Amikacin and Diclofenac Induced Nephrotoxicity: A Drug-Drug Interaction

Harmeet S Rehan, Tarun Arora, Sudhir Kumar, Pranjit S Bhajoni

Abstract
This is a case report of DR, 48yrs male who had deranged kidney function test after administration of both amikacin and diclofenac intravenously simultaneously for acute appendicitis. The nephrotoxicity developed within 48 hrs on intravenous co-administration of amikacin and diclofenac. Serum creatinine levels were raised from 0.9 mg/dl to 1.7 mg/dl. Other biochemical and hematological parameters were within normal limits. On stopping both the drugs, patient's serum creatinine levels reduced to normal levels spontaneously. Causal relationship between both the drugs and raised serum creatinine levels was 'probable' as per WHO causality assessment scale.

Key Words
Amikacin, Diclofenac, Serum Creatinine

Introduction
The nephrotoxic potential of aminoglycosides has been observed on prolonged administration in 10 to 20% of the hospitalized patients who develop acute toxic renal failure. Various studies carried out so far have shown that in as many as 39% of cases of acute renal failure, prior administration of drugs was the cause of failure. Although the incidence of nephrotoxicity with NSAIDS is only 3%-5%, the chances are increased in patients co-administered other nephrotoxic drugs such as aminoglycosides, vancomycin, diuretics, ACE inhibitors, etc. or volume depleted patients or patients with advanced kidney disease. There have been few reports of drug interaction between amikacin and diclofenac leading to nephrotoxicity. Most of the cases of such drug interaction have been seen in preterm infants. The interesting aspect of nephrotoxicity with such interaction is that the aminoglycosides act primarily in the proximal tubules leading to tubular necrosis whereas NSAIDS act mainly on the distal tubules leading to various electrolyte abnormalities. The consequence of such drug interaction can result in early appearance and increased severity of nephrotoxicity.

Case Report
A 48 year male patient diagnosed with acute appendicitis was prescribed inj. amikacin 750 mg and inj. diclofenac 50mg to be administered intravenously twice...
a day on 12th August, 2014. His pretreatment serum creatinine level was 0.9 mg/dl. After 2 days (i.e. on 14th August, 2014) of the treatment his serum creatinine level increased to 1.7 mg/dl (normal range 0.6-1.2 mg/dl). But other investigations including blood urea (12 mg/dl), serum sodium (142 mmol/l) and serum potassium (4.5 mEq/l) were found to be within normal range. Total serum protein level was 6.8 g/dl (normal range 6.0-8.3 g/dl), urine albumin 3.47 g/dl (normal range 3.2-5.0 g/dl) and urine globulin 3.34 g/dl (normal range 3.2-5.0 g/dl) was within normal limits.

On clinical examination, the patient was alert and his pulse and blood pressure was 86/minute regular and 124/82 mmHg respectively. He had no pallor, icterus, lymphadenopathy or clubbing. No abnormality was detected in respiratory, cardiovascular and central nervous system. After raised serum creatinine levels, Inj. amikacin and Inj. diclofenac were stopped. Injection amikacin was replaced by tablet Co-amoxiclav 625 mg per orally twice a day. His serum creatinine levels spontaneously recovered (1.2 mg/dl) after 4 days of stopping drugs (i.e. on 18th August, 2014).

The causality assessment was done as per WHO causality assessment criteria. There was a positive temporal relationship between deranged kidney function test and administration of Inj. amikacin and Inj. diclofenac. There was also a positive dechallenge with both the drugs as the raised serum creatinine returned back to normal (1.2 mg/dl) on stopping both the drugs. Since the adverse event could not be attributed to any other drug and the underlying disease along with the absence of rechallenge makes the causality assessment as 'probable' as per WHO causality assessment criteria.

**Discussion**

The incidence of aminoglycoside induced nephrotoxicity is 10%-15%. The onset of drug induced renal failure is usually slower and the daily rise of serum creatinine level is lower than other causes of acute renal failure. In majority of aminoglycoside induced nephrotoxicity cases, serum creatinine and blood urea nitrogen levels increases within 7 to 10 days of initiation of therapy. Vast majority of patients with aminoglycoside induced nephrotoxicity recover by 4-6 weeks. In the present case a complete recovery of serum creatinine induced nephrotoxicity was observed only after 4 days of stopping the suspected medications. Early recovery could be due to the fact that the rise in serum creatinine level was noticed after 2 days following which suspected medications were withdrawn immediately.

Aminoglycosides, which are strongly cationic drugs, bind to the negatively charged acidic phosphoinositide components of the brush border membrane of proximal tubule. After uptake of aminoglycoside into the proximal tubule cells in the S1 and S2 segments, a number of intracellular processes including inhibition of the mitochondrial transport chain and reabsorption of sodium, potassium, and magnesium are disrupted leading to cell necrosis.

The incidence of nephrotoxicity with diclofenac is around 3%. Usually prolonged administration of non-steroidal anti-inflammatory drugs viz diclofenac can alter renal functions through their inhibitory effects on renal prostaglandins leading to reversible renal ischemia. Toxic doses of diclofenac have been reported to be nephrotoxic both in humans and experimental animals (200 mg/kg in mice). Renal dysfunctions are more prominent in geriatric population, patients with advanced renal disease and co-administration with diuretics, ACE inhibitors and aminoglycosides. Diclofenac-induced nephrotoxicity may involve production of reactive oxygen species leading to oxidative stress and massive genomic DNA fragmentation, which may ultimately translate into apoptotic cell death of kidney cells. Recovery from diclofenac induced nephrotoxicity usually occurs spontaneously after the withdrawal of drug.
Drug interaction between co-administration of amikacin and diclofenac. In addition to the individual potential of amikacin and diclofenac to cause nephrotoxicity when administered together, diclofenac decreases renal clearance of amikacin leading to increased serum levels of amikacin in preterm infants.[4] In adults it is reported that diclofenac 50 mg twice daily when administered with aminoglycosides may lead to nephrotoxicity progressing to acute renal failure.[11]

Amikacin is more frequently associated with deranged serum creatinine than diclofenac. [6, 7] This patient might have developed increased serum creatinine levels on second day itself due to the consequences of drug-drug interaction between amikacin and diclofenac. Clinicians should monitor the kidney function tests more frequently when diclofenac and amikacin are co-administered.

References