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Single Case

Decrease in Mycophenolic Acid Plasma Level by Sacubitril/Valsartan in a Lupus Nephritis Patient: A Case Report

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Keywords
Systemic lupus erythematosus · Lupus nephritis · Hypertension · Pharmacokinetics · Drug-drug interaction

Abstract
Introduction: Mycophenolate mofetil (MMF), an inactive prodrug of mycophenolic acid (MPA), is an immunosuppressive drug used widely in the treatment of lupus nephritis. In this case report, the area under the blood concentration time curve (AUC) of MPA was significantly decreased by the concomitant use of sacubitril/valsartan. ***Case Presentation:*** The patient was a man in his 40s with a diagnosis of lupus nephritis class IVa/c+V. MMF dose was 1.5 g/day at admission, and AUC of MPA on day 14 was 25.1 μg·h/mL. Owing to poor blood pressure control, sacubitril/valsartan was initiated at 97/103 mg/day on day 29. On day 37, AUC of MPA was significantly decreased to 8.7 μg·h/mL, suggesting drug interaction with the newly initiated sacubitril/valsartan. Sacubitril/valsartan was decreased to 49/51 mg/day, and AUC of MPA on day 67 was 37.6 μg·h/mL, achieving the target range. The final MMF dose was set at 1.75 g/day. A possible mechanism of drug interaction between sacubitril/valsartan and MPA involves an organic anion transporting polypeptide (OATP). The inhibition of OATPs by sacubitril may have interrupted the enterohepatic circulation of MPA, resulting in a lower plasma concentration. ***Conclusion:*** Since lupus nephritis is often associated with hypertension, the drug interaction observed in this report may also occur in other cases. However, it is impossible to conclude that the decrease in plasma MPA levels was due to the concomitant use of sacubitril/valsartan, and more cases and basic findings are needed.

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Introduction

Mycophenolate mofetil (MMF), an inactive prodrug of mycophenolic acid (MPA), is an immunosuppressive antimetabolite widely used to treat lupus nephritis because of its efficacy [1, 2]. There is large intra- and inter-individual variability in the pharmacokinetics of MPA, and a correlation has been observed between plasma levels and the therapeutic effect [3, 4]. Therefore, in the treatment of lupus nephritis, it is recommended to perform therapeutic drug monitoring (TDM) and optimize the dosage of MMF to achieve an area under the blood concentration curve (AUC_{0-12}) of 30–45 μg·h/mL [4, 5]. On the other hand, sacubitril/valsartan is composed of 2 molecular moieties in a single crystalline complex: a neprilysin inhibitor prodrug (sacubitril) and the angiotensin-receptor blocker (valsartan). This drug has been recently approved for the treatment of hypertension, although it is very popular in heart failure treatment [6, 7].

Case Report

The patient was a man in his 40s diagnosed with lupus nephritis class II by kidney biopsy in 21 years prior to hospitalization and received steroid pulse therapy 1 g/day for 3 days followed by 60 mg/day of prednisolone (PSL) treatment. He was diagnosed with lupus nephritis class III on a second kidney biopsy at another hospital in 18 years prior to hospitalization and was treated with PSL 20 mg/day and mizoribine 150 mg/day. Owing to low efficacy, PSL 50 mg/day and intravenous cyclophosphamide 350–500 mg/m^2 treatment was started. However, no improvement of proteinuria was observed even after ≥20 doses of intravenous cyclophosphamide. A third kidney biopsy was performed in 11 years prior to hospitalization, which showed lupus nephritis class V. Exacerbation of proteinuria was observed during a routine medical examination. Urine protein/creatinine (Cr) ratio was 5.0 g/gCr. MMF and PSL had been administered for lupus nephritis at this time, and it was decided that the MPA plasma concentration during hospitalization will be measured. A kidney biopsy was repeated on day 8 after admission, which showed lupus nephritis class IVa/c+V. MMF dose was increased to 1.5 g/day on day 9 because the AUC of MPA on day 3 was 16.2 μg·h/mL. TDM was also performed on day 14, and the AUC of MPA was 25.1 μg·h/mL, slightly lower than the target range. Owing to poor blood pressure control, sacubitril/valsartan treatment was initiated at 97/103 mg/day on day 29. The AUC for day 37 was significantly decreased to 8.7 μg·h/mL, suggesting drug interaction with the newly initiated sacubitril/valsartan. Because the nurse was checking by pill count, it was unlikely that the patient had forgotten to take his medication. Since the patient was suspected to be infected with a bacteria based on the findings of fever and elevated C-reactive protein, ceftriaxone (CTRX) 2.0 g/day was initiated on day 36. However, blood culture result for bacterial growth was negative, so CTRX was discontinued on day 42. Mild fever (37.0–37.5°C) persisted, so sacubitril/valsartan dose was reduced to 49/51 mg/day on day 44 because of a suspected drug-related fever. The AUC for day 45 was 13.8 μg·h/mL, so the MMF dose was increased to 2.0 g/day on day 58. As a result, the AUC for day 63 was significantly increased to 52.4 μg·h/mL, and MMF dose was reduced to 1.75 g/day. Finally, the AUC on day 67 was 37.6 μg·h/mL, achieving the target range. No adverse events due to MMF administration were observed during hospitalization. As the blood pressure stabilized and urine protein/Cr ratio was decreased to 1.37 g/gCr, the patient was discharged on day 72. After discharge, the patient was followed up at an outpatient department and showed no adverse or unanticipated events such as an exacerbation of proteinuria. Interventions and outcomes during the clinical course are shown in Figure 1.

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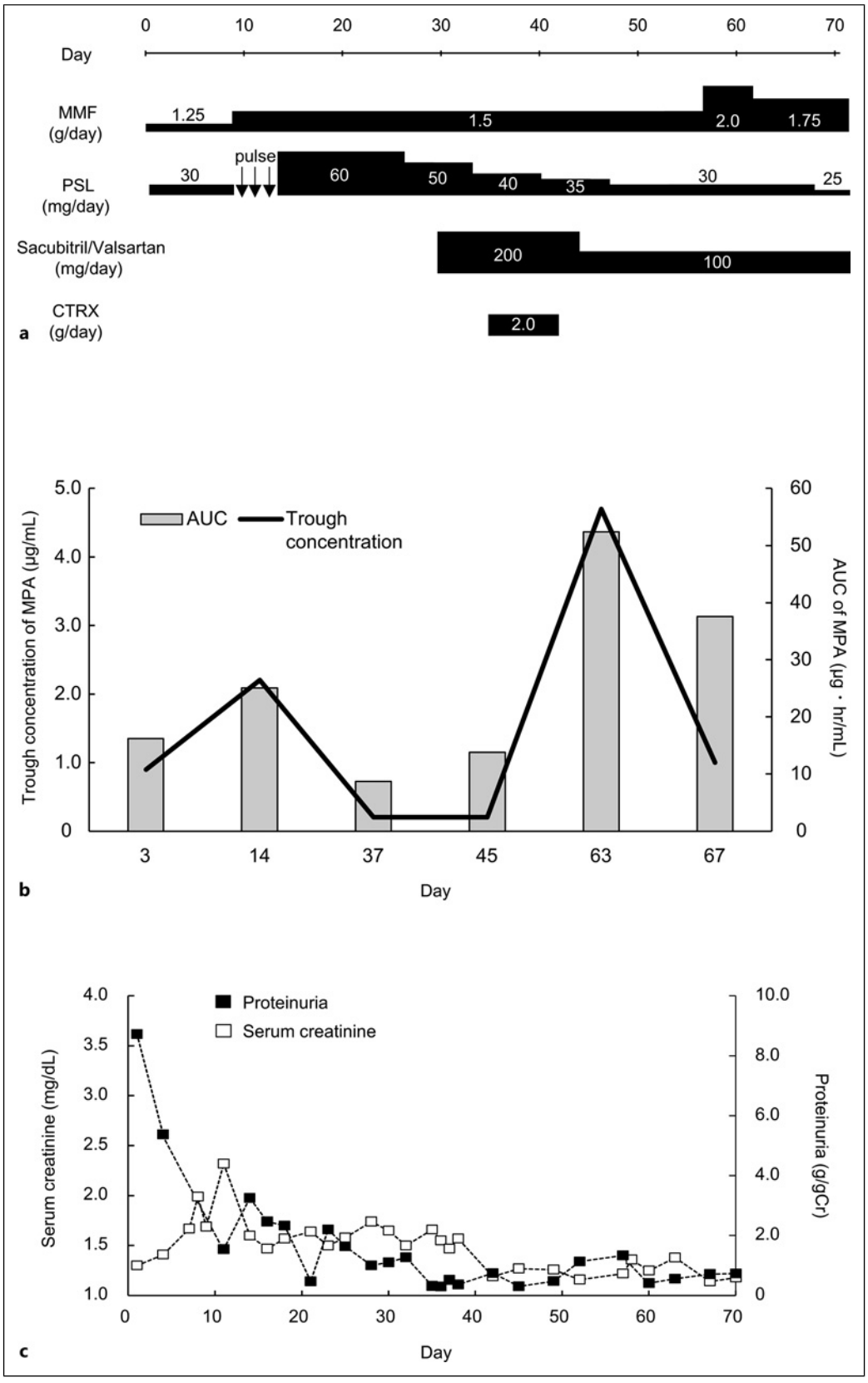

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The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536468).

Discussion

MMF is an immunosuppressive antimetabolite used for lupus nephritis and organ transplantation rejection prevention. In organ transplant patients, the AUC is recommended as an indicator of MPA exposure in the body because trough levels do not correlate with the AUC [8]. Conversely, it is known that trough levels and AUC correlate well in patients with lupus nephritis because their renal function is more stable than that in renal transplant patients [3, 4, 9]. However, whether trough levels should be a predictor of AUC in patients with lupus nephritis remains controversial [10]. We collected plasma samples at 0, 1, 3, and 6 h after MMF administration to estimate AUC_{0-12} values.

In this report, MPA plasma concentration was significantly decreased by concomitant use of sacubitril/valsartan, suggesting the possibility of drug interaction between sacubitril/valsartan and MMF. In addition to sacubitril/valsartan, steroid pulse therapy 1 g/day for 3 days and antibiotic therapy might have affected MPA plasma concentration.

A possible mechanism of drug interaction between sacubitril/valsartan and MPA involves an organic anion transporting polypeptide (OATP). MPA is metabolized to inactive MPA 7-O-glucuronide (MPAG) by glucuronosyltransferase in the liver and intestine [11]. OATP1B1 and 1B3 are involved in the uptake of MPAG from the blood to the liver [12]. MPAG excreted into the bile duct is deconjugated to MPA and reabsorbed in the gastrointestinal tract [11]. In contrast, sacubitril inhibits OATP1B1 and 1B3 in vitro (IC_{50} = 1.91 and 3.81 μM, respectively) [13]. Therefore, the inhibition of OATPs by sacubitril may have decreased the amount of MPAG excreted into the bile duct, resulting in lower plasma concentration by decreasing MPA reabsorption (Fig. 2). However, since sacubitril is rapidly metabolized after administration to sacubitrilat, which exhibits a weak OATP inhibitory effect (IC_{50} ~126 μM) [13], a further study is needed to determine whether OATPs might be involved in this interaction.

In addition, steroid pulse therapy 1 g/day for 3 days and antibiotic therapies might affect the plasma concentration of MPA. High-dose steroids can induce the expression of the drug-metabolizing enzymes in the liver, which might contribute to the decreased AUC of MPA. Cattaneo et al. [14] reported a 50% increase in the AUC of MPA in the low-dose steroid group compared to the high-dose group. CTRX might inhibit the deconjugation of MPA from MPAG by affecting the gut microbiota, leading to decrease in its AUC. Borrows et al. [15] reported that the concomitant use of oral antibiotics (ciprofloxacin and amoxicillin clavulanate) decreased the trough concentration of MPA by 54%, which then normalized within 3 days after the cessation of antibiotic administration, suggesting that the effect was transient. It is possible that CTRX administered intravenously is excreted in the bile duct and affects the gut microbiota.

Serum Cr has been reported as a factor affecting the AUC of MPA [11]. In this report, proteinuria was markedly improved by administration of PSL and MMF, while serum Cr showed almost no changes during hospitalization (Fig. 1c). Therefore, renal function is unlikely to influence the AUC.

Fig. 1. Interventions with outcomes during the clinical course. **a** Changes in pharmacologic therapeutic intervention. **b** Changes in trough concentration and AUC of MPA. **c** Changes in laboratory data associated with renal function. AUC, area under the curve; CTRX, ceftriaxone; Cr, creatinine; MPA, mycophenolic acid; MMF, mycophenolate mofetil; PSL, prednisolone.

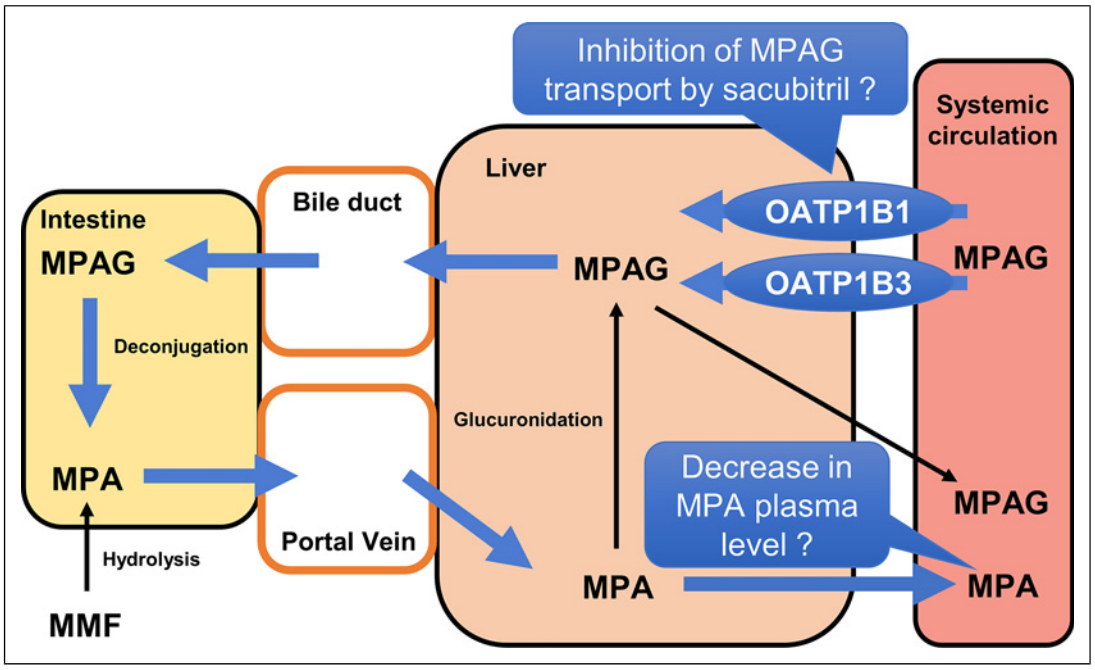

Fig. 2. A possible mechanism of OATPs-mediated drug interaction between sacubitril/valsartan and MMF in the liver. MPA, mycophenolic acid; MPAG, mycophenolic acid 7-O-glucuronide; MMF, mycophenolate mofetil; OATP, organic anion transporting polypeptide.

Since lupus nephritis is often associated with hypertension, the drug interaction observed in this report may also occur in other cases. However, this is a one-patient case report. More cases and basic findings are needed whether plasma MPA level is decreased by the concomitant use of sacubitril/valsartan.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and its amendments. Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

M.K. has received research grants from GlaxoSmithKline, Mitsubishi Tanabe, Astellas, Sanofi, Taisho, Nippon Shinyaku, Taiju Life Social Welfare Foundation, Kowa, Terumo, Kyocera, Chugai, Mochida, Lotte, Hitachi, Takeda, and Yamazaki Baking, outside the submitted work. T.A. has received grants, consulting fee, speakers' bureau, or payment for expert testimony from Astellas, Mitsubishi Tanabe, Chugai, Daiichi Sankyo, Pfizer, Teijin, Novartis, Sanofi, GlaxoSmithKline, AbbVie, AstraZeneca, Nippon Boehringer Ingelheim, Janssen, Gilead Sciences, Eli Lilly, ONO, Takeda, Alexion, Kyowa Kirin, Amgen, UCB Japan, Eisai, Idorsia, and Otsuka, outside the submitted work. The other authors have no competing interests to declare.

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Author Contributions

S.N. wrote the manuscript. S.N., M.M., and I.H. performed TDM of MPA. M.K., M.T., and T.A. took care of the patient and determined MMF dose based on TDM results. M.S. and Y.T. approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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