Short report

Should monitoring of vancomycin be delayed? A case of likely nephrotoxicity occasioned by morbid obesity and minimal monitoring

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The nephrotoxicity of vancomycin was thought to be largely due to impurities in older formulations but recent evidence suggests that even with modern, purified formulations, vancomycin is nephrotoxic, especially at high doses. Recent recommendations advise using actual body weight for obese patients as the basis for dose size and because MICs for important pathogens are increasing, larger doses are frequently recommended nowadays. Therapeutic drug monitoring is important for ensuring appropriateness of dosing and limiting nephrotoxicity but the most recent recommendations advise monitoring should not be performed until steady-state has been achieved.

In late 2009, a 54 year old, morbidly obese patient (approximately 150 kg) was referred to our Hospital because of increasing tiredness, abdominal cramps, ulcerated leg and per rectum bleeding. She had been discharged just 9 days earlier following an admission for pneumonia at which time she had been also been diagnosed with atrial fibrillation and an ischaemic finger for which enoxaparin and warfarin were started. Warfarin was withheld because the INR was 3.4 and haemoglobin concentration had fallen from 143 g l⁻¹ to 103 g l⁻¹ over the preceding 9 days. The provisional diagnosis was a retroperitoneal bleed for which a CT scan (using 100 ml of non-ionic, low osmolar, iopromide contrast) was ordered. This revealed a rectus sheath haematoma. She was taking many drugs including paracetamol/doxylamine/codeine, warfarin, verapamil, digoxin, hydroxychloroquine, prednisolone, nitrazepam, oxazepam, furosemide and nystatin.

At presentation, serum creatinine was 65 µmol l⁻¹, temperature 38°C and CRP was 200 mg l⁻¹. Vancomycin was prescribed because of a history of MRSA. According to Hospital protocol (15 mg kg⁻¹ actual body weight twice daily), 2 g twice daily was ordered and the plan was to administer for 7 days. At that time, the hospital protocol advised not to monitor if treatment was planned for <7 days. However one sample was taken 11 h after the first dose and was reported at 14.2 mg l⁻¹. The temperature did not settle and

vancomycin (as the sole antibiotic) was continued for a total of 17 doses over 10 days (three doses were omitted due to failure of i.v. access). The serum creatinine concentration increased (by >50% over baseline) on days 9 (121 µmol l⁻¹) and 10 (173 µmol l⁻¹) at which time vancomycin was stopped. Serum creatinine peaked on day 15 (252 µmol l⁻¹) (Figure 1) then slowly fell though it did not reach baseline, pre-admission concentrations even 6 months later. Serum vancomycin concentrations were checked 27 h after the last dose (54.8 mg l⁻¹), 24 h later (46.2 mg l⁻¹) and a further 48 h later (29.6 mg l⁻¹).

Vancomycin is primarily renally cleared and the relationship between creatinine clearance (CL_{cr}) and vancomycin clearance is so good, it has been suggested monitoring is not needed because dose can be calculated from CL_{cr} [1]. A recent wide-ranging US review [2] advises trough monitoring be performed at 'steady-state' (generally four doses) and this advice was reiterated in a recent Australian review [3].

Two factors have resulted in larger doses being recommended recently, namely dosing according to actual (rather than ideal) body weight and acceptance of higher therapeutic ranges. The former recommendation came from observations that obese subjects have higher clearances [4, 5] (and hence higher doses or more frequent administration are required to achieve therapeutic concentrations) and the latter from increasing bacterial resistance over recent decades. The acceptance of higher doses has also been encouraged by the perception that vancomycin is not as toxic as was once thought because toxic impurities present in earlier formulations are now removed [6].

Combined, these factors are likely to encourage clinicians to use higher vancomycin doses with minimal monitoring as in our patient. There are however, data suggesting an increased risk of nephrotoxicity when higher doses are used. Lodise *et al.* [7] examined nephrotoxicity in 246 subjects prescribed vancomycin and found

Figure 1

Serum creatinine concentration ($\mu\text{mol l}^{-1}$) ($n = 50\text{--}120$) over the course of 17 doses of 2 g vancomycin (bold line, from day 0 to 10 with 36 h missed due to no i.v. access)

doses $\geq 4 \text{ g day}^{-1}$ increased both the incidence of, and shortened the time to, nephrotoxicity. They also observed that weight $>101 \text{ kg}$ and initial trough vancomycin concentration were also related to risk of nephrotoxicity [8]. These factors were present in our patient.

Given the inherent unreliability in using serum creatinine concentration as a marker of renal function (especially in muscle-wasted subjects) and the ready availability and low cost of vancomycin assays, limiting therapeutic drug monitoring appears illogical. Sampling before steady-state needs to be viewed in that light (*viz.* not at steady-state) but this is done routinely for other drugs (especially warfarin). The concentration 11 h post first dose (14.2 mg l^{-1}) in our case should have cautioned the prescriber that much higher trough values were likely once steady-state was reached.

Our patient had no prior renal impairment or disease but a contrast CT scan of the abdomen was performed on admission. This was a standard scan using a 100 ml of a low-osmolar, non-ionic contrast. A variety of risk factors have been identified for contrast-induced-nephrotoxicity [9]. These include larger doses and use of ionic and high osmolar agents. Our patient had a modest dose of low osmolar, non-ionic contrast. Contrast-induced nephropathy typically appears within 48–72 h of the procedure [10] but in our patient, serum creatinine concentration did not rise to $>50\%$ above baseline until day 9. These factors suggest contrast was not a major factor in the development of renal impairment in our patient.

No other nephrotoxic agents were identified and no specific tests were requested that might have shed light on the nature of the renal injury. Other factors may have contributed to the rise in serum creatinine concentration including low blood pressure which was recorded on a few occasions during the vancomycin treatment period. This

appeared not to be symptomatic, did not require administration of fluids or inotropes, did not necessitate halting verapamil or furosemide and the patient never appeared septic.

We believe the rise in serum creatinine is likely related to the high dose of vancomycin and the resulting renal impairment then reduced clearance resulting in the very high vancomycin concentrations that probably compounded the renal injury. Because monitoring was not performed during days 1–9, we can only speculate as to when the concentration exceeded the recommended therapeutic range. It is certain however that monitoring during this period would have identified the dose was excessive and this might have prevented the subsequent nephrotoxicity.

We recommend earlier monitoring of vancomycin, especially when large doses are prescribed and/or there is doubt about renal function estimates. Prescribers will need to be aware that reported vancomycin concentrations may not have reached steady-state. Delaying monitoring until the fourth dose [2, 3] in the belief that ‘steady-state’ has been achieved is simplistic because vancomycin is renally cleared and hence, half-life can exceed 100 h in severe renal impairment. If interpreted appropriately, early monitoring should facilitate earlier attainment of therapeutic concentrations as well as reducing toxicity. This is not a novel concept in clinical practice and one that should be easily mastered by junior medical staff (perhaps with assistance from pharmacists) because it is the same concept used when initiating warfarin, a very widely used anticoagulant. Earlier monitoring might also be of assistance in patients who have accelerated creatinine clearances that are frequently observed in patients with systemic infections [11] and/or those who fail to thrive. If earlier monitoring can help avoid undue toxicity and shorten the time to attaining therapeutic concentrations, the only argument against performing them would appear to be cost. In our hospital; assaying vancomycin is not expensive, costing approximately the same as 3 g of the drug itself.

Our hospital protocol has been subsequently modified and it currently advises monitoring on day 3 of vancomycin therapy.

Competing Interests

There are no competing interests to declare.

No funding was provided for this work.

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RECEIVED

10 Nov 2010

ACCEPTED

16 Apr 2011

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