

## Clinical manifestation of macrolide antibiotic toxicity in CKD and dialysis patients

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### Abstract

Macrolide antibiotics, erythromycin, clarithromycin and azithromycin are commonly prescribed for upper respiratory infection, and their use has recently been further linked to immunomodulatory effects. With the widespread and expanded use of macrolides, special attention should be paid to their potential adverse effects. We reported two cases of end-stage renal disease (ESRD) patients who developed hallucinations such as vivid images of worms after taking clarithromycin. Similar to previous case reports of clarithromycin neurotoxicity, the visual hallucination resolved upon cessation of clarithromycin. Furthermore, we discussed the pharmacokinetic properties and other toxicities of macrolide antibiotics in patients with chronic kidney disease and ESRD.

**Keywords:** azithromycin; clarithromycin; colchicine; neurotoxicity; peritoneal dialysis

### Introduction

In the past decade, macrolide antibiotics have been increasingly prescribed, and more so for the treatment of community-acquired respiratory tract infection. The recent interest of macrolides linked to its anti-inflammatory effect on airway diseases (notably obstructive airway disease and non-cystic fibrosis bronchiectasis) has brought renewed attention to this class of drugs [1–3]. The prototype macrolide erythromycin has been used since 1952; other commonly used macrolides include clarithromycin and azithromycin. Despite their difference in pharmacologic properties and chemical structures, the three macrolide antibiotics share similar adverse event profiles. Some of the macrolide toxicities are of particular concern among patients with chronic kidney disease.

This in-focus review of macrolide toxicity covers those that have more significant clinical manifestation of chronic kidney disease patients, including those on dialysis. Patients who are at risk of or who have known kidney disease are also included in the discussion.

### Drug properties of macrolides

As a class, macrolides act via the same mechanism, namely, binding to the 50S subunit of the bacterial ribosome and blocking initiation of protein synthesis [4]. They all consist of a large lactone ring. Erythromycin and

clarithromycin have 14-membered lactone ring, whereas azithromycin has a 15-membered ring. Minor structural changes prevent the metabolism of clarithromycin and azithromycin to an inactive compound, improve the acid stability, and provide a broader spectrum of antibacterial activity than erythromycin.

Erythromycin is metabolized by cytochrome P450 (CYP) enzyme CYP3A4 and eliminated primarily by faeces. Since only a small fraction (less than 7.5%) appears in urine as unchanged drug [5], kidney disease has theoretically minimal impact on the pharmacokinetics of erythromycin. However, clinical observation of elevated serum erythromycin concentrations and prolonged half-life in patients with end-stage renal disease (ESRD), associated with reversible hearing loss, led to speculation of altered drug clearance [6, 7]. These results have important clinical implications on drug dosing of erythromycin in ESRD patients. It is now believed that hepatic CYP3A4 metabolic activity, one of the most important enzymes in human drug metabolism, is decreased in uraemia and acutely improved by haemodialysis therapy. Specifically, CYP3A4 activity and elimination of erythromycin is increased by 27% after 2 h of conventional haemodialysis, presumably via removal of a rapid-acting and dialyzable byproduct of uraemia that can inhibit hepatic intrinsic clearance mediated by CYP3A4 [8]. A mounting body of experimental and clinical evidence indicates altered nonrenal clearance, namely, impaired hepatic clearance, of erythromycin in ESRD patients. Reduced hepatic clearance is attributed to downregulation of cytochrome P450 enzymes and

alterations in the transporter system (of drugs into or out of the liver) [9, 10].

Clarithromycin is metabolized by CYP 3A4 to its 14-hydroxy active metabolite, both of which require renal excretion [11]. Because the metabolite 14-hydroxy derivative is primarily excreted in the urine, an increase in area under the plasma concentration-time curve, peak plasma concentrations and elimination half-life are expected in patients with kidney disease (but not those with hepatic impairment). The need to adjust clarithromycin dose for patients with kidney disease is supported by pharmacokinetic studies showing a prolonged elimination half-life of clarithromycin and its metabolite 14-hydroxyclearithromycin when the creatinine clearance is <30 mL/min [11, 12]. Clarithromycin has high lipid solubility which renders it poorly dialyzable.

Azithromycin is excreted in bile and then faeces. Unlike clarithromycin, very little unchanged azithromycin appears in the urine, and there are no biologically active metabolites. Thus, azithromycin dosing modification is not needed in patients with kidney disease. It is also not substantially removed by peritoneal dialysis [13].

### Neurotoxicity of macrolides

Antibiotic-induced neurotoxicity is a well-known complication in patients with chronic kidney disease and ESRD. Common examples include penicillins, cephalosporins, carbapenems and quinolones [14, 15]. Clarithromycin [16], and much less for erythromycin [17, 18], have been reported to cause neurotoxicity, mostly in the form of acute delirium or psychosis. Although uncommon, visual hallucination was the predominant presenting symptom of clarithromycin-induced neurotoxicity in some patients, including both dialysis [19, 20] and non-dialysis populations [21, 22]. Most patients improved spontaneously upon cessation of clarithromycin. **Box 1** and **Box 2** outline two patients with ESRD and clarithromycin neurotoxicity.

**Box 1.** A 55-year-old male patient suffered from ESRD secondary to hypertensive nephrosclerosis and was started on continuous ambulatory peritoneal dialysis (CAPD) for 5 years. He was admitted to hospital because of a history of insomnia, tinnitus and visual hallucination for 3 days. He reported seeing worms crawling in his surrounding environment, rendering him unable to perform CAPD. Five days before admission, he was diagnosed to have *Helicobacter pylori*-related gastritis and started on amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and esomeprazole 20 mg twice daily. Concurrent medications included allopurinol, atenolol, nifedipine sustained release, spironolactone and calcium carbonate. He had no focal neurological deficit or fever. Computed tomography of the brain and electrolytes were unremarkable. He was managed conservatively and symptoms completely subsided after 4 days. There was no recurrence of symptoms in the subsequent 7 years of follow-up. Causality assessment of adverse drug reaction suggested possible (Naranjo probability scale score 4) clarithromycin toxicity; we cannot exclude the alternative explanation by the concurrent use of relatively high-dose amoxicillin.

**Box 2.** A 71-year-old female patient had ESRD due to IgA nephropathy, for which she had received dialysis treatment for >20 years. Due to progressive cognitive impairment, she required assisted CAPD by a domestic helper. Other medical comorbidities included bilateral cataract, ischaemic heart disease and atrial fibrillation. Three weeks before admission, she was admitted to hospital because of CAPD peritonitis due to coagulase-negative staphylococcus and *Moraxella catarrhalis*. She was initially treated with intraperitoneal cefazolin and ceftazidime, without clinical response. Antibiotic regime was switched to intraperitoneal vancomycin 1 g once every 5 days and oral clarithromycin 250 mg twice daily was added to cover *Moraxella* infection based on sensitivity results. She responded well with that regime. Her other medications included aspirin, famotidine, bisoprolol, isosorbide dinitrate, valsartan, alfacalcidol and nystatin. She developed unsteady gait after 10 days of clarithromycin. She then reported seeing worms over her body and in her surrounding environment after 16 days of clarithromycin. She was subsequently admitted to hospital because of a fall, minor head injury and scalp laceration. She had no focal neurological deficit or cerebellar signs. Computed tomography of the brain showed cerebral atrophy but no evidence of acute stroke. Electrolytes were unremarkable. Clarithromycin was stopped and symptoms completely subsided after 1 week. She had no recurrence of symptoms in her subsequent follow-up and remained well on CAPD. Naranjo criteria suggested probable clarithromycin adverse event (score 7).

Steinman and Steinman [19] first reported clarithromycin-induced visual hallucination in a 56-year-old ESRD patient on CAPD. The patient had acute onset of visual hallucination within 24 h after taking clarithromycin 500 mg twice daily for acute bronchitis. His visual hallucination was described as a 'constantly evolving landscape of sharks, priests, red lines and other Technicolor'. Symptoms subsided 3 days after drug cessation. Tse et al. [20] reported another case of visual hallucination in the form of delusion of worms in a 49-year-old male peritoneal dialysis patient after taking clarithromycin 250 mg three times a day for 1 week. This particular patient also had history of acyclovir-induced encephalopathy. He was treated with haloperidol and symptoms completely subsided after 3 weeks. Similarly, both of our patients had visual hallucination in the form of parasitosis.

The mechanism of clarithromycin-induced neurotoxicity remains largely unknown. Proposed neurotoxicity mechanisms include direct toxicity of the lipid-soluble active metabolite of 14-hydroxyclearithromycin on the central nervous system, alterations of cortisol and prostaglandin metabolism, inhibitory action on glutaminergic neurotransmission [23].

In our second patient (**Box 2**) who received a reduced dose of clarithromycin, neurotoxicity developed after 10 days. This might reflect the gradual accumulation of clarithromycin and its metabolite even with adjusted dose. Of note, our second patient had been anuric for years and had no residual renal function. Altered blood-brain barrier in the setting of uraemia may be associated with increased concentration of clarithromycin and its metabolite in the central nervous system, which may be another contributing factor in the development of neurotoxicity.

Bandettini *et al.* [16] analysed 38 patients who developed neurotoxicity after clarithromycin. Most patients had a history of psychiatric illness and only 2 patients had renal insufficiency. This implies that elevated serum drug level secondary to reduced renal excretion is only one possible mechanism of neurotoxicity. In fact, hallucination had been reported in patients taking therapeutic doses of clarithromycin [21, 22]. Clarithromycin has been linked to the development of many acute psychotic manifestations, including the phenomenon of ‘antibiomania’, the feeling of ‘leaving the planet’, and cat-like screeching and movements [24]. According to previous World Health Organization and the Food and Drug Administration, clarithromycin and ciprofloxacin are the most frequent causes linked to antibiotic-induced manic episodes or antibiomania [23]. Other neurotoxic manifestations of clarithromycin include non-convulsive status epilepticus, depersonalization, semicatatonic behaviour, paranoid ideation, delirium and insomnia [16, 25–29]. On the other hand, prolonged duration of treatment may not necessarily result in neurotoxicity. In two series of atypical mycobacterium exit site infection in peritoneal dialysis patients, 10 out of 15 patients received prolonged clarithromycin therapy ranging from 6 to 42 weeks. None of them developed neurotoxicity, although the exact dosages of clarithromycin were not mentioned in either study [30, 31].

### Cardiotoxicity of macrolides

All three macrolides, erythromycin, clarithromycin and azithromycin, have been associated with QT interval prolongation. The single most important concern with drug-induced QT prolongation is risk of fatal polymorphic ventricular tachycardia, or torsades de pointes (characterized by QRS complexes of progressively changing amplitude and contour that seem to twist around the isoelectric line from beat to beat).

The mechanism of QT prolongation after macrolides is blockage of the outward potassium current or channel in myocyte membranes [32]. Although QT interval lengthening is not infrequent after clarithromycin, reports of torsades de pointes after clarithromycin appear to be primarily linked to simultaneous administration of other drugs that prolong the QT interval. Analysis of torsades de pointes associated with macrolide also highlighted the risk factors of concomitant drugs, female gender and increasing age [33]. At least three case reports of torsades de pointes after clarithromycin have been published in patients with creatinine clearance below 30 mL/min when they received clarithromycin at 500 mg twice daily [34, 35]. Such an observation implies the dose effectiveness of clarithromycin, which can accumulate to the high-risk level in the presence of renal failure (when the dose is not adjusted accordingly). Similarly, a dose-response effect of erythromycin has been reported; the effect on the QT interval is directly related to the rate of intravenous infusion of erythromycin [36]. Azithromycin metabolism is not affected by kidney function. For unknown reasons, on the other hand, acute kidney injury has been suggested to be a risk factor for azithromycin-induced torsades de pointes [37].

The observation that prolonged QT interval increased the all-cause mortality and the risk of sudden cardiac death in ESRD patients [38, 39] suggests the possibility of a further increased propensity to macrolide cardiac toxicity in this population.

### Indirect kidney injury after macrolides

Macrolides do not cause direct nephrotoxicity in general [40], but erythromycin and clarithromycin can influence kidney function secondary to interactions with other drugs. These two macrolides are strong inhibitors of CYP3A4 enzymes, and thus lead to accumulation of drugs that require CYP3A4 for their metabolism, potentially causing toxicity. In other words, the potential mechanisms whereby macrolides are linked to adverse kidney events are the indirect effect of increased concentration of concurrent drugs such as statins and calcium-channel blockers.

A recent Canadian population-based cohort study involving 144 336 users of erythromycin, clarithromycin or azithromycin together with statins found a 2-fold increased risk of hospitalization (relative risk 2.17, 95% CI 1.04–4.53) with rhabdomyolysis among those taking statin and coprescription of erythromycin or clarithromycin [41]. The absolute risk increase was 0.02%, 95% CI 0.01–0.03%. The results also confirmed an increased risk of hospitalization with acute kidney injury, hyperkalaemia and all-cause mortality after concurrent use of statins with erythromycin or clarithromycin. This study evaluated statins (atorvastatin, simvastatin or lovastatin) metabolized by CYP3A4 isoenzyme, and confirmed a significantly lower risk of myopathy with concurrent use of azithromycin which does not inhibit CYP3A4. Although only older adults (older than 65 years) were included in the study, it appears prudent to consider a different antibiotic or temporarily stop the CYP3A4-metabolized statin during erythromycin or clarithromycin administration in all patients [41, 42]. Current warnings and recommendations are avoidance of lovastatin and simvastatin with erythromycin or clarithromycin, whereas atorvastatin dose adjustment may be required. Increased monitoring for toxicity is warranted for any such combination.

A much less commonly recognized mechanism by which clarithromycin may cause kidney injury indirectly is via an increase in concentrations of calcium-channel blockers and thus hypotensive insult to the kidneys. This has been shown by two Canadian groups evaluating the use of macrolide and calcium-channel blocker in elderly subjects [43, 44]. The first signal of hypotension risk came from a population-based nested, case-crossover study that included patients who required hospital admission for the treatment of shock or hypotension within 7 days after co-prescription of macrolide antibiotics and calcium-channel blockers (amlodipine, felodipine, nifedipine, verapamil, diltiazem, all of them being metabolized by CYP3A4 enzyme) [43]. This study did not look into nephrotoxicity but confirmed the strongest association of hypotension with concurrent erythromycin (the strongest inhibitor of CYP3A4), followed by clarithromycin. No such association with azithromycin was reported [43]. The second population-based cohort study studied concurrent use of clarithromycin and the previously mentioned calcium-channel blockers [44]. Using azithromycin as a comparator to minimize confounding by indication, the population-based cohort study showed a small but statistically significant greater 30-day risk of hospitalization with acute kidney injury (absolute risk increase 0.22%, 95% CI 0.16–0.27%). The risks of hospitalization with hypotension and all-cause mortality were both increased. The most pronounced effect was observed with concurrent use of clarithromycin and nifedipine [44]. Collectively, these studies indicate a small but significant risk of

combined use of macrolide and calcium-channel blockers among older patients. What are the implications for patients with chronic kidney disease? We suspect chronic kidney disease patients represent another at-risk group given the widespread use of calcium-channel blockers among them and the susceptibility of the injured kidney to hypotensive insults. Nevertheless, this needs to be substantiated in further analysis because <10% of the subjects were suffering from chronic kidney disease in the two Canadian studies [43, 44].

### Drug toxicity after macrolides interaction

In addition to the inhibition of CYP3A4 enzyme, macrolides are also known to inhibit the P-glycoprotein transport system [45]. P-glycoprotein, also known as multidrug transporter 1 and ATP-binding cassette B1 transporter, is located in the apical membrane of the enterocytes and functions as the intestinal drug efflux pump, reducing the absorption of orally administered drugs [46]. Consequently, P-glycoprotein inhibitor may increase the bioavailability of those drugs which are substrate for the P-glycoprotein transport system. P-glycoprotein is also present on the canalicular aspect of the hepatocyte (biliary excretion), as well as an important component of the blood-brain barrier.

Two clinically important P-glycoprotein substrates relevant to kidney disease are colchicine and digoxin.

Colchicine is not uncommonly used in patients with chronic kidney disease and acute gout, when nonsteroidal anti-inflammatory drugs are considered undesirable. Ten per cent or more of colchicine undergoes excretion by the kidneys, besides the metabolism by the cytochrome P450 system. Colchicine accumulation occurs in patients with renal or hepatic dysfunction, and even more so when there is concomitant use of erythromycin or clarithromycin (both of which inhibit the P-glycoprotein transport). This underappreciated but fatal drug interaction is exemplified by a classic case of colchicine toxicity in [Box 3](#).

**Box 3.** An 85-year-old elderly with chronic kidney disease, diabetes and gout was admitted from an aged care home for symptomatic anaemia. Her estimated glomerular filtration rate was 28 mL/min/1.73 m<sup>2</sup> and haemoglobin level was low (7.7 g/dL). An upper endoscopy showed mild gastritis and *Helicobacter pylori*. She was transfused and given eradication therapy which included clarithromycin 500 mg twice daily. Three days later, she developed acute gouty arthritis and was treated with oral colchicine 0.5 mg four times daily. Four days after colchicine use, her platelet count decreased from 230 to 127 × 10<sup>9</sup>/L. She developed sudden cardiac arrest 2 days afterward, when her complete blood count showed a platelet count of 32 × 10<sup>9</sup>/L and white cell count 0.8 × 10<sup>9</sup>/L.

A retrospective analysis of 116 Chinese patients who were prescribed colchicine and clarithromycin during the same hospital admission confirmed a high risk of fatalities (10.2%). Independent predictors of death were renal impairment (defined as serum creatinine level above 140 µmol/L at baseline), longer overlapping therapy of colchicine and clarithromycin, and the development of pancytopenia [47]. Reported manifestations of colchicine toxicity

with concurrent clarithromycin include haematological (pancytopenia, hypocellular bone marrow), gastrointestinal (vomiting, diarrhoea, abdominal pain), neuromyopathy (including rhabdomyolysis), multi-organ dysfunction and death [47, 48]. Although a specific recommendation for colchicine dose reduction (when macrolide such as clarithromycin is coprescribed) has been published [49], the safeguards need to be substantiated in larger clinical trials. In this regard, avoiding combined use of colchicine and P-glycoprotein inhibitor remains the best strategy to prevent drug interaction, and especially among patients with chronic kidney disease.

Digoxin toxicity after macrolide use in patients with chronic kidney disease or ESRD has been characterized more in the literature [50, 51], and continues to be one of the most prevalent adverse drug reactions in clinical practice. This should come as no surprise after considering the pharmacokinetics of digoxin. Over 70% of the body load of digoxin is eliminated unchanged in the urine. Furthermore, patients with chronic kidney disease have decreased extravascular volume of digoxin distribution. These account for the prolonged half-life of digoxin in patients with chronic kidney disease, as well as the need to reduce the loading and maintenance digoxin dose. When macrolides (erythromycin, clarithromycin and azithromycin) are administered together with digoxin, the inhibition of P-glycoprotein will further increase the digoxin levels because digoxin is a substrate for P-glycoprotein.

A study comparing digoxin concentration before and (four to seven days) after clarithromycin treatment in seven elderly found that digoxin level increased significantly; the digoxin clearance and elimination rate constants were 56–60% lower and elimination half-life was 82% longer [52]. Moreover, only one out of the seven patients developed an electrocardiographic sign of digoxin toxicity when she developed acute kidney injury, which further reduced the digoxin clearance [52].

The observation is consistent with the finding of a 15-year population-based nested case-control study evaluating digoxin toxicity after recent macrolide antibiotic use. Indeed, the risk of digoxin toxicity is highest for recent use of clarithromycin (adjusted odds ratio 14.83, 95% CI 7.89–27.86), followed by erythromycin and azithromycin. There was no significant risk for the neutral comparator of cefuroxime [53]. The risk of digoxin toxicity after clarithromycin is 4-fold higher than erythromycin or azithromycin. This is consistent with *in vitro* data showing the highest inhibitory capacity of P-glycoprotein for clarithromycin [45]. Thus, it should be emphasized that use of azithromycin might avoid drug interaction via CYP3A4 inhibition, but azithromycin might still lead to clinically important drug interaction (such as digoxin) by inhibiting P-glycoprotein [54]. Risk of concomitant use of macrolide with digoxin also applies to ESRD patients. Specifically, adding clarithromycin to six ESRD patients taking oral digoxin (on haemodialysis or haemofiltration) was shown to cause 1.8–4.0-fold increase in their serum digoxin levels [51].

Another potential and interesting mechanism of drug interaction between macrolide and digoxin is mediated by human intestinal bacteria. There is evidence that inactivation of digoxin by the gut actinobacterium *Eggerthella lenta* to its inactive metabolite, dihydrodigoxin, contributes to around 10% of digoxin metabolism [55, 56]. Macrolides including azithromycin can kill off a large fraction of *Eggerthella lenta* bacteria and therefore increase the serum digoxin concentration.

**Table 1.** Summary of three macrolides with reference to kidney disease

	Erythromycin	Clarithromycin	Azithromycin
Kidney excretion	Minimal (<7.5% unchanged in urine)	Active metabolites excreted unchanged in urine	Minimal
Recommended dose reduction with kidney disease	No need for dose adjustment but altered nonrenal clearance suggested in ESRD	Decrease by 50% if creatinine clearance <30 mL/min	No need for dose adjustment
Dialyzable	Slightly (5% to 20%)	Minimal	Minimal
CYP3A4 inhibition	+++	+++	–
P-glycoprotein inhibition	+	++++	+
Reported neurotoxicity	+	++	–

## Conclusion

The mode of action is similar for all macrolides, but their pharmacokinetics and adverse events differ slightly, as summarized in Table 1. Patients with chronic kidney disease and ESRD are prone to drug-induced neurotoxicity. In particular, visual hallucination in the form of parasitosis should raise the clinical suspicion of clarithromycin neurotoxicity. Drug interaction with statins, calcium-channel blockers and colchicine is another concerning complication of macrolides. Close monitoring is warranted, and even more so in the setting of chronic kidney disease, ESRD or acute kidney injury.

*Conflict of interest statement.* None declared.

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