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A Case Study of Drug Induced Acute Interstitial Nephritis with combined use of Beta-Lactams, NSAID's and Amikacin

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Abstract: ***The process of wound healing in crush injuries would concede long period due to the large open wound. During this period, the subject will be on antibiotics as a prophylactic therapy to prevent infection and analgesics to relieve the pain for patient comfort. Long-term use of antibiotics (Beta-lactams and Amikacin) and analgesics (NSAIDs) can degrade the functioning of renal organs. Acute Interstitial Nephritis is an entity of Acute Kidney Injury which is manifested mostly with the use of nephrotoxic drugs rather than microbes. This article presents a case of Acute Interstitial Nephritis with the combined use of Amikacin, NSAIDs and Beta-lactams in inpatient who has admitted due to crush injury.***

Keywords: Crush injury, Acute Interstitial Nephritis, Amikacin, NSAIDs, Beta-lactams

1. Introduction

AIN is an entity in which AKI is accompanied by histological findings of interstitial inflammation, edema and tubulitis [1]. It is the underlying cause for up to 3% of all cases of AKI [2]. AIN usually manifests 2 weeks after exposure to a drug but may occur sooner if the patient was previously sensitized [3]. 1/3rd of cases reported were caused due to antibiotics [1]. Clinical presentation of AIN varies with the class of drugs used.

Table 1: Drugs associated with interstitial nephritis

S. No.	*Class of drugs*	*Drugs*
1	Antimicrobials	Acyclovir, Aminoglcosides, Amphotercin-B,Beta-Lactams , Erythromycin, Ethambutol, Indinavir, Sulfonamides, Tetracyclines, Vancomycin.
2	Diuretics	Acetazolamide, Amiloride, Chlorthalidone, Loop Diuretics, Thiazides.
3	Neuropsychiatrics	Carbamazepine, Phenytoin, lithium, Valproic acid, Phenobarbitol.
4	NSAIDS	Aspirin,COX-2Inhibitors, Diclofenac, Diflunisal, Ibuprofen, Indomethacin, Naproxen, Ketoprofen.
5	Miscellaneous	Acetaminophen,Allopurinol, Aspirin,Azathioprine, Lansoprazole,Omeprazole, Captopril, ranitidine, warfarin.

2. Case Presentation

A 55yr old male was presented in emergency ward with a large open wound (crush injury) to his left foot occurred due to trauma. At the time of admission, patient was conscious and has no complaints of vomiting and ear bleed. The social history of patient suggests that he is a mild alcoholic and smoker for not less than 5 years but patient was not diabetic and non-hypertensive. In the emergency ward, analgesics and antibiotics often administered intravenously to help the patient with comfort and also to prevent spread of infection as the wound is open and tissue loss is significant. Physician assessed the injury and determined nerve and vascular damage, found crushed tarsals, severe damage to abductor muscles, flexor muscles, plantar muscles, perforating vessels, superficial nerves and deep nerve branches. Physician recommended for amputation surgery immediately in order to prevent systemic infection.

Pre-Surgical Assessment: Prior to the surgery, lab investigations were performed in-order to assess the functioning of major organs. The reports produced normal liver and kidney functioning. In the Complete Blood Picture, RBC's and Hemoglobin levels found to be low due to loss of blood at the time of trauma. Culture sensitivity tests were done and reported antibiotic sensitivity. Blood transfusions were done to the patient to improve RBC and Hemoglobin levels. The patient regretted and denied the amputation surgery due to emotional imbalances. The surgery has been delayed for 7 days. During this period, patient was on intravenous analgesics and antibiotics which includes-Ceftriaxone-1gm bd, Amikacin – 500mg bd, Metronidazole-500mg bd, Diclofenac – 75mg IM bd, Tramadol – 50mg IM sos. Due to delay in surgery, infection has been spread anterior to the lateral malleus. Finally with the patient compliance surgery was performed and amputated his foot till lateral malleus region.

Post-Surgical Assessment: List of antibiotics and analgesics prescribed after surgery were mentioned in table-2. From day one, after 12 days of continuous intravenous administration of Amikacin – 500mg bd, Metronidazole – 500mg bd and ceftrixone – 1gm bd ; Amikacin and Metronidazole are stopped and ceftriaxone has been changed to oral route with the dose of 200mg bd. Aceclofenac plus paracetamol combination was added to the analgesics diclofenac and tramadol to treat post surgical pain.

Table 2: Antibiotics and Analgesics administered by patient from day one to day25

S No.	*Name of the Drug*	*Dose, Route and Frequency*	*Duration of Administration*
1	Ceftriaxone	1gm IV bd	D1 to D12
2	Amikacin	500mg IV bd	D1 to D12
3	Metronidazole	500mg IV bd	D1 to D12
4	Diclofenac	75mg IM bd	D1 to D25
5	Tramadol	50mg IM sos	D1 to D25
6	Aceclofena+paracetamol	100mg+550 mg oral bd	D13 to D25
7	Ceftriaxone	200mg oral bd	D13 to D25

D – day, IM –Intra Muscular, IV – Intra Venous, bd – twice in a day, sos - when required.

Along with the mentioned drugs in table 2; other medications were also prescribed to treat constipation, cough and occasional fever. These drugs were not mentioned as this article is mainly concentrated on antibiotics and analgesics. After administering ceftriaxone for 25 days, the drug was discontinued and higher antibiotic piperacillin tazobactam combination was prescribed due to delay in wound healing. Amikacin was added again to the therapy. Medications administered from day-26 to day-40 are mentioned in table 3.

Table 3: Antibiotics and Analgesics administered by patient from day 26 to day 40

S No.	*Name of the Drug*	*Dose, Route and Frequency*	*Duration of Administration*
1	Piperacillin+tazobactam	1gm IV bd	D26 to D40
2	Amikacin	500mg IV bd	D26 to D37
3	Diclofenac	75mg IM bd	D26 to D40
4	Tramadol	50mg IM sos	D26 to D40
5	Aceclofena+paracetamol	100mg+550 mg oral bd	D26 to D40

After 40 days of pharmacotherapy, patient had sudden complaints of breathlessness, fever, cough, vomiting and abdominal pain. Lab investigations shown electrolyte imbalances and sudden unexplained rise in serum creatinine, urea levels along with the kidney injury. Protinuria was seen in complete urine examination. There is an abrupt increase in WBCs (esinophilia) and severe anisopoikilocytosis along with microcytic hypochromic anemia has been reported in Complete Blood Picture. In addition to the above clinical features, rashes were also manifested in the patient. The lab findings were mentioned in table 4.

Table 4: Laboratory findings

Lab investigations	*Test value*	*Normal range*
WBCs	16,500 cells/cumm	4000-11000c/cumm
Hemoglobin	5.9gm/dl	11-16gm/dl
Serum creatinine	6.9 mg/dl	0.6-1.4 mg/dl
Blood urea	115mg/dl	14-45 mg/dl
Serum Sodium	136mmols/L	135-155mmols/L
Serum Potassium	4.0mmols/L	3.6-5.5mmols/L
Serum Chlorides	109mmols/L	98-108mmols/L

From the above clinical manifestations, it was found difficult to differentiate sepsis from interstitial nephritis [4]. In order to treat this condition, analgesics and amikacin were stopped immediately. Immunosuppressive agent hydrocortisone therapy was initiated. As the renal functioning was poor, Dialysis was done to patient to remove toxic substances. During the therapy patient became mortal due to complete renal shutdown.

3. Discussion

Interstitial Nephritis affects the interstitium of kidneys surrounding the tubules [5]. Common medications that induces interstitial nephritis are antibiotics mostly beta-lactams, aminoglycosides and NSAIDs. The cumulative doses of those drugs in this case study are mentioned in table 5.

Table 5: Cumulative doses of antibiotics and NSAIDs administered to the patient during the therapy

S No.	*Name of the Drug*	*Cumulative Dose*
1	Ceftriaxone	29.2 gm
2	Piperacillin+tazobactam	35gm
3	Amikacin	24gm
4	Diclofenac	6gm
5	Aceclofena+paracetamol	19.5gm

The mechanisms that leads to kidney damage are:

Beta-lactams – Beta-lactams produce AIN because they behave like haptens, which may bind to serum or cellular proteins to be subsequently processed and presented by MHC molecules as hapten modified peptides and presented by MHC molecules as hapten modified peptides. The most common form of haptenization for pencilloly configuration, which arises from the opening of strained beta-lactam ring, yielding an additional carboxylic function that allows molecule to covalently bind to lateral and terminal amino terminus of proteins. Serum molecule thus facilitates haptenization. This reaction occurs with the prototype benzyl pencillin and virtually all semi-synthetic pencillins, but other derivatives can be formed in small quantities and stimulate variable immune. Because all beta-lactams share the same basic structure, they are all conductive to haptenization[6]. Clinical signs present approximately 14 days after initiation of therapy and include fever, maculopapular rash, eosinophilia, pyuria and hematuria, low level proteinuria and oliguria[3]. Based on hypothesis, administration of ceftriaxone with the cumulative dose of 29.2 gm might have been

sensitized the kidneys, when ceftriaxone was stopped and piperacillin was administered for a period of 14 days , haptenization mechanism might have been generated which reduced renal perfusion and finally lead to interstitial nephritis.

NSAIDs – Non-selective NSAIDs are inhibitors of both COX-1 and COX-2 pathways. COX-1 is responsible for maintainance of renal blood flow. Activation of COX-1 synthesizes the prostaglandins which cause vasodilation of afferent arterioles and it improves renal perfusion. Due to continuous administration of non-selective NSAIDs, COX-1 pathway gets inhibited which reduces renal perfusion and ultimately it leads to interstitial nephritis and renal shutdown [7]. Diclofenac and aceclofenac are non-selective COX inhibitors; this is a possible mechanism which leads to interstitial nephritis in the patients whose age is greater than 50yrs. The onset would be delayed [3].

Amikacin – It is an Aminoglycoside, which directly produces nephrotoxicity as the majority of drug is excreted by renal organs. Toxicity may be related to cationic charge, which facilitates binding of filtered aminoglycosides to renal tubular epithelial cell luminal membranes, followed by intracellular transport and concentration in lysosomes. Cellular dysfunction and death may result from release of lysosomal enzymes into the cytosol[3]. The maximum cumulative dose of amikacin for 10 days is 15g[8], in this case the administered cumulative dose of amikacin was found to be 24g for a period of 30 days through two dosage regimens. Rise in serum creatinine concentrarion and decrease in crearinine clearance after 6 to 10 days of therapy are initial clinical manifestations of toxicity. Dehydration, sepsis, ischemia and other nephrotoxic drugs frequently contribute to and complicate the identification of the causative agent or condition [3].

The combination of above mechanisms can worsen the renal functioning and lead to complete renal shutdown. In this case, symptoms manifested in patient are similar to sepsis, so it is difficult to differentiate the cause of death between sepsis and interstitial nephritis. A test of renal biopsy can specify the reason for death [4]. Unfortunately renal biopsy was not performed to the patient who might have strengthened the evidence.

4. Conclusion

In the cases of crush injury, long-term antibiotic and analgesic therapy is required as the process of wound healing requires certain period of time. This may lead to drug induced interstitial nephritis; along with sepsis the condition becomes life-threatening. To reduce the unwanted effect on kidneys, therapeutic drug monitoring is strictly recommended especially for nephrotoxic agents. Patient induced analgesia is another process to relieve pain in post-surgery patients can be implemented in order to avoid unwanted effects and long-term use of NSAIDs.

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Conflict of Interests

Authors declare that they have no conflict of interests.

Abbreviations

NSAID – Non-Steroidal Anti-Inflammatory Drugs, AKI – Acute Kidney Injury, AIN – Acute Interstitial Nephritis, COX – Cyclo-Oxygenase Pathway.

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