

Case Report

Codeine Toxicity in a Hemodialysis-dependent Child: A Rare Case of Prolonged Neurologic Complications



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ABSTRACT

Background and Aim: Chronic kidney disease (CKD) is one of the most important problems in children, sometimes associated with many co-morbid problems, such as intractable pain. The pharmacokinetics of almost all analgesics are very different in CKD patients compared to the normal population. Because of the accumulation of toxic metabolites, many of the commonly used pain medications have more adverse effects and increased potential for central nervous system toxicity.

Case Presentation: We reported an eleven-year-old girl affected by end-stage renal disease (ESRD) due to focal segmental glomerulosclerosis (FSGS) nephrotic syndrome who presented with decreased level of consciousness, behavioral dysfunction, and neurological complications following a small dose of codeine consumption.

Conclusion: Even small doses of codeine can lead to severe, prolonged neurotoxicity in pediatric ESRD. Appropriate drug selection and dosing in patients with CKD is necessary to ensure optimal outcomes and avoid unwanted complications. Prescribing a standard dose of analgesics without consideration of the patient's renal function state may cause serious complications.

Keywords: Codeine, Opioid, Drug toxicity, Hemodialysis, Pediatric nephrology

Introduction

Approximately one-half of patients with chronic kidney disease (CKD) experience severe pain syndromes. CKD refers to irreversible damage to the kidney tissue, failing its normal function. These patients experience a variety of painful conditions, either nociceptive or neuropathic in nature [1, 2]. Nociceptive pain may include osteoarthritis, renal osteodystrophy, dialysis-related amyloid arthropathy, and

distension of the kidney or liver capsule. This pain may be highly severe, resulting in lower health-related quality of life, psychosocial distress, and other conditions, such as depression and poor sleep [3]. CKD in adults occurs mostly because of diabetic nephropathy and hypertension, but in children, it is more commonly due to congenital anomalies and acquired glomerular diseases [4]. Increased drug level-associated adverse effects may occur due to reduced renal clearance and accumulation of a toxic parent compound and/or its metabolite, or increased free drug levels due to decreased protein bind-



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ing due to hypoproteinemia or hypoalbuminemia and/or acidemia [5]. The need for analgesics is based on the patient's age, sex, stage of renal failure, type of underlying disease, and severity of pain (Table 1). This case report aimed to discuss the importance of cautious use of analgesic medications in children based on the rare documented reports of this condition in children with CKD.

Case Presentation

We reported an 11-year-old girl with end-stage renal disease (ESRD) due to nephrotic syndrome following focal segmental glomerulosclerosis (FSGS), which started when she was 3 years old. She was receiving prednisolone, cyclosporin, tacrolimus, and cyclophosphamide in a consecutive manner, which were discontinued because of non-responsiveness. Her hemodialysis sessions started 3 months before her admission, and she was referred to our tertiary center because of an unusual altered level of consciousness and behavioral dysfunction in the past 10 days. Based on her history, ten days before admission, she had received just one dose of acetaminophen codeine (325 mg/80 mg), and after that, she could not swallow at all and was unable to sit without help. She could not recognize anyone, even her mother and father, and also exhibited bizarre behavior and delusions, and had several episodes of seizures.

Laboratory data showed proteinuria and high levels of urea and creatinine. Hemodialysis sessions began, and simultaneously, a urine sample for a toxicology test was

obtained, which was positive for codeine derivatives. Urine toxicology test was still positive after several hemodialysis sessions.

Brain magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) showed bilateral symmetric cortical and subcortical hyperintensity in the frontal, parietal, and occipital lobes, with no diffusion restriction. Abnormal hyperintensity in the posterior limb of the internal capsule, cerebral peduncles, the middle of the pons, and the tegmental tract was also detected. Diffusion restriction of the posterior limbs of the internal capsules and the middle of the midbrain was also noted (Figure 1).

In the brain MRI and MRV without contrast, there were normal appearing deep and superficial cerebral veins (superior sagittal, straight, inferior sagittal, transverse, and sigmoid Dural venous sinuses). Asymmetry of the transverse and sigmoid sinuses was observed, which could be a normal variation. There was no detectable intracranial venous sinus thrombosis. MRI imaging showed brain stem and midbrain, and parietal involvement. There was no clear explanation for these brain MRI changes.

Post-hypoxic-ischemic encephalopathy, toxic leuko-encephalopathy, ADEM, osmotic demyelination syndrome, and extrapontine myelinolysis were in the list of her differential diagnoses. At first, she received methylprednisolone pulse and IVIG and then continued to receive prednisolone alone, which tapered off and was dis-

Table 1. Stepwise approach for nociceptive pain management in patients with CKD

Severity	Pharmacologic Options For Non-CKD	Special Considerations for CKD
Mild	Nonopioids, adjuvants: NSAIDs, acetylsalicylic acid, and acetaminophen.	Acetaminophen is preferred (dose minimization is warranted). NSAIDs and COX-2 inhibitors likely adversely affect renal hemodynamics equally. Use of short-acting NSAIDs is suggested; consider topical analgesics when appropriate. Consider sulindac or salsalate. Avoid concomitant use of other hemodynamically compromising drugs (e.g. renin inhibitors, ACEIs, ARBs, and radiocontrast agents). Optimize cardiac output and volume status; avoid NSAIDs in volume depletion.
Moderate	Nonopioids, adjuvants, weak opioids (codeine, dihydrocodeine, hydrocodone, tramadol).	Tramadol may be considered. Codeine and dihydrocodeine are not recommended in patients with advanced CKD.
Severe	Nonopioids, adjuvants, moderate to strong opioids (fentanyl, morphine, hydromorphone, methadone, levorphanol, and oxycodone).	Methadone or fentanyl may be acceptable; dose and frequency reduction are advisable. Warning on the use of fentanyl: potential life-threatening respiratory depression in non-tolerant patients and improper dosing. Codeine and dihydrocodeine are not recommended in patients with advanced CKD.

Abbreviations: CKD: Chronic kidney disease; NSAIDs: Non-steroidal anti-inflammatory drugs; ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers.

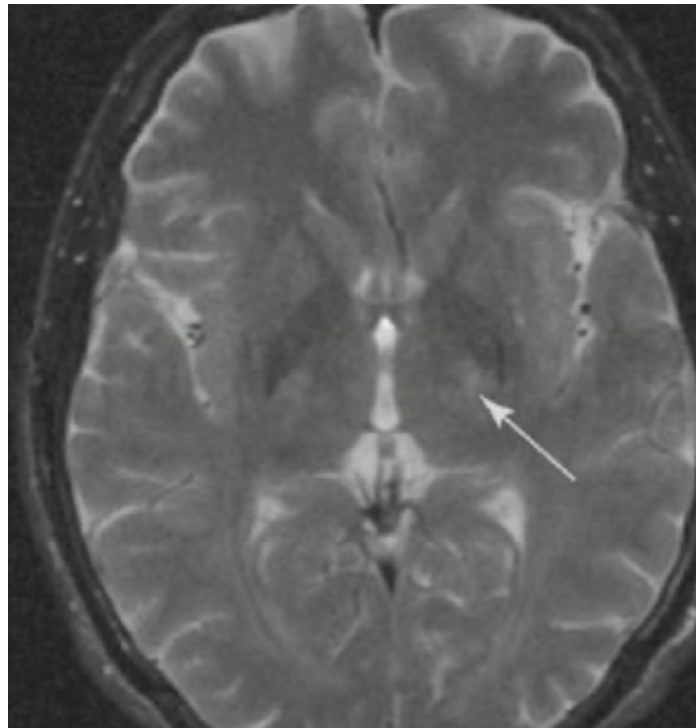


Figure 1. Brain tissue enhancement and diffusion restriction of the posterior limbs of the internal capsules and the middle of the midbrain

continued over 2 months. One month after starting this treatment, she slowly got better and could sit alone and swallow food and drinks, but her level of consciousness came back later, after two months.

Discussion

Patients suffering from CKD and ESRD and those undergoing HD therapy are usually exposed to a significant number of different drugs. The risks of drug-drug interactions (DDI) in poly-medicated patients are well known, particularly in CKD patients [6]. CKD alters drug metabolism through several mechanisms: (a) Decreased absorption from delayed gastric emptying, increased gastric pH, and bowel wall edema; (b) increased volume of distribution and decreased protein binding; (c) altered metabolism with accumulation of active drug; and (d) decreased elimination due to lower glomerular filtration rate and decreased protein binding leading to a higher incidence of adverse effects [7].

Pain is a common problem in patients with ESRD, affecting their quality of life. Some studies report that about 50% of hemodialysis patients experience pain. It also showed that a few patients have been given analgesic treatment to control the pain [8]. Pain is often underestimated and undertreated in patients with CKD or ESRD. CKD patients exhibit a variety of painful

conditions, which may be nociceptive or neuropathic in nature. Pain control in patients with CKD presents a challenge because analgesics are mostly metabolized or eliminated in the kidneys and must be dose-adjusted in these patients [9].

Increased drug levels and associated adverse effects may occur due to their reduced renal clearance and accumulation of a toxic parent compound and/or their metabolites or increased free drug levels due to reduced protein binding associated with hypoproteinemia, hypoalbuminemia, and acidemia [10]. Although the use of non-steroidal anti-inflammatory drugs is the first step in pain treatment, their use is prohibited in kidney failure because it causes more nephrotoxicity and increases the possibility of gastrointestinal bleeding. The preferred medication for analgesia in patients with CKD is acetaminophen [11, 12]. Acetaminophen is thought to cause both liver and renal tubular damage via the toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) [13]. On the other hand, most opioids undergo hepatic biotransformation and are primarily eliminated by renal excretion. Thus, codeine and its active metabolite morphine clearance are decreased in patients with impaired kidney function; they are rarely used in pediatrics [14]. Although adjusting drug dosage in chronic renal failure is usually necessary only when the GFR is less than 30–40

mL/min/1.73 m² in patients with chronic renal failure, it is recommended to be more cautious [1, 15].

In this very rare case report, we presented a child suffering from CKD with neurological complications of codeine toxicity lasting for about 2 months occurring from just one tablet of acetaminophen codeine containing only 80 mg of codeine. Interestingly, several sessions of hemodialysis could not help improve her condition over time.

Conclusion

General prevalence and outcomes of opioid prescription in ESRD patients remain undetermined. Overall, the use of analgesics, such as opioids, morphine, codeine, meperidine, and propoxyphene in patients with advanced kidney failure should be done with strict caution.

Ethical Considerations

Compliance with ethical guidelines

The authors assert that all procedures contributing to this work comply with the ethical standards of [Tehran University of Medical Sciences](#), Tehran, Iran. As our patient was under 16 years of age, her parents or guardians were informed and signed an informed consent form.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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