Drug use in the intensive care unit

To the Editor: Drug use in the intensive care unit poses the increased risk of nephrotoxicity. In this clinical setting two typical errors should be avoided, namely overdosage and underdosage—mainly of the anti-infective drugs. In his valuable review on this topic, Mark A. Perazella suggested adjusting the dose to the patient’s kidney function by using the measured creatinine clearance (CrCl):1 ‘Maintenance dose = standard dose x (patient’s CrCl/normal CrCl), or Maintenance dosing interval = standard dosing interval x (normal CrCl/patient’s CrCl)’. However, the adjusted dose is not equal to that clearance ratio. This has been shown by Luzius Dettli using his classical two-step approach:2 The pharmacokinetic parameters depend on kidney function according to a linear function, and the dose must be adjusted to the pharmacokinetic parameters in direct proportion to that change. With greater drug clearance, the intercept of this linear function is lower and the slope is higher, or the elimination half-life in patients with failing kidney function (T1/2fail) differs from the half-life value in normal individuals (T1/2norm). Bringing both steps into one equation yields the following solution:

\[
\text{Dose} = \left( \frac{\text{Dose Interval}}{\text{Interval norm}} \right) \cdot \left[ 1 - \left( \frac{T_{1/2\text{norm}}}{T_{1/2\text{fail}}} \right) \cdot \left( 1 - \frac{\text{eGFR}_{\text{patient}}}{\text{eGFR}_{\text{norm}}} \right) \right]
\]

In addition, and as proposed in the Kidney Disease: Improving Global Outcomes update, the creatinine clearance could better be replaced by any of the common estimates of the glomerular filtration rate, such as the Cockcroft & Gault equation, the Modification of Diet in Renal Disease equation, or the Chronic Kidney Disease Epidemiology Collaboration formula.3 All three GFR estimates are based on simple serum creatinine measurements.


The Author Replies: Two letters to the editor raise important issues about drug dosing and extracorporeal drug clearance in intensive care unit patients.1,2 Critically ill patients often suffer from acute kidney injury (AKI) and multi-organ failure; they are the most complicated group for whom nephrologists must provide care.3 By the nature of their acute and chronic disease processes, they require numerous pharmaceutical agents. Calculating the appropriate dose is challenging and fraught with difficulty, as most pharmacokinetic parameters are disrupted in critically ill patients with AKI, especially when there is coexistent liver injury. Changes in volume of distribution and altered drug metabolism can lead to either lack of efficacy or overt toxicity. In addition, renal drug excretion is frequently abnormal, difficult to predict, quite dynamic, and further altered when renal replacement therapy is added to the mix.

Dr Keller astutely points out the limitations of creatinine clearance and its use as a ratio to determine drug dose adjustments. I concede this point, but emphasize that my intent was to bring the reader’s attention to the need for dose adjustment in these patients because of their underlying pharmacokinetic disturbances.3 All glomerular filtration rate (GFR) estimates in critically ill patients with AKI and/or multi-organ failure perform poorly, thereby limiting their utility in accurately dosing drugs. The Kidney Disease: Improving Global Outcomes drug dosing recommendations, which were published after my paper was written, are very helpful.4 However, these formulas often significantly overestimate GFR, and the GFR ranges utilized for drug dose adjustment are anything but granular (<10, 10–50, >50). Many of these problems would disappear if we could simply measure drug concentrations. Until this is available for all drugs, the goal of my drug-dosing guides was to familiarize the reader with pharmacokinetic concepts and provide a simple approach to dose adjustment (loading vs. maintenance dose). Most importantly, I emphasize the need for a collaborative working relationship between clinical pharmacists and critical-care nephrologists.

Barrantes and Horwedel appropriately note that attentive care must be undertaken when dosing antibiotics in patients on extended dialysis (ED). While pharmacokinetic drug studies are limited for most continuous renal replacement therapy modalities, ED is an even more understudied area, although it has received recent interest.5 As the authors point out, drug efficacy and toxicity are related not only to the dose administered, but also to the timing of the dose in relation...
to ED. They wisely note that efficacy should also be assessed by monitoring pharmacodynamic drug effects, such as antimicrobial killing.


Mark A. Perazella1
1Yale University School of Medicine, Section of Nephrology, New Haven, Connecticut, USA
Correspondence: Mark A. Perazella, Yale University School of Medicine, Section of Nephrology, BB 122, 330 Cedar Street, New Haven, Connecticut 06520, USA. E-mail: mark.perazella@yale.edu


Combining a fruit and vegetable diet with sodium bicarbonate supplementation seems the best dietary option for chronic kidney disease patients

To the Editor: Goraya et al.1 have, in their interesting paper, shown that short-term (30 days) dietary acid reduction due to fruit and vegetable (F + V) or sodium bicarbonate (NaHCO3) consumption attenuated kidney injury in hypertensive chronic kidney disease (CKD; stadium II) patients undergoing therapy with angiotensin-converting enzyme inhibitors. The F + V diet reduced systolic blood pressure and body weight, but NaHCO3 did not affect these parameters. In a comment on this paper, Uribarri and Oh2 stated that F + V diets rather than NaHCO3 supplementation might be the key to halting CKD progression. The truth seems to lie somewhere in between in that simultaneous use of F + V diets and NaHCO3 is required. In this study, NaHCO3 caused greater aldosterone reduction than the F + V diet. Because aldosterone is involved in kidney injury, long-term NaHCO3 supplementation can be more beneficial than the F + V diet alone. Furthermore, the F + V diet reduces urinary sodium concentration. An epidemiological study reported that lower sodium excretion in healthy patients is associated with higher cardiovascular disease mortality.3 Because the Na+ cation seems more likely to increase blood pressure when combined with the Cl− anion than with HCO3− (ref. 4), providing sodium through bicarbonate rather than kitchen salt seems reasonable. Low long-term dietary compliance is another issue with the F + V diet. Therefore, it seems that CKD patients should use NaHCO3 supplementation as well as F + V diets.

2. Uribarri J, Oh MS. The key to halting progression of CKD might be in the produce market, not in the pharmacy. Kidney Int 2012; 81: 7–9.

Igor Loniewski1
1Sanum Polska, Szczecin, Poland
Correspondence: Igor Loniewski, Sanum Polska, Kurza Stopka S/C, Szczecin, Zachodniopomorskie 70-535, Poland. E-mail: igorloniewski@sanum.com.pl

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