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Individualized drug dosage in patients treated with continuous hemofiltration

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Individualized drug dosage in patients treated with continuous hemofiltration.

Background. Subtherapeutic drug dosing may be even more dangerous than overdosage, especially for intensive care patients requiring hemofiltration.

Proposal. According to Dettli's fundamental equation, body clearance of any drug (Cl) is a linear function of creatinine clearance (Cl = Cl anur + a · C_{Cr}), with [a = (Cl norm − Cl anur)/C_{Cr} norm]. We propose to individualize drug dosage during high-flux hemofiltration by basing it on Dettli's equation and on total C_{Cr} (C_{Cr} tot = C_{Cr} ren + C_{Cr} filt). Using this approach, drug clearance will eventually be overestimated for drugs with substantial tubular secretion and for high-efficiency hemofiltration (C_{Cr} tot > 30 ml/min).

Conclusion. In patients undergoing hemofiltration, the total C_{Cr} approach might be a practical alternative to standardized dosing schemes for deriving an individualized dosage from published pharmacokinetic data and functions.

In renal impairment, dosage reduction is recommended for more than one half of all drugs available. Underdosage of drugs can be even more dangerous than overdosage, especially for anti-infective therapy in critically ill patients. Therapeutic drug-level monitoring very often is available only post hoc, if at all. Hemofiltration experts usually propose to derive drug dosage adjustments from unbound free plasma fraction, or sieving coefficient [1]. However, adsorption by the membrane could substantially contribute to drug elimination [2]. The sieving coefficient might be influenced by alterations in drug protein binding [3]. In addition, this approach does not take into account spontaneous renal function and actual clinical situation.

Hemofiltration is by no means a standardized procedure. The blood flow rate is 50 to 200 ml/min, and the substitution volume ranges from 500 to 3000 ml per hour, with or without a combination of dialysate flow. On the other hand, the pharmacokinetic principles that apply to continuous hemofiltration follow a general rule, much more so than during intermittent hemodialysis. This gives reason for basing drug dosage on the easy-to-measure total serum creatinine clearance (C_{Cr}).

Key words: intensive care, high-flux hemofiltration, creatinine clearance, drug monitoring.

THEORETICAL CONCEPT

According to Dettli's fundamental equation [4], drug clearance (Cl) is a linear function of C_{Cr}. Nonrenal drug clearance values in healthy volunteers can even be used to predict drug clearance for functionally anuric patients (Cl nonren ≅ CL anur).

$$Cl = Cl\ anur + a \cdot C_{Cr}$$

This dependence has been investigated in patients and confirmed for many drugs. Thus, the following holds [a = (Cl norm − Cl anur)/C_{Cr} norm].

The Dettli equation can even be applied to hemofiltration circumstances by introducing the total C_{Cr} concept (C_{Cr} tot). Although for continuous hemofiltration, renal C_{Cr} (C_{Cr} ren) adds up with the extracorporeal C_{Cr} (C_{Cr} filt) to form the total C_{Cr} (C_{Cr} tot = C_{Cr} ren + C_{Cr} filt).

$$C_{Cr}\ tot = \frac{(CreaFiltrate \cdot VolumeFiltrate) + (CreaUrine \cdot VolumeUrine)}{S_{Cr} \cdot 1440}\ [ml/min]$$

At least as a rule of thumb, the 1/Crea method might be used; a serum creatinine of 200 μmol/liter indicates 50% renal impairment [1/Crea ≅ glomerular filtration rate (GFR) percentage].

DISCUSSION

In patients on continuous hemofiltration, serum creatinine should not be higher than 200 to 400 μmol/liter, requiring ultrafiltration rates between 500 and 3000 ml/hr. Accordingly, the total C_{Cr} is to be estimated between 10 and 50 ml/min [5]. This compares with weekly averaged values for the C_{Cr} of only 5 to 10 ml/min by intermittent hemodialysis. Likewise, the usual dose reductions that

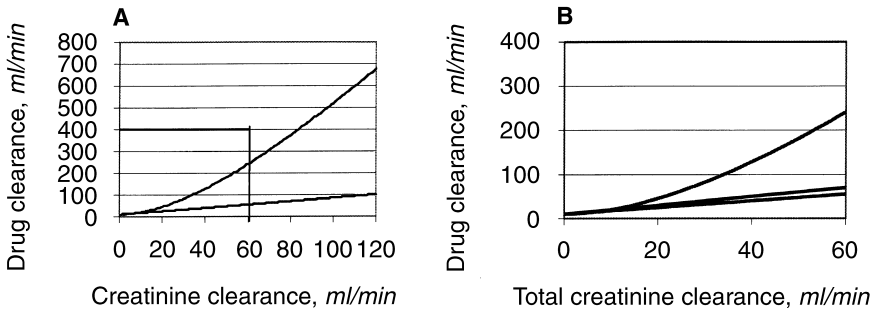

Fig. 1. Drug clearance as a function of creatinine clearance. Fundamental pharmacokinetic principles (*A*) can be applied to the condition of continuous hemofiltration (*B*). The additional line in the right-hand diagram represents the general effect of hemofiltration on drug clearance (Cl = Cl anur + C_{Cr} tot). Two extreme examples are illustrated: (a) The actual effect of hemofiltration on drug clearance might be overestimated for drugs with a high tubular secretion rate (for example, β-lactam antibiotics), and (b) the effect of hemofiltration is underestimated for drugs for which considerable tubular reabsorption takes place (for example, amino acids and vitamin C).

are standardized to intermittent hemodialysis could lead to an inefficiently low dosage in continuous hemofiltration. For meropenem, vancomycin, fluconazole, imipenem, cefepime, and piperacillin, it has been shown that an almost normal dosage is needed in patients on hemofiltration [1, 6–9].

The total C_{Cr} approach can be applied to the hemofiltration situation because high-flux hemofiltration is similar to natural glomerular filtration. Glomerular drug filtration depends on unbound fraction in plasma (fu) and glomerular filtration rate, where ($C_{Cr} \cong$ GFR).

$$\text{Cl filt} = \text{fu} \cdot C_{Cr}$$

The metabolic capacity of the kidneys has long been overlooked [10]. Metabolic clearance as in the case of insulin takes place right after glomerular filtration. By taking into account this effect, renal drug clearance is assessed more accurately from C_{Cr} than from the urinary drug excretion rate.

Any clearance, however, will be estimated too high for deteriorating renal function and too low in the restitution phase of renal failure. If continuous hemodialysis is used instead of or in addition to hemofiltration, total C_{Cr} can overestimate drug clearance, depending on molecular size. The total C_{Cr} approach furthermore has two limitations (Fig. 1). Hemofiltration does not provide clearance by tubular secretion nor does tubular reabsorption take place resulting in the general equation for drug clearance during hemofiltration.

$$\text{Cl} = \text{Cl anur} + C_{Cr}\ \text{tot}$$

If dosage is adjusted according to total C_{Cr}, an overdosage can result, especially with drugs largely eliminated by tubular secretion and in patients with near-normal serum creatinine values.

Overestimation in the case of tubular secretion

Tubular secretion by nonspecific transporters plays an important role in cationic and anionic drugs. The clearance by tubular secretion adds to glomerular filtration. Tubular secretion depends on transport maximum (Tm), Michaelis-constant (Km), and the concentration in plasma (C). The clearance by secretion is a function of GFR because it can occur only into the tubular lumen containing the glomerular ultrafiltrate. The following equations are generally accepted: (Tm = const.) and (Km = const.). The concentration (C) could increase, however, if renal function is impaired; in the most simple case, there is a reciprocal proportionality (b) to the C_{Cr} ($C = b/C_{Cr}$). In this case, drug clearance depends on C_{Cr} according to a nonlinear function. By transformation, it can be shown that a quadratic function holds for the dependence of drug clearance on C_{Cr} [4].

$$\text{Cl} = \text{Cl anur} + \text{fu} \cdot C_{Cr} + [\text{Tm}/(b + \text{Km} \cdot C_{Cr})] \cdot C_{Cr}^2$$

For theoretical reasons, the nonlinear function for drug clearance, including tubular secretion and the dependence on C_{Cr}, is left bent and convex, but it is never right bent or concave.

β-Lactam antibiotics, especially penicillins, are also eliminated by tubular secretion. If the published correlations between drug clearance and C_{Cr} are extrapolated to the effect of hemofiltration, an overestimation of drug clearance results. Because of the convex correlation, the error is low in the case of low C_{Cr} (Fig. 1). On the other hand, creatinine is also eliminated by tubular secretion; thus, C_{Cr} generally overestimates glomerular filtration. These two errors balance, and the wrong dosage will most likely not prove clinically disastrous.

In addition, intestinal secretion of drugs can compensate for missing tubular secretion. The so-called Lauterbach effect partly minimizes the error of overestimation of the hemofiltration effect. Compensatory intestinal secretion (exsorption) has been shown for imipenem or quinolones in renal failure [11, 12].

Underestimation in the case of tubular reabsorption

Tubular reabsorption operates in only very few drugs. It has been shown that elimination of amino acids or vitamin C by hemofiltration is higher than by normal renal function [13, 14]. Because hemofiltration does not

replace tubular reabsorption, losses with hemofiltration could be higher than with normal renal function.

Application to dose adjustment. Individual pharmacokinetic parameters form the basis for an individualized drug dose (D) and interval (τ). A close mathematical relation exists between drug clearance, volume, and half-life ($Cl = 0.693 \cdot Vd/T1/2$) where volume is usually considered constant (Vd = const.). Three different methods exist: (*a*) the proportional dose reduction according to Dettli, (*b*) the half-dosage rule according to Kunin, and (*c*) the target concentration approach according to Holford [15].

$$\text{(a) } D/\tau = (D/\tau)\text{norm} \cdot Cl/Cl\ \text{norm}$$

$$\text{(b) } D/\tau = 1/2\ D\ \text{norm}/T1/2$$

$$\text{(c) } D/\tau = C\ \text{target} \cdot Cl$$

The required parameters (Cl, T1/2) for the three methods can be obtained from the total-clearance approach by applying it to published pharmacokinetic functions and data [15].

CONCLUSION

In patients undergoing hemofiltration, the total C_{Cr} approach might be a practical alternative to standardized dosing schemes. The total C_{Cr} (renal plus extracorporeal C_{Cr}) may make it possible to derive individual pharmacokinetic parameters from published pharmacokinetic facts and functions.

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REFERENCES

1. Joy MS, Matzke GR, Frye RF, Palevsky PM: Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. *Am J Kidney Dis* 31:1019–1027, 1998
2. Leypoldt JK, Gilson JF, Blindauer KM, Cheung AK: Macromolecule adsorption to hemodialysis membranes depends on molecular size. *Blood Purif* 10:53–60, 1992
3. Lau AH, Kronfol NO: Effect of continuous hemofiltration on phenytoin elimination. *Ther Drug Monit* 16:53–57, 1994
4. Keller F, Czock D: Pharmacokinetic studies in volunteers with renal impairment. *Int J Clin Pharmacol Ther* 36:594–598, 1998
5. Clark WR, Mueller BA, Kraus MA, Macias WL: Quantification of creatinine kinetic parameters in patients with acute renal failure. *Kidney Int* 54:554–560, 1998
6. Thalhammer F, Schenk P, Burgmann H, El Menyawi I, Hollenstein UM, Rosenkranz AR, Sunder Plassmann G, Breyer S, Ratheiser K: Single-dose pharmacokinetics of meropenem during continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 42:2417–2420, 1998
7. Tegeder I, Bremer F, Oelkers R, Schobel H, Schuttler J, Brune K, Geisslinger G: Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 41:2640–2645, 1997
8. Allaouchiche B, Breilh D, Jaumain H, Gaillard B, Renard S, Saux MC: Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 41: 2424–2427, 1997
9. Van der Werf TS, Mulder PO, Zijlstra JG, Uges DR, Stegeman CA: Pharmacokinetics of piperacillin and tazobactam in critically ill patients with renal failure, treated with continuous veno-venous hemofiltration (CVVH). *Intensive Care Med* 23:873–877, 1997
10. Lohr JW, Willsky GR, Acara MA: Renal drug metabolism. *Pharmacol Rev* 50:107–141, 1998
11. Nouaille-Degorce B, Veau C, Dautrey S, Tod M, Laouari D, Carbon C, Farinotti R: Influence of renal failure on ciprofloxacin pharmacokinetics in rats. *Antimicrob Agents Chemother* 42:289–292, 1998
12. Mueller BA, Scarim SK, Macias WL: Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. *Am J Kidney Dis* 21:172–179, 1993
13. Story DA, Ronco C, Bellomo R: Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. *Crit Care Med* 27:220–223, 1999
14. Davies SP, Reaveley DA, Brown EA, Kox WJ: Amino acid clearances and daily losses in patients with acute renal failure treated by continuous arteriovenous hemodialysis. *Crit Care Med* 19:1510–1515, 1991
15. Holford N (editor): *Clinical Pharmacokinetics: Drug Data Handbook* (3rd ed). Auckland, Adis, 1998