"Do you think it's a stroke, Doc?"

DALHOUSIE UNIVERSITY Inspiring Minds

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Susan's case

Susan, 48, presents to the ED with a 1 day history of gait disturbance (very unsteady when walking), inability to coordinate, weakness and right-sided headache. On the day prior to presentation she experienced diplopia, which is now resolved. She has no nausea, vomiting, confusion or slurred speech.

Past medical history

- Hydrocephalus (2 ventriculoperitoneal shunts)
- Non-insulin dependent diabetes mellitus (NIDDM)
- Depression
- Migraines
- Neurosarcoidosis

Examination

Susan is afebrile with a temperature of 36.5 °C. Her vital signs are normal, with:

- BP 110/70 mmHg,
- heart rate 68 bpm and
- respiratory rate 16 breaths per minute.

She is awake, alert and orientated. Further examination shows lateral nystagmus and a broad-based gait with ambulation.

Her ECG shows normal sinus rhythm and a CT head scan reveals no evidence of elevated intracranial pressure.

Her serum creatinine is 137 mmol/L (was 78 mmol/L 2 months prior). Complete blood count and differential were within normal limits.

For more on Susan, turn to page 2.

Questions & Answers

1. What is the most likely cause of Susan's presentation?

Susan is likely suffering from gabapentin toxicity due to drug-induced decline in renal function. Her gait disturbance, lateral nystagmus, diplopia, headache and abnormal coordination are all likely early signs of increased gabapentin serum concentrations. Susan has been taking gabapentin for a few years with no prior complaints.

Most commonly, gabapentin toxicity presents as:

- ataxia,
- dizziness,
- somnolence,
- slurred speech,
- diplopia and
- diarrhea.

Chronic ingestion and increasing serum concentrations may present as any of gabapentin adverse effects such as those mentioned above as well as:

- vertigo,
- insomnia,
- confusion,
- fatigue,
- mood changes,
- nausea and
- vomiting.

2. What type of acute renal failure is this?

Renal failure (RF) may occur in three patterns:

1. Pre-renal (decreased perfusion)
2. Intrinsic (structural injury)

Susan's case cont'd...

Medications

- Insulin NPH 30 units q.h.s.
- Insulin lispro p.r.n. for elevated blood glucose
- Metformin 500 mg q.i.d.
- Pioglitazone 30 mg q.d.
- Ramipril 5 mg q.d.
- Atorvastatin 20 mg q.d.
- Levothyroxine 0.175 mg q.d.
- Esomeprazole 40 mg b.i.d.
- Acetazolamide 250 mg q.i.d.
- Bupropion 150 mg b.i.d.
- Quetiapine 100 mg q.am; 200 mg q.pm
- Citalopram 60 mg q.d.
- Gabapentin 600 mg q.am, lunch and supper, 900 mg q.h.s.
- Celecoxib 200 mg b.i.d., started 1 week ago
- Loperamide as needed for diarrhea
- Clonidine 0.05 mg p.r.n. for migraine
- Metoclopramide 10 mg t.i.d. p.r.n. for migraine
- Hydromorphone 2 mg q.6.h to q.8.h p.r.n. for pain

For the resolution of Susan's case, turn to page 4.

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3. Postrenal (obstruction)

Pre-renal failure represents the most common form, (approximately 50% to 80% of cases) and can lead to intrinsic RF if it is not corrected in time. It is reversible when renal blood flow and glomerular filtration rate (GFR) are restored. Pre-renal failure is characterized by inadequate kidney perfusion as a result of decreased circulating volume, intravascular depletion or the use of agents that impaired renal blood flow.

3. *What is the cause of this pre-renal failure?*

Both ACE inhibitors and NSAIDs are common causes of pre-renal failure. ACE inhibitors can induce pre-renal failure in volume-depleted states, although they are otherwise safely tolerated and beneficial in most patients with chronic kidney disease. They prevent the conversion of angiotensin I to angiotensin II; and angiotensin II increases the GFR by constricting the efferent arteriole. Therefore, ACE inhibitors and ARBs decrease the GFR due to efferent arteriole vasodilation.

Prostacyclin, a vasodilator prostaglandin, preserves renal blood flow and GFR by relaxing the renal afferent artery. NSAIDs block prostaglandin production thereby causing afferent arteriolar vasoconstriction and subsequent decreased renal perfusion. COX-2 inhibitors (coxibs) have been shown to have similar renal effects through results from clinical studies, as regulation of renal function is dependent on prostaglandins formed through the COX-2 pathway. Using ACE inhibitors/ARBs and NSAIDs in combination may lower the GFR more than either drug alone due to simultaneous efferent arterial vasodilation and afferent arterial vasoconstriction, placing the patient at an increased risk of pre-renal failure.

Back to Susan

Susan's celecoxib was stopped and her gabapentin dose was reduced to 600 mg t.i.d. Within a couple of days, her symptoms had completely resolved and 10 days after presentation, her serum creatinine had returned to baseline (80 mmol/L).

Take-home message

This case reminds us that whenever patients present with findings that stump us, one of the most important things we should do is to systematically go through the full list of their medications and examine recent changes in these to determine if they can be contributing to the condition. Advice from a clinical pharmacist or toxicologist can be of great value.

4. *Are there risk factors for this drug-induced acute RF?*

Yes, patients with medical conditions that reduce blood flow, such as diabetes, heart failure, atherosclerosis, advanced age, renal and hepatic disease. Concurrent use of diuretics and/or an ACE inhibitor/ARB with a sodium-restricted diet are also risk factors.

5. *What should be done in Susan's case?*

Because Susan has diabetes, she will derive benefit from continuing her ACE inhibitor.

As with traditional NSAIDs, most renal effects with coxibs occur early after starting therapy and are reversible upon discontinuation. Her celecoxib should be discontinued and future use of NSAIDs or COX-2 inhibitors should be avoided or used with caution and close monitoring of serum creatinine.

Susan is currently taking 2,700 mg of gabapentin daily for pain. To avoid further gabapentin toxicity, her dose should be reduced in the short term (300 to 600 mg t.i.d.) and possibly discontinued long-term. Dx

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