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Case Report Open Access

Phenyramidol Induced Acute Tubular Necrosis

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Introduction

Phenyramidol is a moderately effective, non-narcotic analgesic and muscle relaxant. It acts by interneuronal block in the spinal cord and brain stem. The clearance of the drug becomes in the liver via glucuronidation. Conjugated form of the drug is excreted through the kidneys [1]. It is not available in the US or, with the exception of Turkey, in Europe. It is widely used for musculo-skeletal pain such as acute lumbago and chronic back pain in the Asia and Turkey, with or without NSAİDs. It rarely causes gastrointestinal discomfort and there are some reported cases of hepatotoxicity [2]. To the best of our knowledge, nephrotoxicity has not been reported yet. Herein, we reported a case of Acute Tubular Necrosis (ATN) possibly due to the use of phenyramidol for backache.

Case Report

A 30-year-old male was admitted with the complaints of vomiting and fatigue. His complaints had started two days ago. He was hospitalized due to elevation of creatinine (15.6 mg/dL) and urea levels (153 mg/dL) with a diagnosis of Acute Kidney Injury (AKI). A urine analysis shows proteinuria (1 g/day). Urine sediment reveals microscopic hematuria (4 red blood cells per high-power field) and 7 leukocytes per high-power field. Other admission laboratory parameters and final biochemical tests. He denies smoking, drinking alcohol, or using illicit drugs. There was only one month history of low back pain and he was using phenyramidol hydrochloride 400 mg orally, three times daily, for the past month. He does not take any other medications, including over-the-counter Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and is not taking herbal supplements. He also realized that his urine output decreased in the last 24 hours. On physical examination he was ill-appearing; there was no edema or any findings of dehydration. His temperature is 37°C (98.6°F). He has a heart rate of 80 bpm, with a regular rhythm, a blood pressure of 140/82 mm Hg, and a respiratory rate of 16 breaths/min. His lungs are clear to auscultation. Auscultation of his heart demonstrates normal sounds. He has a soft, nontender abdomen, without appreciable masses or organomegaly. The rest of examination, including fundus-ear examination, was unremarkable. There was no rash on his skin. Ultrasonography of the urinary system was unremarkable. Immunological and serological tests including anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody, cryoglobulin, HBsAg, anti-HBs IgG, anti-HCV and anti-HIV were negative. Serum complement C3 and C4 levels were within normal limits.

Immediately after the initial evaluation he was undergone urgent Hemodialysis (HD) because of severe uremia and acidosis. Phenyramidol was discontinued. The patient was not dehydrated. He was adequate hydration. Therefore, pre-renal azotemia was not considered. After three HD sessions, his kidney functions were not improved and he was still oliguric (200 mL/day). AKI was assessed as renal origin. He had Rapidly Progressive Glomerulonephritis (RPGN) statement. Crescentic IgA nephropathy or vasculitis could cause RPGN. Renal biopsy was performed with the possible diagnosis of rapidly progressive glomerulonephritis and acute tubulo-interstitial nephritis. Especially, renal biopsy was performed to exclude RPGN. Result of the biopsy (Cortical tubules are dilated, with some diminishment of their brush border. Some proximal tubules lumens contain necrotic cellular debris) was consistent with ATN. His urine output progressively increased and kidney functions improved without specific therapy after 7 days. At the end of the first month of follow-up, creatinine level was 1.2 mg/dL and all biochemical tests and urinalysis returned to normal range.

Discussion

Phenyramidol is generally well tolerated without serious side effect and available as tablet or ampule for over 50 years [2,3]. It may cause mild gastrointestinal discomfort. There is some reports implicating the hepatotoxicity of this agent [3,4]. Ergun et al. reported that 7 of 38 patients who were treated with phenyramidol (400 mg tablet 3 times/day) had elevated liver enzymes at the end of the chronic treatment phase which was normalized after a week [2]. To the best of our knowledge, nephrotoxicity associated with phenyramidol has not been reported yet.

Drug-induced ATN represents a significant cause of acute kidney injury. ATN is an intrinsic renal failure secondary to ischemic cases or toxic substances. It is characterized by proximal tubular epithelium necrosis. Necrotic cells fall into the tubule lumen and determining acute renal failure. ATN is confined largely to the tubular and interstitial compartments with sparing of the glomeruli and the vasculature. Nephrotoxic mechanisms of ATN include direct drug toxicity, intrarenal vasoconstriction, and intratubular obstruction [5]. Drug induced ATN can result from various drugs, such as aminoglycosides, amphotericin, calcineurin inhibitors, foscarnet, ifosfamide, cisplatin, acyclovir, trimethoprim-sulfamethoxazole, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and radiographic contrast media. Conditions such as multiple myeloma, rhabdomyolysis and intravascular hemolysis can cause ATN. Renal manifestations develop within days or weeks after starting the implicating drug. The clinical presentation most suggestive of the diagnosis is that of a sudden impairment of renal function associated with mild proteinuria and oliguria. It is difficult to diagnose ATN based on clinical and laboratory findings only, and renal biopsy is required for a definitive diagnosis [4]. Only 20 to 30% of patients present with the classic urinalysis of ATN; muddy brown colour and granular casts. The definitive diagnosis has been established by renal biopsy in

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our patient. The adverse reaction appeared after phenyramidol was initiated, resolved promptly on withdrawal of the drug, and no other medications were likely to be the cause. Mechanism of toxicity due to phenyramidol is not known. Clinical signs developed a few weeks after the start of to take phenyramidol in our patient. Therefore, tubular accumulation is thought as the mechanism of toxicity. The clearance of the drug becomes in the liver via glucuronidation. Conjugated form of the drug is excreted through the kidneys [1]. These conjugated products may accumulate in the tubules.

This drug is used by physicians, especially in primary care, for the locomotor system pain in the countries of Middle East and Asia for nearly 50 years. It has been used as the first choice by some physicians because of its less adverse effects compared to NSAIDs. In our patient, Phenyramidol was chosen as the first choise by primary care physician for back pain. It is not available in the US or, with the exception of Turkey, in Europe.

Phenyramidol is a relatively nontoxic drug. To date, there have been no reports implicating the nephrotoxicity of this agent. This report presents the first case of phenyramidol induced nephrotoxicity. Therefore, phenyramidol should be considered as a drug that may cause nephrotoxicity. If kidney dysfunction develops during phenyramidol treatment, the drug should be stopped and alternative agents should be used.

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