Drug Interaction between Ticlopidine and Cyclosporine

Uchenwa Iroaga, Jennifer Newman, and David J. Hollomby

INTRODUCTION

Cyclosporine is an immunosuppressant that is widely used for patients undergoing organ transplantation. Optimal long-term use of the drug entails careful monitoring of blood or plasma concentrations. The concurrent administration of other drugs may lead to alterations in cyclosporine concentrations and either a potential risk of graft rejection or toxic effects from excess cyclosporine. Ticlopidine is an antiplatelet agent that may interact with cyclosporine, affecting its concentration in whole blood.

A limited number of reports have suggested a potential interaction between cyclosporine and ticlopidine. Birmele and others documented this interaction in an 18-year-old man who was treated with cyclosporine for corticodependent nephrotic syndrome and who received ticlopidine 500 mg daily. The authors observed a dramatic decrease in the mean blood level of cyclosporine, and the dosage of cyclosporine had to be increased. When ticlopidine was discontinued, the cyclosporine blood level increased. A reintroduction test of ticlopidine yielded the same results. Verdejo and others reported a probable interaction between ticlopidine 250 mg daily and cyclosporine in a patient who had received cyclosporine for a period of 3 months. At follow-up, no significant modifications to the cyclosporine dosage were made, although the mean whole-blood trough level of cyclosporine was significantly decreased.

Practitioners need to be aware of this potential interaction, as it may lead to changes in cyclosporine concentrations and changes in the patient’s clinical status. We report here a case of decreased cyclosporine concentration after initiation of ticlopidine therapy.

CASE REPORT

On March 1, 1999, a 59-year-old woman was admitted to hospital with a 5-day history of shortness of
breath and retrosternal heaviness at rest lasting up to 2 h; the symptoms were not relieved by nitroglycerin. Her medical history consisted of a liver transplant in 1986, a kidney transplant in 1990, type 2 diabetes mellitus, hypertension, coronary artery disease, and gout. Her medications on admission included cyclosporine 50 mg bid, mycophenolate 1 g bid, prednisone 10 mg every other day, estrogen 0.625 mg daily, medroxyprogesterone 2.5 mg bid, metoprolol 50 mg bid, furosemide 40 mg daily, glyburide 2.5 mg bid, allopurinol 300 mg daily, colchicine 0.6 mg pm, vitamin E 800 IU daily, acetaminophen 325 mg pm, and zopiclone 7.5 mg qhs. In hospital, coronary angiography showed severe stenosis of the right coronary artery. Percutaneous coronary angioplasty with stent placement was performed, and on March 6, a 4-week course of ticlopidine 250 mg bid was prescribed. Within 2 days of commencing ticlopidine, the patient’s 12-h whole-blood trough level of cyclosporine dropped from more than 50 ng/mL to undetectable levels (less than 25 ng/mL), as determined by radioimmunoassay of whole blood (Diasorin Inc., Stillwater, Minnesota). The detection range for the assay was 25 to 800 ng/mL, and the coefficient of variation for the assay was 5%.

The patient’s medication administration record was checked to ensure that there had been no change in dosing time, and the hospital laboratory’s cyclosporine result was verified for the specific patient. The patient’s medication profile was reviewed for potential interactions with cyclosporine that would have resulted in the decrease in cyclosporine levels, but none of the potential interactions are well documented in the literature. In addition, the patient had been receiving cyclosporine since her liver transplant in 1986, with no dosage adjustments in more than 3 months, and had been taking her other medications for many years. According to her physician, the target cyclosporine level at the time was 50 to 100 ng/mL, so the dose was increased from 50 to 100 mg bid on March 11 and to 125 mg bid on March 13. The patient also received pulse corticosteroid treatment with methylprednisolone 250 mg on 2 separate days (March 11 and 12), as treatment for signs of graft rejection; this drug may have augmented the increase in cyclosporine concentrations. Subsequently, the patient’s cyclosporine concentrations rose steadily, to reach the target range at the time of discharge. The duration of ticlopidine therapy was extended by 1 to 2 weeks at a follow-up appointment and was probably discontinued on April 20 (7 weeks after admission). The patient’s cyclosporine concentrations during concurrent therapy ranged from 86 to 105 ng/mL (Table 1). Once the ticlopidine was discontinued, the cyclosporine concentrations increased to 134 ng/mL over the next month.

### DISCUSSION

Two mechanisms for the potential interaction between cyclosporine and ticlopidine have been proposed: altered metabolism and reduced absorption. Because cyclosporine is a substrate of the cytochrome (CYP) P450 3A4 enzyme system, its metabolism may be affected by CYP P450 3A4 inhibitors or inducers. Ticlopidine is a potential inducer of the CYP P450 3A4 system; induction results in an increase in the rate of cyclosporine metabolism and a subsequent decrease in whole-blood concentrations. The induction process has been indirectly measured by means of urinary excretion of 6-ß-hydroxycortisol, a marker of induction of hepatic CYP P450 3A. Boissonnat and others showed that urinary excretion of 6-ß-hydroxycortisol was significantly higher in subjects receiving ticlopidine than in those receiving placebo. Reduced absorption may also be responsible for the interaction between ticlopidine and cyclosporine; however, there is no evidence to support this postulated mechanism.

We believe that this case represents an example of the potential interaction between cyclosporine and ticlopidine. Literature reports suggest that this interaction has

<table>
<thead>
<tr>
<th>Time after Admission, wk</th>
<th>Dosage (mg/day)</th>
<th>Whole-Blood Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>100, 200, or 250*</td>
<td>Not detectable†</td>
</tr>
<tr>
<td>3</td>
<td>250</td>
<td>105</td>
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<tr>
<td>11</td>
<td>250</td>
<td>134</td>
</tr>
</tbody>
</table>

*The dosage was 100 mg daily from day 1 (the day of admission) to day 10; on day 11, the dosage was changed to 200 mg daily, and on day 13, the dosage was changed to 250 mg daily.
†Minimum detectable concentration in the testing laboratory was 25 ng/mL.
‡Concurrent ticlopidine discontinued at about 7 weeks after admission.
a fairly rapid onset, can occur at various ages, can affect both men and women, and may occur at daily doses of 250 or 500 mg ticlopidine. This case exhibits similar characteristics; however, a major limitation is the lack of measurement of cyclosporine concentrations immediately after withdrawal of ticlopidine. As a result, the effect on cyclosporine concentrations of withdrawing the ticlopidine is unclear in this case.

The concurrent administration of ticlopidine and cyclosporine can be successfully managed in a number of ways. First, it is necessary to ensure that appropriate indications exist for the use of both medications and that alternative therapeutic options have been considered. If concurrent therapy is required, cyclosporine concentrations should be followed closely during initiation and discontinuation of this combination of drugs. Patients should also be monitored for signs and symptoms of graft rejection. As in our case, the cyclosporine dose can be adjusted according to the patient’s target whole-blood concentration.

In conclusion, the potential interaction between cyclosporine and ticlopidine may lead to a decrease in whole-blood concentrations of cyclosporine in patients receiving both drugs. Close monitoring of cyclosporine concentrations should be performed upon initiation and withdrawal of ticlopidine.

References

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