

Pharmacokinetics of a Once Daily Dosing Regimen of Gentamicin in a Patient with Delayed Wound Healing

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ABSTRACT

Background: Gentamicin is used for the treatment of serious gram-negative infections and has low therapeutic index. This may lead to several side effects, though therapeutic drug monitoring (TDM) is important in gentamicin therapy.

Aim: To report the pharmacokinetics of gentamicin using a once-daily dosing regimen.

Clinical presentation and intervention: The patient was a 78-year-old male. His weight was 78 kg and he was 1.75 m in height. He was admitted to the hospital complaining of an infected wound secondary to chronic limb ischaemia. Once-daily dosing of gentamicin (360 mg by infusion over 30 minutes) was prescribed to this patient, in combination with flucloxacillin. A gentamicin blood sample was taken every day for four days (day 1 = 1.4 mg/L, day 2 = 2.1 mg/L, day 3 = 2.1 mg/L, day 4 = 1.6 mg/L). The patient's serum creatinine was 88 µmol/L during the four days. The Hartford nomogram was used to estimate the dosage and interval for administration of gentamicin.

Conclusion: The Hartford nomogram is a valid tool to monitor the once-daily dosing regimen of gentamicin.

Keywords: Pharmacokinetics; Dosing Regimen; Gentamicin; Wound Healing.

INTRODUCTION

Gentamicin is an aminoglycoside and is commonly used for the treatment of serious gram-negative infections. Loading and maintenance doses are ciprofloxacin for the patient. On the day of admission, calculated depending on the patient's weight and renal function¹. Gentamicin has a low therapeutic index, which may lead to dose-related side effects, such as nephrotoxicity or ototoxicity.

Consequently, therapeutic drug monitoring (TDM) is important in gentamicin therapy to avoid these toxic side effects. Once daily dosing of gentamicin is preferred rather than conventional multiple dosing as it may reduce the accumulation of gentamicin in renal tissue. In addition, some trials have reported similar efficacy with less nephrotoxicity in once daily dosing compared with multiple dosing².

CASE SUMMARY

Patient identity

Patient is a 78-year-old male, weighing 78 kg and is 1.75 meters in height.

Presenting complaint

The patient was admitted to the accident and emergency (A&E) unit complaining of an infected wound of his second toe on the right foot.

History of presenting complaint

A month prior to admission, he grazed the second toe on his right foot. He was renewing the dressing triage

twice weekly. Three days prior to admission, a nurse

used for the treatment of serious gram-negative general practitioner (GP). The GP prescribed infections. Loading and maintenance doses are ciprofloxacin for the patient. On the day of admission, calculated depending on the patient's weight and renal the wound looked worse and was painful and leaking.

Past medical history

The patient's medical history included a femoral artery stenosis of the left foot ten months prior to admission, bypass surgery of the left foot nine months prior,

Drug History

The patient's drug history included:

- Paracetamol 1 g qid
- Clopidogrel 75 mg od
- Ciprofloxacin 500 mg bid (started three days before admission)

Medications prescribed for the patient in the hospital included:

- Enoxaparin 40 mg sc od
- Flucloxacillin 2 g IV as a first dose, then 1 g IV qid
- Gentamicin as the chart (table 1)
- Clopidogrel 75 mg od
- Morphine sulfate 5-10 mg IV prn
- Morphine sulfate 10 mg po bd

Table 1. Gentamicin IV Chart

Sample number	Date	Gentamicin dose	Time given	Time sample taken	Sample result	Predicted concentration
1	D1	360 mg by infusion over 30 minutes	22:00	13.5 hours after dose given	1.4 mg/L	1.75 mg/L
2	D2	360 mg by infusion over 30 minutes	22:00	11 hours after dose given	2.1 mg/L	2.686 mg/L
3	D3	360 mg by infusion over 30 minutes	22:00	11 hours after dose given	2.1 mg/L	2.686 mg/L
4	D4	360 mg by infusion over 30 minutes	22:00	13.5 hours after dose given	1.6 mg/L	1.781 mg/L

D=day

DIAGNOSIS

The diagnosis was delayed wound healing secondary to chronic limb ischemia.

The examinations/investigations

Upon examination, the patient's temperature was 38.4°C, his heart rate (HR) was 108 beats per minute; his respiratory rate was 24 breathes per minute; his electrolytes test results were normal; his urea test result was 9.5 mmol/L; his liver function tests results (LFTs) were normal; and his white blood cell count (WCC) test result was $17.6 \times 10^9/L$. His c-reactive protein test result was 240 mg/L and his prothrombin time (PT) test result was 14s. On the day of admission and four days later, the patient's serum creatinine was 88 micromol/L.

On day two, his blood culture was received in the evening, but there was no date, time or consultant name on the sample; therefore, the culture was repeated. According to this sample, the result was an 'anaerobic - gram positive (+ve) cocci- may be staphylococci'

The management

The initial management plan was to relief the pain, asking for consultant review, and to take a blood culture. Once daily dosing of gentamicin was prescribed for this patient in combination with flucloxacillin. A gentamicin blood sample was taken every day for four days. The gentamicin doses, when the doses were administered, when the samples were taken, and the sample results are illustrated in the table above (table 1). On day five, the patient was transferred to another hospital.

Pharmacokinetics calculations

The Cockcroft and Gault equation was used²:

$$CrCl \text{ (ml/min)} = \frac{F \times [(140 - \text{age in years}) \times \text{weight (kg)}]}{\text{plasma creatinine (micromol/L)}}$$
 where F = 1.04 for females, 1.23 for males. The creatinine clearance (CrCl) for this patient was 67.593 ml/min.

The estimated gentamicin clearance was calculated using this equation³:

Gentamicin clearance (ml/min) = $[0.82 \times \text{Creatinine CL (ml/min)} + (0.11 \times \text{weight (kg)})]$. The result was 64.006 ml/min.

The volume of distribution (V) for gentamicin is around 0.3 L/kg as it mainly distributes into extracellular fluid². So, V in this patient was 23.4 L.

Using the equation⁴ $K \text{ (h}^{-1}\text{)} = \frac{\text{clearance L/h}}{V L}$, the elimination rate constant (K) for gentamicin in this patient was 0.164 h^{-1} .

Gentamicin half-life ($t_{1/2}$) was estimated using this equation⁴: $t_{1/2} = \frac{0.693}{k} = 4.23 \text{ hr}$.

In sample (1) the concentration of gentamicin was 1.4 mg/L. The sample was taken 13.5 hours after the dose was administered. The predicted concentration (C) at that time was calculated using the equation⁴

$C = \frac{s \cdot IR}{CL} (1 - e^{-k \cdot T_{inf}}) e^{-k(t - T_{inf})}$, where IR = the infusion rate, s = salt factor (s = 1), T_{inf} = the duration of the infusion, and t = the time after the start of the infusion. The result was 1.75 mg/L. In samples (2) and (3) the concentration of gentamicin was 2.1 mg/L. The samples were taken 11 hours after the dose was administered. The predicted concentration (C) at this time was calculated using this equation⁴: $C = \frac{s \cdot IR}{CL} (1 - e^{-k \cdot T_{inf}}) \left[\frac{1}{1 - e^{-kt}} \right] e^{-k(t - T_{inf})}$. The result was 2.686 mg/L. In sample (4) the concentration of gentamicin was 1.6 mg/L. The sample was taken 13.5 hours after the dose was administered. Using the last equation, the predicted concentration (C) at that time was 1.781 mg/L.

According to the guidelines in *Therapeutics: A Handbook for Prescribing in Adults*⁵, 360 mg administered once daily was the appropriate dose for this patient during the four days.

Using the last equation, the estimated concentration of this dose (360 mg once daily)

eight hours after administration was 4.41 mg/L, the estimated peak concentration after one hour was 13.901 mg/L, and the estimated trough concentration after 24 hours was 0.361 mg/L.

DISCUSSION

On admission, a combination therapy of flucloxacillin and gentamicin was started. Flucloxacillin is a beta-lactam antibiotic. It is not inactivated by penicillinases enzymes, thus it is effective against beta-lactamase-producing staphylococci infections including cellulitis and osteomyelitis¹. One study explained why flucloxacillin is the empirical choice for putative staphylococci aureus infections in intensive care units (ICU) in the Netherlands. Research found only a 1% flucloxacillin resistance among the clinical staphylococci aureus isolates from ICU patients over a 13-year period in the Netherlands⁶.

Gentamicin is an aminoglycoside antibiotic. It is commonly used to treat serious infections and is considered the aminoglycoside of choice in the United Kingdom¹. In one study, once daily administration of gentamicin showed substantial killing of staphylococci aureus at 24 hours⁷. In the Netherlands, a combination therapy of flucloxacillin and gentamicin is commonly used in the case of a life-threatening infection⁶. One study demonstrated the combination of flucloxacillin and gentamicin entirely inhibits exotoxin production during the logarithmic phase of growth in staphylococci aureus and decreased it by approximately 80% during the stationary phase of growth. This effect of the combination is possibly a result of the inhibition of protein synthesis by the aminoglycoside⁸.

Combination therapy of flucloxacillin and gentamicin appears to be appropriate for the patient's treatment. However, the blood culture was not acceptable because there was no date, time or consultant name on the sample. Therefore, it was important to repeat the sample and determine the most appropriate antibiotic therapy, according to the new blood culture result.

The patient was given an initial dose of 360 mg gentamicin. The patient is a 78-year-old male and weighs 78 kg. On admission, his serum creatinine concentration was 88 µmol/L. By using 'Cockcroft Gault', the patient's creatinine clearance (CrCl) was 67 mL/min. Consequently, 360 mg once daily was suitable for him⁵.

After gentamicin administration, a blood sample was taken after 13 hours. In that sample, the patient's gentamicin concentration was 1.4 mg/L. Therefore, it was suitable to continue with a maintenance dose of 360 mg once daily⁵.

Age, severity of illness and renal impairment are factors that may lead to reduction in gentamicin

clearance. This elderly patient had a mild decline in kidney function and the infection was severe during the first three days, which explains why the predicted concentration was slightly more than the measured concentration in samples^{2,3,4}. This emphasises the need for gentamicin monitoring and dose adjustment depending on the individualised patient parameters.

During the four days, there was no reduction in renal function, as indicated by stable serum creatinine (88 micromol/L). This indicates the advantage of a significant drug-free interval during a once-daily gentamicin dosing regimen.

The estimated peak concentration after the dose of 360 mg once daily was 13.901 mg/L, which is sufficiently above the minimum inhibitory concentration (MIC) to provide a positive clinical outcome, which is 5 to 6 mg/L⁹. A high peak concentration gives the advantage of enhancing efficacy.

The upper-limit trough concentration of 1 mg/L is recommended for a once-daily dosing regimen⁹. The estimated trough concentration after the dose of 360 mg once daily (0.361 mg/L) was less than 1 mg/L, which indicates decreasing toxicity risk and suggests that the use of the Hartford nomogram was valid in this patient.

This report relating to a patient with a mild renal dysfunction indicates the importance of therapeutic drug monitoring for gentamicin when it is prescribed, to achieve an effective and safe dosage regimen.

CONCLUSION

Our data showed that the Hartford nomogram is a valid tool for monitoring the once daily dosing regimen of gentamicin.

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