BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

Acyclovir-induced acute renal failure and the importance of an expanding waist line

Ahmed Seedat,[1] Georgia Winnett[2]

[1]Department of General Medicine, Basildon and Thurrock University Hospitals NHS, Foundation Trust, Basildon, UK
[2]Department of Renal Medicine, Basildon and Thurrock University Hospital NHS, Foundation Trust, Basildon, UK

Correspondence to Dr Seedat Ahmed, aseedat@doctors.org.uk

Summary

A 23-year-old gentleman with no significant medical history other than obesity was admitted with a history of balance problems, double vision and strange behaviour following a fall from bed. Systems examination was unremarkable. The patient was given intravenous acyclovir and intravenous ceftriaxone given the suspicion of encephalitis/meningitis. Investigations including routine bloods, CT/MRI Head and lumbar puncture were unremarkable. Within 48 h of commencing intravenous acyclovir, there was a marked deterioration in renal function. On stopping acyclovir therapy, renal function improved back to baseline. No other cause for deterioration in renal function was identified. The most likely cause for acute renal failure was secondary to acyclovir therapy. This has been well documented and is due to intratubular crystal precipitation. Moreover, in this case nephrotoxicity is likely secondary to the large boluses of intravenous acyclovir that had been given as prescribed according to the total body weight.

BACKGROUND

Acyclovir-induced acute renal failure, which is caused due to intratubular crystal precipitation has been well documented. The basis for a diagnosis of crystal-induced nephropathy is supported by the clinical history and time course of acyclovir administration. Moreover, in this case nephrotoxicity is likely secondary to the large boluses of intravenous acyclovir that had been given as prescribed according to the total body weight (TBW).

Drug administration in obese patients is difficult because there is very limited data on which to base dosing guidelines and recommended doses are based on pharmacokinetic data obtained from individuals with normal weights. Subsequently, mistakes in determining appropriate doses are often made. Moreover, comorbidities in these patients and the function of organs involved in drug elimination (eg, kidney and liver) can be affected making pharmacokinetics more difficult.

CASE PRESENTATION

A 23-year-old white British gentleman was admitted with a history of balance problems, double vision and strange behaviour following a fall from the bed 1 week before.

The only significant medical history of note was depression. He had never smoked, denied recreational drug use and was currently living with his parents and working as an IT technician. There had been no recent travel.

On examination, the patient was morbidly obese weighing 111.5 kg, otherwise systems examination was unremarkable.

INVESTIGATIONS

Bloods on admission: Na 141 mmol/l, K 4 mmol/l, urea 3.7 mmol/l, creat 75 umol/l, C-reactive protein (CRP) <2 mg/l, Hb 14.8 g/dl, white cell count (WCC) 9.5×10^9 per litre, plt 266×10^9 per litre, normal liver function tests.

On day 2 bloods showed: Na 142 mmol/l, K 4.2 mmol/l, urea 5.2 mmol/l, creat 172 umol/l, CRP 3 mg/l, Hb 14.7 g/dl, WCC 10.8×10^9 per litre, plt 231×10^9 per litre.

On day 4 bloods showed Na 139 mmol/l, K 4.7 mmol/l, urea 13.5 mmol/l, creat 692 umol/l, CRP 74 mg/l, Hb 12.3 g/dl, WCC 10×10^9 per litre, plt 209×10^9 per litre.

Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody and cytomegalovirus PCR were negative. Serum complement was normal.

A lumbar puncture was performed. Cerebrospinal fluid (CSF) results showed no organisms, white blood cell 0/mm^3, red blood cell 139/mm^3, glu 4.1 mmol/l, pro 0.49 g/l.

CT Head performed on admission was normal.

An MRI brain was normal.

Ultrasound of the kidneys, ureter and bladder was performed, which showed that both kidneys were of normal size and echotexture. There was no evidence of hydronephrosis.

DIFFERENTIAL DIAGNOSIS

- Meningitis
- Encephalitis
- Acute renal failure secondary to acyclovir therapy

TREATMENT

Given the suspicion of meningitis/encephalitis, the patient was given intravenous acyclovir 10 mg/kg eight hourly and ceftriaxone 2 g intravenous six hourly empirically. Following deterioration of renal function, acyclovir therapy was stopped. The patient had received four doses of 1.1 g intravenous acyclovir, 4.4 g in total. Antibiotic therapy was stopped shortly afterwards (completed three doses) as there was no further evidence to support a diagnosis of meningitis or encephalitis.

OUTCOME AND FOLLOW-UP

On cessation of acyclovir therapy, renal function improved back to baseline. The patient developed fatigability in addition to diplopia and was started with steroid therapy as there was a suspicion of myasthenia gravis. Spirometry, nerve conduction study, electromyography, CSF oligoclonal bands and acetylcholine receptor antibodies were unremarkable. MRI whole spine was normal. Once medically stable, the patient was discharged on reducing doses of steroids. He was followed up as an outpatient under the care of the neurologists and was eventually referred for neuropsychological assessment to ascertain if there was an organic or psychological cause for his symptoms.

DISCUSSION

Acyclovir-induced acute renal failure has been well documented and is due to intra-tubular crystal precipitation. Acyclovir is rapidly excreted in the urine and has a relatively low solubility. Acyclovir therapy may lead to a deposition of acyclovir crystals in the tubules resulting in intratubular obstruction and foci of interstitial inflammation.[1] There has been some evidence in animal models that acute kidney injury can occur secondary to acyclovir administration without crystal obstruction from effects on renal microcirculation, although the exact mechanism is unknown.[2] There has been sufficient evidence to show that kidney injury secondary to crystal obstruction is the most common mechanism and thus the likely diagnosis in this case.

Renal function typically deteriorates soon after therapy is initiated.[2] Patients may complain of nausea, flank or abdominal pain, presumably induced by urinary tract obstruction.[1] Decline in renal function is usually seen within 24–48 hours following administration, and may be severe[2]; however, complete recovery typically occurs within four to nine days once acyclovir is discontinued.[1]

In some cases, birefringent needle-shaped acyclovir crystals can be seen in the urine, particularly under polarised light. Treatment is largely supportive with adequate hydration and wash-out of crystals with loop diuretics.[1]

In this case, nephrotoxicity secondary to acyclovir therapy may be due to prescribing drugs according to the TBW resulting in very large doses of the drug being given. The global epidemic of obesity has wider implications than just increased mortality and morbidity. Physicians have to be mindful of necessary changes to some conventional therapies when faced with the obese patient. Drug therapy in these individuals is particularly relevant. Drug dosing can be difficult as there are very limited data on which to base dosing guidelines.[3 4]

Drug administration in obese patients is difficult because recommended doses are based on pharmacokinetic data obtained from individuals with normal weights.[5] Subsequently, mistakes in determining appropriate doses can be made. Moreover, comorbidities in these patients and the function of organs involved in drug elimination (eg, kidney and liver) can be affected making pharmacokinetics more difficult.

There are a number of physiological changes occurring in obesity, which can alter both the pharmacokinetics and pharmacodynamic properties of drugs. These include increased adipose tissue, slightly increased lean tissue mass, increased cardiac output, increased glomerular filtration rate and fatty infiltration of liver.[3]

Table 1 Weight calculations for drug dosing

Weight	How to measure	Use
Total body weight (TBW)	Weigh patient	Loading dose for some lipophilic drugs
Ideal body weight (IBW)	Male=50 kg+0.9 kg for each cm>150 cm height Female=45 kg+0.9 kg for each cm>150 cm height	Maintenance dose of drugs where clearance is not changed in obesity
Lean body weight	IBW+1/3×(TBW−IBW) Estimate of fat-free mass	Maintenance doses of most drugs with increased clearance in obesity

Obese patients have a dramatic increase in fat mass as well a small increase in lean tissue. This can make it difficult to determine a dosing weight for an obese patient.[3] A number of different weight calculations have been devised to help with this conundrum (table 1).

Pharmacokinetics in obesity

Oral availability in obese patients does not appear to be different from non-obese patients.[3 6]

Volume of distribution determines loading dose and is dependent on whether the drug in question is hydrophilic or lipophilic. With hydrophilic drugs generally there is no change in volume of distribution. These drugs have limited distribution in body fat and no increase in loading dose is required. Lipophilic drugs are less straightforward. Some exhibit a large increase in volume of distribution, distributed into excess fat, while others show no significant change.[3 6]

Clearance determines maintenance dosing and clearance of many drugs is increased in obesity. This is mainly due to increased glomerular filtration rate. With regard to hepatic clearance in obesity, Cytochrome P450 enzyme activity is increased. Some studies have shown increased clearance via CYP3A4 and increased glucoronidation.[3] However, patients with severe fatty infiltration of liver have poor hepatic function and reduced drug clearance.[6]

Drugs to be aware of:

- *Acyclovir*

Should be adjusted for obese patients and it is generally recommended that ideal body weight (IBW) is used.[7]

- *Low molecular weight heparin (LMWH)*

TBW should be used to calculate the treatment dose of LMWH up to 150 kg. Beyond this safety data are lacking.[8]

- *Digoxin*

Should be adjusted for obese patients and it is generally recommended that lean body weight is used.[7]

- *Gentamicin*

For obese patients requires a dosing weight to be calculated.

Dosing weight=0.4(TBW−IBW)+IBW[9]

Learning points

- Acyclovir-induced acute renal failure has been well documented and is most likely due to intratubular crystal precipitation. Fortunately, complete recovery in renal function is common on cessation of the offending medication.
- The importance of monitoring renal function in hospitalised patients on acyclovir is strongly supported by this case.

BMJ Case Reports 2012; doi:10.1136/bcr-2012-006264

- Drug dosing in obesity:
  - May require dose adjustments.
  - Important to monitor the effects of medication both clinically and if possible with therapeutic drug range monitoring.
  - Maximum recommended doses should not be exceeded.
  - Depending on the drug in question may need to consider prescribing according to ideal body weight, lean body weight or calculate a dosing weight based on recommended formulae.

Competing interests None.

Patient consent Obtained.

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