ISSN: 2474-3674

Applewhite A et al. Int J Crit Care Emerg Med 2025, 11:169
DOI: 10.23937/2474-3674/1510169
Volume 11 | Issue 1
Open Access

International Journal of Critical Care and Emergency Medicine

CASE REPORT

Seville Orange-Induced Tacrolimus Toxicity in a Heart Transplant Recipient: A Case Report

Andres Applewhite[1]*, Oscar Pena[2] and Rohan M. Goswami[3]

[1]Department of Internal Medicine, Saint Vincent's Medical Center, Affiliate of the Frank H. Netter MD School of Medicine at Quinnipiac University, Bridgeport, Connecticut, USA

[2]Department of Internal Medicine, Saint Vincent's Medical Center, Affiliate of the Frank H. Netter MD School of Medicine at Quinnipiac University, Bridgeport, Connecticut, USA

[3]Division of Advanced Heart Failure and Transplant Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, Florida, USA

***Corresponding author:** *Andres Applewhite, Department of Internal Medicine, Saint Vincent's Medical Center, Affiliate of the Frank H. Netter MD School of Medicine at Quinnipiac University, Bridgeport, Connecticut, USA*

Abstract

This case report presents a 67-year-old African American male who underwent an orthotopic heart transplant without complications and maintained excellent adherence to his post-transplant regimen. However, 7 years post-transplant, he developed symptoms suggestive of Tacrolimus toxicity with tremors, nausea, diarrhea, and vomiting. Upon investigation, it was revealed that the patient had been consuming Seville oranges in an attempt to increase his vitamin C levels. Subsequent analysis identified Seville oranges as the culprit, containing furocoumarins known to inhibit CYP isozyme 3A4 and P-glycoprotein, thereby affecting Tacrolimus metabolism. This case underscores the importance of patient education regarding dietary restrictions post-transplant to prevent potentially life-threatening drug interactions.

Keywords

Tacrolimus toxicity, Seville oranges, Heart transplant, Drug interactions, CYP isozyme 3A4

Introduction

Orthotopic heart transplantation stands as the definitive treatment for end-stage heart failure patients who have exhausted conventional medical intervention [1]. Despite advancements in surgical techniques and immunosuppressive therapies, heart transplant recipients face ongoing challenges in maintaining graft function and preventing rejection [2]. Among the various immunosuppressive agents available, tacrolimus, a calcineurin inhibitor, has emerged as a cornerstone in post-transplant management due to its potent immunosuppressive properties and favorable outcomes [3].

Tacrolimus exerts its immunosuppressive effects by inhibiting the activity of calcineurin, a phosphatase enzyme crucial for activating T-lymphocytes. By disrupting the intracellular signaling cascade, tacrolimus effectively suppresses the immune response against the allograft, thereby reducing the risk of rejection [3,4]. However, the therapeutic use of tacrolimus is fraught with challenges, primarily stemming from its narrow therapeutic window and susceptibility to pharmacokinetic variability [5].

Maintaining tacrolimus within the optimal therapeutic range is essential to balance its immunosuppressive efficacy against the risk of toxicity and rejection. Deviations from the target range, whether due to subtherapeutic or supratherapeutic levels, predispose transplant recipients to adverse outcomes, including rejection, graft dysfunction, and drug-related complications [6,7]. Consequently, meticulous monitoring of tacrolimus levels and dose adjustments based on individual pharmacokinetic parameters are integral components of post-transplant care [8].

Citation: Applewhite A, Pena O, Goswami RM (2025) Seville Orange-Induced Tacrolimus Toxicity in a Heart Transplant Recipient: A Case Report. Int J Crit Care Emerg Med 11:169. doi.org/10.23937/2474-3674/1510169

Accepted: May 26, 2025: **Published:** May 28, 2025

Tacrolimus metabolism is influenced by drug interactions and dietary factors, especially those involving cytochrome P450 enzymes, particularly CYP3A4. Inhibitors or inducers of CYP3A4 can affect tacrolimus's bioavailability and clearance. For example, the interaction between citrus fruits like pomelo and clementine and certain hybrids like Beni-Madonna, grapefruit, and Seville oranges contain furanocoumarins that inhibit CYP3A4 and P-glycoprotein potentially leading to elevated tacrolimus levels by increasing its plasma concentration and thereby increase toxicity risk [9,10].

Furanocoumarin inhibition of CYP3A4 reduces the clearance of calcineurin inhibitors, leading to an increase in their levels and potential toxicity. Conversely, decreasing the effect of P-glycoprotein, which is responsible for pumping tacrolimus out of epithelial cells in the intestine, would increase its absorption, resulting in a higher concentration level [6,9-11].

Against this backdrop, we present a compelling case of tacrolimus toxicity induced by Seville orange consumption in a heart transplant recipient. This case underscores the intricate interplay between pharmacotherapy and dietary factors in transplant medicine and highlights the importance of comprehensive patient education and multidisciplinary collaboration in optimizing transplant outcomes. By elucidating the complexities of tacrolimus management and its potential interactions, we aim to enhance awareness and promote tailored approaches to post-transplant care.

Case Presentation

A 67-year-old male with a past medical history of hypertension, chronic kidney disease, and dilated cardiomyopathy status post orthotopic heart transplant seven years prior, who had diligently adhered to his immunosuppressive regimen and attending all follow-up appointments, presented to the emergency department with worsening tremors, nausea, malaise, and decreased urine output over the past several days. Initial laboratory evaluation revealed a markedly elevated serum creatinine of 8.8 mg/dL (baseline 1.4 mg/dL), blood urea nitrogen (BUN) of 78 mg/dL, and a dangerously high potassium level of 7.1 mmol/L. His tacrolimus level was critically elevated at 34 ng/mL (therapeutic range: 5-12 ng/mL).

Shortly after arrival, the patient became progressively confused and lethargic, raising concerns for uremic encephalopathy and life-threatening hyperkalemia. He was promptly admitted to the intensive care unit (ICU), where emergent hemodialysis was initiated via a temporary right internal jugular dialysis catheter due to worsening metabolic derangements and the high risk of cardiac arrhythmias. Following dialysis and supportive care, the patient showed gradual clinical improvement. His mental status normalized, serum potassium and creatinine levels trended downward, and he was successfully weaned off continuous cardiac monitoring.

When patient's mentation returned to baseline, a detailed dietary history revealed that he had been consuming large quantities of oranges, which were in season at his local supermarket, in an effort to boost his Vitamin C levels to "increase his immunity." Further questioning, accompanied by image identification, confirmed that he had been ingesting Seville oranges, a specific strain known to contain furocoumarins, which inhibit CYP3A4 and P-glycoprotein-key enzymes involved in the metabolism and absorption of tacrolimus. Unaware of the interaction, the patient had unknowingly entered a vicious cycle: as his symptoms worsened, he consumed more oranges, further elevating his tacrolimus levels and exacerbating his condition.

The patient was later transferred out of the ICU to the general medicine ward for further optimization of his immunosuppressive regimen, dietary counseling, and close nephrology follow-up.

Discussion

This case illustrates the potential for Seville oranges to induce Tacrolimus toxicity due to their high furanocoumarin content. Furanocoumarins inhibit the CYP3A4 enzyme and P-glycoprotein, crucial pathways for Tacrolimus metabolism. This enzyme-inhibition mechanism results in elevated Tacrolimus blood levels, increasing the risk of toxicity. This pharmacokinetic interaction is well-documented for several citrus fruits, each with unique but similar effects on Tacrolimus metabolism [10,11].

Other citrus like Grapefruit is the most extensively studied citrus fruit in terms of drug interactions. It contains high levels of furanocoumarins, which inhibit CYP3A4 significantly, similar to Seville oranges. Patients consuming grapefruit have been shown to exhibit elevated levels of Tacrolimus, increasing toxicity risks. The grapefruit-Tacrolimus interaction is so well-established that it is commonly cited in transplant guidelines, whereas the risks associated with Seville oranges are less frequently discussed, despite their similar biochemical impact [12-14].

Pomelo: Like grapefruit, pomelo inhibits CYP3A4 and can lead to increased Tacrolimus levels. Pomelo may have a somewhat lower furanocoumarin concentration than grapefruit but can still significantly elevate Tacrolimus levels when consumed in large amounts. Pomelo interactions are less commonly noted in clinical guidelines than grapefruit, although the potential for toxicity is well-recognized [15].

Beni Madonna (hybrid citrus): Beni Madonna is another citrus fruit known to contain furanocoumarins,

though in lower amounts than grapefruit. While not as common in Western diets, Beni Madonna has been linked to similar enzyme inhibition, increasing Tacrolimus levels when consumed in large quantities. Due to its lesser availability, clinical guidelines and patient education often overlook Beni Madonna, but it presents a comparable risk profile when consumed frequently by transplant patients [10].

This is the first case reported of Seville oranges causing tacrolimus toxicity. These oranges are notable for their use in cooking rather than regular consumption, unlike other citrus fruits. However, as seen in this case, they can be easily mistaken as a safe option, especially for patients unaware of their drug interaction potential. The case highlights the lesser-known risk of Seville oranges and emphasizes the importance of education on all potential food interactions for transplant patients [16].

Conclusion

This case underscores the critical need for comprehensive dietary education in post-transplant patients, particularly regarding lesser-known food-drug interactions. Despite being a rare occurrence, the interaction between Seville oranges and Tacrolimus led to a severe adverse effect, highlighting that even less commonly consumed citrus fruits can impact Tacrolimus metabolism and lead to toxicity. By inhibiting CYP3A4 and P-glycoprotein, Seville oranges caused elevated Tacrolimus levels, resulting in symptoms of toxicity in the patient. This case serves as an essential reminder for healthcare providers to educate patients not only on well-known interactions, like grapefruit but also on other citrus fruits that contain furanocoumarins.

In conclusion, while Tacrolimus remains a cornerstone immunosuppressant in transplant medicine, its management is complex due to its narrow therapeutic window and sensitivity to various dietary and drug interactions. This report highlights the need for a proactive, multidisciplinary approach to patient education, emphasizing the potential risks associated with seemingly innocuous dietary choices. By enhancing patient awareness of these risks, we can help optimize post-transplant care, prevent drug-related complications, and support better long-term outcomes for transplant recipients.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest

The authors declare no conflicts of interest related to this case report.

Funding

No external funding was received for the publication of this case report.

Acknowledgments

The authors would like to acknowledge the patient for granting consent for the publication of this case report and the medical staff involved in the patient's care.

References

1. Ahmed T, Jain A (2023) Heart transplantation. StatPearls.
2. Tonsho M, Michel S, Ahmed Z, Alessandrini A, Madsen JC (2014) Heart transplantation: Challenges facing the field. Cold Spring Harb Perspect Med 4: a015636.
3. Wallemacq PE, Verbeeck RK (2001) Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. Clin Pharmacokinet 40: 283-295.
4. Araya AA, Tasnif Y (2023) Tacrolimus. StatPearls.
5. Nezam D, Porcher R, Grolleau F, Morel P, Titeca-Beauport D, et al. (2022) Kidney histopathology can predict kidney function in ANCA-associated vasculitides with acute kidney injury treated with plasma exchanges. J Am Soc Nephrol 33: 628-637.
6. Nguyen TVA, Nguyen HD, Nguyen TLH, Le VT, Nguyen XK, et al. (2023) Higher tacrolimus trough levels and time in the therapeutic range are associated with the risk of acute rejection in the first month after renal transplantation. BMC Nephrol 24: 131.
7. Schumacher L, Leino AD, Park JM (2021) Tacrolimus intrapatient variability in solid organ transplantation: A multiorgan perspective. Pharmacotherapy 41: 103-118.
8. Campagne O, Mager DE, Tornatore KM (2019) Population pharmacokinetics of tacrolimus in transplant recipients: What did we learn about sources of interindividual variabilities? J Clin Pharmacol 59: 309-325.
9. Loer HLH, Feick D, Rüdesheim S, Selzer D, Schwab M, et al. (2023) Physiologically based pharmacokinetic modeling of tacrolimus for food-drug and CYP3A drug-drug-gene interaction predictions. CPT Pharmacomet Syst Pharmacol 12: 724-738.
10. Ushijima K, Mizuta K, Otomo S, Ogaki K, Sanada Y, et al. (2018) Increased tacrolimus blood concentration by Beni-Madonna - a new hybrid citrus cultivar categorized as “Tangor”, in a liver transplant patient: Likely furanocoumarin-mediated inhibition of CYP3A4 or P-glycoprotein. Br J Clin Pharmacol 84: 2933-2935.
11. Miedziaszczyk M, Bajon A, Jakielska E, Primke M, Sikora J, et al. (2022) Controversial interactions of tacrolimus with dietary supplements, herbs and food. Pharmaceutics 14: 2154.
12. Fukatsu S, Fukudo M, Masuda S, Yano I, Katsura T, et al. (2006) Delayed effect of grapefruit juice on pharmacokinetics and pharmacodynamics of tacrolimus in a living-donor liver transplant recipient. Drug Metab Pharmacokinet 21: 122-125.
13. Seden K, Dickinson L, Khoo S, Back D (2010) Grapefruit-drug interactions. Drugs 70: 2373-2407.
14. Zhai X, Chen C, Xu X, Ma L, Zhou S, et al. (2019) Marked change in blood tacrolimus concentration levels due to grapefruit in a renal transplant patient. J Clin Pharm Ther 44: 819-822.

15. Egashira K, Ohtani H, Itoh S, Koyabu N, Tsujimoto M, et al. (2004) Inhibitory effects of pomelo on the metabolism of tacrolimus and the activities of CYP3A4 and P-glycoprotein. Drug Metab Dispos 32: 828-833.

16. Malhotra S, Bailey DG, Paine MF, Watkins PB (2001) Seville orange juice-felodipine interaction: Comparison with dilute grapefruit juice and involvement of furocoumarins. Clin Pharmacol Ther 69: 14-23.