

Immunosuppressants

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This edition of the Med-Psych Drug-Drug Interactions Update begins a change in format. Starting with this column, each column will feature one drug-drug interaction (DDI) topic that will be explored in depth. This edition features DDIs associated with the commonly used immunosuppressants. These drugs are frequently encountered by consultation-liaison psychiatrists in tertiary care settings. Generally, most of these drugs have narrow safety and therapeutic windows; therefore, other drugs that change their serum levels can have deleterious effects. In this review, the DDI profiles of cyclosporine, tacrolimus, sirolimus, and the corticosteroids are explored.

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Cyclosporine

Cyclosporine is a calcineurin inhibitor that is metabolized by cytochrome P450 3A4 (3A4). It is also a moderate inhibitor of 3A4. Cyclosporine has a narrow therapeutic index; inadequate serum levels lead to transplant failure, and toxic levels potentially lead to delirium, nephrotoxicity, and organ failure.

There are numerous reports in the literature of interactions between cyclosporine and other agents. Many drugs inhibit cyclosporine metabolism through inhibition of 3A4. Inhibitors verified from in vivo studies include norfloxacin, ketoconazole, fluconazole, calcium-channel blockers, clarithromycin, muromonab-CD3, nefazodone, fluvoxamine, grapefruit juice, and oral contraceptives. Other potential/probable inhibitors include any 3A4 inhib-

itor, including erythromycin, ciprofloxacin, itraconazole, and ritonavir. Although fluoxetine is only a moderate inhibitor of 3A4, there has been one reported case of cyclosporine levels doubling after initiation of fluoxetine treatment at 20 mg/day.¹

Page et al.² noted that co-administration of azithromycin and cyclosporine led to an increase in cyclosporine levels. While azithromycin only mildly inhibits 3A4, the authors hypothesized that the marked increase in cyclosporine levels may have been due to azithromycin's inhibition of the P-glycoprotein (P-gp) efflux pump.

It is of interest that cyclosporine is itself an inhibitor of P-gp. We reviewed P-gp in a previous column.³ Cyclosporine's inhibition of P-gp can lead to higher levels—and possible toxicity—of many drugs, including many cancer chemotherapy agents.⁴ This inhibition can also have positive effects, such as increasing the bioavailability of a particular drug, such as docetaxel.⁵

Since cyclosporine is a very expensive drug, many have proposed using 3A4 inhibitors to reduce the cost of the drug. This strategy has been discussed before in this column.⁶ Essentially, clinical researchers have generally discouraged this strategy because of the narrow therapeutic/toxic index of cyclosporine.^{7–9}

Patients receiving immunosuppressants such as cyclo-

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sporine are often given lipid-lowering agents, such as HMG-CoA reductase inhibitors (“statins”), to treat hyperlipidemia associated with immunosuppressant use.¹⁰ Most of the HMG-CoA reductase inhibitors are metabolized by 3A4 (except for pravastatin). As a moderate 3A4 inhibitor, cyclosporine may increase the levels of the “statin” drugs and place a patient at risk for the rhabdomyolysis and myopathy that can result from HMG-CoA reductase inhibitor toxicity.¹¹

Drugs that induce 3A4 or speed up metabolism of cyclosporine and reduce serum levels may lead to transplant failure. Carbamazepine¹² and rifampin (multiple case reports) have been reported to decrease serum cyclosporine levels. Indeed, any 3A4 inducer (such as efavirenz, modafinil, phenobarbital, phenytoin, dexamethasone and prednisone) is probably at risk for causing cyclosporine levels to decrease. There have been many reports of transplant rejection when patients added St. John’s wort to their immunosuppressant regimen.¹³ This has been discussed in a previous edition of this column¹⁴ and is possibly due either to St. John’s wort being a 3A4 inducer or to a P-gp effect. Finally, ticlopidine has been shown to decrease cyclosporine levels by an unknown mechanism.¹⁵

Tacrolimus

Tacrolimus, previously known as FK506, is a macrolide immunosuppressant that, like cyclosporine, is metabolized at 3A4 and is a moderate inhibitor of 3A4. Tacrolimus has a narrow therapeutic window and is associated with nephrotoxicity and cognitive impairment in overdose. The list of suspects that can raise tacrolimus levels is similar to that of cyclosporine. In addition, clotrimazole has been noted to cause a significant increase in tacrolimus levels,¹⁶ possibly through 3A4 inhibition. Butani and colleagues¹⁷ observed that concomitant administration of tacrolimus and felodipine caused a significant increase in tacrolimus levels in a renal transplant recipient—again, probably through 3A4 inhibition by felodipine.

Homma et al.¹⁸ reported that co-administration of tacrolimus and the proton pump inhibitor (PPI) lansoprazole, in a patient with a cytochrome P450 2C19 polymorphism, caused a significant increase in tacrolimus levels. The PPIs are metabolized by both 3A4 and 2C19. It was hypothesized that since this patient was a poor metabolizer at 2C19 because of the polymorphism, the bulk of the metabolic work shifted to 3A4, causing competition. There was no such interaction observed with the concomitant administration of tacrolimus and rabeprazole. Rabeprazole has al-

ternate metabolic pathways for elimination in addition to the P450 system.

Taber et al.¹⁹ reported concomitant administration of tacrolimus and chloramphenicol causing a 5-fold increase in tacrolimus levels in a patient. The patient experienced headache, lethargy, fatigue, and tremors. These symptoms resolved when the chloramphenicol was stopped. Chloramphenicol undergoes glucuronidation but has been found to inhibit 2C11, 2C6, and 3A2. While no specific studies have found chloramphenicol to inhibit 3A4, this case demonstrates a significant interaction between tacrolimus and chloramphenicol that could be due to inhibition of glucuronidation.

Similar to the concern with cyclosporine and the HMG-CoA reductase inhibitors, Kotanko et al.²⁰ reported a case of severe rhabdomyolysis when tacrolimus and simvastatin were co-administered. Tacrolimus is an inhibitor of 3A4 and inhibited the metabolism of simvastatin, which led to toxic levels. Although cyclosporine and tacrolimus are moderate inhibitors of 3A4, tacrolimus appears to be a relatively more potent inhibitor. Vasquez and Pollak²¹ reported that tacrolimus increased cyclosporine levels when used together.

Tacrolimus, through an unknown mechanism, appears to inhibit the phase 2 glucuronidation enzyme UGT1A1. Gornet et al.²² reported that toxicity ensued when tacrolimus was used with irinotecan (a topoisomerase I inhibitor with antitumor activity, also known as CPT-11). It appeared that tacrolimus inhibited irinotecan’s metabolism through UGT1A1, which makes the more active antitumor agent/metabolite SN-38.

Tacrolimus also appears to be a substrate for P-gp.²³ This would imply that inhibitors (i.e., quinidine or verapamil) or inducers (i.e., St. John’s wort) of P-gp could alter levels of tacrolimus.

Potential inducers of tacrolimus metabolism—identical to the list noted for cyclosporine—can decrease tacrolimus levels. Rifampin caused a decrease in tacrolimus concentrations,²⁴ and Bolley and colleagues²⁵ reported a significant decrease in tacrolimus levels when a renal transplant patient self-medicated with St. John’s wort.

Sirolimus

Sirolimus is a macrolide immunosuppressant that is metabolized at 3A4 and has been discovered to inhibit 3A4 activity.²⁶ Sirolimus also has a narrow therapeutic window and is associated with cognitive impairment and nephrotoxicity, although notably less nephrotoxicity than cyclo-

sporine, in overdose. Any potent inhibitor of 3A4 is a potential inhibitor of sirolimus. Specifically, Böttiger et al.²⁷ reported that co-administration of diltiazem and sirolimus led to increased sirolimus levels and decreased clearance. The same effect is seen with ketoconazole.²⁶ Induction of sirolimus metabolism has the potential to lead to transplant failure. Again, potential inducers include all drugs noted previously that potently induce 3A4. Sirolimus also has a synergistic effect when co-administered with cyclosporine, leading to an increase in concentrations of both drugs. This unusual effect may be because both are not only metabolized by 3A4 (thus competing at metabolic sites) but are also P-gp substrates and may competitively inhibit each other at this efflux pump.²⁸

Corticosteroids

Prednisone is usually used in long-term immunosuppression as part of a therapeutic regimen that includes cyclosporine. Prednisone is metabolized through 3A4 and is also a 3A4 inducer. Concomitant administration of ketoconazole, a potent 3A4 inhibitor, and prednisone causes a decrease in prednisolone (prednisone’s major active metabolite) clearance, raising levels and toxicity.²⁹ However, concomitant administration of itraconazole, also a potent

3A4 inhibitor, and prednisone had no effect on prednisone levels.³⁰ Both diltiazem and mibefradil (now off the U.S. market) are calcium-channel blockers and inhibitors of 3A4. When either of these drugs was administered with prednisone, an increased prednisone level was observed.^{29,31} Potential inducers of prednisone metabolism include any agent that induces 3A4. Specifically, a decrease in transplant survival has been found in patients that receive prednisolone with phenobarbital or phenytoin, both 3A4 inducers.²⁹

Summary

Potent inhibitors and inducers of 3A4 metabolism or the P-glycoprotein efflux pump may greatly affect immunosuppressants, leading to toxicity or transplant failure. The addition of a potent inhibitor may make it possible to decrease the dose of an administered immunosuppressant—and thus reduce the cost of immunosuppressant therapy—but the risks of exploiting the drug interaction may outweigh the benefits. Nefazodone and fluvoxamine have been implicated in interactions with these drugs. We would recommend serial monitoring of serum immunosuppressant and creatinine levels when using any drugs that may inhibit or induce the immunosuppressant drugs.

TABLE 1. Immunosuppressants

Drug	Metabolism Site	Enzyme(s) Inhibited	Enzyme(s) Induced	P-gp Substrate
Cyclosporine	3A4	3A4 ^a , P-gp ^b	—	Yes
Methylprednisolone	3A4	3A4	3A4	—
Muromonab-CD3	Not phase 1 or 2	3A4 ^c , P-gp ^c	—	—
Prednisone	3A4	—	3A4	Yes ^c
Sirolimus	3A4	3A4 ^d	—	Yes
Tacrolimus	3A4	3A4 ^a , UGT1A1	—	Yes

^aModerate inhibition.
^bCyclosporine is a potent P-gp inhibitor. The ability of other immunosuppressants to inhibit P-gp is less clear.
^cPossible, but more research necessary to confirm.
^dWeak inhibition.

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