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The Effect of Diphenyl-Dimethyl-Dicarboxylate on Cyclosporine-A Blood Level in Kidney Transplants with Chronic Hepatitis

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An adequate blood level of cyclosporine-A (CsA) is essential to keep graft function in kidney transplants. Due to a narrow therapeutic index and highly variable pharmacokinetic properties associated with CsA, drug interactions may have a significant impact on the immunosuppressive efficacy or toxicity of CsA. Numerous drug interactions of potential clinical significance involving CsA have been reported.

Diphenyl-dimethyl-dicarboxylate (PMC), a hepatotonic drug, is a substance derived from the synthesis of Schizandrae fructus elements. We have experienced two cases of drug interaction between CsA and PMC in kidney transplants with chronic hepatitis. In both cases, CsA troughs decreased markedly to a subtherapeutic level following administration of PMC.

We, therefore, suggest that PMC could decrease the CsA trough level and thus a close monitoring of the CsA trough level is necessary during a PMC therapy.

Key Words: *Diphenyl-dimethyl-dicarboxylate, Cyclosporine, Drug interaction*

INTRODUCTION

Diphenyl-dimethyl-dicarboxylate (PMC:Nissel™, Taerim Pharma Co., Korea), a hepatotonic drug, is a substance derived from the synthesis of *Schizandrae fructus* elements[1]. Although this drug is used in clinical medicine, its action and interactions with other drugs have not been elucidated.

We have encountered two cases of drug interaction between CsA (Sandimmun™, Sandoz Pharmaceuticals, Basle) and PMC in kidney transplants with chronic hepatitis. Both cases showed a reduction of CsA trough to a subtherapeutic level following PMC treatment.

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CASE REPORT

CASE 1

A 52-year-old female underwent a successful living-unrelated donor renal transplantation. Two months following transplantation, serum transaminases showed a persistent elevation. Viral markers tested at 17 months after transplantation were HBsAg/sAb/cAb (−/+/+), anti-HCV (+) and CMV Ab IgG/IgM (+/−). Thirty months following transplantation, PMC (75mg/day, each tablet contains 25mg of PMC) was given orally for 6 successive weeks. Immunosuppression was maintained by administering CsA 175mg and prednisolone 7.5mg daily. Laboratory tests on starting PMC treatment indicated a CsA trough level of 97.7ng/ml (by monoclonal antibody radioimmunoassay, whole blood) and a serum creatinine level of 1.8mg/dl. Alanine transferase (ALT) measured 2 weeks before PMC therapy was 71IU/L. The CsA trough level fell to 78.0ng/ml after 4 weeks and 49.0ng/ml after 6

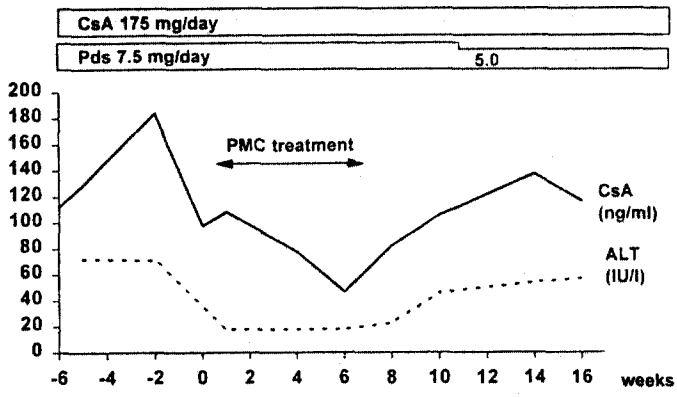

Fig. 1. CsA trough levels before, during and after PMC administration (Case 1).

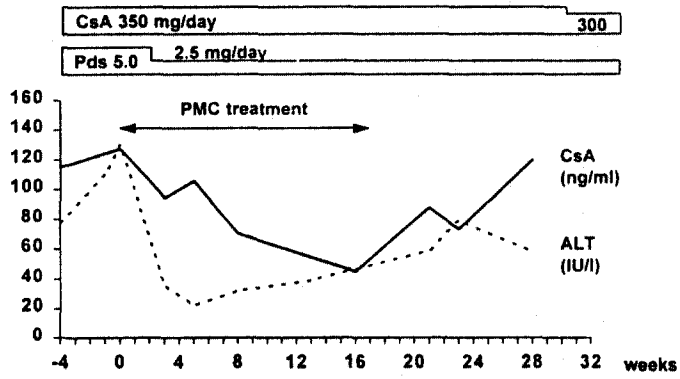

Fig. 2. CsA trough levels before, during and after PMC administration (Case 2).

weeks of PMC treatment, and no drugs were added or withdrawn. Upon cessation of PMC treatment, the CsA trough rose gradually, reaching 106.6mg/ml after 4 weeks and 137.4ng/ml after 8 weeks (Fig. 1).

CASE 2

A 53-year-old male kidney transplant showed intermittent elevations in transaminases 1 month after transplantation. Viral markers tested at 36 months following transplantation were HBsAg/sAb/cAb (−/−/+), anti-HCV (+) and CMV Ab IgG/IgM (+/+). Thirty-six months after transplantation, PMC (75mg/day) was given orally for 17 successive weeks. Immunosuppression was maintained by giving CsA 350mg and prednisolone 5mg daily. Laboratory tests on starting PMC treatment indicated CsA trough level of 127.5ng/ml, an ALT of 130 IU/L and a serum creatinine of 1.8mg/dL. The CsA trough level fell to 70.5 and 45.0ng/ml after 8 and 16 weeks of PMC therapy, respectively, despite the same dose of CsA being given. At the second week of PMC treatment, the dose of prednisolone was reduced to 2.5mg/day. Seven weeks after discontinuation of PMC treatment, the CsA trough rose 73.3ng/ml and, 12 weeks after, it reached 120.0ng/ml (Fig. 2).

DISCUSSION

The vast majority of the drugs that interact with CsA cause either an increase or decrease in CsA

blood level, thereby exposing the patient to the risk of development of renal dysfunction associated with a high CsA level, or graft rejection due to a subtherapeutic level. These effects are primarily attributed to the inhibition or induction of the p-450 microsomal enzyme system which metabolizes CsA[2]. Induction of the p-450 microsomal enzyme system by drugs such as phenytoin[3], phenobarbital[4], carbamazepine[5] and rifampin[6] may significantly decrease the blood concentration of CsA. Whether steroids could also decrease the CsA blood level[7] remains unclear.

PMC has been suggested to be effective in treating toxic hepatitis induced by CCl4 in animal model[8] and in chronic hepatitis in humans[9]. Although PMC is clinically used, the mechanism of action and its interaction with other drugs have not been identified. We experienced two cases of drug interaction between CsA and PMC in kidney transplants with chronic hepatitis. The duration of PMC therapy was 6 weeks in one case and 17 weeks in the other. In both cases, the CsA trough decreased to a subtherapeutic level during PMC treatment. However, the dose of CsA was not increased becaues of the possibility of CsA hepatotoxicity. No drugs influencing the CsA trough level were added or were discontinued during this period, except prednisolone.

In case 2, the dose of oral prednisolone was decreased from 5 to 2.5mg/day on the second week of PMC treatment. This, however, might not alter the interaction between CsA and PMC, as the CsA level readily reverted to the control level after the cessation of PMC treatment.

Although no episode of acute rejection was observed in the present study, some risks of acute rejection due to reduced CsA level may be considered in PMC therapy in humans. To identify the mechanism of interaction between PMC and CsA, analysis of the p-450 microsomal enzyme activity and the CsA metabolites in animal model may be required.

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