TCP Transl Clin Pharmacol
2016;24(4):153-156
http://dx.doi.org/10.12793/tcp.2016.24.4.153

TUTORIAL

Pitfalls in the calculation of hemodialysis clearance and in the assessment of dialysis efficacy

Arthur J. Atkinson, Jr.
Department of Pharmacology, Feinberg School of Medicine, Northwestern University Chicago, Illinois, USA
*Correspondence: Arthur J. Atkinson, Jr.; E-mail: art_atkinson@msn.com

Keywords
Hemodialysis
Hemodialytic clearance
Drug toxicity
Drug replacement doses
Recovery method
A-V Difference method

pISSN: 2289-0882
eISSN: 2383-5427

The therapeutic technique of hemodialysis and the concept of clearance have both followed a long but instructive course of development. In addition, it recently has been shown that physiological changes occurring during hemodialysis have important clinical consequences both in the treatment of drug toxicity and in the selection of appropriate replacement doses of therapeutic drugs. Two major approaches for calculating hemodialysis clearance are currently used. The first approach, termed the *recovery method* is the "gold standard" that is recommended for use in the current US FDA draft guidance on the conduct of pharmacokinetic studies in patients with impaired renal function. The second approach, termed the *A-V difference* method, is used more commonly. Unfortunately, this method results in erroneous plasma clearance estimates when improper values for dialyzer flow are chosen. This constitutes a major pitfall that should be avoided in future studies.

Early Experience with Hemodialysis

John Jacob Able can be credited with pioneering the technique of hemodialysis. In his landmark 1914 paper, he and his colleagues described the construction of the dialysis apparatus, the preparation of the necessary anticoagulant, and the results of his use of the technique to remove salicylate that he had administered to dogs.[1] He assessed the efficacy of this procedure by measuring the amount of salicylate actually recovered as a percentage of the administered dose and concluded that salicylate removal by hemodialysis was over several hours comparable to that eliminated in the urine of an unanesthetized dog that had also received an intravenous dose of salicylate. At this early stage, Able already envisioned that hemodialysis would prove clinically useful in "toxic states in which the eliminating organs, more especially the kidneys, are incapable of removing (toxic substances) from the body at an adequate rate".

Georg Haas can be credited with first evaluating hemodialysis in humans. His first studies in uremic patients involved only a 15-minute dialysis period but did demonstrate that indican, used as a marker, could be removed from 150 ml of blood.[2] As in Able's work hirudin, extracted and purified from leeches, was used as the anticoagulant but proved quite toxic. However, following the introduction of heparin, Haas carried out further studies with this new anticoagulant and demonstrated that hemodialysis could not only remove urea and other substances but could relieve uremic symptoms.[3] The efficacy of repeated dialysis sessions was limited and it has been speculated retrospectively that this reflected the inefficiency of the dialysis membranes that he used compared to cuprophane which only became available in 1937.[4]

The modern era of hemodialysis began in 1943 with the publication by Kolff and Berk of a case report that described the repeated hemodialysis of a 29-year-old uremic woman with chronic nephritis.[5] These authors employed a large-area cellophane dialysis membrane and were able to remove 24 to 40 gm of urea during each dialysis. The patient's blood urea nitrogen fell substantially and her uremic symptoms improved markedly. Unfortunately, vascular access problems terminated her therapy after 12 hemodialysis sessions. In a postscript, these authors describe two additional patients and dialysis time was reported in one so that the urea clearance achieved by the dialyzer can be estimated at about 74 ml/min, within the normal range of 60-100 ml/min/1.7 m^2. However, dialysis clearance was not actually calculated by any of these pioneering authors.

The Clearance Concept

The incorporation of clearance estimates in hemodialysis studies is a direct outgrowth of the earlier use of urea clearance to assess renal function. In 1916, Addis and Watanabe ligated the ureters of rabbits and reported its effect on renal function.[6] They calculated the following ratio from simultaneous measurements of blood urea concentrations and urea output in urine:

Copyright © 2016 Arthur J. Atkinson, Jr.
It is identical to the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/).
This paper meets the requirement of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z.39.48-1992 (Permanence of Paper).

$$\frac{\text{Gm. of urea in 1 hr's. urine}}{\text{Gm. of urea in 100 cc. of blood}} \quad (1)$$

However, it was only in 1928 that Möller et al. introduced both the term *clearance*,[7] defined et al. "the cubic centimeters of blood, the urea content of which is excreted in 1 minute", and the familiar equation for calculating it:

$$CL = \frac{U\,V}{B} \quad (2)$$

In this equation, B and U are the concentrations of urea in blood and urine, respectively, and V is the volume of urine secreted per minute. Both Equations 1 and 2 define *blood* rather than *plasma* clearances and can be categorized as *recovery clearances* in that their calculation requires actual measurement of the urea in urine over a specified period of time.

A second method for calculating clearance stems from the work of Adolf Fick who in 1870 calculated cardiac output by sampling blood from the right and left ventricles at the same time that pulmonary oxygen absorption or carbon dioxide[8] elimination was measured. For example in the case of oxygen, the following equation can be used to calculate cardiac output (Q) from the rate of oxygen absorption from the lungs (VO_2) and oxygen concentration in the right (CA), and left (CV) ventricles:

$$Q = \frac{VO_2}{(C_A - C_V)} \quad (3)$$

Conversely if flow rate is known, the rate of oxygen absorption of a substance can be calculated by simply rearranging Equation 3:

$$VO_2 = Q\,(C_A - C_V) \quad (4)$$

Equation 4 is equivalent to the numerator in Equation 2, so an alternate equation for calculating clearance is:

$$CL = \frac{Q\,(C_A - C_V)}{C_A} \quad (5)$$

This approach has been termed the *A - V difference method.* Plasma blood flow is usually chosen for Q when plasma clearance is calculated. As subsequently discussed, this can lead to significant errors in clearance estimates.

Assessment of Dialysis Efficiency

In the first dialysis machines, the dialysis bath fluid was continuously recirculated through the dialyzer so that during hemodialysis the concentration of dialyzable substances rose continuously in the bath fluid against which the patient's blood was being dialyzed. For this reason, Equation 5 needed to be modified to account for this decrease in efficiency and the concept of dialysance was introduced. Wolff et al. defined dialysance (D) by the following equation.[9]

$$D = \frac{Q\,(C_A - C_V)}{(C_A - C_D)} \quad (6)$$

The continuously increasing concentration of dialysate in the dialysis bath (C_D) reduces the concentration gradient between dialysate in blood en tering the dialysis cartridge and in the dialysis bath fluid. As a result the clearance of dialysate falls with time. However, the advent of single pass dialysis machines enhanced dialysis efficiency and enabled Equations 2 and 5 to be used to calculate dialysis clearance.

Hemodialysis of Drugs

Based on the demonstration by Able et al.[1] that salicylate was dialyzable, Doolan et al.[10] reported the first use of hemodialysis to treat a patient who had ingested a lethal dose of acetylsalicylic acid. Dialysis could be continued for only 1 hour and the amount of salicylate that could be removed was insufficient to prevent a fatal outcome. However, these investigators conducted additional studies in which they demonstrated that the percentage of an administered acetylsalicylic acid dose that could be removed from hemodialysis patients during 4 hours of hemodialysis was comparable to that excreted over 24 hours in the urine of healthy subjects. In addition, they were able to calculate the dialysance of salicylate from Equation 6.

Over the next 30 to 40 years, hemodialysis was increasingly employed to treat patients with drug overdose and data on drug clearance by hemodialysis was compiled. Extensive tables were published that not only listed the dialysis clearance of toxins but of many therapeutic drugs.[11,12] Criteria, including drug binding to plasma proteins and distribution volume, were established to assess the ability of hemodialysis to remove clinically significant amounts of a drug or toxin. Dialysis modifications like charcoal hemoperfusion were also introduced that could enhance removal of certain drugs.

Total clearance (CL_E) of substances during hemodialysis equals the sum of the existing renal clearance (CL_R), non-renal clearance (CL_{NR}), and dialysis clearance (CL_D):

$$CL_E = CL_R + CL_{NR} + CL_D \quad (7)$$

Levy[13] has proposed that CL_D needs to be >30% of CL_R + CL_{NR} in order to be quantitatively significant. However, a fair comparison requires that CL_D be calculated as a *plasma clearance* if the baseline values of CL_R and CL_{NR} are calculated as plasma clearances. Conversely, CL_D should be calculated as a *blood clearance* if the renal and nonrenal clearances are calculated as blood clearances.

Misconceptions and Errors in the Calculation of Dialysis Clearance

The recovery method provides the "gold standard" estimate of CL_D. and is recommended in the current US FDA guidance for conduct of pharmacokinetic studies in patients with impaired

renal function.[14] It is based on a restatement of Equation 2 so that:

$$CL_D = \frac{R}{\bar{A}\,\tau} \quad (8)$$

where R is the amount of drug recovered in the dialysis bath fluid, Ā is the average drug concentration in blood (CL_D = blood clearance) or plasma (CL_D = plasma clearance) entering the dialyzer, and τ is the dialysis time. Alternatively, the denominator can be calculated as AUC_A: the AUC of the drug concentration in plasma or blood that enters the dialyzer during the dialysis period.

However, there are inherent misunderstandings and difficulties in the use of Equation 5 to calculate CL_D by the A-V difference method. First of all, contrary to some authors either blood or plasma concentrations can be used to calculate (A-V)/A because it is a ratio that remains unchanged regardless of whether blood or plasma concentrations are used. However, a more significant error occurs when plasma flow through the dialyzer is used to calculate clearance. This is best understood by reference to Figure 1 that shows the four equations that are generally used in these calculations. The use of blood flow for calculating blood clearance does not pose any problem. However, the use of plasma flow for calculating plasma clearance can lead to erroneous results and is only valid for drugs that are completely excluded from erythrocytes. For example, if blood concentrations are greater than plasma concentrations, plasma clearance will be *greater* than blood clearance when calculated by the recovery method. So a value of Q_{EFF} greater than plasma flow is needed if the recovery and A-V difference methods of estimating plasma clearance are to agree.

Most drugs distribute into erythrocytes and in that location are accessible to dialysis. This can be examined *in vitro* by separately measuring drug concentrations in whole blood and plasma and then calculating the [RBC]/[P] ratio for each patient, where [RBC] is the drug concentration calculated to be in erythrocytes.[15] This result was used to calculate the *effective blood flow* (Q_{EFF}) through the dialyzer from the following equation:

$$Q_{EFF} = [(1 - Hct) + (RBC/P)\ Hct]\ Q_{MEAS} \quad (9)$$

where Hct is the patient's hematocrit and Q_{MEAS} is the measured blood flow through the dialyzer. In one study, Q_{MEAS} averaged 195 mL/min, whereas Q_{EFF} averaged 217 mL/min.[15] Because dialysis clearance was primarily calculated as a recovery clearance, Equation 5 could be rearranged to provide a third estimate of 223 mL/min for dialyzer blood flow (Q_{PK}) that was internally consistent with the overall pharmacokinetic analysis. So if Q_{MEAS} had been used to calculate dialysis clearance from Equation 5, a 14% underestimate would have been obtained. Use of Q_{EFF} in this equation would have come closer to the benchmark value but would still be somewhat of an underestimate. An even greater error would have been made if Q_{MEAS} had been used to calculate plasma clearance. This would have given a value of 148 mL/min for Q_{PLASMA} and resulted in a 33% underestimate of CL_D. Lee et al. subsequently obtained similar results in a study of the hemodialysis clearance of ethambutol.[16] In this case, CL_D calculated from Equation 5 using plasma flow averaged 21% less than when it was calculated by the recovery method.

	PLASMA CLEARANCE	BLOOD CLEARANCE
RECOVERY METHOD	$CL_P = \frac{R}{\bar{A}_P\ \tau}$	$CL_B = \frac{R}{\bar{A}_B\ \tau}$
A - V DIFFERENCE METHOD	$CL_P = Q_{EFF}\left(\frac{A-V}{A}\right)$	$CL_B = Q_B\left(\frac{A-V}{A}\right)$

Figure 1. The four main ways of calculating dialysis clearance. The recovery methods for plasma and whole blood are shown in the top row. In these equations R represents total drug recovery in the dialysis bath fluid, $\bar{A}_B$ and $\bar{A}_P$ are the respective blood and plasma concentrations of solute entering the dialyzer, and τ is the dialysis time. The A-V difference methods for calculating whole blood and plasma dialysis clearance are shown in the bottom row. Because (A-V)/A is a ratio, it can be calculated from either plasma or blood concentrations as long as all concentrations are consistently either the one or the other. When Q represents blood flow through the dialyzer blood clearance is calculated. When plasma concentrations are less than blood concentrations, plasma clearance calculated by the recovery method is greater than blood clearance (upper left). So Q in the A-V difference equation (lower left) needs to be greater than blood flow in order to obtain the recovery method result. Thus, as described in the text, erroneous clearance values can be obtained when plasma flow through the dialyzer is used to calculate dialyzer plasma clearance.

Impact of Physiologic Changes During Hemodialysis

It is usually assumed that the distribution kinetics of drugs remain unaltered during hemodialysis. However, Stec et al. found that during hemodialysis there was an average 77% reduction in the intercompartmental clearance between plasma and the more slowly equilibrating and larger of the two peripheral compartments of their distribution model.[15] Subsequent simultaneous studies of inulin and urea kinetics in dogs indicated that substantial decreases in slow intercompartmental clearances of these compounds (urea: 82%, inulin: 47%) reflected a 90% reduction in blood flow to this compartment which largely represents skeletal muscle.[17] There are two consequences of this physiological perturbation that have implications for patient care.

First, the skeletal muscle compartment contains the major portion of most drugs after distribution equilibrium is reached. So major reductions in this compartment's blood flow and intercompartmental clearance serve as a virtual tourniquet that retards the return of drugs from this compartment to the intravascular space and most vital organs.

This may enhance the efficacy of hemodialysis in treating toxicity from drugs that in the un-

perturbed state have distribution volumes that are large enough so that hemodialysis would ordinarily be thought to be an ineffective therapeutic intervention. For example, hemodialysis was used to treat a woman who had ingested an estimated 7 gm of procainamide and subsequently became lethargic and hypotensive and developed junctional tachycardia.[18] After 4 hours of hemodialysis, her procainamide blood concentration had fallen from 25.7 to 15.5 μg/mL and the patient was hemodynamically stable although only 340 mg of procainamide had been removed by dialysis. The apparent distribution volume based on this and the accelerated plasma concentration drop was 0.76 L/kg, compared to an expected value of 2.0 L/kg. This presumably reflected a tourniquet effect that retarded the return of drug from skeletal muscle to the intravascular compartment and thereby enhanced the efficacy of hemodialysis in this patient.

Secondly, when hemodialysis removes a significant quantity of a drug, one way of estimating a replacement dose is to multiply the concentration drop by the expected distribution volume of the drug in healthy subjects. However, if this tourniquet effect causes the apparent distribution volume to be much less than the expected value, an excessive replacement dose will be administered. Replacement based on the amount of drug recovered in the dialysate would theoretically be more accurate but is not feasible during routine patient care.

Acknowledgement

Otto Linet, M.D. provided invaluable help in translating the cited German references.

Conflict of Interest

Nothing to declare

References

1. Able JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the circulating blood of living animals by dialysis. J Pharmacol Exp Ther 1914;5:275-317.
2. Haas G. Veersuche der blutauswaschung am lebenden mit hilfe der dialysis. Klin Wochenschr 1925;4:13-14.
3. Haas G. Über blutwashung. Klin Wochenschr 1928;7:1356-1362.
4. Wizemann V. Hemodialysis: 70 years. Clin Investig 1994;72:720-721.
5. Kolff WJ, Berk HTJ. The artificial kidney: a dialyzer with a great area. Acta Med Scand 1944;117:121-134.
6. Addis T, Watanabe CK. A method for the measurement of the urea-excreting function of the kidneys. J Biol Chem 1916;28:251-259.
7. Möller E, McIntosh JF, Van Slyke DD. Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. Definition and calculation of the maximum and standard blood urea clearances. J Clin Invest 1928;6:427-465.
8. Fick A, Über die measung des blutquantums in der herzventrickeln. Sitzungen der phys-med gesellsch zu Wûrzburg 1870;16: XIV. Sitzung am 8 Juli 1870.
9. Wolf AV, Remp DG, Kiley JE, Currie GD. Artificial kidney function: kinetics of hemodialysis. J Clin Invest 1951;30:1062-1070.
10. Doolan PK, Walsh WP, Kyle LH, Wishinsky H. Acetylsalicylic acid intoxication. A. Proposed method of treatment. JAMA 1951;146:105-106.
11. Cutler RE, Forland SC, St John Hammond PG, Evans JR. Extracorporeal removal of drugs and poisons by hemodialysis and hemoperfusion. Ann Rev Pharmacol Toxicol 1987;27:169-191.
12. Takki S, Gambertoglio JG, Honda DH, Tozer TN. Pharmacokinetic evaluation of hemodialysis in acute drug overdose. J Pharmacokinet Biopharm 1978;6:427-442.
13. Levy G. Pharmacokinetics in renal disease. Am J Med 1977;62:461-465.
14. CDER. Draft Guidance for Industry. Pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing and labeling. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM204959.pdf Accessed 10 October 2016
15. Stec GP, Atkinson AJ Jr, Nevin MJ, Thenot JP, Ruo TI, Gibson TP, et al. N-Acetylprocainamide pharmacokinetics in functionally anephric patients before and after perturbation by hemodialysis. Clin Pharmacol Ther 1979;26;618-628.
16. Lee CS, Marbury TC, Benet LZ. Clearance calculations in hemodialysis: Application to blood, plasma, and dialysate measurements for ethambutol. J Pharmacokinet Biopharm 1980;8:69-81.
17. Bowsher DJ, Krejcie TC, Avram MJ, Chow MJ, Del Greco F, Atkinson AJ. Reduction in slow intercompartmental clearance of urea during dialysis. J Lab Clin Med 1985;105:489-497.
18. Atkinson AJ Jr, Krumlovsky FA, Huang CM, del Greco F. Hemodialysis for severe procainamide toxicity: clinical and pharmacokinetic observations. Clin Pharmacol Ther 1976;20:585-592.