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Synthetic Cannabinoids and Renal Transplant

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Abstract

Synthetic cannabinoids, also known as 'spice' or 'K2', have recently increased in popularity as a drug of abuse among young adults. It has been associated with unexplained acute kidney injury and electrolyte abnormalities in otherwise healthy individuals. The mechanism of this phenomenon is not fully understood although some reports suggest that it may be potentially due to synthetic cannabinoids having increased potency causing an accumulation of harmful levels of toxicity. It is not understood if the use of this drug should preclude deceased donor renal transplantation and currently there are no reports on the use of K2's effect on donor graft function. Herein, we summarize the first reported case of renal transplantation from a deceased donor in whom K2 was a known mortal factor and outline the similar abnormal graft functions of the two recipients.

Keywords: Drugs; End stage renal disease; Transplantation; Urine

Introduction

Synthetic cannabinoids (SCs) have recently emerged as popular drugs of abuse among young adults; only marijuana being used more frequently [1]. SC-containing mixtures produce psychoactive effects overlapping with those of cannabis and have also been shown to be more potent agonists, possibly leading to greater cannabinomimetic toxicity [2]. SC has been associated with various neurological, psychiatric, cardiovascular, gastrointestinal, and renal toxicities although the mechanism in which it does so is not fully understood [3]. Increasing literature exists regarding the renal and metabolic complications, and no reports exist concerning SC use in donors or recipients of renal transplant. We present the first reported case of delayed graft function of renal transplantation from a deceased donor with SC use and briefly summarize pertinent available data.

Case Report

A 29-year-old African American (AA) man presented to the emergency department in cardiac arrest subsequent to SC ingestion. He had return of spontaneous circulation and after appropriate critical care management, the patient underwent rewarming and brain death testing. He was ultimately declared brain dead secondary to myocardial infarction. His hospital course was complicated by acute kidney injury (AKI) while continuing to produce adequate urine volume. The first kidney transplant was accomplished two days after brain death declaration and the second was accomplished on the subsequent day.

Our first recipient was a 41-year-old AA man with autosomal dominant polycystic kidney disease with end stage renal disease (ESRD). The surgery was uncomplicated with no perioperative concerns. Postoperatively, his creatinine levels steadily increased from 13 to 15.4 within a span of four days and he had low urine output. He subsequently received dialysis and a renal biopsy was performed which did not show evidence of acute rejection or ischemic pathology. Renal function slowly began to improve afterward; creatinine after dialysis hovered near 8 for the subsequent 3 days, then decreased significantly from 7.8 to 4.2 on the fifth day after dialysis. He was discharged postoperative day 15. The patient's 3-month protocol Ultrasound guided percutaneous renal biopsy demonstrated Borderline Sub-Clinical acute rejection with focal areas of tubulitis, C4d negative with less than 10% fibrosis. This was treated with oral corticosteroid taper and the patient's renal status has been relatively stable since.

The second recipient was a 47 year old AA man with ESRD secondary to diabetes mellitus (DM) and hypertension on hemodialysis for approximately eight years. Transplant was uncomplicated with no operative or postoperative concerns. However, similarly to the first recipient, his creatinine levels remained highly elevated with slower than normal return of kidney function. He also received hemodialysis and renal biopsy which again did not show acute rejection ischemic pathology; creatinine after dialysis hovered near 8 for the subsequent 5 days, then decreased significantly from 6.4 to 2.8 over the next 4 days. He was discharged postoperative day 19. The patient continued to have multiple bouts of AKI and acute cellular rejection throughout the following months after the procedure. The most recent Ultrasound guided percutaneous renal biopsy performed 8 months since the transplant demonstrated steroid-resistant Grade 1A T-cell mediated acute cellular rejection (Figures 1 and 2).

Discussion

The use of SCs has been increasing due in part to their low cost, easy accessibility, and being undetectable on routine drug screens [4]. They have been distributed under the names 'Spice' and 'K2,' and very little is known about the pharmacology of SCs. The products are marketed as natural herbal incense and have been sold legally in convenience stores and online. However, the contents within SC products are poorly labeled and include a mixture of psychoactively inert herbs sprayed with SC compounds [5]. The lack of quality control leads to significant differences in SC concentrations between batches, with most products containing more than 1 structure of SCs that can interact in unpredictable and potentially harmful ways [6]. Furthermore, although they have been marketed as 'synthetic marijuana,' SCs have been shown to be much more potent cannabinoid receptor agonists and more toxic than THC in natural cannabinoids.

Many reports have demonstrated a variety of adverse health effects associated with SC abuse. In 2013 the Centers for Disease Control and Prevention (CDC) published a study identifying AKI as an unanticipated

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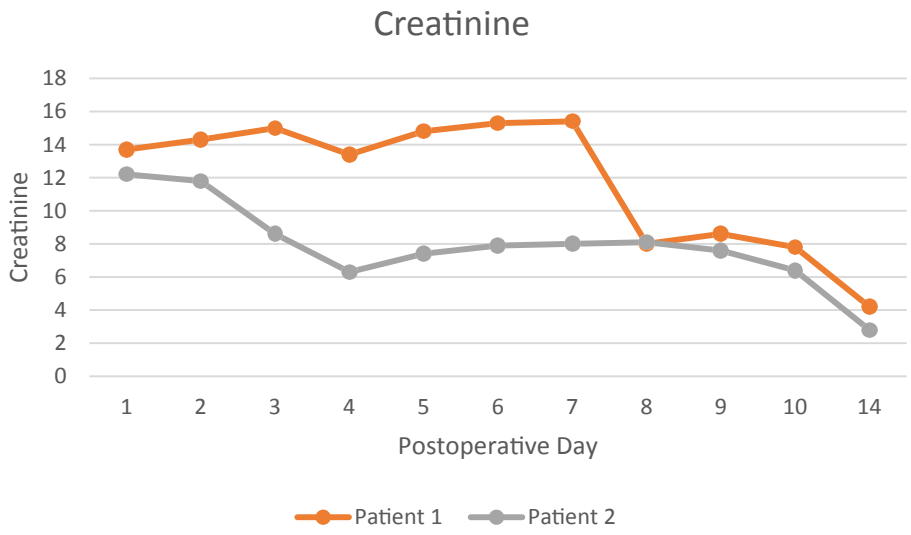

Figure 1: Post-transplantation creatinine.

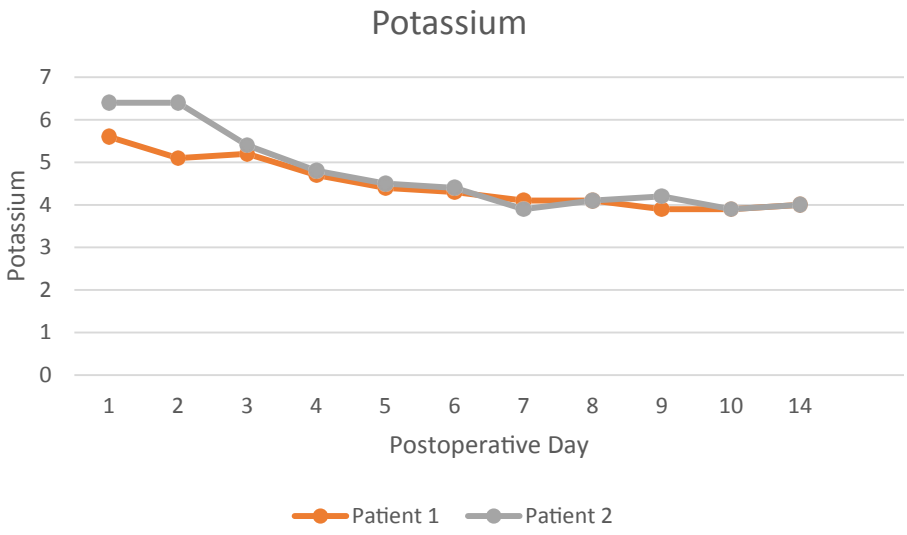

Figure 2: Post-transplantation potassium

complication of SC abuse and over 21 cases of SC-associated AKI have been reported with nearly 25% of patients requiring renal replacement therapy [7]. Although the pathogenesis remains uncertain, the reported cases seem to be due to a nephrotoxic etiology rather than ischemic one [8].

While a number of cases have been reported demonstrating the association of SC-abuse and AKI, there currently have been no reports on its renal effect post extraction. The number of donors who have overdosed on SCs is not known and may not be particularly common. However, with the increasing rise in popularity of SC abuse there, most likely will also be a rise in the number of SC-related mortality in a population of mostly young and healthy individuals. It is then imperative to outline SCs effects on graft function considering the known association with AKI so that future transplant guidelines can be created.

The current Organ Procurement and Transplant Network (OPTN) guidelines state that the absolute exclusion criteria include: Uncontrolled hypertension or history of hypertension with end-organ damage, HIV infection, diabetes mellitus, evidence of acute symptomatic infection (until resolved) [9]. Additionally, the OPTN guideline state some relative contraindications, including: ABO or HLA incompatibility without a planned management protocol and informed consent, proteinuria and/or hematuria, impaired renal function (defined as GFR <80 mL/min/1.73 m^2 or inappropriately low function for age and sex), marked urologic, renal vascular abnormalities, or multiple renal vessels (e.g. three or more, depending on surgeon experience), any chronic, active viral infection (human T-lymphotropic virus (HTLV), HBV, and HCV), history of malignancy, especially lung, breast, renal or urologic, gastrointestinal, or hematologic cancers and melanoma, chronic illness,

particularly pulmonary, liver, autoimmune, neurologic, or cardiac disease , hypertension, nephrocalcinosis, bilateral kidney stones, or recurrent nephrolithiasis, current pregnancy, disorders requiring anticoagulation, active peptic ulcer disease, history of sickle cell trait, morbid obesity, most commonly defined as BMI >35 kg/m^2, strong family history of diabetes mellitus, family history of renal cell cancer and active illicit substance or alcohol abuse [9]. Our case demonstrates that renal transplant from donors with suspected or confirmed use of SC is feasible but not without potential complication. SC use may be associated with delayed graft function (DGF), a complication known to be associated with an increased incidence of acute rejection (AR) and poorer overall graft survival [10]. Both recipients had DGF requiring hemodialysis and one of the recipients has had multiple hospital admissions due to episodes of steroid-resistant acute cellular rejection even many months after the procedure. Whether SC contributed to an increased risk for AR is indeterminate.

Limitations of our observation is that the donor would fall under the category of donations after brain death (DBD) which is known to be associated with higher rates of delayed graft function [11]. However, the donor maintained adequate urine output throughout his hospital course and a preoperative kidney biopsy was normal. The renal perfusion pump for both recipients were found to be normal without evidence of acute tubular necrosis indicating an ischemic episode. Another limitation is that while our observation demonstrates an association with SC use and renal transplantation, we cannot demonstrate causation as is the case in other reports on SC-associated renal complications.

Conclusion

Renal transplant in patients with known SC use is feasible but may prolong return of graft function. As there are currently no reports of SC usage's effects on renal transplant, this case may serve as an example of another potentially unforeseen adverse reaction to SC use and raise awareness to the fact that recipients may require more careful observation and aggressive treatment strategies. It seems most likely that the delayed graft function is associated with the nephrotoxic characteristics of SCs in accordance with the numerous reports of SC-related AKI. What is still not understood however is the mechanism in which SCs are able to do this, and what remains to be proven is whether SCs use is a causation rather than only an association of kidney injury. More robust study should be done to understand the mechanism of this effect in order to provide broad transplantation recommendations moving forward.

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