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Clindamycin: An Unusual Cause of Acute Kidney Injury

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Statistical Analysis C
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Conflict of interest: None declared

Patient: Male, 52
Final Diagnosis: Clindamycin induced acute kidney injury
Symptoms: Nausea • fatigue • anorexia • hematuria • decreased urine output
Medication: Clindamycin
Clinical Procedure: None
Specialty: Nephrology and Internal Medicine

Objective: Mistake in diagnosis

Background: Medications are one of the most common causes of acute kidney injury (AKI). Elderly patients with diabetes mellitus and chronic kidney disease seem to be at particularly high risk for development of medication-induced AKI. Among antibiotics, the most commonly implicated agents are aminoglycosides, cephalosporins, trimethoprim-sulfamethoxazole, acyclovir, and amphotericin. Despite its widespread use, clindamycin has been rarely associated with AKI.

Case Report: A 52-year-old male patient with type II insulin dependent diabetes mellitus without diabetic nephropathy was treated with clindamycin for chronic osteomyelitis. Five days following initiation of therapy, he developed nausea, poor appetite, decrease in urine output, and profound generalized weakness. His symptoms were initially attributed to gastrointestinal side effects of clindamycin and he was advised to take it with food and to hydrate himself vigorously. Despite this change, his symptoms progressed and he developed hematuria and AKI which prompted hospital admission. Extensive workup for AKI that included evaluation for pre-renal, intrinsic renal, and post-renal etiologies failed to point to other etiologies apart from clindamycin-induced AKI. Following cessation of medication and temporary renal replacement therapy (RRT), his renal function returned to baseline.

Conclusions: We present a case of clindamycin-induced AKI that was diagnosed after a delay due to uremia symptoms being mistakenly attributed to gastrointestinal side effects of clindamycin. Although rare, clindamycin can be a cause of AKI and clinician should be aware of this association in order to recognize and treat it in timely manner.

MeSH Keywords: Abnormalities, Drug-Induced • Acute Kidney Injury • Clindamycin • Diabetes Mellitus, Type 2 • Hematuria • Oliguria • Uremia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/913779

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Background

Acute kidney injury (AKI) is a complex clinical syndrome characterized by abrupt decrease in renal function with consequent dysregulation of electrolytes, extracellular volume, and excretion of urea and other nitrogenous waste products [1]. Several criteria have been established to define AKI including criteria from KDIGO (Kidney Disease: Improving Global Outcomes), RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease) and AKIN (Acute Kidney Injury Network) among others [2,3]. The KDIGO guidelines define AKI as follows: 1) an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or 2) an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or 3) urine volume <0.5 mL/kg/hour for 6 hours [1].

Clindamycin is a lincosamide antibiotic that works primarily by binding to the 50s ribosomal subunit of bacteria. It is considered to be bacteriostatic but in high enough concentration it can be bactericidal for anaerobes such as *Bacteroides fragilis* [4,5]. Clindamycin is well absorbed after oral administration and reaches 90% bioavailability. Its broad spectrum of activity against anaerobes, staphylococci (including methicillin resistant *Staphylococcus aureus*), viridans group streptococci, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, make it an excellent choice for treatment of various infections. Clindamycin is actively transported into polymorphonuclear leucocytes and macrophages, so it has good penetration into abscesses. Penetration to bone is excellent as well. However, because it does not achieve significant levels in cerebrospinal fluid, it cannot be used to treat central nervous system infections. It is metabolized in the liver and excreted in urine. The half-life in patients with normal renal function is about 2 hours, which increases to 6 hours in those with chronic kidney disease. It is not dialyzable by hemodialysis or peritoneal dialysis [6].

Unlike other antibiotics, such as beta lactams, acyclovir, aminoglycosides, and amphotericin, clindamycin has been rarely associated with AKI.

Case Report

A 52-year-old black man with history of type II insulin dependent diabetes mellitus was admitted to hospital for nausea, poor appetite, decreased urine output, hematuria, and profound generalized weakness that started 5 days prior. Three weeks before his current hospital admission, he was hospitalized for a week for treatment of diabetic foot ulcer and chronic osteomyelitis. At that time, he underwent left fourth and fifth metatarsal, cuboid, and lateral cuneiform bone amputation and received clindamycin. Postoperatively, he recovered uneventfully and was discharged on clindamycin 600 mg orally, every 8 hours. Other medications included insulin glargine. He denied use of over-the-counter medications or herbal remedies. He was a non-smoker, did not drink alcohol, or use any illicit drugs. Five days before readmission, he contacted his primary care physician complaining about nausea and poor appetite. This was attributed to clindamycin gastrointestinal side effects and he was advised to take medication with meals and to hydrate himself. No blood work was done at that time. Despite taking medication with meals and hydrating himself vigorously, his symptoms progressed further, his generalized weakness worsened, and he developed hematuria. His condition thus prompted evaluation and hospital admission. He denied fever, chills, headache, confusion, vomiting, shortness of breath, palpitations, or abdominal pain. He did not have diarrhea or skin rashes. His vital signs on admission were normal. Physical examination revealed an ill appearing man in no distress. Mucous membranes were moist, skin turgor was normal, and there was no clinically evidence of dehydration. His orthostatic vital signs were normal. His mental status was normal, there was no pericardial rub, and heart sounds were normal. His lungs were clear bilaterally on auscultation. His abdomen was soft and non-tender. He had no edema or skin rashes.

At baseline, his creatinine was normal (0.9 mg/dL), glomerular filtration rate (GFR) was 115 mL/min/1.73 m^2 and he had proteinuria of 30 mg/dL, but he was not on angiotensin converting enzyme (ACE) inhibitors. Significant laboratory findings on admission included: sodium 125 mEq/L, potassium 6.7 mEq/L, chloride 90 mEq/L, bicarbonate 17.1 mEq/L, blood urea nitrogen 89 mg/dL, creatinine 12.6 mg/dL, glucose 263 mg/dL, and phosphate 7.8 mg/dL. Complete blood cell count (CBC) was normal including differential. There was no eosinophilia. Urine analysis revealed specific gravity of ≤1.005, large amount of blood, protein 100 mg/dL, small leukocyte esterase, urine white blood cell count (WBC) of 7–20 hpf (high power field), red blood cell count (RBC) of 7–20 hpf and few bacteria. Urine cultures remained without growth. Urine toxicology was negative. Urine sediment (which was spun at this point), showed muddy brown casts. There were no urine eosinophils seen. Urine protein-to-creatinine ratio was 2914.1 mg/g. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were normal. Complement levels were normal. Glomerular basement membrane (GBM) IgG antibodies (Ab) was <0.2 unit (negative), antimyeloperoxidase Ab was <5.0 units (negative), proteinase-3 Ab was <5.0 units (negative). Chest x-ray on admission was normal, there was no infiltrates, effusion, or pulmonary vascular congestion. Electrocardiography (ECG) showed an old right bundle branch block but no ischemic changes, PR interval was normal and there were no peaked T waves. An indwelling urinary catheter was placed immediately with zero urine output. Bedside ultrasound revealed an empty urinary bladder with the tip of the catheter in the bladder. Kidney ultrasounds revealed normal appearing kidneys without hydronephrosis.

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The patient was diagnosed with oliguric AKI and was admitted to the critical care unit. Intravenous (IV) normal saline was administered as well as insulin, albuterol, bicarbonate, and kayexalate for the management of hyperkalemia. Clindamycin was stopped. Following IV hydration he remained oliguric with less than 50 mL of urine output for 24 hours.

Despite IV fluid challenge, he remained oliguric with worsening metabolic acidosis and persistent hyperkalemia; he eventually required initiation of replacement therapy (RRT). Throughout the hospital course, the patient required intermittent hemodialysis. He refused renal biopsy. Over the following 4 weeks, his renal function returned to baseline, dialysis was stopped, and he completed treatment for osteomyelitis with ceftriaxone without complication. By demonstrating improvement following clindamycin cessation and concomitantly ruling out other etiologies of AKI we confidently concluded that our patient indeed had clindamycin-induced AKI.

Discussion

Development of AKI has been associated with an increase in in-patient morbidity, mortality, and healthcare spending [7–9]. Drug-induced nephrotoxicity is a common problem in clinical practice and its incidence might be as high as 60% [8,9]. Elderly, patients with chronic kidney disease and diabetes mellitus are particularly prone to medication-induced AKI. Common adverse drug reactions associated with clindamycin are predominantly gastrointestinal and include nausea, diarrhea, and vomiting. Rash, pain at the injection site, clostridium difficile colitis, and allergic reactions are common as well. AKI associated with the use of clindamycin is exceedingly rare.

We performed a literature search on PubMed database for articles using the following words alone or in combination: clindamycin side effect, AKI due to clindamycin, drug related AKI, acute interstitial nephritis (AIN) due to clindamycin, and acute tubular necrosis (ATN) due to clindamycin. While our search yielded no single case report published, we found 2 retrospective studies from China that described case series of biopsy proven AKI due to clindamycin [10,11]. The study by Wan et al. [10] reported 50 patients and the study by Xie et al. [11] reported a case series consisting of 24 patients with biopsy proven clindamycin-induced AKI.

In the retrospective case series described by Wan et al. [10] and Xie et al. [11] the median patient age was 42.1 years and 41.1 years, respectively. In the study by Wan, females were more likely to develop AKI (29 females versus 21 males) while Xie et al. demonstrated opposite results, with men more likely to develop clindamycin-induced AKI (14 males versus 10 females). All reported patients thus far have been Asian, while our patient was African-American and the first reported case from North America. The most common symptoms on admission in the other 2 studies [10,11] were abdominal discomfort, nausea, and vomiting, similar to what our patient experienced. The median onset of AKI following clindamycin administration in the other 2 studies was between 1 and 4 days. Our patient was diagnosed 14 days into clindamycin treatment, however, his symptoms (that were mistakenly attributed to gastrointestinal side effect of clindamycin) started much earlier. It does seem that clindamycin-induced AKI tends to occur early into the treatment course. The most common findings on urinalysis in patients with clindamycin-induced AKI seems to be proteinuria (62%) and hematuria (between 42–62%) [10,11]. Our patient demonstrated both hematuria and worsening proteinuria (from 30 mg/dL on discharge to 100 mg/dL on re-admission). In the study by Wan and colleagues [10] they performed renal biopsy in all 50 patients diagnosed with clindamycin-induced AKI. All patients (100%) had evidence of ATN on biopsy. Renal tubulitis was identified in 82% of cases. Our patient refused renal biopsy; hence, we cannot with full certainty determine the exact pathophysiological mechanism of AKI. While renal biopsy is a gold standard to diagnose drug-induced AKI, it is also associated with the risk for complications that can lead to a patient's unwillingness to undergo such a procedure, which is what happened in our case. Despite not being able to, with certainty, diagnose the precise mechanism of clindamycin-induced AKI in our patient (due to the lack of biopsy findings) we are confident that clindamycin, indeed, was a cause, since extensive workup for other etiologies remained negative.

The mechanism by which antibiotics can cause AKI depends on the specific medication and might include glomerular injury, AIN, ATN, tubular damage secondary to crystallization of the drug within the tubules, or hemodynamic protuberances. Table 1 presents a selected list of the most commonly used antibiotics and their mechanism of causing AKI. On the other hand, ACE inhibitors and non-steroidal anti-inflammatory drugs are known to alter intra-glomerular hemodynamics [9,12]. Clindamycin-induced AKI might be secondary to ATN, AIN, or crystal nephropathy.

Since our patient refused a renal biopsy, we cannot confidently conclude what was the exact mechanism of his clindamycin-induced AKI. However, we believe that mechanism was ATN or crystal nephropathy. He had hematuria (more common in ATN) and did not have fever, rash, or eosinophilia or urine eosinophils (more common with AIN) [13,14]. While this did not rule out AIN, it did make it less likely. Additionally, AIN rarely leads to oliguric AKI [14] unlike what we saw in this case. Furthermore, he had muddy brown cast on urine microscopy which is consistent with ATN [15]. In previously published retrospective studies, clindamycin-induced AKI was characterized by transient gross hematuria and oliguric AKI [10,11] which our patient demonstrated.

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Table 1. Summary of commonly used antibiotics and mechanism of causing AKI.

Antibiotic class/mechanism of injury	AIN	ATN	CN	Glomerular injury
Antibacterial	β-lactams Sulfonamides Ciprofloxacin Vancomycin	Aminoglycoside	Sulfonamide Ciprofloxacin Polymixin	–
Antiviral	Acyclovir	Tenofovir	Foscarnet Acyclovir Ganciclovir	Interferon
Antifungal	–	Amphotericin B	–	–
Antiprotozoal	–	Pentamidine	–	Quinidine

AKI – acute kidney injury; AIN – acute interstitial nephritis; ATN – acute tubular necrosis; CN – crystal nephropathy.

Another possibility is crystal nephropathy. Due to clindamycin achieving high concentration in the urine, it might precipitate and lead to tubular obstruction and consequent injury and hematuria [11]. Similar to previously reported cases, our patient developed severe AKI, required RRT temporarily, and improved completely 4 weeks following the cessation of clindamycin.

Conclusions

Albeit rare, clindamycin can be a cause of AKI. The most common side effects of clindamycin, such as nausea, abdominal discomfort, and vomiting are at the same time clinical manifestation of AKI and uremia. Clinician must be vigilant in recognizing these symptoms so that the symptoms of uremia are not attributed to medication side effects which can contribute to a delay in diagnosis. Patients with clindamycin-induced AKI tend to have gross hematuria, and initially AKI is severe with the majority of patients requiring RRT. Despite its dramatic presentation and severity, all reported cases of clindamycin-induced AKI were improved and were successfully weaned off RRT. Early recognition of this rare side effect of a commonly used antibiotic and timely discontinuation of the medication might improve morbidity and mortality associated with this syndrome.

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