CASE REPORT

Concomitant gentamicin-induced nephrotoxicity and bilateral ototoxicity

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Abstract

Co-occurrence of aminoglycoside-induced ototoxicity and nephrotoxicity is rare, possibly as a result of divergent mechanisms of tissue damage despite similarities in the anatomy of the inner ear and the proximal renal tubular epithelium. We present the case of a 63-year-old hypertensive woman who developed nonoliguric acute exacerbation of chronic renal failure and sudden onset of sensorineural deafness after receiving daily injections of gentamicin. Coexisting ototoxicity and nephrotoxicity from aminoglycosides can occur, though rare. Adverse effects of aminoglycosides are better prevented by a careful exercise of discretion by prescribers.

Key words: Acute kidney injury, aminoglycosides, co-occurrence, gentamicin, nephrotoxicity, ototoxicity

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Introduction

Aminoglycosides are known to cause nephrotoxicity, ototoxicity, and, more rarely, neuromuscular blockade. Gentamicin-induced nephrotoxicity ranges between 8% and 26%, while by audiometry about 25% of patients on aminoglycoside therapy develop ototoxicity.[1,2] However, concomitant renal toxicity and ototoxicity from aminoglycosides are rare. Gentamicin remains a first-line antibiotic for many severe infections due to its clinical effectiveness, low rates of resistance, affordability, and low risk of *Clostridium* difficile. This has made it one of the most frequently used aminoglycosides. Monitoring of plasma concentrations is effective in avoiding gentamicin-induced nephrotoxicity and ototoxicity, but this is not readily affordable in our environment.[3]

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Case Report

The patient is a 63-year-old poorly compliant hypertensive of 6 years duration who presented with hiccups; vomiting of 3 weeks duration; a abnormally elevated serum urea and creatinine (urea 47 mmol/L and creatinine 308 μmol/L); and sudden loss of hearing in both ears following administration of multiple injectables (gentamicin-included) on account of a febrile illness for about 2 weeks at a private hospital. The total daily dose of the gentamicin administered was, however, not specified. About the same time, she developed sudden onset of inability to hear in both ears. There was no associated earache, tinnitus, ear discharge, or vertigo. There was no significant change in her urine volume [Table 1].

At presentation, she was dehydrated and restless with blood pressure of 100/40 mHg. Urine culture yielded growth of *Escherichia coli* sensitive to imipenem, ceftriaxone, and chloramphenicol. Renal scan showed loss of corticomedullary

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differentiation bilaterally. There was no hydroureter or hydrocalyx. She had hypokalemia (2.5 mmol/L) and hyponatremia (129 mmol/L). Her corrected serum calcium was 2.39 mmol/L. Urinalysis showed 1 + glycosuria and 3 + proteinuria. Pure tone audiometry and tympanometry confirmed bilateral sensorineural deafness [Figure 1].

She was managed on intravenous ceftriaxone 1 g daily and rehydrated with normal saline. Hypokalemia was corrected with oral potassium chloride. She received a total of 4 sessions of hemodialysis with significant improvement in renal function. She was discharged home after the 3rd week of admission for follow-up in the renal and otorhinolaryngology clinics.

Three months after discharge, her renal function stabilized; with serum urea 4.2 mmol/L, creatinine 124 μmol/L, potassium 3.5 mmol/L, sodium 132 mmol/L, and bicarbonate of 24 mmol/L. However, the sensorineural deafness persisted.

Table 1: The fluid input and urine output chart of index patient showing predominantly nonoliguric level of urine output

Day	Input (ml)	Urine output (ml)
2	2450	880
3	700	590
4	1920	810
5	1400	880
6	890	1080
7	1300	880
8	1050	870
9	1300	760
10	900	590
11	1600	730
12	900	700
12	1300	850
14	700	420
15	1250	1250

Discussion

Our index patient had coexisting nephrotoxicity and ototoxicity. A direct and dose-dependent relationship between nephrotoxicity and ototoxicity in the same patient has not yet been established despite earlier suggestions.[4]

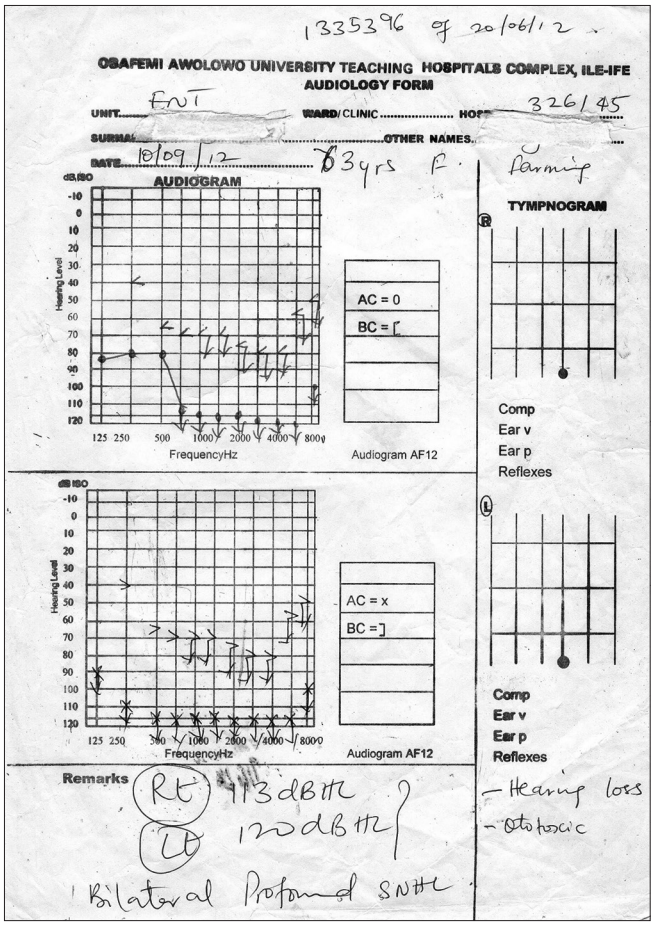

Figure 1: Audiogram of index patient showing bilateral profound sensorineural hearing loss

Table 2: Pharmacokinetics of gentamicin recommended initial dosages for specific clinical indications

Gentamicin/ tobramicin	Gram-positive infections	Gram negative infections (sepsis/pneumonia)	Dosage monitoring
Traditional initial dose	1 mg/kg/dose	1.5-2 mg/kg/dose	Obtain serum peak and trough concentrations after the 3rd dose following initiation of therapy and any dosing adjustments in therapy
Desired peak	3-5 mg/L	8-10 mg/L (10-12 times MIC of infecting organism)	Draw trough concentration just prior to next dose Draw peak concentration 30-45 minutes after the end of an intravenous infusion
Desired trough	<1 mg/L	<2 mg/ml	Once achieved, monitor periodically (e.g., 2-3 times weekly) throughout therapy with changes in renal function If stable renal function, monitor at least once weekly
Extended interval dose	NA	7 mg/kg/dose	Random serum concentration monitoring approximately 6-12 h after the 1st dose Interpret by using an established nomogram or based on MIC data. For amikacin therapy, divide serum concentration by 2 before using nomogram Monitor periodically if unstable renal function or prolonged therapy (>7-10 days)
Desired peak	NA	10-12 times MIC of infecting organism	
Desired trough	NA	<1 mg/ml	

MIC=Minimal inhibitory concentration; NA=Not available

Studies showed that ototoxicity results mainly from apoptosis unlike dose-dependent necrosis in nephrotoxicity.[5]

Several factors have been reported as increasing the risk of gentamicin nephrotoxicity and ototoxicity, viz.: Elevated trough gentamicin levels, plasma concentration-time area under the curve, duration of treatment on aminoglycoside, concomitant vancomycin, frusemide use, volume depletion, elevated baseline serum creatinine, increasing age, presence of co-morbidities, liver dysfunction, sepsis, hypokalemia, hypomagnesaemia, the type of aminoglycoside, the frequency of aminoglycoside dosing, and the timing of aminoglycoside administration.[6,7] In our index patient, identified risk factors include old age, volume depletion (dehydration and suboptimal blood pressure), background chronic kidney disease, and multiple dosing of gentamicin.

Gentamicin nephrotoxicity presents commonly as non-oliguric acute kidney injury as seen in our index patient [Table 1]. This usually occurs in association with the appearance of enzymuria.

The onset of renal failure from aminoglycoside toxicity is usually slower, and the daily rise of serum creatinine tends to be lower than other causes of acute kidney injury characteristically taking 7–10 days to increase after initiation of aminoglycoside therapy with associated aminoaciduria, glycosuria, hypomagnesemia, hypocalcemia, and hypokalemia.[8,9]

Our index patient developed acute kidney injury about the 7th day of treatment with gentamicin. Hypokalemia (2.5 mmol/L) and glycosuria were also demonstrated in her blood and urine, respectively.

Recovery from aminoglycoside nephrotoxicity is usually slow, often taking 4–6 weeks, particularly in elderly individuals. In patients with underlying chronic kidney disease, recovery of renal function may be incomplete.[10] Recovery of renal function was quite prolonged in our index patient resulting in a prolonged hospital stay, of a total of 22 days. It might even have been longer without dialytic intervention. Gentamicin causes predominantly irreversible cochlear damage but when reversible, recovery may start from 24 h after stopping the aminoglycoside.[11]

The treatment of aminoglycoside nephrotoxicity is supportive; discontinue the aminoglycoside and other nephrotoxic agents, maintain fluid and electrolyte balance, and control sepsis. Parenteral vitamin B complex and a combination of Vitamin E and selenium have been suggested.[12]

While it is natural to favor outright avoidance of aminoglycosides where culture sensitivity results are indicative (especially in resource-poor settings), it may just be safer to use the lowest possible dose, shortest course of therapy, and administer once daily doses, particularly in high-risk individuals such as patients in the extremes of age, presence of diabetes mellitus, and electrolyte imbalance (hypokalemia and hypomagnesemia).[6,7] Other important safety measures include serial monitoring of renal function, avoidance of combination of aminoglycosides with other nephrotoxins, adequate hydration, modification of the dose according to the glomerular filtration rate, and avoidance of use in patients with liver disease.[13]

Where economic conditions are more favorable or the use of aminoglycoside becomes imperative, serum drug levels may be monitored for safety. A recent review by Wargo and Edwards dealt with newer strategies to prevent patients from developing aminoglycoside-induced nephrotoxicity.[14] One of such strategies is individualized pharmacokinetic monitoring (IPM) in patients who are receiving aminoglycosides. Streetman *et al.* showed that patients who received IPM were significantly less likely to develop aminoglycoside-associated nephropathy.[15] IPM allows tailoring of aminoglycoside dosage to each patient to achieve optimal therapeutic goals while avoiding (or minimizing) toxicity; this is best achieved when the patients' peculiar clinical characteristics and drug serum trough and peak levels are carefully taken into consideration. For instance, a patient could indeed receive intravenous gentamicin once every 3–5 days with trough level monitoring to achieve excellent therapeutic outcomes.

Pharmacokinetic monitoring protocol for serum levels of aminoglycosides varies from center to center. The more popular protocols include the standard initial dose protocol and the extended interval dose protocol [Table 2].[16,17] However, their practicability in our environment would require an upgrade of our microbiology facilities, establishment of a standard drug toxicology unit, continuous medical education, and skill acquisition programs for our medical doctors, pharmacists, and laboratory personnel.

Conclusion

Aminoglycoside-induced nephrotoxicity is avoidable. The indications for the use of aminoglycosides must be strongly established, and the predisposing factors for renal failure and ototoxicity must be vigorously sought out and eliminated, where possible. The use of aminoglycosides in the elderly should best be discouraged because of the likelihood of underlying age-related reduced renal reserve and impaired hearing ability.

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Conflicts of interest

There are no conflicts of interest.

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