Case Series

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The hidden pharmacokinetic challenge: diarrhea's influence on cyclosporine therapy: a case series

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Background: Cyclosporine is used as an immunosuppressive drug to improve graft survival rates in the field of organ transplantation. Therapeutic drug monitoring [TDM] of cyclosporine in transplant patients is crucial for optimizing drug dosage and minimizing the risks. Diarrhea is a common gastrointestinal condition, resulting in pharmacokinetic, malabsorption, and clinical consequences for people who rely on cyclosporine medication.

Case presentations: The case series discusses three pediatric patients who underwent therapeutic drug monitoring of cyclosporine to guide their treatment. The first two cases involved post-renal transplant patients with glomerulonephritis, while the third case involved a patient with tubulointerstitial kidney disease. TDM was employed to guide dose adjustments. The first patient initially received 15 mg/kg but showed high trough concentration. The dosage was gradually reduced, while diarrhea was managed. The second and third patients exhibited a similar trend which also necessitated dose adjustments.

Clinical discussion: Diarrhea was identified as a factor impacting cyclosporine levels. This case series evaluated the impact of diarrhea on cyclosporine therapeutic levels in three pediatric renal transplant patients. TDM in cyclosporine therapy is significant due to its narrow therapeutic index and variable pharmacokinetics. Elevated trough concentrations led to a gradual dose reduction to achieve the target levels.

Conclusion: This case series highlights the importance of TDM-guided dosing of cyclosporine, particularly in patients with diarrhea, to maintain target trough concentrations.

Keywords: cyclosporine, diarrhea, therapeutic drug monitoring, trough

Introduction

Cyclosporine, a powerful immunosuppressive drug, has transformed the field of organ transplantation by dramatically increasing graft survival rates. Under usual circumstances following transplant, the therapeutic dose for initiation is 15 mg/kg PO in both pre-transplant and post-transplant, which is then tapered to 5 mg/kg PO BID after a week. Monitoring therapeutic levels of cyclosporine in transplant patients are crucial for optimizing drug dosage and minimizing the risks of acute rejection, nephrotoxicity, and dose-dependent adverse reactions such as hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and tremor[1]. However, its therapeutic effectiveness is inextricably linked to maintaining ideal blood levels within a restricted therapeutic window. Cyclosporine levels can be influenced by a variety of variables, including nutrition, drugs, and physiological circumstances. Among these causes, diarrhea is a substantial but frequently overlooked contribution to changes in cyclosporine levels.

HIGHLIGHTS

- Cyclosporine-mediated immunosuppressive therapy in organ transplantation patients may induce conditions like diarrhea which complicate the therapy.
- Diarrhea can affect cyclosporine drug absorption and pharmacokinetics, potentially leading to increased risks of drug toxicity and treatment failure.
- Therapeutic drug monitoring of cyclosporine is effective particularly in patients with diarrhea, to maintain target drug concentrations.

Diarrhea is a common gastrointestinal condition marked by frequent, loose, or watery feces. While it may appear to be a minor nuisance for many, it has far-reaching consequences for people who rely on cyclosporine medication. Diarrhea incidence among cyclosporine-treated patients ranges from 14% to 47%, attributed to various factors such as gastrointestinal irritation, increased bile production, altered intestinal motility, and microbial flora changes, along with impaired water and electrolyte absorption[2–4]. The link between diarrhea and cyclosporine levels is complex, involving pharmacokinetic changes, malabsorption dynamics, and clinical consequences that require further investigation.

Understanding how diarrhea affects cyclosporine pharmacokinetics and therapeutic outcomes allows healthcare practitioners to

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enhance patient management techniques, limit risks, and ensure therapeutic goals are met in this tough clinical circumstance. For solid organ transplantation/rejection prophylaxis, standard dosing of cyclosporine varies based on the route of administration and patient age. In infants ≥6 months, children, and adolescents, intermittent IV cyclosporine is typically dosed at 5–6 mg/kg/day, continuous IV cyclosporine at 2–4 mg/kg/day, and oral cyclosporine initially at 15 mg/kg/day (range: 14–18 mg/kg/day) administered 4 to 12 hours pre-transplantation. Afterward, oral dosing is adjusted, with the initial dose continued daily for 1 to 2 weeks, and then tapered by 5% per week to a maintenance dose of 5–10 mg/kg/day[5]. Drug levels guide dosage adjustments, with goal trough concentrations ranging from 100 to 300 ng/mL[6].

This article intends to provide physicians and healthcare workers with the knowledge they need to manage the complexity of cyclosporine medication in the setting of diarrhea by clinical insights and practical advice. By shedding light on this often-overlooked element of cyclosporine medication, we want to improve patient care and clinical outcomes for those facing the combined difficulties of transplantation and gastrointestinal problems. The case series has been reported in line with the PROCESS 2020 criteria[7].

Case-1

A 12-year-old girl was diagnosed with glomerulonephritis and underwent renal transplantation. Following surgery, she was initiated on a cyclosporine capsule of 15 mg/kg, methylprednisolone injection of 20 mg/kg intravenous (IV), and an anti-thymocyte globulin injection of 1.5 mg/kg IV for immunosuppression, and TDM was employed to guide therapy and to reduce the dangers associated with cyclosporine treatment. The patient was started on cyclosporine capsule 15 mg/kg/day post-transplantation for 2–3 weeks. At the end of the induction phase (3rd week), the trough concentration measured was 380 ng/mL. The patient was advised to taper the dose slowly to 12 mg/kg/day orally by the end of the 6th week and was instructed to check plasma concentrations every week to change dosage as needed to reach the intended trough concentration. This dosing resulted in a trough concentration of 390 ng/mL. In the 7th week, plasma concentration was still high (415 ng/mL) and she presented with loose stools. Due to high trough concentration, the dose was further reduced to 10 mg/kg/day. By the 8th week, she was given oral rehydration solution (ORS) and IV fluids for diarrhea, but the plasma concentration was 440 ng/mL which was significantly high. Therefore, she was urged to reduce the dose further to 8–10 mg/kg due to the higher trough concentration. By the 9th week, trough concentration was reduced to 400 ng/mL, followed by 340 ng/mL by the 10th week after cessation

Of a diarrheal episode. Cyclosporine trough concentrations have subsequently decreased and now range between 202 and 300 ng/mL by the end of the 20th week. Since the patient was well-maintained at that dosage, the patient continued with this regimen (Fig. 1).

Case-2

A 10-year-old boy was diagnosed with glomerulonephritis and had a kidney transplant after that. He was initiated on a cyclosporine capsule of 15 mg/kg, a methylprednisolone injection of 20 mg/kg IV, and an anti-thymocyte globulin injection of 1.5 mg/kg IV. This patient was also encouraged to start TDM for cyclosporine since this would benefit the patient especially to increase tolerance (avoid adverse effects, including nephrotoxicity and excessive immunosuppression) and prevent rejection (graft survival) by monitoring. The patient was given a cyclosporine capsule of 15 mg/kg daily, and at the end of the induction phase (3rd week), trough concentration was found to be 368 ng/mL. Due to higher plasma concentration, dosage was reduced to 10–12 mg/kg/day for another 3–4 weeks. This resulted in a trough concentration of 290 ng/mL by the end of the 7th week. In contrast to this, the following week, the boy was admitted to the hospital for diarrhea and was given ORS and IV fluids. The trough concentration measured then was found to be 460 ng/mL. Diarrhea was treated with ORS and the conventional management. Dosing was further reduced to 8 mg/kg daily to moderate the plasma levels of cyclosporine. Despite dose reduction, the plasma concentrations were high. And by the 16th week, plasma concentrations had declined to 223 ng/mL after cessation of a diarrheal episode (Fig. 1).

Case-3

An 11-year-old boy was diagnosed with tubulointerstitial kidney disease (TKD) and was subjected to renal transplantation since TKD is a rare genetic cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD)[8]. Post-operation, he was initiated on a methylprednisolone injection of 20 mg/kg IV, an anti-thymocyte globulin injection of 1.5 mg/kg IV, and oral cyclosporine of 10 mg/kg daily. TDM of cyclosporine was started, and plasma levels were measured every 4–7 days to avoid adverse effects and reach the target trough concentration. By the end of the 3rd week, the trough concentration measured was 376 ng/mL. The dose was further reduced to 8 mg/kg/day for the next 3 weeks. By the end of the 6th week, the child was admitted for a fever and diarrhea and was administered ORS, IV fluids, and metronidazole three times a day for 5 days. The plasma concentration measured then was found to be 423 ng/mL; hence, the dosage of cyclosporine was reduced further to 6 mg/kg daily which still showed elevated levels of cyclosporine. The cyclosporine levels turned to the normal range after cessation of a diarrheal episode. The patient was discharged by the following week and was continued on oral cyclosporine 8 mg/kg/day and reached the target trough concentration (Fig. 1).

Discussion

Three cases were presented to illustrate how diarrhea impacted the levels of cyclosporine in our patients. Dose adjustments were made based on these alterations, deviating slightly from the standard dosage schedule. This was necessary due to the absence of a firmly established dosing protocol and our limited experience with cyclosporine therapeutic drug monitoring (TDM). Without TDM, these patients would have experienced elevated cyclosporine levels, leading to either undesired changes in therapy or the potential development of cyclosporine resistance[9]. However, in our cases, the root cause of cyclosporine toxicity was diarrhea which was identified and treated restoring normal cyclosporine plasma levels. This strategy proved essential as all the patients showed elevated levels despite tapering the doses.

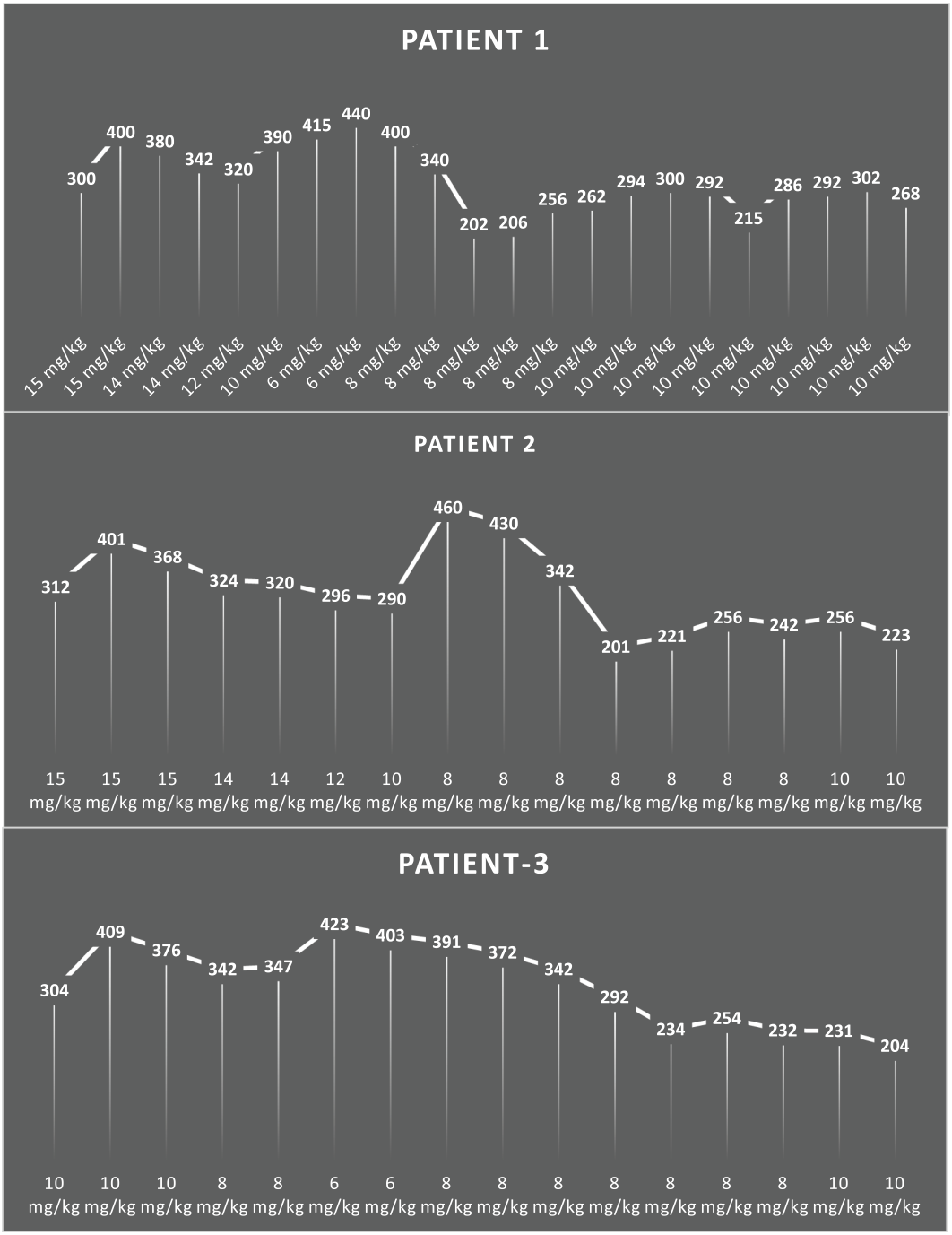

Figure 1. Trend in cyclosporine values through the treatment period. Figure. 1 shows the relation between the various doses of cyclosporine and blood levels. The first peak is normal and indicates the induction phase. The second prominent peak indicates the disproportionate rise in blood levels of cyclosporine following diarrhea.

These scenarios also emphasize that TDM alone might not be adequate to monitor cyclosporine levels, but a good clinical watchout for such disease-based interactions is also necessary.

Diarrhea can significantly affect the absorption of orally administered medications, including cyclosporine. Rapid gastrointestinal transit time and increased luminal fluid volume associated with diarrhea may lead to decreased drug absorption due to reduced contact time with the intestinal mucosa[10]. Another point to be ascertained is the role of concomitant drugs in influencing the pharmacokinetics of cyclosporine. Among antithymocyte globulin and methylprednisolone, the latter is found to have some interactions which are clinically insignificant and might show a transient rise without warranting any cessation of therapy[11]. In our case, the rise in cyclosporine levels was sustained, and the downward trend was seen only after initiating anti-diarrheal therapy. Additionally, alterations in intestinal

permeability and disruption of the enterocyte barrier function during diarrheal episodes may further increase drug absorption[12]. Several studies have documented the impact of diarrhea on cyclosporine bioavailability. For example, a study by Jain *et al* demonstrated a significant increase in cyclosporine absorption in patients with diarrhea compared to those without gastrointestinal symptoms[13]. Similarly, Kahan *et al* reported a reduction in cyclosporine trough levels during episodes of diarrhea in renal transplant recipients, highlighting the clinical relevance of this phenomenon[14].

Cyclosporine undergoes extensive enterohepatic circulation, with biliary excretion playing a crucial role in its elimination pathway. Less than 5% of cyclosporine metabolites are excreted in urine after metabolizing the cytochrome P450 system, namely CYP3A4 and CYP3A5. The varying expression of CYP3A4 and CYP3A5 isoenzymes is suggested to contribute to the unexpected bioavailability of cyclosporine, and in that case, doses should be adjusted accordingly; TDM is of paramount importance[15–16]. Diarrhea-induced dehydration and electrolyte imbalances may disrupt this process, leading to increased cyclosporine reabsorption in the intestines and reduced fecal excretion[17]. Consequently, reduced enterohepatic recirculation could contribute to increased cyclosporine levels observed in patients experiencing diarrhea. All these intricate molecular mechanisms showed that beyond drug interactions, disease interaction between diarrhea and cyclosporine is of clinical concern when treating patients with cyclosporine.

The impact of diarrhea on cyclosporine levels has important clinical implications for transplant recipients and other patients reliant on cyclosporine therapy. Suboptimal drug levels resulting from diarrhea may increase the risk of allograft rejection or transplant failure[18]. Conversely, elevated cyclosporine concentrations due to reduced clearance during diarrheal episodes may predispose patients to toxicity and adverse effects, including nephrotoxicity and hypertension[19]. In cases of persistent or severe diarrhea, alternative routes of drug administration, such as intravenous or sublingual formulations, may be considered to bypass the gastrointestinal tract and ensure adequate drug absorption[20].

Ensuring sufficient exposure to cyclosporine medication can be achieved through the straightforward use of therapeutic drug monitoring (TDM). This tool facilitates the assessment of cyclosporine serum concentrations and guides making dosage adjustments. Despite advances in our understanding of the interaction between diarrhea and cyclosporine levels, several questions remain unanswered. Future research should focus on determining the particular processes driving diarrhea-induced cyclosporine pharmacokinetic changes, as well as devising techniques to attenuate these effects and improve treatment results. Longitudinal studies that use pharmacokinetic modeling and simulation techniques may give useful insights into individual variability in medication response and enable individualized treatment options for patients at risk of diarrhea-related problems.

Conclusion

Cyclosporine, an important immunosuppressive drug for organ transplantation, has provided ameliorated graft survival, despite having condition like diarrhea can complicate its management. Diarrhea can affect cyclosporine levels through changes in drug absorption and pharmacokinetics, potentially leading to increased risks of drug toxicity and treatment failure. This article intends medical professionals to be equipped with perspicacity and practical advice to manage cyclosporine therapy in patients suffering from diarrhea, emphasizing the importance of therapeutic drug monitoring (TDM) to adjust dosages accurately. Even though the progress has been made in understanding these interactions, further research is required to explore the mechanisms behind diarrhea-induced changes in cyclosporine pharmacokinetics and to develop and execute strategies for better management, including individualized treatment plans.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient's parents/legal guardian in their native language for the publication of this case series. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author's contribution

Conceptualization, writing and reviewing: R.M.R.; Conceptualization, supervision, resources, writing original draft: J.W.G.; Conceptualization, data curation, writing and reviewing: B.R.P., A.M.S.; Conceptualization, writing and reviewing: P.T.

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The authors declare there are no competing interests. All authors reviewed the final version of the manuscript and consented to publish.

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Anonymized data will be made available on request. All values have been provided in the form of the graph, as shown in the figure.

Assistance with study

None.

Presentation

None.

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