

4. Doctor's Companion by Medhand Mobile Library

This app allows access to 161 book titles which makes checking up on information easy. One of the all time favourite is that of the 5 Minute Clinical Consult which is updated annually. This eBook provides information on medical conditions in an easy to read and accessible format. Unfortunately most are paying titles.

In conclusion, despite a busy clinic, it would be difficult to justify that one has no time to look for good medical information. With iPad, tablet and mobile computing devices becoming ubiquitous and more and more medical apps available, such evidence-based medical information should be available literally at your fingertips.

References:

- (1) Systolic Blood Pressure Intervention Trial (SPRINT)
A Randomised Trial of Intensive Vs. Standard Blood Pressure Control, The SPRINT Research group, NEJM, Vol 373, No 22, p2103-2116, Nov 25, 2015.
- (2) Primary vs. Secondary Sources of EBM, Dr. Sohail Bajammal, OCT 2011

■ CM

Q&A WITH THE EXPERTS:

Acyclovir Toxicity in Patients with Chronic Kidney Disease

by Dr See Toh Kwok Yee, MCFP(S), Editor

Herpes zoster is characteristically a medical affliction of the elderly and is commonly seen in General Practice. GPs usually start an antiviral agent to reduce the duration of active zoster, zoster associated pain, and to prevent postherpetic neuralgia. Acyclovir is the treatment of choice due to physician familiarity and cost.

Among the elderly, aside from the often-encountered comorbidities like Hypertension, T2DM and Dyslipidemia, the presence of renal insufficiency should always be borne in mind and taken into consideration in prescribing drugs especially those with serious toxic effects.

Acyclovir has an oral bioavailability of 10 - 20% and is excreted in the kidneys. Patients with chronic kidney disease (CKD) are vulnerable to drug toxicity due to their reduced ability to eliminate unchanged acyclovir in the urine [1]. Therefore, its half-life elimination can increase from 2 – 3.5 hours in normal renal function to > 24 hours in anuric patients, leading to drug overdosage.

College Mirror (CM) is accorded the privilege of a Q&A session with the following distinguished panel of specialists to seek their expert opinions on the use of Acyclovir in elderly patients with CKD:

Dr. Clara Lee Ying Ngho

Division of Nephrology, University Medicine Cluster, National University Health System, Singapore, Singapore

Dr. Joy Vijayan

Division of Neurology, University Medicine Cluster, National University Health System, Singapore, Singapore

Dr. Huma Jaffar

Division of Dermatology, University Medicine Cluster, National University Health System, Singapore, Singapore

Dr. Horng-Ruey Chua

Division of Nephrology, University Medicine Cluster, National University Health System, Singapore, Singapore

Q1.

Are there clinical or laboratory parameters the GP must be mindful of when prescribing acyclovir in CKD patients?

Clinical

1. Consider if acyclovir is indicated

The Centre for Disease control and Prevention (CDC) guidelines recommend that antivirals should be started within 72 hours of onset of rash to be most effective. It has also been reported that antivirals are no longer helpful once zoster lesions have crusted.

However, CKD and ESRD patients are at higher risk for prolonged zoster associated pain, disseminated herpes zoster and post-herpetic neuralgia. As such, we suggest that acyclovir be considered in all CKD and ESRD patients with herpes zoster even beyond the 72 hours window.

Patients with kidney transplants are also at higher risk of morbidity and complications. The live vaccine which may prevent VZV primary infection and reactivation are also contraindicated in these patients on immunosuppressive therapy. Therefore acyclovir is indicated for herpes zoster in these individuals. Such patients should be asked to notify their respective specialists-in-charge as soon as possible.

2. In elderly patients especially with CKD, assess for risk factors which predispose to acute kidney injury (AKI)

- Hypotension or severe dehydration in relation to acute illnesses.
- Concurrent use of other nephrotoxins (NSAIDs, colchicine).
- Baseline high doses of renin-angiotensin-aldosterone system blockers including ACE-inhibitors or angiotensin-receptor blockers (ARB).

(continued on the next page)

(continued from Page 19: Q&A with the Experts)

Patients in a dehydrated state with poor urine output are at risk for precipitation of acyclovir crystals in the renal tubules, which can lead to an obstructive nephropathy. Other potential mechanisms of injury include acute interstitial nephritis and acute tubular necrosis. The above factors will contribute to development of AKI.

3. In advanced CKD or even ESRD patients, it is imperative to take a history for

- Severity of CKD. How advanced is advanced? The patient may be able to quote you the estimated glomerular filtration rate (eGFR). Common terms used include “percentage function left”.
- Modality of dialysis, if any. This is important as acyclovir is cleared better with hemodialysis than peritoneal dialysis. The drug clearance is certainly even poorer if the patient has advanced disease not yet on dialysis.

4. Drug interactions

Few drugs interact with acyclovir. However, the following are examples where caution must be exercised

- Mycophenolate mofetil:
This immunosuppressant is encountered in patients with post solid organ transplant and patients with rheumatoid arthritis. Acyclovir increases the serum concentration of mycophenolate, predisposing to cytopenias and gastrointestinal upset. Likewise, mycophenolate can increase the serum concentration of acyclovir, predisposing to toxicity
- Zidovudine:
A antiretroviral medication used in management of HIV/AIDS, its central nervous system (CNS) depressant effect is enhanced by acyclovir and can result in cognitive impairment and drowsiness.

If gabapentin and opiate analgesics are prescribed concomitantly in a CKD patient with herpes zoster, dose adjustment must be made as all 3 drugs can cause neurotoxicity.

Laboratory

Serum creatinine and electrolytes should preferably be checked before starting acyclovir in every patient. If this is not practicable, taking a detailed history can be helpful.

For instance, patients with Diabetes mellitus (DM), which is the major cause of CKD in Singapore, risk factors for CKD should be sought for. These include the presence of neuropathy, hypertension, longer duration of DM, poor glycemic control, cardiovascular disease, proliferative retinopathy, and older age.

Q2.

What are the dose titrations that need to be made in CKD and is there a quick reference the GP can use?

Kidney Disease Improving Global Outcome (KDIGO) group guidelines recommend using the Cockcroft-Gault Equation or Modification of diet in renal disease (MDRD) equation to calculate estimated creatinine clearance or eGFR for drug dosing, respectively. The Cockcroft-Gault and MDRD calculators are available online.

- www.mdcalc.com

Clinicians are reminded to note the following limitations.

- The MDRD eGFR equation is also not valid for eGFR > 60 or < 10 ml/min/1.73 m2.
- The CKD stage is arbitrarily set based on a numerical CrCl cut-off, but elimination of acyclovir does not necessarily follow a linear decrement as CrCl falls.

Acyclovir is 60% dialyzable on regular haemodialysis (HD) but, on the other hand, peritoneal dialysis (PD), is very inefficient in removing the drug.

Based on available guidelines, we recommend the following dose adjustment [2,3]:

Oral acyclovir dosing

- CrCl > 50 mL/min/1.73m2: 800 mg 5 times daily
- CrCl 30 – 50 mL/min/1.73m2: 800 mg 8h
- CrCl 10 – 29 mL/min/1.73m2: 800mg 12h
- CrCl < 10 mL/min/1.73m2: 800 mg daily
- ESRD
 - o HD (assuming thrice weekly sessions): 800 mg daily, to be administered post-HD on dialysis days
 - o PD: 400 – 600 mg daily, higher doses of 500 – 600 mg can be administered if the patient has residual renal function of more than 500 mL/day

IV dosing is not covered in this discussion. If the patient is ill, he should be admitted.

Online guides to acyclovir dosing include

- UpToDate 2016
- www.drugs.com
- <http://mims.com/>

Q3.

A serious toxic effect of acyclovir is neurotoxicity. What are the salient features and what immediate steps should the GP take?

The GP needs to differentiate acyclovir induced encephalopathy from VZV associated encephalitis.

Clinical features	Acyclovir induced encephalopathy	VZV associated encephalitis
Fever and headache	Uncommon	Common
Mental status	Steady deterioration with a temporal association between symptoms and acyclovir use Vivid hallucinations, death delusions	Fluctuates
Focal neurological signs	Uncommon; myoclonus	Common
Seizures	Generalised	Can be focal

Basic laboratory investigations	Leucocytosis uncommon, but can occur.	Leucocytosis common Occasionally, lumbar puncture, electroencephalography (EEG) and magnetic resonance imaging (MRI) of the brain are required to make a definitive diagnosis.
---------------------------------	---------------------------------------	--

It can be difficult to distinguish the two based only on clinical features alone as intercurrent sepsis can mar the picture. If the patient becomes confused, we advise temporarily stopping acyclovir and an immediate referral to the nearest Accident and Emergency department be made.

A memo must be provided detailing the patient’s medications, including date of onset, duration of exposure, and dosing. This information is critical for the hospital colleagues receiving the patient.

Q4. What are the sequelae and mortality rates with acyclovir induced neurotoxicity?

Sequelae include seizures degenerating into status epilepticus, coma and even death.

In patients with significant residual renal function, forced diuresis and IV hydration can be attempted for removal of acyclovir, but the efficacy is unclear.

The margin of error is small should we attempt to aggressively hydrate a patient with moderate to advanced CKD.

In patients with advanced CKD or ESRD, haemodialysis is the preferred treatment for severe acyclovir toxicity.

Mortality risks appeared to increase with age, co-morbidity and prior cerebral insults.

Q5. Are the same precautions necessary with the use of other available antiviral agents such as valacyclovir and famciclovir?

The same precautions apply to valacyclovir and famciclovir.

Valacyclovir is a pro-drug of acyclovir, with markedly greater bioavailability than acyclovir (55% vs. 15%). Its subsequent pharmacology follows that of acyclovir.

Famciclovir is a pro-drug of peniclovir and undergoes extensive metabolism to peniclovir upon oral administration. Peniclovir is predominantly excreted by the kidney.

Q6. How should a patient be followed-up after he has been prescribed acyclovir?

Neurotoxicity has been reported in CKD and ESRD patients even when dose adjusted acyclovir is prescribed[1]. Hence all patients need close clinical monitoring for the duration of acyclovir therapy.

Therefore, it is our opinion that a review of the patient after 2 – 3 days of therapy is advisable to look out for unusual symptoms. The repeat visit will also allow the clinician to adjust the dose according to the laboratory results which by now should have become available.

Q7. Should the Zoster vaccine be routinely recommended to elderly patients with CKD?

CDC guidelines recommend that ESRD patients aged ≥ 60 years receive a single dose of the zoster vaccine, regardless of whether they report a prior episode of herpes zoster. This is a live vaccine and is contraindicated in allogenic transplant recipients who are on immunosuppression or who are HIV positive.

Studies have shown that the zoster vaccine reduces the occurrence of herpes zoster by approximately 50%, with the highest benefit (64%) in patients aged 60 – 69. For patients who were vaccinated but still developed herpes zoster, the duration of pain was reduced by approximately 10%.

CM thanks the panel for their insightful and informative contribution.

REFERENCES

1. Almond, M.K., S. Fan, and S. Dhilon, Avoiding acyclovir toxicity in patients with chronic renal failure undergoing haemodialysis. *Nephro*, 1995.69: p. 428-32.
2. Joint Formulary Committee 2015 62nd edition, British National Formulary, British Medical Association and Royal Pharmaceutical Society of Great Britain: London.
3. Aronoff, G.R., Prescribing in Renal Failure: Dosing Guidelines for Adults, in American College of Physicians, 4th Edition. 1999: Philadelphia.

■ CM