Editors' view

Drugs and the kidney: more than a question of dose

Derek G. Waller, Assistant Editor-in-Chief, British Journal of Clinical Pharmacology

Division of Unscheduled Care, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD

The current issue of the *Journal* is devoted to several papers that examine the complex interplay among drug therapies and the kidney. The determination of renal function to guide dosage adjustment for drugs prescribed for patients with impaired renal function was considered recently in the *Journal* [1]. In his editorial, Aronson produced cogent arguments for retaining the Cockcroft and Gault equation for estimating creatinine clearance as a surrogate for glomerular filtration rate, rather than eGFR (estimated glomerular filtration rate). Nevertheless, the most recent edition of the British National formulary [2] has acknowledged the almost universal availability of the eGFR and has accepted its use as an appropriate tool to guide dosage adjustment in many cases. In this issue of the *Journal* Gupta and colleagues [3] have recommended dosage reduction of peginterferon alfa-2b based on measured creatinine clearance. The suggested adjustment is a 50% reduction for severe renal impairment (creatinine clearance 10–29 ml min⁻¹) and a 25% reduction for moderate insufficiency (creatinine clearance 30–50 ml min⁻¹). Although the C_{max} for the drug was almost doubled in those with severe renal impairment compared to those with normal or moderately impaired renal function, there was no excess of adverse events in this group of patients. This probably reflects the small number of people in the study, while the short duration of the observations (weekly injection for 4 weeks) or the therapeutic index of the drug could also be important. For drugs with significant toxicity and a narrow therapeutic index, the precision of using calculated creatinine clearance or eGFR instead of measured creatinine clearance for avoiding adverse effects remains unresolved.

Ciclosporin has a narrow therapeutic index and is used in many regimens for immunosuppression after

renal transplantation. Its metabolism depends on CYP3A4 and it is potentially nephrotoxic. Fanta and colleagues [4] have explored the pharmacokinetics of ciclosporin in children awaiting renal transplantation. They conclude that the hepatic metabolizing capacity of the liver is mature by the age of 6–12 months, and that drug dosing after this age can be determined by adjustment for body weight.

Drug interactions can complicate the application of recommendations for dosage adjustment. Pescovitz and colleagues [5] have studied the pharmacokinetics of mycophenolate mofetil in combination with either ciclosporin or sirolimus in renal allograft recipients. The use of ciclosporin reduced exposure to mycophenolic acid by 39–50% while increasing exposure to its glucuronide metabolite compared with sirolimus. In this case the influence of renal function on drug exposure was not important, but these observations illustrate the potential complexity of dosage adjustments in patients taking multiple drug regimens.

Other papers in this issue of the *Journal* examine the important question of the effect of dialysis on drug dosing [6, 7]. The increasing use of renal replacement therapy makes this type of study essential in improving our ability to maximize drug efficacy and minimize toxicity in a group of patients who often require multiple drugs for co-morbid conditions.

Many drugs can injure the kidneys, although there is a limited number of mechanisms by which they produce nephrotoxicity. These include renal vasoconstriction, thrombotic microangiopathy, changes in intraglomerular haemodynamics, immune-mediated glomerulonephritis, tubular cell toxicity, interstitial nephritis, and crystal formation in the tubules. There are four major clinical presentations: acute renal insufficiency, nephrotic

syndrome, renal tubular dysfunction, and chronic renal insufficiency. For some drugs, such as aminoglycosides, cisplatin, and ciclosporin, the risks are well documented. Preventive strategies include ensuring adequate hydration and monitoring blood concentrations of the nephrotoxin. It is equally important to ensure appropriate dosage adjustment of the potential nephrotoxin if there is pre-existing renal impairment, when the kidney is more vulnerable to the nephrotoxic effects of drugs. These measures are often sufficient to minimize the risk of significant damage [8]. However, idiosyncratic nephrotoxic damage can occur from the use of drugs for which there is no indication for regular monitoring of renal function. It is then possible that the connection between the drug and its adverse effect will not be made. Omeprazole has been linked to the development of interstitial nephritis. Härmark and colleagues [9] have used a Danish pharmacovigilance database to report a link between several proton pump inhibitors and severe renal impairment. In the five of seven cases in which a renal biopsy was undertaken, it showed acute interstitial nephritis. The value of spontaneous reporting in evaluating adverse effects is again demonstrated by this study, although the frequency of the problem can only be determined by more robust post-marketing surveillance.

By contrast, not all apparent changes in renal function represent drug nephrotoxicity. Creatinine is largely eliminated by glomerular filtration, but partially by tubular secretion via an active cation transporter. Cimetidine and trimethoprim have long been recognized to increase plasma creatinine concentration by inhibiting its tubular secretion. Tschuppert and colleagues [10] have shown a similar effect with the antiarrhythmic drug dronedarone, which reduced creatinine clearance by an average of 18% compared with placebo. However, there was no effect on glomerular filtration rate determined by renal sinistrin clearance. The consequent increase in plasma creatinine concentration may have implications for determining drug dosing in renal impairment.

Renal disease increases the risk of cardiovascular disease by 10–20 times [11], and the presence of microalbuminuria in people with hypertension, even in the absence of diabetes, is a powerful marker of increased vascular risk [12]. Atthobari and colleagues [13] take a novel approach to the consequences of population risk factor screening for cardiovascular disease. Their starting point was a concern that screening exposes well people to medicalization and increased use of prescribed drugs. They examined whether screening an asymptomatic population increases prescribing of medications unrelated to the risk factors they identified.

They conclude that screening leads to appropriate prescribing for cardiovascular risk reduction, but does not lead to undue medicalization of the screened population. However, the screened population had the same rate of drug prescription for primary prevention as the unscreened comparator group, suggesting that opportunistic case finding may be as effective as unselected screening. The authors advocate targeted screening of high-risk populations, such as those with microalbuminuria, to improve the cost-effectiveness of screening.

Furosemide has been around for many years, and remains a key drug for the management of significant fluid retention. However, we are still exploring the most effective ways to use it, and in this issue of the *Journal* high-dose continuous infusion of furosemide in infants [14] and the potential for sublingual administration [15] have been examined. High-dose infusions are underused, and the study by van der Vorst and colleagues gives reassurance about both efficacy and lack of toxicity in infants following cardiac surgery. Haegli and colleagues open up the possibility that furosemide should be added to the small group of drugs for which buccal or sublingual absorption may be both effective and useful. In the case of furosemide, its variable and unpredictable absorption after oral administration makes it difficult to use for resistant oedema. Sublingual absorption opens up the option of treatment without the need for intravenous infusion in selected cases.

The kidney will continue to be a central theme in the quest for the safest and most effective use of many therapeutic agents. This issue of the *Journal* both advances our knowledge and shows how much more there is to discover.

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