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I read with interest the article on safe drug prescribing for patients with renal insufficiency.[1] The authors have succinctly summarized various medications that require adjustment in dosage in renal failure and others that do not require such adjustments, but I take issue with certain recommendations in Table 4 of the paper.

First, the authors describe morphine as a medication not requiring dosage adjustment in renal failure unless given in a palliative care setting. Although morphine is rapidly metabolized by the liver, it is excreted mainly in the urine as its active metabolites, morphine-3-glucuronide (M-3G) and morphine-6-glucuronide (M-6G). Both M-3G and M-6G readily cross the blood–brain barrier and bind with strong affinity to opiate receptors, exerting strong analgesic effects. In patients with renal failure or in the elderly, the ratios of M-3G and M-6G to morphine increase, making opioid toxicity, prolonged narcosis and respiratory depression more likely.[2,3] Morphine dosage must therefore be carefully controlled and adjusted in patients with renal failure.

The authors also state that angiotensin-converting enzyme (ACE) inhibitors require dosage adjustment in renal failure whereas angiotensin receptor blockers (ARBs) do not. Although these generalizations are mostly accurate, subtle pharmacokinetic differences in some agents may make them exceptions to the rule. For example, although most ACE inhibitors require dosage adjustment because they are exclusively eliminated through the kidney, fosinopril has both a renal and hepatobiliary route of elimination and thus may not require dosage adjustment in chronic renal insufficiency.[4] Similarly, most ARBs do not require dosage adjustment in renal failure because of their hepatobiliary route of elimination, but 60% of candesartan cilexetil is mainly excreted in the urine as candesartan. In patients with renal insufficiency it may be prudent to employ lower starting doses of this medication.[5]

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[One of the authors responds:]

Bruce Lange's comments regarding COX-2 selective NSAIDs are quite correct and readers would be well advised to add this addendum to Table 5.[1]

Strictly speaking, radiocontrast agents are diagnostic tools and not drugs and therefore were not included in this article on safe drug prescribing. However, radiocontrast agents certainly can cause nephrotoxicity in patients with renal insufficiency. I do not think that the current published studies regarding the use of *N*-acetylcysteine in patients with renal insufficiency have conclusively established that this drug absolutely reduces the incidence of contrast nephropathy.[2] Because *N*-acetylcysteine is relatively harmless, I think that it is being used widely without adequate data.

Malvinder Parmar's comments regarding morphine dosage adjustments are quite correct when morphine is used on a regular basis. However, when morphine is used on a sporadic basis, as in postoperative pain control, I do not believe that dosage adjustment is practically required. Dosage adjustments are required when morphine is used on a regular basis such as in a palliative care setting (as reflected in Table 4).

An excellent review article by Song and White states that angiotensin receptor blockers do not require dosage adjustment in patients with renal insufficiency.[3] This includes candesartan cilexetil. Furthermore, a subsequent article by See and Stirling extensively reviewed the pharmocokinetics of candesartan cilexetil and did not find a significant alteration in patients' blood pressure response (in those with renal insufficiency) after they received multiple doses of candesartan cilexetil .[4]

As the treatment of many nonemergent conditions does not require an immediate or maximal drug response, I would hope that clinicians would start drugs at the lowest convenient dose, regardless of renal function, and increase to produce the desired response.

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tPA for acute stroke: balancing baseline imbalances

In a recent *CMAJ* article,[1] David Gladstone and Sandra Black stated that the National Institute of Neurological Disorders and Stroke (NINDS) study[2] provided valid evidence that patients treated with tissue plasminogen activator (tPA) within 3 hours of symp-