the loss of drugs through the ultrafiltrate are subjects requiring further research, especially in a clinical setting.

COMPLEMENT REMOVAL THROUGH HEMOFILTRATION

An area which has been the subject of current perfusion research is the reduction of the systemic inflammatory response by use of hemofiltration. The primary mediator of this inflammatory response is activated complement.

Complement activation is an important component of the humoral immune system. Activation of the complement cascade

causes leucocyte activation, opsonization (rendering of bacterial cells subject to phagocytosis), and neutralization of pathogens.

As with other defense systems of the body, activation of complement may occur during CPB, leading to post-bypass morbidity. Split products C3a, C4a, and C5a which are known anaphylatoxins are formed upon activation of the complement cascade. They have been found to cause bronchoconstriction, pulmonary vasoconstriction, histamine release, platelet and leucocyte aggregation, and increased vascular permeability, leading to a post-bypass systemic inflammatory response (23).

Much research has been conducted in an effort to attenuate either the activation of the inflammatory response or the effects seen upon activation. Some of the most promising results have come from studies using ultrafiltration or MUF to remove inflammatory mediators such as C3a, C4a, C5a, and Interleukin-8 (6,7,9,24). The utilization of MUF requires the patient to have been weaned from bypass, yet there is some evidence that the greatest release of complement and cytokines occurs during the rewarming phase (7,25). For this reason, it has been proposed that ultrafiltration also be used throughout the entire rewarming period, whether or not MUF is used after termination of bypass (9).

Due to the fact that C3a, C4a, and C5a have molecular weights of 8900, 8000, and 17000 Daltons respectively, it appears that all would be readily removed by a hemofilter with a pore size ranging from 55,000 to 65,000 Daltons (26). In the case of C5a, however, it is readily bound to neutrophils, preventing its filtration. Therefore, even with ultrafiltration, an inflammatory response may still be seen. Additionally, no data is available regarding the possible binding of cytokines and complement split products to proteins, thereby making them unfilterable. As a result, while ultrafiltration can surely play a role in attenuating the inflammatory response, it is unlikely to abolish it completely.

Finally, consideration must also be given to the biocompatibility of the hemofilter used. Studies have shown that membranes made of cellulose-based materials cause a much higher degree of complement activation than those composed of synthetic compounds such as polyacrylonitrile or polysulfone (4,27). Accordingly, most of the major suppliers of hemofilters (Minntech, Cobe, Amicon/Bard, Gambro, Bentley) use synthetic materials in their products (28).

SUMMARY

While ultrafiltration and modified ultrafiltration can play an important part in attenuating the inflammatory response seen after CPB in many patients, care must be taken during their use. A therapeutic dose of a drug, whether it is an anesthetic, antiarrhythmic, or even an ion such as calcium, may be reduced below the therapeutic level by extended periods of hemofiltration. Further research is necessary in order to determine precise clinical values for sieving coefficients as well as supplemental doses of drugs based upon the percentage removed during hemofiltration.

Through their work, Golper and Bennett have provided vital information regarding drug losses in dialysis. Similar experimentation must be done with hemofilters which are being used more and more frequently in CPB surgery. Without this knowledge, it is impossible for anyone to know what percentage of a drug dosage is actually seen by the patient.

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