Corticosteroid Interactions with Cyclosporine, Tacrolimus, Mycophenolate, and Sirolimus: Fact or Fiction?

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OBJECTIVE: To review the current clinical evidence on the effects of corticosteroid interactions with the immunosuppressive drugs cyclosporine, tacrolimus, mycophenolate, and sirolimus.

DATA SOURCES: Articles were retrieved through MEDLINE (1966–February 2008) using the terms corticosteroids, glucocorticoids, immunosuppressants, cyclosporine, tacrolimus, mycophenolate, sirolimus, drug interactions, CYP3A4, P-glycoprotein, and UDP-glucuronosyltransferases. Bibliographies were manually searched for additional relevant articles.

STUDY SELECTION AND DATA EXTRACTION: All English-language studies dealing with drug interactions between corticosteroids and cyclosporine, tacrolimus, mycophenolate, and sirolimus were reviewed.

DATA SYNTHESIS: Corticosteroids share common metabolic and transporter pathways, the cytochrome P450 and P-glycoprotein (P-gp/ABCB1) systems, respectively, with cyclosporine, tacrolimus, and sirolimus. As a group, corticosteroids induce the CYP3A4 and P-gp pathways; however, a few exceptions exist and the impact on a patient's immunosuppressant regimen may be critical. Corticosteroids also have demonstrated an induction effect on the uridine diphosphate–glucuronosyltransferase enzymes and multidrug resistance–associated protein 2 involved in mycophenolate's disposition. Successful corticosteroid withdrawal regimens have been reported; however, only few studies have examined the effects of steroid withdrawal on the remaining immunosuppressive regimens. To date, the clinical impact of steroid withdrawal on disposition of other immunosuppressive agents is not well characterized, and reports of such drug–drug interactions are conflicting.

CONCLUSIONS: While our understanding of the clinical impact of steroid–immunosuppressant interactions is limited, it remains a fact that corticosteroids have complex induction and inhibition interactions with common metabolic and transport pathways. Given the complex interaction of corticosteroids on crucial metabolic enzymes and transporter proteins, monitoring of immunosuppressive agents during steroid withdrawal is warranted to ensure optimal treatment outcomes.

KEY WORDS: corticosteroids, cyclosporine, glucocorticoids, immunosuppressants, mycophenolate, sirolimus, tacrolimus.

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The discovery and use of 4 classes of immunosuppressive agents (ie, calcineurin inhibitors, mammalian target of rapamycin [mTOR], antimetabolites, corticosteroids) have led to tremendous improvements in short-term outcomes of solid organ transplantation. The goal of immunosuppression is to prevent rejection of the transplanted organ while minimizing drug-related toxicity. The calcineurin inhibitors, cyclosporine and tacrolimus, are potent inhibitors of T cells, acting at a point of activation between receptor ligation and transcription of early genes.[1] Mycophenolic acid, a reversible inhibitor of inosine monophosphate dehydrogenase, blocks the proliferation of lymphocytes by inhibiting guanosine production,[2] while the mTOR inhibitors, sirolimus and everolimus, inhibit the mTOR signaling protein, resulting in blocked cell proliferation induced by growth factors and cytokines.[3] Of note, everolimus is currently not used in the US, but is approved in Europe for heart and kidney transplantation.[4,5] Corticosteroids regulate transcription factors such as activator protein 1, interleukins, and nuclear factor-κB by inhibiting gene transcription.[6,7] Employing a multidrug regimen is therefore logical from an immunomechanistic standpoint, given the potentially synergistic mechanisms of these agents.

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The disposition of immunosuppressive agents is dependent on metabolic pathways (phase I and II) as well as transporter systems. Phase I metabolism is typically mediated by cytochrome P450 enzymes; CYP3A4 is the major isoenzyme that metabolizes corticosteroids, calcineurin inhibitors, and mTOR inhibitors.[8-12] A common phase II conjugation pathway involves uridine diphosphate–glucuronosyltransferase (UGT), which metabolizes mycophenolic acid, the active moiety of mycophenolate mofetil.[2] P-glycoprotein (P-gp), also known as the adenosine triphosphate–binding cassette subgroup B (ABCB1), is the main transporter protein for corticosteroids, calcineurin inhibitors, and mTOR inhibitors; and the multidrug resistance–associated protein 2 (MRP2) exports glucuronidated metabolites of mycophenolic acid. Drug–drug interactions occur when an inducer or inhibitor of any of the above pathways is added or deleted from the immunosuppressive regimen.

The gold standard for immunosuppressive maintenance regimens in renal, cardiac, hepatic, and pancreatic transplantation usually consists of triple therapy including a corticosteroid, calcineurin inhibitor, and either mycophenolate mofetil or azathioprine. It is well known that corticosteroids are associated with an increased risk of morbidity and mortality from adverse effects such as diabetes, hypertension, and hyperlipidemia.[13-15] Recently, new protocols without steroids or with early steroid withdrawal have shown to be as effective as steroid-containing regimens in preventing rejection and reducing cardiovascular risk factors in recipients of solid organ transplants.[16-21]

This article reviews current clinical evidence on the effects of corticosteroid interactions with the immunosuppressive drugs cyclosporine, tacrolimus, mycophenolic acid, and sirolimus and provides recommendations on any dosage adjustments required subsequent to corticosteroid withdrawal from or addition to an immunosuppressive regimen.

Key Pathways

METABOLIC PATHWAYS

The key pathways involved in metabolism and transport of immunosuppressive agents are briefly reviewed (Table 1).[22-56]

Cytochrome P450

The CYP3A enzyme subfamily represents the most abundant of the cytochrome P450 enzymes found in humans and is a key catalyst for biotransformation of many drugs.[57] This is a major site of drug–drug interactions and therefore a possible source of adverse interactions, because changes in cytochrome P450 activities may affect the metabolism of various drugs that share a common metabolic pathway.

CYP3A4, the most plentiful isoenzyme expressed in the human liver and small intestine, is inducible by corticosteroids in humans and isolated hepatocytes.[58] The induction of CYP3A4 by corticosteroids presents an important, and often overlooked, factor in immunosuppressive therapy; high-dose intravenous corticosteroids are eventually tapered or discontinued depending on the protocol.

Uridine Diphosphate–Glucuronosyltransferases

The UGT system fulfills a crucial role in phase II biotransformation of potentially toxic endogenous and exogenous compounds.[59,60] These enzymes catalyze glucuronidation, rendering molecules more hydrophilic to facilitate

Table 1. Summary of Immunosuppressant Metabolism and Transport Pathways

Drug	Pathways			
	CYP3A4	UGT	P-gp	MRP2
Methylprednisolone	substrate,[22] weak competitive inhibitor[22-24]	NA	substrate,[25] inhibitor,[26] inducer[27]	NA
Prednisone	substrate (as prednisolone), inducer,[22] competitive inhibitor[22,24]	NA	substrate,[25] inducer[28]	NA
Prednisolone	substrate,[22] weak competitive inhibitor[22,24]	NA	substrate[25]	NA
Dexamethasone	substrate,[22] inducer,[22,29,30] competitive inhibitor[22]	inducer[31-35]	substrate,[25,36] inducer[37-41]	inducer[42-45]
Cyclosporine	substrate,[46,47] inhibitor[48]	NA	substrate,[36,49] inhibitor,[28] inducer[50]	inhibitor[51]
Tacrolimus	substrate[11,12]	substrate?[15] inhibitor?[52]	substrate,[36,49] inhibitor[28]	NA
Mycophenolate mofetil	NA	substrate[53]	NA	substrate (mycophenolic acid and glucuronide metabolites)[2,53]
Sirolimus	substrate[54]	NA	substrate,[54,55] inhibitor[56]	NA

MRP2 = multidrug resistance–associated protein 2; NA = information not available or not applicable; P-gp = P-glycoprotein; UGT = uridine diphosphate–glucuronosyltransferase.

their excretion. At least 18 UGT isoforms have been identified and are found mainly in liver, gastrointestinal tract, kidney, and biliary tissues.[59,60]

Mycophenolic acid, the active drug moiety of mycophenolate mofetil, is metabolized in the liver, gastrointestinal tract, and kidneys by UGTs to the major metabolite 7-*O*-mycophenolic acid glucuronide (MPAG) and minor metabolite acyl glucuronide of mycophenolic acid (AcMPAG).[2,53] Metabolism of mycophenolic acid to MPAG is primarily mediated by UGT1A7, 1A8, 1A9, and 1A10, whereas AcMPAG is predominantly formed by UGT2B7.[53]

To date, no relationship has been identified between the metabolism of cyclosporine, tacrolimus, and sirolimus versus the metabolism of UGT in vivo; however, high dosages of corticosteroids upregulate expression of UGT in rat and human hepatocytes and liver microsomes.[31-35]

TRANSPORT PATHWAYS

P-Glycoprotein

P-gp, an energy-dependent efflux pump, is extensively distributed and expressed in cells lining the intestine and liver, renal proximal tubular cells, and capillary endothelial cells comprising the blood–brain barrier.[61,62] P-gp serves as a protective mechanism by pumping xenobiotics back into the intestinal lumen to reduce intracellular drug concentrations.[61] P-gp also acts as a detoxifying transporter by secreting metabolites and natural toxic substances into urine via renal proximal tubules.[28] Many drugs are bisubstrates for both CYP3A4 and P-gp; therefore, potential interactions and synergy between the systems may occur.[37,63-65]

Cyclosporine is a substrate and competitive inhibitor of CYP3A4 and P-gp in vitro.[8] However, cyclosporine is also associated with increased intestinal CYP3A4 activity and decreased intestinal and hepatic P-gp activity in vivo.[66,67] While tacrolimus is also a substrate and competitive inhibitor of CYP3A4 and P-gp,[23,68] it has less inhibition of intestinal P-gp than of CYP3A.[66,69] In vivo studies in patients and healthy volunteers showed that clinically relevant doses of tacrolimus do not alter CYP3A4 or P-gp activity.[26,66,67]

Sirolimus has been shown to be both a substrate[3,54,55,70] and inhibitor[56] of P-gp. Sirolimus modulates drug transport mediated by P-gp by competitive inhibition, a mechanism different from that by which immunosuppression occurs.[71]

Corticosteroids have been shown to be both substrates and potent inducers of the P-gp system.[50] The most commonly used corticosteroid preparations in transplantation are methylprednisolone and prednisone (converted to prednisolone in vivo). Dexamethasone, although not used in the prevention of solid organ transplant rejection, is used in conjunction with other agents to treat posttransplant proliferative disorders, which occur in less than 2% of solid organ transplant recipients.[72] Despite similar mechanisms of action, subtle differences in their molecular structures affect P-gp transporter affinity.[7,25] For example, all are substrates; however, methylprednisolone and prednisolone are transported more efficiently by P-gp compared with dexamethasone or prednisone, due to the presence of a hydroxyl group.[25] Methylprednisolone,[27] prednisone,[28] and dexamethasone[37-40] are also inducers of P-gp. To our knowledge, no study has reported the effects of prednisolone on P-gp. Given that methylprednisolone and prednisone (metabolic precursor of prednisolone) are both inducers, it is likely that prednisolone may also have an inductive effect.

Multidrug Resistance–Associated Protein 2

The MRP2, an organic anion transport protein, is another important factor in determining drug disposition. It is mainly expressed in bile canalicular membrane, apical membrane of enterocytes, and renal proximal tubules for biliary and renal exports of anionic compounds and conjugation products.[73] MRP2 contributes to disposition of mycophenolic acid, MPAG, and AcMPAG and may impact mycophenolic acid pharmacokinetics significantly, as enterohepatic recirculation of mycophenolic acid is mediated by biliary excretion and deglucuronidation of MPAG.[53] It has been suggested that the pharmacokinetic interaction between cyclosporine and mycophenolic acid is via inhibition of MRP2 by cyclosporine.[51,53]

Drug Interactions

Current evidence for drug interactions between corticosteroids and immunosuppressive medications is summarized in Table 2.[22,24,66,74-89]

CORTICOSTEROIDS AND CYCLOSPORINE

Pichard et al.[22] evaluated cyclosporine interactions with corticosteroids (dexamethasone, prednisolone, prednisone, methylprednisolone) in primary cultures of human hepatocytes and liver microsomes and found all of the corticosteroids to be competitive inhibitors of cyclosporine oxidase, while only dexamethasone and prednisone were also found to be inducers. Dexamethasone and prednisone were also found to be inducers of CYP3A. Theoretically, all drugs characterized as inducers or inhibitors of cyclosporine oxidase could modify hepatic metabolism and blood concentration of cyclosporine in vivo.

One clinical study specifically evaluated the effect of corticosteroid withdrawal on cyclosporine concentration, although several studies alluded to possible drug interactions. Gotti et al.[84] reported no significant change in mean cyclosporine trough concentrations 3 years after steroid withdrawal; however, only 5 transplant recipients were studied.

Another small pilot study of 23 patients initiated on an 8-week corticosteroid withdrawal protocol reported on one patient with declining renal function one year after cy-

closporine initiation and renal biopsy revealing signs of cyclosporine nephrotoxicity.[90] Mean baseline cyclosporine trough concentrations ± SD were 120 ± 35 ng/mL, and the authors reported no change in cyclosporine dosage and trough concentrations throughout the study.

A number of studies have examined the effects of corticosteroids on cyclosporine concentrations in patients receiving methylprednisolone, prednisolone, or prednisone.[74,75,78,85,86] Conflicting data regarding corticosteroids increasing or decreasing cyclosporine concentrations have been reported. Some investigators observed an increased whole blood concentration of cyclosporine after high doses of corticosteroids[74,75]; results were attributed to an inhibitory effect of the corticosteroid on hepatic metabolism of cyclosporine.[22] Earlier studies reported increasing cyclosporine concentrations subsequent to administration of intravenous methylprednisolone (IVMP). Klintmalm et al.[74] reported a 135–430% increase of whole blood cyclosporine concentrations in 12 of 15 rejection episodes treated with IVMP, Huisman et al.[75] reported a significant increase in cyclosporine concentration in 12 of 14 patients, and Hall[76] reported decreases in cyclosporine clearance by greater than 25% in 5 of 11 patients. Although the studies did not evaluate the metabolic pathway of CYP3A, it is possible that results are in agreement with the findings of Pichard et al.[22] that methylprednisolone inhibits cyclosporine oxidase, thus leading to the rise in cyclosporine concentration.

In contrast, other investigators observed decreased whole blood concentrations of cyclosporine, suggesting that corticosteroids induce hepatic drug metabolism.[24,77] Ptachcinski et al.[77] reported increased clearance of cyclosporine after high doses of IVMP compared with administration of maintenance steroids. The authors speculated that hepatic enzyme induction was probably the main cause. Other studies observed no significant pharmacokinetic interactions; Ubhi et al.[78] reported a significant increase of 100 ng/mL in cyclosporine concentrations in only 3 of 17 rejection episodes and attributed the increase to factors other than IVMP therapy. The authors concluded that there was no apparent clinical interaction between IVMP and cyclosporine. Another study also reported no significant change in cyclosporine bioavailability and clearance index (calculated from cyclosporine trough concentrations; Table 2) with tapering methylprednisolone doses in 97 renal transplant recipients over one year.[66]

The discrepancy between the findings may be attributed to the analytical methods for cyclosporine measurement. Klintmalm et al.[74] used the original radioimmunoassay to measure cyclosporine concentrations; therefore, accumulation of cross-reactive metabolites may have contributed to the higher cyclosporine concentrations, while Ptachcinski et al.[77] and Pichard et al.[22] used the more specific analysis of high-performance liquid chromatography. However, Huisman et al.[75] did find a significant increase in cyclosporine values using both methods.

Table 2. Summary of Current Evidence for Interactions Between Corticosteroids and Immunosuppressive Agents

Combination	Results
Methylprednisolone–tacrolimus	↑ bioavailability and clearance index[a] of tacrolimus with ↓ steroid dose[66]
Methylprednisolone–cyclosporine	↑ cyclosporine concentrations and ↓ cyclosporine clearance subsequent to IVMP administration[74-76] ↓ cyclosporine concentrations from ↑ cyclosporine clearance[77] ↔ clinical effect[78] ↔ bioavailability and clearance index[a] of tacrolimus with ↓ steroid dose[66]
Methylprednisolone–MPA	↑ MPA 12-h exposure, trough and peak concentrations, ↓ mycophenolic acid clearance, and ↑ MPAG trough concentrations as methylprednisolone is tapered/withdrawn[79] no impact of methylprednisolone on MPA pharmacokinetic parameters[80]
Methylprednisolone–sirolimus	↔ effect when methylprednisolone boluses administered concomitantly[81]
Prednisone/prednisolone–tacrolimus	↑ systemic exposure to tacrolimus upon withdrawal of prednisolone; ↑ in tacrolimus concentrations in 43% and 61% of pts. after withdrawal of 5 and 10 mg of prednisolone, respectively[82] ↑ prednisone dose, ↑ tacrolimus dosage required[83]
Prednisone/prednisolone–cyclosporine	↔ effect on mean cyclosporine trough concentrations 3 y after steroid withdrawal[84] prednisone ↑ CYP3A and cyclosporine oxidase in vitro, may ↓ cyclosporine concentrations [22] cyclosporine may inhibit prednisone/prednisolone[85,86]
Prednisone/prednisolone–MPA	↔ effect of prednisone on mycophenolic acid trough concentrations[87]
Prednisone/prednisolone–sirolimus	↓ prednisolone elimination[88]
Dexamethasone–tacrolimus	↓ tacrolimus concentration after low (1 mg/kg/day) and high (75 mg/kg/day) dose dexamethasone in rats[89]
Dexamethasone–cyclosporine	dexamethasone ↑ CYP3A and cyclosporine oxidase in human hepatocytes, may ↓ cyclosporine concentrations [22,24]
Dexamethasone–MPA	NA
Dexamethasone–sirolimus	NA

IVMP = intravenous methylprednisolone; MPA = mycophenolic acid; MPAG = 7-*O*-mycophenolic acid glucuronide; NA = information not available or not applicable.
[a]Bioavailability and clearance index = trough concentration (µg/L)/dose/weight(mg/kg)•100.

To complicate matters further, cyclosporine may inherently inhibit the metabolism of prednisone and prednisolone.[85,86,91] One study followed 16 kidney transplant recipients who were on prednisone, allocated to either cyclosporine or azathioprine treatment arms, for 3 weeks.[85] Prednisone dosage was gradually decreased from 2 to 0.5 mg/kg/day after the first week of treatment. Only prednisolone concentrations were measured. The authors found that prednisolone's elimination rate was significantly lower by an average of 22% ($p < 0.05$) in the cyclosporine-treated group, thus providing support that cyclosporine increases prednisolone's bioavailability, possibly through inhibition of CYP3A4 and P-gp.

The inconsistent cyclosporine–corticosteroid interaction data could be attributed to study design, type and dosage of corticosteroid used, subject characteristics, and cyclosporine pharmacokinetic variability. While all of the commonly used corticosteroids are substrates and competitive inhibitors of CYP3A4, their inductive properties differ. The extent of inhibition/induction may also be time-dependent, as it generally takes longer to manifest induction effects.[50] In addition, interaction at the P-gp level likely plays a role in this complex pharmacokinetic interaction (Table 1).

CORTICOSTEROIDS AND TACROLIMUS

An interaction between steroids and tacrolimus has been described in both in vitro and in vivo animal studies.[11,89,92-94] In addition, 2 reviews of other drug interactions associated with tacrolimus have been published.[50,95] Corticosteroids may either induce or inhibit CYP3A4. Christians et al.[50] demonstrated that time is an important factor to consider in evaluating whether the net effect is CYP3A inhibition or induction. The authors concluded that after the initiation of corticosteroid therapy or an increase in dosage, inhibition is more important than induction properties; however, the impact of induction gradually increases, becoming more prominent than inhibition after several hours to days. Depending on the type of corticosteroid used, different effects on the expression of CYP3A and P-gp have been reported in in vitro experiments; dexamethasone, prednisone, and cortisone increased the activity of CYP3A, but prednisolone and methylprednisolone did not. Whether this difference translates to clinical use is unknown.[22]

Given that tacrolimus is metabolized almost entirely (>90%) by CYP3A in the liver and, to a lesser extent, in intestinal mucosa, coadministration of inhibitors/inducers of these systems potentially leads to significant pharmacokinetic interactions.[50,96] An interaction between tacrolimus and P-gp has also been shown.[36,49,50,97] The presence of P-gp substrates, inhibitors, and/or inducers is crucial in determining whether an interaction is likely to occur. Information on drugs categorized as P-gp subtrates, inhibitors, or inducers can be found in more detail elsewhere.[61,65]

Numerous in vitro studies have examined the effect of dexamethasone on P-gp,[25,37-40] but few have examined in vivo effects in rats. In one study, dexamethasone rapidly increased P-gp expression more than 4.5- and 2-fold in liver and lungs, respectively, and returned to control values 6 days after dexamethasone administration.[38] Another study found a 5-fold increase in male rats subsequent to dexamethasone administration; however, a 60% reduction in P-gp expression was found in female rats.[40] Several plausible mechanisms have been proposed regarding the impact of sex differences on pharmacology, such as lower oral bioavailability, menstrual cycle, and higher intestinal P-gp activity in females.[50] These factors, whether alone or in combination, may account for sex differences.

The pharmacokinetics of tacrolimus in rats after a low (1 mg/kg/day) and high (75 mg/kg/day) dexamethasone dose given intraperitoneally for 4 days were evaluated.[89] Blood concentrations and bioavailability of orally administered tacrolimus after both doses of dexamethasone were significantly decreased ($p < 0.01$). This paralleled a case report of a 20-year-old man whose tacrolimus trough concentration markedly decreased, by approximately 80%, subsequent to pulse methylprednisolone therapy and gradually returned to baseline levels (before steroid therapy) over 11 days.[89] These results indicate that a decrease in tacrolimus concentrations after high-dose steroids is likely a consequence of P-gp and CYP3A induction in liver and intestine and that these changes are reversible after corticosteroid cessation.

The interactions between tacrolimus and corticosteroids in clinical studies are generally in accord with animal model findings[89] (Table 2). An increase in tacrolimus bioavailability and clearance index, calculated from tacrolimus trough concentrations (Table 2), was noted with tapering methylprednisolone doses in 203 renal transplant recipients over one year.[66] A parallel increase in hematocrit and serum albumin was also observed. However, cyclosporine bioavailability was not altered in 97 subjects in the same study. The authors suggested that tacrolimus is more sensitive to interactions at the CYP3A4 and P-gp level.

In renal transplant patients who had been on a tacrolimus-based immunosuppression regimen for at least 3 months, van Duijnhoven et al.[82] evaluated tacrolimus trough concentrations and doses before and after withdrawal of prednisolone (5 and 10 mg) prospectively and retrospectively. The median tacrolimus dose-normalized concentration increased by 11% in the prospective and 14% in the retrospective part of the study after withdrawal of prednisolone 5 mg. Similarly, a withdrawal of prednisolone 10 mg led to increases of 36% and 33%, respectively. Assessment of the area under the curve (AUC) revealed an 18% increase ($p = 0.05$) after the withdrawal of prednisolone 5 mg, compatible with a reduced metabolism after steroid withdrawal. The study suggests that the effect

of corticosteroid withdrawal is steroid-dose dependent and that the tacrolimus dosage should be adjusted once steroid withdrawal has been initiated (Table 2).

The effect of steroid tapering was assessed in 83 renal transplant recipients on a tacrolimus-based regimen.[83] Patients were divided into 3 groups according to steroid dose (low: 0–0.15 mg/kg/day; intermediate: 0.16–0.25 mg/kg/day; high: >0.25 mg/kg/day). Tacrolimus concentration–dose ratios were assessed for each dosage group after 1 and 3 months of treatment. Patients received IVMP 500 mg at transplantation, which was slowly tapered to oral prednisone 5 mg daily at 3 months after transplantation. At higher doses of steroids, higher dosages of tacrolimus were required to achieve target trough concentrations. The authors speculated that the most likely interaction mechanism was specific enzymatic induction of CYP3A and/or P-gp. Thus, given the apparent interaction upon steroid administration, careful monitoring of tacrolimus blood concentrations during steroid tapering is warranted (Table 2).

CORTICOSTEROIDS AND MYCOPHENOLATE

Mycophenolic acid, the active form of mycophenolate, is metabolized solely by the UGT enzyme system via glucuronidation. Induction of UGTs by corticosteroids has been reported (Table 1)[31-33,79,98]; however, data regarding the impact of corticosteroids on the specific UGTs that metabolize mycophenolic acid are scarce and warrant further investigation (Table 2). One trial compared 26 renal transplant patients on triple-drug immunosuppression therapy (cyclosporine, mycophenolate mofetil, methylprednisolone) who underwent steroid tapering and eventual withdrawal over a period of 21 months with 12 patients on the same regimen without steroid withdrawal (control group).[79] The authors did not specify when IVMP, given intraoperatively, was switched to the oral formulation. Upon study initiation, the mycophenolic acid AUC was lower when high doses of steroids were being administered but progressively increased as methylprednisolone was being tapered and eventually withdrawn. Apparent plasma clearance of mycophenolic acid showed progressive and significant decline ($p < 0.01$) in patients who discontinued methylprednisolone compared with the controls. The authors concluded that steroids interfere with mycophenolic acid bioavailability in solid organ transplant recipients, and changes in mycophenolic acid concentration may be clinically relevant.

Another trial followed 100 recipients of de novo kidney transplants over 12 months, all of whom were also taking tacrolimus and methylprednisolone.[80] The steroid dose was tapered over subsequent months and corticosteroid treatment was completely withdrawn in 26 subjects. The authors reported no impact of methylprednisolone dose or withdrawal on mycophenolic acid trough concentrations or total exposure, concluding that only a randomized, prospective study could assess the corticosteroid–mycophenolic acid interaction.

In another study, 52 renal transplant patients continued on triple immunosuppression therapy (cyclosporine, mycophenolate mofetil, prednisone) for 3 months after transplant; at 6 months, 19 discontinued cyclosporine and 14 discontinued prednisone.[87] Mycophenolic acid trough concentrations determined at 6 and 9 months in the 14 patients who discontinued steroids but had no other changes in their immunosuppressive regimen revealed no statistically significant differences and no acute rejections. This implies that mycophenolic acid exposure may compensate for the lower overall level of immunosuppression obtained from a regimen without steroids[79]; whether this confers a lower risk of acute graft rejection still needs to be investigated.

While dexamethasone is known to induce MRP2 in rat hepatocytes,[42-44] currently there are no clinical studies investigating the impact of corticosteroids on MRP2 induction in humans. Pharmacokinetic interaction between corticosteroids and mycophenolic acid at the transporter level remains unknown.

CORTICOSTEROIDS AND SIROLIMUS

Sirolimus pharmacokinetics are expected to change when drugs affecting hepatic and intestinal CYP3A4 and P-gp are administered concomitantly.[54,99] To our knowledge, no pharmacokinetic studies on the effects of corticosteroid tapering on sirolimus concentrations have been published. However, available data regarding the effect of coadministered corticosteroids on sirolimus trough concentrations are conflicting.[81,88,100] Jusko et al.[88] evaluated the pharmacokinetic interaction of prednisolone and sirolimus during a 2-week course of sirolimus 1–13 mg/m^2 in 40 kidney transplant patients maintained on cyclosporine. The investigators reported a decrease in prednisolone elimination in relation to sirolimus dosage. Prednisolone AUC increased significantly from day –1 to day 14, with a mean ratio ± SD of 1.27 ± 0.30 ($p = 0.0001$), although time to maximal concentration, half-life, and mean residence time remained unchanged. The clinical significance of this finding and its effect on a steroid-tapering regimen remains to be evaluated.

A retrospective analysis was used to investigate the effect of corticosteroids on sirolimus trough concentrations when dual and triple immunosuppressive regimens were compared.[100] Addition of steroids to a dual regimen containing cyclosporine or mycophenolate mofetil resulted in significantly lower dose-normalized sirolimus and mycophenolic acid trough concentrations as compared with steroid-free regimens ($p < 0.01$ and $p < 0.05$, respectively).

The study did not include doses and levels of the other immunosuppressive agents coadministered with sirolimus or the different corticosteroids used; both of these factors may be crucial in determining the magnitude of the interaction.

Contrary to the first 2 studies, another investigation reported that steady-state sirolimus trough concentrations were not affected by bolus methylprednisolone doses (ranging from 500 mg to 3000 mg over 1–5 days) when administered to 14 renal transplant patients.[81] The authors acknowledged transience of high-dose methylprednisolone treatment and variability in timing of steroid dosing and sirolimus concentration measurement in this retrospective study.

To date, few studies have investigated corticosteroid–sirolimus interactions, and results are inconsistent. Prospective studies examining the effect of corticosteroid tapering on sirolimus concentrations need to be conducted to assess the clinical relevance of the potential interactions.

Discussion

Cyclosporine, tacrolimus, sirolimus, and corticosteroids share common metabolic and transporter pathways and, as the studies reviewed here have demonstrated, all are at risk of drug interactions. The impact of corticosteroids on drug-metabolizing enzyme and transporter protein activities is complex (Table 1). Depending on the type of corticosteroid used, study design, and time of dosing, corticosteroids have been shown to induce and/or inhibit metabolism of the immunosuppressants (Table 2). Therefore, a corticosteroid withdrawal regimen should prompt the clinician to expect decreased or increased concentrations of the remaining immunosuppressants. In addition, one study demonstrated that P-gp is significantly upregulated in peripheral T cell subsets from liver and lung transplant patients[101]; however, another found that hepatic expression of CYP3A4 increased during the first year after liver transplant, while P-gp did not.[102] Lemahieu et al.[66] also evaluated activities of hepatic and intestinal CYP3A4 and P-gp in renal transplant recipients and reported a decrease of CYP3A4 and P-gp activities over time (1 y after transplant) compared with healthy controls. The authors suggested that corticosteroid withdrawal likely explained the observation. However, the clinical relevance of alteration in metabolic and transport pathways following corticosteroid withdrawal is still debated.

Although more studies are needed to evaluate the in vivo interaction, steroid withdrawal is likely an important factor to consider in the pharmacokinetics of cyclosporine and its implications may be key in preventing nephrotoxicity or rejection in these patients. Whether declining renal function seen early in the withdrawal studies can be attributed to initiation of an acute rejection episode or whether it is an early sign of cyclosporine nephrotoxicity also needs to be evaluated. Similarly, corticosteroids are frequently coadministered with tacrolimus and there is growing evidence suggesting an interaction. Most transplant patients are maintained at target tacrolimus concentrations of 10–15 ng/mL one month after transplant, with lower concentrations thereafter.[23] The inductive effect of corticosteroids on CYP3A and tapering of corticosteroids may be responsible for reduced oral clearance of tacrolimus over time. The interaction may be dependent on the specific corticosteroid used, but overall, clinicians should closely monitor tacrolimus concentrations during and after the steroid withdrawal phase; dose reduction may be necessary.

Available data on steroid–sirolimus interactions are scant and conflicting; however, 2 studies appear to indicate a potential pharmacokinetic interaction.[88,100] This may therefore warrant a sirolimus dosage increase or decrease and closer monitoring once corticosteroids are introduced or tapered, respectively, from the regimen.

While corticosteroids are shown to induce UGT enzymes, the main metabolic pathway of mycophenolic acid, direct studies on pharmacokinetic interactions between corticosteroids and mycophenolic acid are limited. Dexamethasone has been shown to induce various UGT isoforms in vitro[31-33,98]; however, current clinical data on the impact of corticosteroid dosage or withdrawal on mycophenolic acid pharmacokinetics are inconsistent.[79,80,87] Similarly, clinical evidence of corticosteroids' impact on mycophenolic acid transport via MRP2 is lacking. It appears unnecessary to adjust the mycophenolate mofetil/mycophenolic acid immunosuppressive regimen with corticosteroid dosage changes; however, further trials are necessary to confirm this.

While therapeutic drug monitoring of immunosuppressants is often employed in management of transplant patients, it is still evolving and debate continues about defining adequate or excessive concentrations in different transplant recipients at various times after transplant. In 2002, the International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group published a consensus document on the measurement and interpretation of immunosuppressive drugs[103]; however, rising changes and issues surrounding the therapeutic drug monitoring of these drugs prompted a review. A recent update of the group's symposium acknowledges the inhibitory and inductive impact of steroids, as a group, on the metabolic pathways and the potential drug–drug interaction with immunosuppressant drugs.[104] However, no differentiation between the steroids and no recommendations were outlined. Although cyclosporine and tacrolimus concentrations are measured routinely, anticipating a change (upon steroid dosage adjustment) helps to guide clinicians and avoid unnecessary adverse events. On the other hand, it may be premature to suggest adjustment of mycophenolic acid and sirolimus dosages during steroid withdrawal. One must also bear in

mind that even in cases of complete corticosteroid withdrawal, which is increasingly adopted in some transplant populations (eg, liver, heart), a concern other than steroid-induced pharmacokinetic interactions may be potential severe leukopenia, due to removal of steroid-induced leukocytosis effects in patients on agents with bone marrow suppression activity (eg, mycophenolic acid, azathioprine, ganciclovir, thymoglobulin). To date, the influence of corticosteroid addition or withdrawal has not been routinely considered in clinical practice. Only by bringing forward the possible interactions of steroids with other immunosuppressant agents can we assess the significance of the impact of corticosteroid interactions on patient care.

The majority of corticosteroid withdrawal studies have focused on acute rejection, and rightly so; however, it is equally important for clinicians to keep in mind that pharmacokinetic interactions may occur upon removing a drug that induces the CYP3A4, P-gp, and UGT systems. With the available studies, it is yet difficult to recommend the incremental reductions that are necessary for the remaining immunosuppressive agents. The large interpatient variability found among those taking immunosuppressive drugs may also hinder such empiric recommendations. Many more studies examining the specific corticosteroid–immunosuppressant interactions are required before clinicians can take a proactive approach to dose adjustment of the remaining immunosuppressants once the plan is to alter the corticosteroid regimen. Overall, a trend of increased immunosuppressive exposure seems to be apparent from the results of the few studies evaluating the concentrations of immunosuppressive agents subsequent to instituting a corticosteroid withdrawal regimen. Future studies should compare transplant recipients who undergo steroid withdrawal versus those with no withdrawal while monitoring concentrations of the other immunosuppressants (eg, cyclosporine, tacrolimus, mycophenolic acid, sirolimus) throughout the entire period, with dosages adjusted only if necessary (eg, toxicities). Such well-controlled studies, although challenging to conduct, would provide crucial information regarding the impact of corticosteroid withdrawal on the pharmacokinetics of other immunosuppressants. These studies could be part of larger clinical trials addressing optimal immunosuppressant protocols for solid organ transplant recipients.

Summary

While our understanding of the clinical impact of steroid–immunosuppressant interactions is limited, it remains a fact that corticosteroids have complex induction and inhibition interaction with common metabolic and transport pathways. This underscores the utility of therapeutic drug monitoring in guiding and individualizing immunosuppressive therapy, especially when corticosteroids are tapered or withdrawn. No conclusive evidence-based recommendations for immunosuppressant dosage adjustments can be made at this time. Only well-designed and properly conducted studies can adequately complete the clinician's armamentarium in dealing with changing immunosuppressant protocols and provide a definitive answer to whether there are interactions between corticosteroids and cyclosporine, tacrolimus, mycophenolate, and sirolimus.

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References

1. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715-29. DOI 10.1056/NEJMra033540
2. Product monograph. Cellcept (mycophenolate mofetil). Nutley, NJ: Roche Laboratories, March 2003.
3. Kahan BD, Napoli KL. Sirolimus. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. Applied pharmacokinetics & pharmacodynamics. Principles of therapeutic drug monitoring. 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006:595-616.
4. Hiatt WR, Nissen SE, Cardiovascular and Renal Drugs Advisory Committee, US Food and Drug Administration. New drug application 21-628, certican (everolimus), for the proposed indication of prophylaxis of rejection in heart transplantation: report from the Cardiovascular and Renal Drugs Advisory Committee, US Food and Drug Administration, November 16, 2005, Rockville, MD. Circulation 2006;113:e394-5. DOI 10.1161/CIRCULATIONAHA.105.607630
5. Novartis Pharmaceutical Corporation. New Novartis drug Certican approved in first European market. www.novartis.nl/pdf/nieuws/juli2003/pr230703certicanapprovalsweden.pdf (accessed 2008 Feb 18).
6. Karin M. New twists in gene regulation by glucocorticoid receptor: is DNA binding dispensable? Cell 1998;93:487-90. DOI S0092-8674(00)81177-0
7. Smith L. Corticosteroids in solid organ transplantation: update and review of the literature. J Pharm Pract 2003;16:380-7.
8. Johnston A, Holt DW. Cyclosporine. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. Applied pharmacokinetics & pharmacodynamics. Principles of therapeutic drug monitoring. 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006:512-28.
9. Chapman TM, Perry CM. Everolimus. Drugs 2004;64:861-72; discussion 873-4.
10. Product monograph. Prograf (tacrolimus). Markham, ON: Fujisawa Canada Inc., February 2004.

11. Sattler M, Guengerich FP, Yun CH, Christians U, Sewing KF. Cytochrome P-450 3A enzymes are responsible for biotransformation of FK506 and rapamycin in man and rat. Drug Metab Dispos 1992;20:753-61.
12. Shiraga T, Matsuda H, Nagase K, et al. Metabolism of FK506, a potent immunosuppressive agent, by cytochrome P450 3A enzymes in rat, dog and human liver microsomes. Biochem Pharmacol 1994;47:727-35. DOI 0006-2952(94)90136-8
13. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: changing paradigms, improving outcomes, and remaining questions. Clin J Am Soc Nephrol 2006;1:1080-9. DOI 10.2215/CJN.01800506
14. Bestard O, Cruzado JM, Grinyo JM. Corticosteroid-sparing strategies in renal transplantation: are we still balancing rejection risk with improved tolerability? Drugs 2006;66:403-14.
15. Fireman M, DiMartini AF, Armstrong SC, Cozza KL. Immunosuppressants. Psychosomatics 2004;45:354-60.
16. Hollander AA, Hene RJ, Hermans J, van Es LA, van der Woude FJ. Late prednisone withdrawal in cyclosporine-treated kidney transplant patients: a randomized study. J Am Soc Nephrol 1997;8:294-301.
17. Lemieux I, Houde I, Pascot A, et al. Effects of prednisone withdrawal on the new metabolic triad in cyclosporine-treated kidney transplant patients. Kidney Int 2002;62:1839-47. DOI 10.1046/j.1523-1755.2002.00611.x
18. Rigotti P, European Tacrolimus/MMF Transplantation Study Group. Patients with high cholesterol levels benefit most from early withdrawal of corticosteroids. Transplant Proc 2002;34:1797-8. DOI S0041134502030828
19. Ramirez CB, Sebayel MI, Kizilisik T. Early steroid withdrawal after liver transplantation. Transplant Proc 1998;30:3182-3.
20. Rosenbaum DH, Adams BC, Mitchell JD, et al. Effects of early steroid withdrawal after heart transplantation. Ann Thorac Surg 2006;82:637-44; discussion 644. DOI 10.1016/j.athoracsur.2006.03.067
21. Vazquez de Prada JA, Celemin I, de la Torre JM, et al. Corticosteroid withdrawal after heart transplantation. Transplant Proc 1999;31:2212-4.
22. Pichard L, Fabre I, Daujat M, Domergue J, Joyeux H, Maurel P. Effect of corticosteroids on the expression of cytochromes P450 and on cyclosporin A oxidase activity in primary cultures of human hepatocytes. Mol Pharmacol 1992;41:1047-55.
23. Christians U, Pokaiyavanichkul T, Chan L. Tacrolimus. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. Applied pharmacokinetics & pharmacodynamics. Principles of therapeutic drug monitoring. 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006:529-62.
24. Pichard L, Fabre I, Fabre G, et al. Cyclosporin A drug interactions. Screening for inducers and inhibitors of cytochrome P-450 (cyclosporin A oxidase) in primary cultures of human hepatocytes and in liver microsomes. Drug Metab Dispos 1990;18:595-606.
25. Yates CR, Chang C, Kearbey JD, et al. Structural determinants of P-glycoprotein–mediated transport of glucocorticoids. Pharm Res 2003;20:1794-803.
26. Lemahieu WP, Maes BD, Verbeke K, Vanrenterghem YF. Alterations of CYP3A4 and P-glycoprotein activity in vivo with time in renal graft recipients. Kidney Int 2004;66:433-40. DOI 10.1111/j.1523-1755.2004.00750.x
27. Konishi H, Sumi M, Shibata N, Takada K, Minouchi T, Yamaji A. Decrease in oral bioavailability of ciclosporin by intravenous pulse of methylprednisolone succinate in rats. J Pharm Pharmacol 2004;56:1259-66. DOI 10.1211/0022357044481
28. Joy MS, Nickeleit V, Hogan SL, Thompson BD, Finn WF. Calcineurin inhibitor–induced nephrotoxicity and renal expression of P-glycoprotein. Pharmacotherapy 2005;25:779-89.
29. Watkins PB, Murray SA, Winkelman LG, Heuman DM, Wrighton SA, Guzelian PS. Erythromycin breath test as an assay of glucocorticoid-inducible liver cytochromes P-450. Studies in rats and patients. J Clin Invest 1989;83:688-97.
30. McCune JS, Hawke RL, LeCluyse EL, et al. In vivo and in vitro induction of human cytochrome P4503A4 by dexamethasone. Clin Pharmacol Ther 2000;68:356-66. DOI 10.1067/mcp.2000.110215
31. Soars MG, Petullo DM, Eckstein JA, Kasper SC, Wrighton SA. An assessment of UDP-glucuronosyltransferase induction using primary human hepatocytes. Drug Metab Dispos 2004;32:140-8. DOI 10.1124/dmd.32.1.140
32. Kanou M, Usui T, Ueyama H, Sato H, Ohkubo I, Mizutani T. Stimulation of transcriptional expression of human UDP-glucuronosyltransferase 1A1 by dexamethasone. Mol Biol Rep 2004;31:151-8.
33. Djebli N, Picard N, Rerolle JP, Le Meur Y, Marquet P. Influence of the UGT2B7 promoter region and exon 2 polymorphisms and comedications on acyl-MPAG production in vitro and in adult renal transplant patients. Pharmacogenet Genomics 2007;17:321-30. DOI 10.1097/FPC.0b013e32801430f8
34. Li YQ, Prentice DA, Howard ML, Mashford ML, Desmond PV. The effect of hormones on the expression of five isoforms of UDP-glucuronosyltransferase in primary cultures of rat hepatocytes. Pharm Res 1999;16:191-7.
35. Wishart GJ, Dutton GJ. Regulation of onset of development of UDP-glucuronosyltransferase activity towards *O*-aminophenol by glucocorticoids in late-foetal rat liver in utero. Biochem J 1977;168:507-11.
36. Ueda K, Saeki T, Hirai M, et al. Human P-glycoprotein as a multi-drug transporter analyzed by using transepithelial transport system. Jpn J Physiol 1994;44(suppl 2):S67-71.
37. Schuetz EG, Beck WT, Schuetz JD. Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells. Mol Pharmacol 1996;49:311-8.
38. Demeule M, Jodoin J, Beaulieu E, Brossard M, Beliveau R. Dexamethasone modulation of multidrug transporters in normal tissues. FEBS Lett 1999;442:208-14. DOI S0014-5793(98)01663-9
39. Zhao JY, Ikeguchi M, Eckersberg T, Kuo MT. Modulation of multidrug resistance gene expression by dexamethasone in cultured hepatoma cells. Endocrinology 1993;133:521-8.
40. Salphati L, Benet LZ. Modulation of P-glycoprotein expression by cytochrome P450 3A inducers in male and female rat livers. Biochem Pharmacol 1998;55:387-95. DOI S0006-2952(97)00436-X
41. Yokogawa K, Shimada T, Higashi Y, et al. Modulation of mdr1a and CYP3A gene expression in the intestine and liver as possible cause of changes in the cyclosporin A disposition kinetics by dexamethasone. Biochem Pharmacol 2002;63:777-83. DOI S000629520100911X
42. Pulaski L, Kania K, Ratajewski M, Uchiumi T, Kuwano M, Bartosz G. Differential regulation of the human MRP2 and MRP3 gene expression by glucocorticoids. J Steroid Biochem Mol Biol 2005;96:229-34. DOI 10.1016/j.jsbmb.2005.03.004
43. Courtois A, Payen L, Guillouzo A, Fardel O. Up-regulation of multidrug resistance–associated protein 2 (MRP2) expression in rat hepatocytes by dexamethasone. FEBS Lett 1999;459:381-5.
44. Turncliff RZ, Meier PJ, Brouwer KL. Effect of dexamethasone treatment on the expression and function of transport proteins in sandwich-cultured rat hepatocytes. Drug Metab Dispos 2004;32:834-9.
45. Micuda S, Fuksa L, Brcakova E, et al. Zonation of multidrug resistance-associated protein 2 in rat liver after induction with dexamethasone. J Gastroenterol Hepatol 2007. DOI 10.1111/j.1440-1746.2007.05066.x
46. Kelly PA, Wang H, Napoli KL, Kahan BD, Strobel HW. Metabolism of cyclosporine by cytochromes P450 3A9 and 3A4. Eur J Drug Metab Pharmacokinet 1999;24:321-8.
47. Kronbach T, Fischer V, Meyer UA. Cyclosporine metabolism in human liver: identification of a cytochrome P-450III gene family as the major cyclosporine-metabolizing enzyme explains interactions of cyclosporine with other drugs. Clin Pharmacol Ther 1988;43:630-5. DOI 0009-9236(88)90006-9
48. Brunner LJ, Bennett WM, Koop DR. Cyclosporine suppresses rat hepatic cytochrome P450 in a time-dependent manner. Kidney Int 1998;54:216-23. DOI 10.1046/j.1523-1755.1998.00970.x
49. Saeki T, Ueda K, Tanigawara Y, Hori R, Komano T. Human P-glycoprotein transports cyclosporin A and FK506. J Biol Chem 1993;268:6077-80.
50. Christians U, Jacobsen W, Benet LZ, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2002;41:813-51. DOI 411103
51. Hesselink DA, van Hest RM, Mathot RA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance–associat-

ed protein 2. Am J Transplant 2005;5:987-94. DOI 10.1046/j.1600-6143.2005.00779.x.
52. Zucker K, Tsaroucha A, Olson L, Esquenazi V, Tzakis A, Miller J. Evidence that tacrolimus augments the bioavailability of mycophenolate mofetil through the inhibition of mycophenolic acid glucuronidation. Ther Drug Monit 1999;21:35-43.
53. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clin Pharmacokinet 2007;46:13-58.
54. Zimmerman JJ. Exposure–response relationships and drug interactions of sirolimus. AAPS J 2004;6:e28. DOI 10.1208/aapsj060428
55. Miller DS, Fricker G, Drewe J. P-glycoprotein–mediated transport of a fluorescent rapamycin derivative in renal proximal tubule. J Pharmacol Exp Ther 1997;282:440-4.
56. Anglicheau D, Pallet N, Rabant M, et al. Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine–sirolimus interaction. Kidney Int 2006;70:1019-25. DOI 10.1038/sj.ki.5001649
57. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211-21. DOI 10.1056/NEJMra032424
58. Guengerich FP. Cytochrome P-450 3A4: regulation and role in drug metabolism. Annu Rev Pharmacol Toxicol 1999;39:1-17. DOI 10.1146/annurev.pharmtox.39.1.1
59. Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. Pharmacogenomics J 2003;3:136-58. DOI 10.1038/sj.tpj.6500171
60. Kiang TK, Ensom MH, Chang TK. UDP-glucuronosyltransferases and clinical drug–drug interactions. Pharmacol Ther 2005;106:97-132. DOI S0163-7258(04)00200-1 [pii]; 10.1016/j.pharmthera.2004.10.013
61. Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet 2001;40:159-68.
62. Watkins PB. The barrier function of CYP3A4 and P-glycoprotein in the small bowel. Adv Drug Deliv Rev 1997;27:161-70. DOI S0169-409X(97)00041-0
63. Benet LZ, Izumi T, Zhang Y, Silverman JA, Wacher VJ. Intestinal MDR transport proteins and P-450 enzymes as barriers to oral drug delivery. J Control Release 1999;62:25-31. DOI S0168-3659(99)00034-6
64. Suzuki H, Sugiyama Y. Role of metabolic enzymes and efflux transporters in the absorption of drugs from the small intestine. Eur J Pharm Sci 2000;12:3-12. DOI S0928-0987(00)00178-0
65. Matheny CJ, Lamb MW, Brouwer KR, Pollack GM. Pharmacokinetic and pharmacodynamic implications of P-glycoprotein modulation. Pharmacotherapy 2001;21:778-96.
66. Lemahieu WP, Maes BD, Vanrenterghem Y. Different evolution of trough and dose levels during the first year after transplantation for tacrolimus versus cyclosporine. Transplant Proc 2005;37:2051-3. DOI 10.1016/j.transproceed.2005.03.095
67. Lemahieu WP, Maes BD, Verbeke K, Vanrenterghem Y. CYP3A4 and P-glycoprotein activity in healthy controls and transplant patients on cyclosporin vs. tacrolimus vs. sirolimus. Am J Transplant 2004;4:1514-22. DOI 10.1111/j.1600-6143.2004.00539.x
68. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 2004;43:623-53.
69. Saitoh H, Saikachi Y, Kobayashi M, et al. Limited interaction between tacrolimus and P-glycoprotein in the rat small intestine. Eur J Pharm Sci 2006;28:34-42. DOI 10.1016/j.ejps.2005.12.006
70. Product monograph. Rapamune (sirolimus). Philadelphia: Wyeth Pharmaceuticals Inc., March 2005.
71. Arceci RJ, Stieglitz K, Bierer BE. Immunosuppressants FK506 and rapamycin function as reversal agents of the multidrug resistance phenotype. Blood 1992;80:1528-36.
72. Tsao L, Hsi ED. The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. Arch Pathol Lab Med 2007;131:1209-18.
73. Suzuki H, Sugiyama Y. Single nucleotide polymorphisms in multidrug resistance associated protein 2 (MRP2/ABCC2): its impact on drug disposition. Adv Drug Deliv Rev 2002;54:1311-31.
74. Klintmalm G, Sawe J. High dose methylprednisolone increases plasma cyclosporin levels in renal transplant recipients (letter). Lancet 1984;1:731.
75. Huisman RM, van Son WJ, Tegzess AM. Interaction of intravenous methylprednisolone with oral CsA. Nephrol Dial Transplant 1990;5:905-6.
76. Hall TG. Effect of methylprednisolone on cyclosporine blood levels (abstract). Pharmacotherapy 1990;10:248.
77. Ptachcinski RJ, Venkataramanan R, Burckart GJ, et al. Cyclosporine–high-dose steroid interaction in renal transplant recipients: assessment by HPLC. Transplant Proc 1987;19:1728-9.
78. Ubhi CS, Woodhouse L, Giles GR. Interaction of intravenous methylprednisolone with oral cyclosporin. Nephrol Dial Transplant 1990;5:376-8.
79. Cattaneo D, Perico N, Gaspari F, Gotti E, Remuzzi G. Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. Kidney Int 2002;62:1060-7. DOI 10.1046/j.1523-1755.2002.00531.x
80. Kuypers DR, Claes K, Evenepoel P, et al. Long-term changes in mycophenolic acid exposure in combination with tacrolimus and corticosteroids are dose dependent and not reflected by trough plasma concentration: a prospective study in 100 de novo renal allograft recipients. J Clin Pharmacol 2003;43:866-80.
81. Backman L, Kreis H, Morales JM, Wilczek H, Taylor R, Burke JT. Sirolimus steady-state trough concentrations are not affected by bolus methylprednisolone therapy in renal allograft recipients. Br J Clin Pharmacol 2002;54:65-8. DOI 10.1046/j.1365-2125.2002.01594.x
82. van Duijnhoven EM, Boots JM, Christiaans MH, Stolk LM, Undre NA, van Hooff JP. Increase in tacrolimus trough levels after steroid withdrawal. Transpl Int 2003;16:721-5. DOI 10.1007/s00147-003-0615-1
83. Anglicheau D, Flamant M, Schlageter MH, et al. Pharmacokinetic interaction between corticosteroids and tacrolimus after renal transplantation. Nephrol Dial Transplant 2003;18:2409-14.
84. Gotti E, Perico N, Perna A, et al. Renal transplantation: can we reduce calcineurin inhibitor/stop steroids? Evidence based on protocol biopsy findings. J Am Soc Nephrol 2003;14:755-66.
85. Langhoff E, Madsen S, Flachs H, Olgaard K, Ladefoged J, Hvidberg EF. Inhibition of prednisolone metabolism by cyclosporine in kidney-transplanted patients. Transplantation 1985;39:107-9.
86. Ost L. Effects of cyclosporin on prednisolone metabolism (letter). Lancet 1984;1:451.
87. Gregoor PJ, de Sevaux RG, Hene RJ, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. Transplantation 1999;68:1603-6.
88. Jusko WJ, Ferron GM, Mis SM, Kahan BD, Zimmerman JJ. Pharmacokinetics of prednisolone during administration of sirolimus in patients with renal transplants. J Clin Pharmacol 1996;36:1100-6.
89. Shimada T, Terada A, Yokogawa K, et al. Lowered blood concentration of tacrolimus and its recovery with changes in expression of CYP3A and P-glycoprotein after high-dose steroid therapy. Transplantation 2002;74:1419-24. DOI 10.1097/01.TP.0000038287.39271.8F
90. Budde K, Geissler S, Hallebach G, et al. Prospective randomized pilot study of steroid withdrawal with mycophenolate mofetil in long-term cyclosporine-treated patients: 4-year follow-up. Transplant Proc 2002;34:1703-5. DOI S0041134502029901
91. Jeng S, Chanchairujira T, Jusko W, Steiner R. Prednisone metabolism in recipients of kidney or liver transplants and in lung recipients receiving ketoconazole. Transplantation 2003;75:792-5. DOI 10.1097/01.TP.0000055099.97542.5D
92. Ali Shah I, Whiting PH, Omar G, Thomson AW, Burke MD. Effects of FK 506 on human hepatic microsomal cytochrome P-450–dependent drug metabolism in vitro. Transplant Proc 1991;23:2783-5.
93. Moochhala SM, Lee EJ, Earnest L, Wong JY, Ngoi SS. Inhibition of drug metabolism in rat and human liver microsomes by FK 506 and cyclosporine. Transplant Proc 1991;23:2786-8.
94. Piekoszewski W, Chow FS, Jusko WJ. Pharmacokinetic and pharmacodynamic effects of coadministration of methylprednisolone and tacrolimus in rabbits. J Pharmacol Exp Ther 1994;269:103-9.
95. van Gelder T. Drug interactions with tacrolimus. Drug Saf 2002;25:707-12.

96. Lampen A, Christians U, Guengerich FP, et al. Metabolism of the immunosuppressant tacrolimus in the small intestine: cytochrome P450, drug interactions, and interindividual variability. Drug Metab Dispos 1995;23:1315-24.
97. Yokogawa K, Takahashi M, Tamai I, et al. P-glycoprotein–dependent disposition kinetics of tacrolimus: studies in mdr1a knockout mice. Pharm Res 1999;16:1213-8.
98. Nawrocki A, Korecka M, Solari S, Kang J, Shaw LM. Mycophenolic acid. In: Burton ME, Shaw LM, Schentag JJ, Evans WE, eds. Applied pharmacokinetics & pharmacodynamics. Principles of therapeutic drug monitoring. 4th ed. Baltimore: Lippincott Williams & Wilkins, 2006: 563-94.
99. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. Clin Pharmacokinet 2001;40:573-85.
100. Cattaneo D, Merlini S, Pellegrino M, et al. Therapeutic drug monitoring of sirolimus: effect of concomitant immunosuppressive therapy and optimization of drug dosing. Am J Transplant 2004;4:1345-51. DOI 10.1111/j.1600-6143.2004.00517.x
101. Donnenberg VS, Burckart GJ, Griffith BP, Jain AB, Zeevi A, Berg AD. P-Glycoprotein (P-gp) is upregulated in peripheral T-cell subsets from solid organ transplant recipients. J Clin Pharmacol 2001;41:1271-9.
102. Thorn M, Lundgren S, Herlenius G, Ericzon BG, Loof L, Rane A. Gene expression of cytochromes P450 in liver transplants over time. Eur J Clin Pharmacol 2004;60:413-20. DOI 10.1007/s00228-004-0786-4
103. Holt DW, Armstrong VW, Griesmacher A, et al. International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology Working Group on Immunosuppressive Drug Monitoring. Ther Drug Monit 2002;24:59-67.
104. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. Ther Drug Monit 2006;28:720-5. DOI 10.1097/FTD.0b013e31802c5cf5

Interacciones de Corticosteroides con Ciclosporina, Tacrolimus, Micofenolato, y Sirolimus: ¿Verdad o Ficción?

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EXTRACTO

OBJETIVO: Revisar la evidencia clínica actual de los efectos de las interacciones de los corticosteroides con los fármacos inmunosupresores ciclosporina, tacrolimus, micofenolato, y sirolimus.

FUENTES DE INFORMACIÓN: Los artículos se extrajeron a partir de la base de datos de MEDLINE (1966–febrero de 2008) con los siguientes términos de búsqueda en inglés: corticosteroids, glucocorticoids, immunosuppressants, cyclosporine, tacrolimus, mycophenolate, sirolimus, drug interactions, CYP3A4, P-glycoprotein, y UDP-glucuronosyltransferases. Se realizaron búsquedas manuales de la bibliografía para obtener artículos relevantes adicionales.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Se revisaron todos los estudios en inglés que trataban sobre las interacciones farmacológicas entre los corticosteroides y los inmunosupresores (ciclosporina, tacrolimus, micofenolato, y sirolimus).

SÍNTESIS: Los corticosteroides comparten vías metabólicas y de transporte comunes, los sistemas citocromo P450 (CYP) y P-glicoproteína (P-gp/ABCB1), respectivamente, con ciclosporina, tacrolimus, y sirolimus. Como grupo, los corticosteroides inducen las vías CYP3A4 y P-gp; sin embargo, existen algunas excepciones cuyo impacto sobre el régimen inmunosupresor del paciente puede ser crítico. Los corticosteroides también han demostrado un efecto inductor sobre las enzimas UDP-glucuronosil-transferasa y la proteína 2 asociada a la resistencia multifármaco involucrada en la disposición de micofenolato Se han notificado regímenes de retirada de corticosteroides exitosos; sin embargo, sólo algunos estudios han examinado los efectos de la retirada de esteroides sobre los regímenes inmunosupresores concomitantes. Hasta la fecha, no se ha caracterizado en detalle el impacto clínico de la retirada de esteroides sobre la disposición de otros agentes inmunosupresores y los informes de dichas interacciones farmacológicas son contradictorias.

CONCLUSIONES: Mientras nuestro conocimiento del impacto clínico de las interacciones entre esteroides e inmunosupresores sea limitado, sigue siendo un hecho las complejas interacciones de inducción e inhibición de los corticosteroides con las vías metabólicas y de transporte comunes. Dada la compleja interacción de los corticosteroides con las enzimas metabólicas y las proteínas de transporte cruciales, debe garantizarse la monitorización de los agentes inmunosupresores durante la retirada de esteroides para asegurar un tratamiento óptimo.

Traducido por Enrique Muñoz Soler

L'Interaction des Corticostéroïdes avec la Cyclosporine, le Tacrolimus, le Mycophénolate, et le Sirolimus: Réalité ou Fiction?

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RÉSUMÉ

OBJECTIF: Revoir les données cliniques probantes de l'interaction rapportée entre les corticostéroïdes et les immunosuppresseurs dont notamment la cyclosporine, le tacrolimus, le mycophénolate sodique, et le sirolimus.

SOURCES D'INFORMATION: Une recherche dans la banque de données MEDLINE (1966–février 2008) a été effectuée avec les mots-clés suivants: corticostéroïdes, glucocorticoïdes, immunosuppresseurs, cyclosporine, tacrolimus, mycophénolate, sirolimus, interaction médicamenteuse, CYP3A4, p-glycoprotéine, y glucuronosyltransférase-UDP. Les bibliographies des articles identifiés ont été vérifiées pour tenter de cibler des références additionnelles.

SÉLECTION DE L'INFORMATION: Tous les articles de langue anglaise dont le sujet principal était l'interaction entre les corticostéroïdes et les immunosuppresseurs ont été retenus et révisés.

RÉSUMÉ: La cyclosporine, le tacrolimus, le sirolimus, et les corticostéroïdes partagent la voie métabolique du cytochrome P450 ainsi que le système de transport transmembranaire de la p-glycoprotéine. En général, les corticostéroïdes induisent le cytochrome P450 3A4 et la p-glycoprotéine; toutefois, quelques exceptions existent et l'impact net sur le régime immunosuppresseur d'un patient peut varier. Les corticostéroïdes démontrent aussi un effet inducteur sur les enzymes glucuronosyltransférases-UDP et la protéine 2 du gène MRP qui est elle-même impliquée dans la disposition du mycophénolate. Plusieurs succès thérapeutiques de sevrage des corticostéroïdes ont été rapportés; toutefois, il existe uniquement quelques études qui ont examiné les effets spécifiques du retrait des corticostéroïdes sur les régimes d'immunosuppresseurs. A ce jour, l'impact clinique du retrait des stéroïdes sur la cinétique des immunosuppresseurs n'est pas bien caractérisé et les publications à cet égard présentent des résultats contradictoires.

CONCLUSIONS: Bien que notre compréhension de l'impact clinique de l'interaction médicamenteuse entre les corticostéroïdes et les immunosuppresseurs soit limitée, il n'en demeure pas moins que les corticostéroïdes possèdent des effets inducteurs et inhibiteurs sur plusieurs voies communes métaboliques et de transport transmembranaire. Ces interactions complexes peuvent aisément justifier le monitorage des immunosuppresseurs afin de s'assurer de l'optimisation des traitements.

Traduit par Sylvie Robert