Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

Department of Clinical Pharmacology, Christchurch Hospital, Private Bag 4710, Christchurch

Drug Information Service **Phone**: 80900 **Fax**: 80902
Drug Utilisation Review **Phone**: 89971 **Fax**: 81003

January 2014 No. 003/14

Renal clearance - "fu" is now "f_e" – what does this mean?

For each of the medications listed in the Preferred Medication List (the "Pink Book" 2014) there is a comment on the metabolism and the "fu" for the medication. This "fu" is the abbreviation for the ***f****raction of the medication excreted* ***u****nchanged* in the urine, but this is now changing to "

Background

- The extent that a medication is cleared renally varies from those that are exclusively renally cleared (for example lithium, fu = 1) to those that are exclusively metabolised by the liver (for example phenytoin, fu = 0).
- Internationally fu has a different meaning. In pharmacology it stands for the ***f****raction* ***u****nbound of a medication in the blood*, i.e. it refers to the degree of plasma protein binding. The ***f****raction of the medication* ***e****xcreted unchanged in urine* is abbreviated to "f_e" internationally. In keeping with this, we are now changing our use of "fu" to "f_e"

Know your f_e

- Before prescribing any renally eliminated medication the patient's renal function and the f_e of a medication must be considered.
- The dose of a medication required for a therapeutic effect can be compared with the dose that produces toxicity. This ratio is the *therapeutic index* for a medication.
- A medication with a high f_e and a low therapeutic index can be associated with toxic concentrations with even mild renal impairment in the absence of appropriate dose-reduction.

Low therapeutic index medications with f_e > 0.5 (dose MUST be adjusted for renal function)

ACE inhibitors
Allopurinol
Aminoglycosides (e.g. gentamicin, tobramycin, amikacin)
Digoxin
Contrast agents
Certain cytotoxics (e.g. methotrexate, cisplatin)
Lithium
Metformin
Vancomycin

Other medications have a higher therapeutic index and dose-adjustment in renal impairment may reduce the incidence of side effects.

High therapeutic index medications with f_e > 0.5 (dose adjust to reduce side effects)

Aciclovir
Some beta-blockers (e.g. atenolol, sotalol)
Cephalosporins (e.g. cefuroxime, cephazolin)
Fluconazole
H2-antagonists (e.ranitidine, cimetidine)

NB: these lists are not comprehensive. Please be familiar with medications you prescribe, look them up, discuss them with the ward pharmacist, and/or consult Drug Information (ph 80900) if unsure.

Calculating dose-rates in patients with renal impairment

(Refer to the renal dosing section in the Pink Book 2014 – p164)
This should be done when prescribing medications with f_e > 0.5, in renal impairment. The estimated glomerular filtration rate (eGFR) provided from the lab report is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which calculates the GFR assuming a standard body weight and height (i.e. a body surface area of 1.73m^2).
Alternatively, the creatinine clearance can be calculated using the modified Cockcroft and Gault equation which is a better reflection of GFR at the extremes of age and weight (*use for elderly patients and over/under weight patients*).

1. Check the f_e for the medication (see page 165 in the Pink Book)
2. Calculate creatinine clearance (CrCl):

$$CrCl\ (ml/min) = \frac{(140 - age) \times\ ideal\ body\ weight*\ (kg)}{plasma\ creatinine\ (\mu mol/L) \times\ 0.8}\ (\times\ 0.85\ if\ female)$$

*****Ideal body weight (kg) = 50kg (male) or 45 kg (female) + 0.9 kg for each cm over 150cm in height

3. For medications with an f_e > 0.9 calculate the dose–rate (DR) to give the renal adjusted dose:

$$DR\ (patient) = \frac{CrCl\ (ml/\min\ )}{100\ (ml/\min\ )} \times\ DR(normal)$$

4. If the f_e < 0.9, use the following equation:

$$DR\ (patient) = \left[(1 - fe) + fe\left(\frac{CrCl\ (ml/\min\ )}{100\ (ml/\min\ )}\right)\right] \times\ DR(normal)$$

Fraction Unbound – fu

- This relates to the protein binding of medication. Unlike f_e, this generally does not need to be taken into consideration when prescribing most medications.
- When drug concentrations are measured in the plasma, this generally means the total concentration of the drug – i.e. both 'free' drug and that which is protein bound. It is only the free drug that acts on receptors, regardless of how much drug is protein bound. In states of hypoalbuminaemia, a total drug plasma concentration may appear to be within the therapeutic range, but this may mask a high free drug concentration.
- When looking at concentrations of drugs that have a high level of protein binding and a narrow-therapeutic index (such as *phenytoin*), it is important to also check a plasma albumin concentration, and if this is low, check a free drug concentration.