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The Sri Lanka Prescriber

The Sri Lanka Prescriber is the only national, independent drugs and therapeutics bulletin in the country. Published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo, in collaboration with the State Pharmaceuticals Corporation (SPC), it has served as a source of unbiased, evidence-based information for several decades.

The Sri Lanka Prescriber evolved from the pocket size bulletins published by the Department of Pharmacology, Formulary Notes, which began publishing in 1966, continued as 'The Prescriber' from 1973. The Sri Lanka Prescriber started publication in the current format in 1993, which is also a continuation of the two previous bulletins. The Sri Lanka Prescriber continues with an updated scope and an Editorial Board from 2025.

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Dedicated to supporting informed prescribing decisions, the Sri Lanka Prescriber offers content relevant to clinicians, pharmacists, academics and students in medicine and allied health fields.

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- Independent drug reviews and cost-effectiveness evaluations
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SCAN ME

Prescribing in Chronic Kidney Disease

This article intends to introduce the basic principles of prescribing in patients with chronic kidney disease. It summarizes the definition and staging of chronic kidney disease (CKD) and the changes in handling of medicines that occur in the body as kidney function declines. It provides guidance on factors to consider when prescribing medicines for patients with CKD and discusses key considerations in dialysis and transplantation.

Case: A 48-year-old woman in referred for evaluation of abnormal kidney function tests. She has type 2 diabetes, hypertension and dyslipidaemia. Her blood pressure is 120/80 mmHg. Her serum creatinine is 1.9 mg/dL. Serum sodium is 138 mmol/L and serum potassium is 4.8 mmol/L. Urinalysis reveals 1+ albumin, no red cells no pus cells and no casts. Her urine albumin:creatinine ratio is 35 mg/mmol. She reveals that her serum creatine had been 1.8 mg/dL 6 months before. Her medications include metformin 1g b.d., empagliflozin 10 mg/d, gliclazide 40 mg/d, losartan 25 mg b.d., and atorvastatin 20 mg nocte.

What is Chronic Kidney Disease?

Chronic kidney disease (CKD) is an abnormality of kidney structure or function, present for a minimum of three months, with implications for health [1]. Kidney function is evaluated by measurement or, more often, estimation of glomerular filtration rate (GFR). Structural abnormality may manifest in several ways, but is most often identified and quantified by the presence and degree of albuminuria. CKD can be staged based on the GFR and degree of albuminuria (Figure 1). In health the GFR averages 120 mL/min/1.73m^2, and albuminuria is quantified as a urine albumin:creatinine ratio of less than 3 mg/mmol.

The least severe stage of CKD, G1, is characterized by a preserved GFR and moderate to severe albuminuria only. Such patients have a low risk of progressing to more severe stages. The most advanced stage is CKD G5, where GFR is <15 mL/min. Within this stage, some patients will require kidney replacement therapy (KRT) for survival. They are referred to as having end-stage kidney disease. These KRTs include peritoneal dialysis, haemodialysis and kidney transplantation.

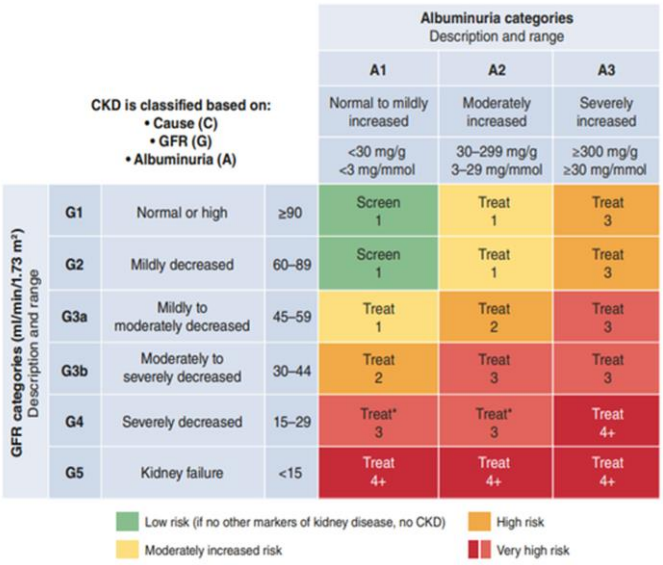

Figure 1: KDIGO staging of chronic kidney disease based on eGFR and albuminuria. Colour coding indicates the risk of progression to end stage kidney disease [1]

In whom should we suspect CKD?

The commonest causes of CKD are diabetes mellitus and hypertension. Other risk factors include urological diseases, atherosclerotic disease, and a family history of kidney disease. In Sri Lanka, CKD of unknown aetiology is seen in certain geographical areas, particularly among agricultural workers. Some medications such as nonsteroidal anti-inflammatory drugs and proton pump inhibitors are known to cause CKD. It is worthwhile screening patients with these risk factors for CKD.

How can we know the GFR?

When it comes to prescribing, it is the GFR that is most relevant to the prescriber. Usually, GFR is estimated rather than measured. This is because GFR measurements are practically difficult and cumbersome. Measurements of GFR are only done in situations where GFR must be known very accurately or its estimation is challenging.

In the practical setting GFR is estimated by measuring serum biomarkers which are usually cleared by the renal filtration and therefore accumulate in kidney disease. These are serum creatinine, and less commonly, serum cystatin-C. The values are then used to calculate the eGFR based on validated formulae. Of these the currently recommended formula for use is the CKD-EPI formula which uses age, sex and serum creatinine or cystatin-C [2]. Online calculators are available. (https://www.kidney.org/professionals/gfr_calculator)

Both creatinine based and cystatin-C based estimations have their limitations. This is due to the non-GFR determinants of serum levels of each marker. Some examples are listed in Table 1.

Table 1: Determinants of serum creatinine and cystatin-C

Non-GFR determinants of serum creatine
Creatinine generation
Increased creatinine production
● Increased muscle mass (e.g. body building) ● Creatine supplementation ● High protein diet (especially red meat)
Decreased creatinine production
● Severe malnutrition ● Anorexia nervosa ● Limb amputation
Non-GFR dependent elimination
Reduced tubular secretion e.g. co-prescription of medicines such as trimethoprim which compete with creatinine for renal elimination
Non-GFR determinants of serum cystatin-C
Increased production
● Chronic inflammation ● Obesity ● Diabetes ● Smoking ● Hyperthyroidism ● Steroids ● Malignancy
Decreased production
● Hypothyroidism

Generally, one or the other can be used, creatinine being preferred due to availability, cost and familiarity. A more accurate estimation can be made by averaging the eGFR values derived using both serum creatinine and cystatin-C when non-GFR determinants do not affect either significantly.

The eGFR values derived from these equations are reported as for a body surface area of 1.73m^2. Particularly in extremes of body habitus, it is more accurate to use height and weight to adjust the eGFR for the body surface area, or measure GFR.

The most accurate GFR value is from its measurement. This can be done by measuring the urinary or plasma clearance of other markers such as ^{51}Cr-EDTA and ^{99m}Tc-DTPA (radionuclide markers) or iohexol and iothalamate (non-radionuclide markers). These may be of use in determining doses of medicines in cases where precise dosing is required, such as for some cancer treatments.

How does kidney disease affect the pharmacokinetics of medications?

Kidney disease can affect all aspects of pharmacokinetics, i.e. of absorption, distribution, metabolism and excretion [3]. Absorption may be reduced by gut oedema, reduction in gastric pH and gastroparesis. Polypharmacy may interfere with the absorption of one another (e.g. phosphate binders reduce absorption of certain antibiotics). In CKD, volume of distribution often increases due to fluid retention. This can lead to lower levels of water-soluble medications. On the other hand, a lower volume of distribution may be seen for fat soluble medicines, especially as kidney disease progresses. The main effects of CKD, however, are on metabolism and excretion. CKD can result in reduced metabolism (e.g. insulin) or activation (e.g 25-hydroxy vitamin D) of medicines. Perhaps unexpectedly, CKD can also reduce hepatic clearance of medicines usually cleared by the liver by 5-50%. This may be due to reduced cytochrome P 450 dependent metabolism, and is aggravated by polypharmacy. Medicines, metabolites and excipients which are renally eliminated accumulate as kidney function declines due to reduced excretion. Table 2 summarizes some of the effects of kidney disease on the pharmacokinetics of medications.

Table 2: Effects of chronic kidney disease on pharmacokinetics of medicines [3]

Absorption	Distribution	Metabolism	Elimination
Gut oedema	Increased volume of distribution - due to salt and water retention or hypoalbuminemia → Lower plasma level of water-soluble medicines	Reduced renal catabolism E.g. insulin	Reduced renal filtration or secretion May affect parent drug, its metabolites or stabilizing excipients
Drug interactions (e.g. phosphate binders	Reduced volume of distribution - due to reduced body fat → Higher plasma levels of fat-soluble medicines (e.g. digoxin, insulin)	Reduced renal activation E.g. 25-hydroxy vitamin D	
Reduction in gastric pH- due to disease or medications e.g. calcium, iron, ketoconazole		Reduced hepatic clearance (by 5-50%) - due to reduced cytochrome P dependent hepatic metabolism (worsened by polypharmacy)	
Co morbidities (e.g. gastroparesis			

What are the points to consider when prescribing a medicine to a patient with CKD?

The main consideration when prescribing in CKD is to minimize renal and systemic harm while ensuring adequate dosing for therapeutic effect. Here are some of the questions which need to be considered to ensure these aims are met.

1. **What is the GFR?**

   The GFR can be calculated using the equations described above. Most medicines do not require dose adjustment if the GFR >30mL/min/1.73m^2. However, there are exceptions, so it is good practice to consult a formulary until one is acquainted with these.

   Certain medicines which act on the kidney or from within its filtrate require adequate amounts of medicines to be filtered at the glomerulus for them to be effective e.g. nitrofurantoin for treatment of lower UTI, thiazides. These medicines will not be effective at lower GFRs and should be substituted.

2. **Is the medicines needed? Is it known to be harmful to the kidneys, if so is there a less harmful alternative? What is the risk vs its benefit**

   Medicines with known nephrotoxicity are best avoided in patients with CKD. This is because these patients have low renal reserves and therefore are more vulnerable to clinically relevant disease following exposure to nephrotoxic medications. While this is often the rule, there may be instances where the benefits of a potentially nephrotoxic medicines may outweigh the risks. Wherever possible a medicine that is not harmful to the kidneys is preferred.

3. **Does the dosing schedule need to be adjusted?**

   As renal clearance declines, the half-life of a renally eliminated medicines (or metabolite) will be prolonged, potentially causing harm. The aim is to maintain the effectiveness of the medicines while minimizing both non-renal and renal toxicity.

   Usually loading doses of medicines do not need to be changed. However, the medicine will remain longer within the system if it is renally cleared. When considering maintenance dosing,

2 approaches may be considered to avoid accumulation of a medicine (or metabolite). These are to reduce the dose of the medicine or extend the dosing interval. These two methods can be combined.

How this is approached will depend on the mechanism of action of the medicine (i.e. concentration-dependent vs time-dependent) and the therapeutic index, with concern highest for medicines with narrow therapeutic index.

For medicine with concentration-dependent effects efforts must be made to achieve the required peak dose. Often the same dose may be administered at reduced frequencies.

For medicines with time-dependent effects, dosing options include:

1. smaller doses of medicine at the same frequency
2. usual dose of medicine at a lesser frequency
3. smaller doses at lower frequency
4. a continuous infusion

It is best to consult a renal formulary for the appropriate dose and schedule.

4. Are additional steps required to minimise and identify toxicity?

Therapeutic drug monitoring can be used to guide dosing of medications and reduce toxicity (e.g. phenytoin, gentamicin concentrations).

If a patient is on a medicine which is known to be harmful to the kidney, they should be closely monitored for changes in serum creatinine or electrolytes which will indicate further injury. It is important to be aware of the vicious cycle of nephrotoxicity where kidney damage leads to further accumulation of the medicine leading to further kidney damage.

It is worth considering that combinations of medicines may be more toxic than a single agent and that these should be avoided when possible (e.g. aminoglycosides and loop diuretics).

What special considerations must be made for patients on dialysis?

Estimations of GFR based on serum creatinine or cystatin levels cannot be used in dialysis as these reflect the dialysis schedule rather than the renal clearance. Instead, it is assumed that a patient on dialysis will have a GFR of < 15mL/min and medicines are dosed accordingly. Even if patients are on dialysis, efforts must be made to preserve residual kidney function because patients with preserved residual kidney function have better outcomes. Here too risk vs benefit must be carefully evaluated when deciding on the use of medicines with potential for further kidney damage. It must be kept in mind that some medicines may be removed during dialysis. These will need to be administered or topped up post-dialysis. Once again, it is best to refer to a renal formulary. The clearance will vary depending on the modality of dialysis i.e. peritoneal dialysis, haemodialysis or haemodiafiltration.

What special considerations must be made for patients with kidney transplants?

Patients who have had a transplant are considered to have CKD, and at present their eGFR is calculated using the same formulae. Usually, they will be on three types of immunosuppression including prednisolone, an anti-proliferative (mycophenolate mofetil or azathioprine) and a calcineurin inhibitor (tacrolimus or ciclosporin). Patients must be fully adherent to their regimen to prevent rejection. It must be kept in mind that if acutely unwell they may need to increase their dose of steroid and that certain medicines (e.g. clarithromycin, diltiazem, fluconazole, rifampicin) will interact with the metabolism of calcineurin inhibitors and affect drug levels leading to either toxicity or under-dosing, and alternatives are preferred where possible. If this is not possible blood levels of calcineurin inhibitors should be closely monitored.

Key messages

- Use the CKD EPI 2021 formula to estimate GFR
- Be aware of instances when eGFR based on creatinine may be inappropriate
- Use a formulary to identify medicines with known nephrotoxicity
- Weigh risk vs benefit when considering administration of nephrotoxic medications, and avoid wherever possible
- Use a formulary to plan the most appropriate dosing schedule

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Self-Assessment Questions – Prescribing in Chronic Kidney Disease

A patient's eGFR is 32 ml/min//1.73m2 as per the CKD-EPI formula. As she has had abnormal kidney function for at least 6 months she has CKD. This places her in CKD stage G3b based on GFR. She also falls into stage A3 based on the level of albuminuria.

Which of the following aspects of pharmacokinetics do you expect to be affected?

A. Absorption
B. Distribution
C. Metabolism
D. Elimination
E. All of the above

Answer E.

Consider the case presented above. Which of the medications should be changed? Select all that are relevant.

A. Metformin
B. Losartan
C. Empagliflozin
D. Atorvastatin
E. Gliclazide

It is best to consult a renal formulary when prescribing in CKD. In this case A and B should be changed. Metformin is excreted by the kidney and accumulates in kidney disease. Its dose must be halved when the eGFR falls below 45 ml/min and stopped below 30 mL/min. The maximum dose she should be on is 1g daily. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are reno-protective in albuminuric CKD, and must be prescribed at maximum tolerated dose for full effect. This would be 50 mg b.d. and as her symptoms, blood pressure and serum potassium levels are stable this can be done. Empagliflozin provides cardiorenal protection and must be continued until dialysis or transplantation. Similarly, atorvastatin must be continued. Gliclazide, is metabolized in the liver and is safe for use in patients with CKD, though as GFR falls risk of hypoglycaemia due to reduced insulin catabolism increases.

Pharmacogenomics and precision medicine: implications for prescribing

Introduction

Patients receiving the same medicine at the same dose often show marked differences in response. Some achieve satisfactory therapeutic benefit, while others experience little or no effect, and a small proportion develop serious adverse reactions. Traditionally these differences have been attributed to age, co-morbidities, organ function, drug interactions and adherence. However, an additional major determinant is genetic variation.

Pharmacogenomics refers to the study of how inherited genetic variation affects an individual's response to medicines. Precision medicine is a broader concept that incorporates pharmacogenomics together with clinical, environmental and lifestyle factors to guide personalised treatment decisions. For prescribers, pharmacogenomics has a practical goal: to improve efficacy and safety of medicines by tailoring therapy to an individual patient's genetic profile. This can influence three key aspects of prescribing: 1) choice of medicine, 2) dose selection and 3) prediction and prevention of adverse reactions. Several pharmacogenomic associations are now well established internationally, and growing evidence from South Asian populations indicates that clinically relevant genetic variants are common in this region, with differences in prevalence in comparison to other major global ethnicities. Understanding the basic principles of pharmacogenomics is therefore becoming increasingly important for clinicians.

Mechanisms underlying pharmacogenomic variation

Genetic variation affects the response to medicines mainly through changes in metabolism, transport, or targets. These variations typically occur as single nucleotide polymorphisms (SNPs) or other genetic variants in genes encoding proteins involved in pharmacokinetics or pharmacodynamics.

Metabolism of medicines

Many medicines are metabolised by hepatic enzymes belonging to the cytochrome P450 (CYP450) family. Genetic variants in these enzymes can alter metabolic capacity. Individuals may therefore be classified as:

- Poor metabolisers – markedly reduced enzyme activity
- Intermediate metabolisers – reduced activity
- Normal metabolisers – typical activity
- Ultra-rapid metabolisers – increased enzyme activity

Reduced metabolism may lead to the accumulation and toxicity of medicines, whereas increased metabolism may lead to subtherapeutic levels and treatment failure (vice versa in the case of pro-drugs). Examples of clinically important CYP enzymes include: CYP2C9, CYP2C19 and CYP2D6. Variants affecting these enzymes influence the metabolism of many commonly prescribed medicines including anticoagulants, antiplatelet agents, antidepressants and analgesics.

Transport of medicines

Transporters regulate the movement of medicines into and out of cells. Genetic variation in transporter proteins can therefore alter absorption, distribution and elimination of medicines.

One clinically important transporter is SLCO1B1, which encodes a hepatic transporter responsible for the uptake of several statins into liver cells. Reduced transporter function can increase circulating statin concentrations and increase the risk of statin-induced myopathy. Transporter variants may therefore influence both efficacy and toxicity of medicines.

Targets of medicines

Genetic variation may also occur in targets of medicines, such as receptors or enzymes that medicines interact with. Changes in these proteins can alter binding and pharmacological response. This mechanism is particularly relevant in oncology, cardiovascular pharmacology and immunomodulatory therapy. Such variations may lead to reduced therapeutic response despite adequate drug concentrations, highlighting the importance of pharmacodynamics in pharmacogenomics.

Case scenario 1: Statin intolerance

A 56-year-old man with type-2 diabetes and dyslipidaemia is started on simvastatin for primary prevention of cardiovascular disease. Two months later he complains of muscle pain and fatigue. His creatine kinase is elevated. The statin is stopped and symptoms resolve. When a lower dose is attempted, the symptoms recur. Because of suspected

statinintolerance, pharmacogenomic testing is performed. The patient is found to carry a reduced-function variant in the *SLCO1B1* gene.

Pharmacogenomic mechanism

The *SLCO1B1* gene encodes a hepatic transporter responsible for uptake of statins into hepatocytes. Reduced transporter function leads to decreased hepatic uptake of statins, increased circulating statin concentrations and increased exposure of skeletal muscle to statins. This mechanism explains the increased risk of statin-associated myopathy in patients carrying reduced-function *SLCO1B1* variants.

Relevance to Sri Lanka

Pharmacogenomic studies conducted in Sri Lankan populations have demonstrated that genetic variants affecting statin transport and metabolism are present at clinically relevant frequencies [1]. In a Sri Lankan pharmacogenomic study, the *SLCO1B15* (rs4149056) variant, which reduces hepatic statin uptake and increases the risk of statin-associated myopathy, was observed with a minor allele frequency (MAF) of approximately 18%. These findings suggest that genetic determinants of statin efficacy and toxicity are relatively common in Sri Lankan patients, which may partly explain the variability in statin response and susceptibility to muscle toxicity observed in clinical practice.

Case scenario 2: Clopidogrel treatment failure

A 63-year-old man undergoes percutaneous coronary intervention with stent placement following an acute coronary syndrome. He is discharged on dual antiplatelet therapy with aspirin and clopidogrel. Six months later he presents with recurrent chest pain. Coronary angiography demonstrates stent thrombosis despite adherence to medication. Because of suspected inadequate platelet inhibition, pharmacogenomic testing is performed. The patient is found to carry a loss-of-function variant in the *CYP2C19* gene.

Pharmacogenomic mechanism

Clopidogrel is a pro-drug that requires activation by hepatic enzymes, primarily CYP2C19. Loss-of-function variants reduce formation of the active metabolite. As a result, platelet inhibition is reduced, antiplatelet effect is inadequate and risk of thrombotic cardiovascular events increases. This is a classic example of pharmacogenomic variation affecting activation of a medicine.

Relevance to Sri Lanka

Pharmacogenomic studies conducted in Sri Lanka have shown that *CYP2C19* variants affecting clopidogrel activation occur frequently in the population [2]. In a study of Sri Lankan individuals, two variants associated with reduced CYP2C19 enzyme activity were particularly common:

- *CYP2C19* rs12769205 – MAF ~42%
- *CYP2C19* rs4244285 – MAF ~42%

These variants impair the metabolic activation of clopidogrel and are associated with reduced antiplatelet effect. Because clopidogrel remains widely used in the management of acute coronary syndromes and after coronary stenting, these findings suggest that a significant proportion of Sri Lankan patients may have reduced responsiveness to clopidogrel, potentially contributing to variability in treatment outcomes.

Case scenario 3: Warfarin sensitivity

A 72-year-old woman with atrial fibrillation is started on warfarin for stroke prevention. Within the first week her INR rises markedly, despite receiving a low initial dose. She develops minor bleeding manifestations. Because of the unusually high sensitivity to warfarin, pharmacogenomic testing is performed. The patient is found to carry variants in *CYP2C9* and *VKORC1* associated with increased sensitivity to warfarin.

Pharmacogenomic mechanism

Two key genetic mechanisms contribute to warfarin dose variability in the above scenario.

1. *CYP2C9* variants - CYP2C9 is the main enzyme responsible for metabolising warfarin. Reduced activity leads to slower metabolism and higher plasma drug concentrations.
2. *VKORC1* variants - Warfarin inhibits vitamin K epoxide reductase, encoded by the *VKORC1* gene. Variants in this gene alter the sensitivity of the enzyme to warfarin inhibition.

Patients with these variants often require lower maintenance doses and are at increased risk of bleeding if standard doses are used.

Relevance to Sri Lanka

Warfarin pharmacogenomic studies conducted in Sri Lankan populations have demonstrated that variants

affecting both warfarin metabolism and pharmacodynamic response are present locally [3]. Variants affecting warfarin metabolism include:

- *CYP2C9*3* – MAF ~10%
- *CYP2C91*4* – MAF ~2–3%
- *CYP2C9*2* – MAF ~2%

Variants affecting warfarin pharmacodynamic response through the *VKORC1* gene were also identified, including:

- *VKORC1* rs7294 – MAF ~47%
- *VKORC1* rs9934438 – MAF ~10%
- *VKORC1* rs8050894 – MAF ~10%

These findings indicate that genetic factors contributing to warfarin dose variability are common in Sri Lankan patients, supporting the potential value of genotype-guided dosing strategies in the future.

Clinical Implications

Increasing evidence from studies conducted in Sri Lankan populations indicates that several clinically relevant pharmacogenomic variants are present locally, highlighting the importance of considering genetic factors when interpreting variability in treatment response. While routine pharmacogenomic testing is not yet implemented in clinical practice, awareness of these mechanisms can help clinicians recognise situations where genetic variation may contribute to unexpected toxicity of medicines or treatment failure.

The case scenarios presented here illustrate pharmacogenomic influences on commonly used cardiovascular medicines such as statins, clopidogrel and warfarin. However, pharmacogenomic variability is also relevant to several other therapeutic areas. For example, studies in Sri Lankan populations have identified variants affecting the metabolism and toxicity of fluoropyrimidine chemotherapy, where reduced activity of the enzyme dihydropyrimidine dehydrogenase (DPYD) may predispose patients to severe toxicity when treated with medicines such as 5-fluorouracil or capecitabine.

Similarly, variants affecting thiopurine metabolism, particularly involving enzymes such as NUDT15, may increase the risk of severe myelosuppression in patients receiving medicines such as azathioprine or mercaptopurine. Genetic variation may also influence the response to tamoxifen, a medicine commonly used in the treatment of hormone receptor–positive breast cancer. Reduced activity of the CYP2D6 enzyme may impair the conversion of tamoxifen to its active metabolite, potentially reducing therapeutic efficacy. Pharmacogenomic variability has also been reported in relation to immunomodulatory and biologic therapies, where genetic differences may influence both treatment response and susceptibility to adverse effects. These examples illustrate that pharmacogenomics is relevant across multiple clinical specialties, including cardiology, oncology, rheumatology and transplant medicine. At present, pharmacogenomic testing may be most useful in situations where:

- a medicine has a narrow therapeutic index
- serious toxicity is unpredictable and potentially preventable
- a drug is a pro-drug requiring metabolic activation
- a patient experiences unexpected toxicity or treatment failure

As genomic technologies become more accessible and cost-effective, pharmacogenomic information is likely to play an increasing role in guiding safer and more effective prescribing. In the interim, understanding the mechanisms by which genetic variation influences response to medicines can help clinicians better interpret variability in therapeutic outcomes and support the gradual integration of precision medicine into clinical practice.

Challenges to implementation

Although pharmacogenomics offers significant potential, several challenges remain before it can be widely implemented in routine clinical practice.

1. Limited clinical outcome data - Many studies describe the frequency of genetic variants, but fewer studies evaluate whether genotype-guided therapy improves clinical outcomes.
2. Access to testing - Pharmacogenomic testing requires specialised laboratory facilities and may not be readily available in many healthcare settings.
3. Cost considerations - The cost-effectiveness of pharmacogenomic testing varies depending on the medicine, the clinical scenario and the prevalence of relevant variants.
4. Clinician awareness - Many clinicians have limited formal training in pharmacogenomics. Increasing awareness and education is therefore essential for successful implementation.

Future directions

Despite these challenges, pharmacogenomics is likely to play an increasingly important role in prescribing. Possible future developments include:

- targeted pharmacogenomic testing in high-risk clinical situations
- integration of pharmacogenomic information into electronic prescribing systems
- development of population-specific prescribing guidelines
- increased collaboration between clinicians, clinical pharmacologists and genetic laboratories

Ultimately, pharmacogenomics has the potential to improve safety, treatment effectiveness and healthcare efficiency.

Conclusion

Pharmacogenomics is an important component of precision medicine and provides a scientific framework for understanding variability in response to medicines. Genetic variation may affect metabolism, transport and pharmacological targets, leading to differences in efficacy and toxicity. Clinically relevant examples include therapy using warfarin, clopidogrel, statins, fluoropyrimidines and thiopurines. Although routine pharmacogenomic testing is not yet widely implemented in many healthcare systems, awareness of these mechanisms can help clinicians interpret unexpected responses to medicines and support the gradual integration of personalised prescribing into clinical practice. As genomic technologies become more accessible, pharmacogenomics is likely to become an increasingly important tool in improving the safety and effectiveness of pharmacotherapy.

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Self-assessment questions - Pharmacogenomics and precision medicine: implications for prescribing

1. Which mechanism best explains statin-associated muscle toxicity related to pharmacogenomic variation?
   A. Increased renal clearance of statins
   B. Reduced hepatic uptake of statins due to transporter variants
   C. Increased statin absorption from the intestine
   D. Increased statin metabolism in the liver
   E. Reduced protein binding of statins

2. Reduced response to clopidogrel is most commonly related to genetic variation in which mechanism?
   A. Reduced platelet receptor binding
   B. Reduced intestinal absorption
   C. Reduced hepatic activation of the pro-drug
   D. Increased renal excretion
   E. Increased plasma protein binding

3. Warfarin dose variability is mainly explained by variation in which two pathways?
   A. Warfarin absorption and protein binding
   B. Warfarin metabolism and drug target sensitivity
   C. Renal excretion and transporter activity
   D. Warfarin absorption and renal elimination
   E. Warfarin transport and protein binding

Self-assessment questions (MCQs) - Answers

Question 1 – Answer B
Variants in the SLCO1B1 transporter gene reduce uptake of statins into hepatocytes. This increases circulating statin concentrations and raises the risk of muscle toxicity.

Question 2 – Answer C
Clopidogrel is a pro-drug requiring metabolic activation by the CYP2C19 enzyme. Variants reducing enzyme activity lead to lower active metabolite concentrations and reduced platelet inhibition.

Question 3 – Answer B
Warfarin response is influenced by variants affecting CYP2C9-mediated metabolism and VKORC1-mediated target sensitivity, which together explain much of the variability in warfarin dose requirements.

Regulatory News from the National Medicines Regulatory Authority (NMRA)

Finerenone

- Available strengths – 10mg, 20mg
- Dosage form – Film coated tablet
- Pharmacotherapeutic group – Non-steroidal mineralocorticoid receptor antagonist, diuretics
- ATC code – C03DA05

Pharmacodynamics

Finerenone is a non-steroidal selective mineralocorticoid receptor antagonist. In physiological conditions the receptor is activated by aldosterone and cortisol and regulates gene transcription. Activation of the complex leads to recruitment of transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators.

At recommended doses finerenone inhibits the action of aldosterone. Finerenone has a high potency and selectivity for the mineralocorticoid receptor. Since finerenone is non-steroidal it does not have sex hormone related adverse effects such as gynecomastia. Binding finerenone to the receptor causes inhibition of transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators.

Pharmacokinetic properties

Absorption

Finerenone is almost completely absorbed after oral administration. Absorption is rapid with maximum plasma concentrations (C_{max}) appearing between 0.5 and 1.25 hours after tablet intake in the fasted state. The absolute bioavailability of finerenone is 43.5% due to first-pass metabolism in the gut-wall and liver. Although with high fat, high calorie food finerenone AUC is increased by 21% and C_{max} reduced by 19%, with prolonged time to reach C_{max}, this is not considered as clinically relevant, and finerenone can be taken with or without food.

Distribution

The volume of distribution at steady state of finerenone is 52.6 L. The human plasma protein binding of finerenone in vitro is 91.7%, with serum albumin being the main binding protein.

Metabolism

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. All metabolites are pharmacologically inactive.

Elimination

The elimination of finerenone from plasma is rapid with an elimination half-life (t½) of about 2-3 hours. About 80% of the administered dose is excreted via urine and approximately 20% of the dose is excreted via faeces. Excretion is almost exclusively in the form of metabolites.

Indication and dosage

Treatment of chronic kidney disease with albuminuria associated with type-2 diabetes mellitus

eGFR (mL/min/1.73m^2)	Starting dose (Once daily)
≥ 60	20mg
≥ 25 to < 60	10mg
< 25	Not recommended

It is recommended in chronic kidney disease associated type-2 diabetes mellitus when the serum potassium is less than 4.8mmol/L and may be considered with careful monitoring between 4.8 to 5 mmol/L. If serum potassium is more than 5mmol/L, initiation of finerenone is not recommended.

Contra-indications

- Hypersensitivity to the active substance or excipients
- Concomitant use of strong CYP3A4 inhibitors (e.g. Ketoconazole, Clarithromycin)
- Addison's disease

Special warnings and precautions for use

- Hyperkalemia.
- Renal impairment
- Hepatic impairment
- Heart failure
- Moderate and weak CYP3A4 inhibitors
- Strong and moderate CYP3A4 inducers
- Grapefruit

Adverse effects

- Hyperkalemia
- Hyponatremia
- Hyperuricemia
- Hypotension
- Pruritus

Interactions

Since finerenone is almost metabolized via cytochrome p450 mediated oxidative metabolism via CYP3A4,

1. CYP3A4 inhibitors – Increases finerenone concentration, thus strong CYP3A4 are contra-indicated in concomitant use with finerenone.
2. Moderate inhibitors such as verapamil causes significant increase in plasma finerenone concentration, increasing the risk of hyperkalemia, thus monitoring of serum potassium is required.
3. Weak inhibitors may cause increase in serum potassium thus monitoring may be required.
4. Concomitant use of grapefruit tends to increase plasma concentration thus should be avoided.
5. Strong and moderate inducers of CYP3A4 – Reduces the therapeutic concentration of finerenone and should be avoided (e.g. Carbamazepine, Phenytoin, Phenobarbital).
6. Other medications that increases the concentration of potassium (e.g. ACEI, ARB)

Use in special populations

Pregnancy

Avoid unless benefit outweighs potential risks. Animal studies have shown embryo foetal developmental toxicity at exposures in excess to the maximum human exposure.

Lactation

Avoid unless benefit outweighs potential risks. It is unknown whether finerenone or its metabolites are excreted in human breast milk. Available pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk.

Fertility

No human data on the effect of finerenone on fertility is available. Animal studies with finerenone did not indicate a risk of impaired male fertility. Women of childbearing potential should use effective contraception during treatment with finerenone.

References

1. Specifications of products characteristics approved by the NMRA

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Medication Safety Corner: Carbamazepine and Steven Johnson Syndrome

Introduction

Carbamazepine (CBZ) is a commonly used anti-seizure medicine in both paediatric and adult populations, especially in focal seizures, and in other conditions such as bipolar affective disorder and trigeminal neuralgia. It is known to cause hypersensitive skin syndromes including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) as adverse effects [1]. SJS and TEN are life threatening conditions, with a mortality rate of 1-5% in SJS and 25-30% in TEN [2].

Stevens Johnson Syndrome and TEN are mucocutaneous disorders, for which common aetiological agents include medicines, such as allopurinol, carbamazepine, lamotrigine and phenytoin [3]. The classification is based on the percentage of the skin detachment area (SJS <10%, TEN >30%, SJS/TEN overlap between 10-30%). Common mucocutaneous manifestations include, painful erythematous rash, painful ulcers in the mouth, eyes and throat, bullae around the face and the trunk area, with the skin lesion often testing positive for Nikolsky sign. These are accompanied by systemic manifestations such as fever [4]. The SCORTEN severity illness score is widely used to predict the mortality. The most common cause of death is sepsis induced multiorgan failure [2].

Incidence and Risk Factors

Although hypersensitivity reactions with CBZ seen in around 10% of patients, CBZ induced SJS/TEN are much rarer [3]. The risk of development is highest during the first few months of starting the medicine and is 10 times higher in the South Asian countries [5] and studies have shown strong genetic link with HLA-B*15:02 allele and CBZ induced SJS/TEN [6]. This association is most prevalent in Southeast Asian countries such as Thailand, Malaysia, Philippines, China and Taiwan. Hence the FDA has recommended HLA-B*15:02 screening for individuals of Asian ancestry prior to initiation of therapy. Recent studies suggest HLA- B*15:21 is also another significant risk allele in the South Asian population [7]. Retrospective case-control studies in patients of European, Korean and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA- A*31:01, an inherited allelic variant of the HLA-A gene, in patients using CBZ [8].

Mechanisms

Although the exact mechanism is not fully understood, it is believed that the medicine bind with T cell receptors (TCR) and initiate the immune reaction. Four hypotheses have been proposed to explain how the immune system is activated in an HLA molecule-dependent manner:

- the “hapten/ prohapten” theory,
- the “p-i” concept,
- the “altered peptide repertoire” model
- The “altered TCR repertoire” model

Recent studies suggest that the CBZ molecule binds to the HLA-B∗15:02 molecule, forming a complex that is presented to the TCR. The activation of the HLA and TCR complex leads to recruitment and expansion of specific CD8+ cytotoxic T cells, resulting in cellular death. In SJS/TEN this will lead to death of keratinocytes leading to skin and mucosal manifestations. The occurrence of this condition predominantly in certain populations suggests that the genetic background and the frequency of the HLA-B∗15:02 allele plays a key role [8].

Management

Management should be multidisciplinary. Immediate discontinuation of CBZ and providing supportive care which includes intravenous fluids, nutritional support, eye care, wound care and pain relief, together with oxygen if required. Daily skin care needs to be provided. If the lesions are complicated with infection, antibiotics need to be prescribed based on clinical suspicion. Sometimes steroids and in severe and refractory instances intravenous immunoglobulin, plasmapheresis, TNF alpha blockers may be used [2,4].

Systemic steroids: Recent studies suggested a beneficial role for corticosteroid treatment. A European multi-center retrospective study and a recent meta-analysis of observational studies showed the beneficial effects of corticosteroids [9,10].

Intravenous immunoglobulins: The exact mechanism how IVIG acts in SJS is not known. The largest retrospective study in this field, the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) showed IVIG did not improve mortality compared with supportive care alone [9]. However, recent meta-analyses have shown that high-dose IVIG (≥ 2 g/kg) has a beneficial effect in decreasing the mortality of SJS/TEN [11].

Plasmapheresis: Several studies have shown that plasmapheresis is effective in the treatment of SJS/TEN. Its purpose is to remove pathogenic factors such as a medicine, its' metabolites, and disease-induced cytokines/chemokines from the patient's blood. Plasmapheresis sessions are carried out every other day or daily. It is a safe treatment and can be performed with minimal adverse effects. However, evidence remains equivocal [4].

Prevention

Prevention of CBZ induced SJS/TEN includes rational prescribing of the medicine, especially in high-risk individuals, where benefits outweigh the risk and screening for HLA–B*15:02 and avoiding CBZ in an individual with a previous history of SJS or adverse skin reaction [12]. Patients positive for HLA–B*15:02 should also be cautious with structurally similar medicines, such as oxcarbazepine, aromatic anti-seizure medications such as phenytoin, and fosphenytoin (Figure 1) [6].

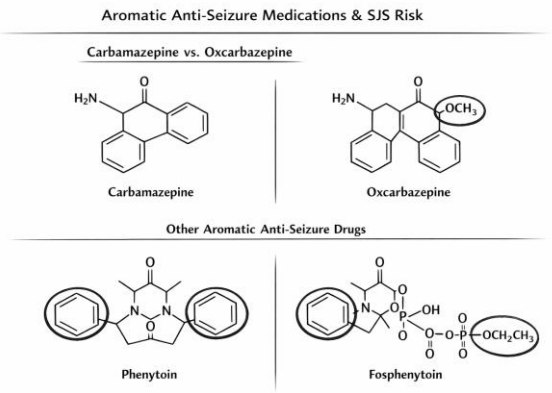

Figure 1: Structure of Carbamazepine and related medicines

Studies done in Sri Lanka has revealed that the prevalence of HLA–B*15:02 is about 4.5% [13].

Message to clinicians

- Screening for genetic markers such as HLA-B*15:02 will help to identify individuals at increased risk of developing CBZ-induced SJS, if the facilities permit, especially if the individual has an ancestry where HLA-B*15:02 is common [6,12].
- Patients should be counselled to immediately report rash or mucosal symptoms during the first few months of therapy.
- It is best to avoid re-administration of CBZ in patients with a previous history of SJS or adverse skin reaction [12].
- In patients who are positive for HLA-B*15:02 or HLA-A*31:01, alternative medications should be used as first-line therapy [6].

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