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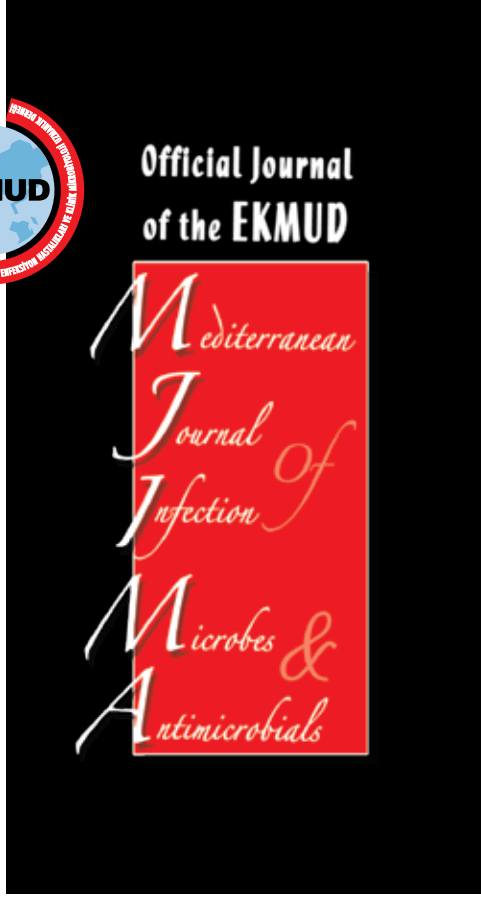

Hypophosphatemia Due to Adefovir Treatment

Adefovir Tedavisine Bağlı Hipofosfatemi

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ABSTRACT

Adefovir dipivoxil is an orally effective prodrug excreted unchanged in urine by glomerular filtration and tubular secretion. While it effectively suppresses hepatitis B virus replication, it may cause nephrotoxicity characterized by severe hypophosphatemia. In this report, we present a case of isolated hypophosphatemia due to long-term use of adefovir dipivoxil (10 mg/day). Due to the risk of hypophosphatemia with extended use, calcium and serum levels and symptoms suggesting nephrotoxicity should be followed in patients using adefovir dipivoxil for an extended period.

Key words: Adefovir, hypophosphatemia, adverse drug reaction

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ÖZET

Adefovir dipivoksil oral yoldan kullanılan bir ön ilaç olup, glomerüler filtrasyon ve tübüler sekresyonla değişmeden vücuttan atılır. Etkin olarak hepatit B virüsü replikasyonunu baskılasa da, ağır nefrotoksisiteye neden olabilir. Uzun süreli kullanımda hipofosfatemi gelişebilme ihtimalinden dolayı serum kalsiyum ve fosfor düzeyleri uzun süreli adefovir dipivoksil kullananlarda takip edilmelidir.

Anahtar kelimeler: Adefovir, hipofosfatemi, advers ilaç reaksiyonu

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INTRODUCTION

Adefovir dipivoxil (ADV) is an orally effective prodrug that is a phosphonate nucleotide analog of adenosine monophosphate[1]. It is effective against human immunodeficiency virus (HIV) and hepatitis B virus (HBV)[2]. It causes termination of the HBV DNA strand by inhibiting both reverse transcriptase and DNA polymerase[3]. It is well tolerated at a 10 mg daily dose[4]. ADV may cause renal tubulopathy in patients[5]. There are several features of nephrotoxicity due to ADV. It is usually caused by a daily dose ≥ 30 mg, and it causes proximal tubular dysfunction. Proximal tubular dysfunction is generally seen after 20 weeks of treatment, with a gradual onset[5,6]. Although no evidence of proximal tubular dysfunction was found in long-term safety studies with a 10 mg dose, in a few case reports, severe Fanconi syndrome was reported at this dose[6,7]. Fanconi syndrome was reported in many studies with HIV patients due to high-dose ADV treatment and in several studies with chronic HBV patients using 10 mg/day ADV. In patients with Fanconi syndrome, proteinuria, aminoaciduria, hypophosphatemia, and hypouricemia occur due to generalized proximal tubular dysfunction and muscle weakness, fatigue, skeletal pain, and pseudofractures due to electrolyte disturbances. Treatment includes correction of metabolic acidosis and normalization of serum phosphate levels[3,5-7]. In patients using ADV, renal functions, serum alkaline phosphatase (ALP), calcium, and phosphate levels should be monitored regularly due to the risk of nephrotoxicity[5,6]. Predisposing factors for renal failure should be searched in patients if use of the drug for more than one year is being considered[4].

CASE REPORT

ADV 10 mg/day was introduced to a 48-year-old male patient due to chronic hepatitis B. At the beginning of therapy, laboratory results were as follows: HBsAg positive, HBeAg positive, alanine aminotransferase (ALT): 87 u/L, HBV DNA: 247.000.000 copy/mL, phosphate: 3.4 mg/dL, calcium: 10.4 mg/dL, and creatinine: 0.7 mg/dL.

During the follow-up, ALT normalized and HBV DNA became negative, but the phosphate level was not measured. Due to the presence of virological and biochemical response to the drug and absence of an increase in blood creatinine level during the follow-up, treatment was continued. After three years of treatment, serum phosphate level was 3.4 mg/dL. The patient presented to our clinic after five years of treatment with diffuse skeletal pain and malaise. Laboratory test results were: creatinine: 0.9 mg/dL, phosphate: 2.7 mg/dL, and ALP: 80 u/L; urine biochemistry was normal. He denied using a drug other than ADV, and there was no history of a familial disease. He was consulted to the Physical Therapy and Endocrinology Departments. Serum parathormone, vitamin D, thyroid stimulating hormone (TSH), and free T3 levels were measured to exclude other causes of hypophosphatemia, and all were within normal limits. ADV treatment was continued and the patient was seen at monthly follow-ups. The phosphate level was found to be 2.4 mg/dL, 2.1 mg/dL, and 1.8 mg/dL in the first, second, and third months, respectively. Lumbar osteopenia was detected in bone densitometry, and this result was reported to the Drug Surveillance Unit of the Ministry of Health. Treatment was changed to entecavir 0.5 mg/day. At the monthly follow-ups, bone pain and malaise complaints regressed and phosphate level after the third month of entecavir treatment was 3 mg/dL.

DISCUSSION

Renal tubular toxicity due to antiviral treatment may be seen with ADV, tenofovir disoproxil and cidofovir[3,5]. ADV is excreted unchanged in urine by glomerular filtration and tubular secretion[8]. Although this drug effecti-

vely suppresses HBV replication, it may cause nephrotoxicity characterized by severe hypophosphatemia[9].

Nephrotoxicity due to ADV is usually late-onset and dose-dependent[7]. In HIV treatment, it is usually seen due to long-term and high-dose usage[10,11]. In a double-blind comparative study of 60 mg/day and 120 mg/day ADV, nephrotoxicity was seen less often in patients using low doses[12]. In two large studies, 10 mg/day ADV led to important improvements in liver histology and ALT levels, and there was no evidence of nephrotoxicity[13,14]. However, in a study involving 125 patients, 3% of patients using ADV 10 mg/day showed mild to moderate renal dysfunction and another study detected mild nephrotoxicity in 5% of patients[15,16]. Jung et al., Lee et al. and Girgis et al. reported severe hypophosphatemia (1.3-2 mg/dL) and Fanconi syndrome in patients using ADV 10 mg/day[2,6,8]. Our patient also had hypophosphatemia due to ADV at a dose of 10 mg/day.

Fanconi syndrome is characterized by proximal renal tubular dysfunction, which causes proteinuria, aminoaciduria, hypophosphatemia, hypouricemia, glucosuria, and proximal renal tubular acidosis. Muscle weakness, fatigue and pseudofractures are seen due to electrolyte imbalance[6,7]. Although fatigue, bone pain, hypophosphatemia, and normal serum levels of calcium, parathormone, and vitamin D suggested Fanconi syndrome, normal ALP and uric acid levels and absence of proteinuria and aminoaciduria in urine were inconsistent. Osteomalacia frequently accompanies Fanconi syndrome, and bone densitometry in our patient revealed osteopenia in the lumbar region[7].

Other than antiviral drugs, valproate, aminoglycoside, tetracycline, iphosphamide, cisplatin, 6-mercaptopurine, and methyl-3-chromamine may lead to hypophosphatemia and Fanconi syndrome[6,16]. Our patient was not using any drug other than ADV.

Standard treatment for hypophosphatemia due to ADV includes switching ADV to an antiviral agent other than tenofovir disoproxil[7,17]. We changed ADV to entecavir and followed phosphate levels at monthly visits. Phosphate levels increased during the follow-up and normalized (3 mg/dL) three months later.

In conclusion, according to our literature search, there has been no previous case of isolated hypophosphatemia, as seen in our patient, although in recent years ADV was reported to cause nephrotoxicity at high doses and Fanconi syndrome at 10 mg/day. Many clinicians generally do not follow calcium and phosphate levels routinely because incidence of nephrotoxicity is low using conventional doses. However, due to the risk of hypophosphatemia with extended use, calcium and serum levels and symptoms suggesting nephrotoxicity should be followed in patients using ADV for a long period. An antiviral agent other than tenofovir disoproxil should be preferred in such cases as soon as an adverse effect is detected.

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