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Pharmacokinetic Drug–Drug Interactions Between Immunosuppressant and Anti-Infective Agents: Antimetabolites and Corticosteroids

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Infections account for 15–20% of deaths in transplant recipients, requiring rapid and appropriate therapeutic interventions. Many anti-infective agents interact with immunosuppressive regimens used in transplantation, placing patients at increased risk for adverse drug reactions and prolonged hospitalizations. There is established data regarding the level of evidence and magnitude of interactions between calcineurin inhibitors and mammalian target of rapamycin inhibitors with anti-infective agents. Less is known about the interactions with anti-proliferative agents and corticosteroids, with gaps in knowledge on the appropriate management of these interactions. The objective of this review was to highlight the pharmacokinetic drug–drug interactions between antimetabolites and corticosteroids with commonly used anti-infective agents.

MeSH Keywords: Anti-Infective Agents • Antimetabolites • Corticosteroids • Drug Interactions

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Background

Infections remain a significant complication after solid organ transplantation (SOT). Use of various induction regimens, administration of novel immunosuppressive agents, and incorporation of newer prophylactic strategies continue to change the spectrum and severity of infections in SOT recipients [1]. Corticosteroids and anti-proliferative agents, azathioprine (AZA), and mycophenolic acid (MPA) are cornerstone therapies for rejection prevention in patients undergoing SOT [2]. Corticosteroids are utilized for immunosuppression induction to prevent acute rejection, and for chronic anti-rejection maintenance therapy. Anti-proliferative agents are primarily utilized for anti-rejection maintenance prophylaxis [2]. The use of these treatments in conjunction with specific antimicrobial agents introduces the potential for drug–drug interactions. This review highlights clinically important pharmacokinetic interactions between these classes of immunosuppressants and select antimicrobials, focusing on mechanisms, magnitude of effects, and management strategies.

Interactions with Antimetabolites

In general, long-term data demonstrating a decrease in the risk of rejection and improved survival with mycophenolate mofetil (MMF) compared with AZA has prompted many transplant centers to replace routine use of AZA with MMF [3–6]. Azathioprine is a prodrug converted rapidly by plasma esterases or non-enzymatically via glutathione to 6-mercaptopurine, which is further converted to thioinosine-monophosphate, its active metabolite. Only about 10% of AZA is eliminated as unchanged drug in the urine. The majority of AZA's metabolism is based on plasma esterases or non-enzymatic processes [2].

Antivirals

Ribavirin

Ribavirin is a nucleoside analogue, which inhibits viral replication of a wide spectrum of RNA and DNA viruses. In solid organ transplant patients, ribavirin is utilized for the treatment of patients infected with hepatitis C (HCV), respiratory syncytial virus, and other viral infections [7–9]. Ribavirin has a well-established inhibitory effect on inosine monophosphate dehydrogenase (IMPDH). This enzyme is key to the metabolism of AZA. Inhibition of IMPDH leads to an increase in 6-methyl-thioinosine monophosphate, which has been associated with myelotoxicity [10].

Several case reports have described patients with normal thiopurine methyltransferase genotype, and who received chronic AZA treatment and developed severe pancytopenia resulting in the discontinuation of ribavirin and AZA [11,12]. A case series of eight patients on AZA treated for HCV with ribavirin showed significant pancytopenia with a mean cell count nadir of 4.6±1.6 weeks following initiation of ribavirin. Three of the patients underwent bone marrow aspiration and were found to be profoundly hypocellular. Following the withdrawal of ribavirin and AZA, full blood count recovery was seen at 5±1 week and hematologic toxicity was not seen following reintroduction of ribavirin or AZA alone in any patient. Within the case series, two patients' plasma concentrations of methylated derivatives and 6-thioguanine nucleotide were evaluated. From baseline to cell count nadir there was an average threefold increase in methylated derivatives plasma concentration and 44% reduction in plasma 6-thioguanine nucleotide concentrations [13]. The concomitant use of AZA and ribavirin should be avoided given the significant risks for pancytopenia.

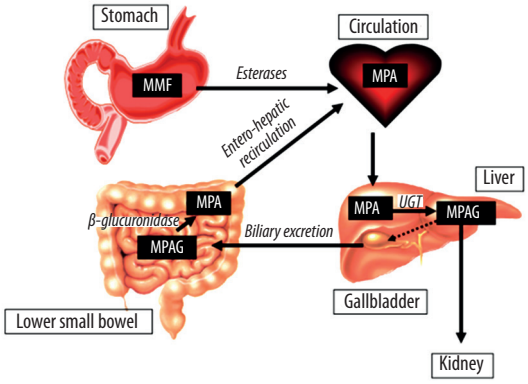

Figure 1. Summary of mycophenolate mofetil and mycophenolic acid metabolism [21,26]. MMF – mycophenolate mofetil; MPA – mycophenolic acid; MPAG – mycophenolic acid glucuronide; UGT – uridine diphosphate-glucuronosyltransferases.

Mycophenolate mofetil is a 2-morpholinoethyl ester prodrug, with a complex metabolism pathway (Figure 1). After absorption from the stomach, MMF is rapidly hydrolyzed by esterases to its active metabolite MPA. This represents the first MPA peak plasma concentration. Once in the liver, MPA is metabolized primarily by uridine diphosphate-glucuronosyltransferases (UGTs), specifically UGT1A9, to form MPA's phenolic glucuronide metabolite, MPAG, which is devoid of pharmacologic activity. MPAG is excreted via renal mechanisms as well as into the bile and ultimately into the distal small bowel and colon [14]. Colonic and intestinal gram-negative aerobic and anaerobic flora produce β-glucuronidase, which cleaves MPAG's glucuronide conjugate converting it back to MPA. Once de-conjugated, MPA may be reabsorbed back into the circulation [15]. The biliary excretion of MPAG and the subsequent MPA enterohepatic recirculation involve several transport mechanisms including

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P-glycoprotein (P-gp), organic anion-transporting polypeptide (OATP), and multi-drug resistant protein 2 (MRP2) [16]. This recirculation results in MPA's second peak plasma concentration and may account for as much as 40% of the MPA exposure measured by the area under the curve (AUC) [14].

While a limited number of pharmacokinetic drug–drug interactions have been reported with MMF, potential mechanisms involve alterations in absorption or enterohepatic recycling, competition of renal tubular excretion of MPAG, and changes in UGT activity [17]. Although antiretroviral and HCV therapies can influence these pathways, no pharmacokinetic drug interactions have been reported to date. A pharmacokinetic analysis of MMF before, during, and after treatment with ombitasvir, paritaprevir/ritonavir and dasabuvir found no significant changes in MPA concentrations [18]. Regardless, caution and clinical monitoring is prudent when co-administering MMF with antivirals that may influence MPA elimination pathway.

Antibiotics and Alteration of Intestinal Flora

Oral antibiotics, including fluoroquinolones, metronidazole, and amoxicillin-clavulanate, can inhibit or eliminate normal intestinal bacterial flora, which express enzymes responsible for MPAG de-glucuronidation, leading to alterations in MPA levels (Table 1). Two case reports showed a 39% and 63% drop in MPA AUC with amoxicillin-clavulanate and a doubling of the MPA exposure five days following the discontinuation of amoxicillin-clavulanate [19]. While use of oral fluoroquinolones have resulted in decreased MPA levels secondary to destruction of normal intestinal flora, further interruption of the pathway converting MPAG to MPA has been shown, *in vitro*, to be more pronounced with ciprofloxacin compared to levofloxacin [20]. Further studies have evaluated the effects of norfloxacin (NOR), metronidazole (MET), or the combination of both antibiotics (NOR+MET) on MPA exposure [21]. The 48-hour MPA AUC was reduced on average by 10%, 19%, and 33% (p=0.01)

Table 1. Documented pharmacokinetic drug interactions between anti-infective agents and both mycophenolic acid and corticosteroids.

Drug	Interaction drug (specific medication studied)	Effect	Magnitude [68]	Level of evidence	Recommendations
AZA	Ribavirin	Increased AZA metabolite exposure	Major	Established	Avoid concomitant use. Monitor for myelotoxicity (e.g., anemia, thrombocytopenia)
MMF	**Anti-anaerobic/anti-parasitic agents** [19–22,69]				
	Metronidazole	Decreased MPA exposure	Minor	Possible	Increase MMF dose by 25%. Monitor MPA levels (controversial)*
	Amoxicillin/ clavulanate	Decreased MPA exposure	Moderate	Probable	Increase MMF dose by 25%. Monitor MPA levels (controversial)*
	Norfloxacin	Decreased MPA exposure	Minor	Possible	Monitor for signs and symptoms of clinical immunosuppression failure. Monitor MPA levels (controversial)*
	Ciprofloxacin	Decreased MPA exposure	Moderate	Possible	Monitor for signs and symptoms of clinical immunosuppression failure. Monitor MPA levels (controversial)*
	Levofloxacin	Decreased MPA exposure	Minor	Possible	Monitor for signs and symptoms of clinical immunosuppression failure. Monitor MPA levels (controversial)*
	Anti-tubercular agents [23–27]				
	Rifampin	Decreased MPA exposure	Minor	Possible	Avoid concomitant use; if possible use rifabutin. Monitor MPA levels (controversial)*
	Antifungal agents [28]				
	Isavuconazole	Increased exposure of MPA and decreased MPAG exposure	Moderate	Established	Reduce MMF dose by 25% and/or monitor for signs and symptoms of MMF toxicity

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Table 1 continued. Documented pharmacokinetic drug interactions between anti-infective agents and both mycophenolic acid and corticosteroids.

Drug	Interaction drug (specific medication studied)	Effect	Magnitude [68]	Level of evidence	Recommendations
Corticosteroids	**Antifungal agents** [28,33–43]				
	Azole antifungals				
	Ketoconazole (methylprednisolone)	Increased Dexamethasone, methylprednisolone, prednisone, prednisolone exposure	Moderate	Established	Consider decreasing methylprednisolone dose by 50% or switching to prednisone or prednisolone. Avoid dexamethasone if possible. Monitor for steroid related adverse effects (e.g., hyperglycemia, mental status changes, WBC)
	Itraconazole (methylprednisolone, dexamethasone)				
	Isavuconazole (prednisone)	Minimal increased prednisone exposure	Minor	Established	No change to prednisone regimen. Monitor for steroid related adverse effects
	Anti-tubercular agents [44–46,48,51,52]				
	Rifampin (methylprednisolone, prednisone, prednisolone)	Decreased methylprednisolone, prednisone, prednisolone exposure	Moderate	Probable	Avoid concomitant use; if possible use rifabutin, may require doubling prednisone or prednisolone dose
	Isoniazid (prednisolone)	Decreased INH exposure	Moderate	Probable	Consider INH monitoring when using prednisolone in combination with INH
	Macrolides [53–55]				
	Erythromycin (methylprednisolone)	Increased methylprednisolone exposure	Moderate	Probable	Consider using prednisone when prolonged courses of macrolides are warranted; consider azithromycin
	Clarithromycin (methylprednisolone)				
	Antiviral agents [56–66]				
	Ritonavir (fluticasone, triamcinolone, beclomethasone, prednisone)	Increased fluticasone, triamcinolone, beclomethasone, prednisone exposure	Moderate	Probable	Avoid use of corticosteroids with significant CYP3A4 metabolism such as fluticasone and triamcinolone. Utilize beclomethasone or prednisone and consider 25% dose reduction. Monitor for signs and symptoms of Cushing's syndrome and adrenal suppression
	Cobicistat (fluticasone)	Increased fluticasone exposure	Moderate	Possible	Avoid use of corticosteroids with significant CYP3A4 metabolism such as fluticasone and triamcinolone. Utilize beclomethasone or prednisone and consider 25% dose reduction. Monitor for signs and symptoms of Cushing's syndrome and adrenal suppression

* Correlation of MPA concentrations and AUC to clinical outcomes is not well established, therefore dose adjustment and therapeutic drug monitoring controversial.

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in patients who received NOR, MET, and NOR+MET, respectively. Similarly, the 48-hour MPAG AUC was also reduced on average by 10%, 27% (p=0.03), and 41% (p=0.01) for the same respective treatments [19–22]. These data suggest a positive correlation between antibacterial spectrum of activity and reduction of enterohepatic recirculation of MPA. Although uncommonly performed and resource intensive, monitoring of MPA concentrations could be considered in special cases when broad spectrum antibiotic therapy is utilized.

Anti-Tubercular Agents

Rifampin is a potent inducer of cytochrome P450 (CYP) 3A4, P-gp, monoamine oxidase B, and glutathione S-transfereases. Rifampin increases UGT expression, particularly intestinal UGT1A7 and UGT1A8, as well as hepatic and intestinal UGT1A9, which accounts for 55% of MPAG production [23–25]. Rifampin induces MRP2 and P-gp, which are responsible for MPAG's biliary and renal excretion, as well as MPA's enterohepatic recirculation [24,25].

One case report showed a three-fold increase in MMF dosing was needed to maintain a MPA concentration of 2.5 mcg/mL following rifampin administration [26]. The corresponding dose-corrected 12 hour MPA AUC increased 221% while MPA total body clearance decreased by 68.9% after rifampin discontinuation [26]. These findings may have been due to intestinal, hepatic, and renal UGT1A9 augmentation, increased renal MRP2, and possible interruption of intestinal flora. Rifampin may increase MPAG levels in the circulation and gut lumen, subsequently increasing renal elimination, and ultimately reducing MPA reabsorption from the distal gut [26,27].

Antifungals

Isavuconazole

Isavuconazole is second-generation triazole indicated for the treatment of invasive aspergillosis and mucormycosis infections. A prospective pharmacokinetic interaction study of 22 patients evaluated interactions between isavuconazole and MMF [28]. Isavuconazole increased MPA mean $AUC_{0-\infty}$ by 35% and decreased C_{max} by 11%. Conversely, MPAG mean $AUC_{0-\infty}$ decreased by 24% and C_{max} decreased by 32%. Isavuconazole pharmacokinetics were largely unchanged with the addition of MMF.

Isavuconazole's secondary metabolism is mediated in part by the UGT pathway and is also a mild inhibitor of this pathway. The increased MMF exposure in conjunction with isavuconazole administration is likely the result of the inhibition of the UGT pathway. Effects of other antifungal agents on MMF concentrations are not reported but are unlikely due to the lack of interaction with the UGT pathway [29]. A dose reduction of MMF by 25% and/or close monitoring for signs and symptoms of toxicity are reasonable approaches when administering isavuconazole.

Corticosteroids

Corticosteroids may undergo 6β-hydroxylation via the CYP3A4 metabolic pathway, and are inducers of MRP2, as well as substrates, inhibitors, and inducers of OATP and P-gp [16]. Detection of pharmacokinetic interactions with corticosteroids is difficult as serum concentrations are not routinely measured and patients are often receiving concomitant inhibitors and/or inducers of drug transporters and CYP enzymes. Therefore, potential interactions are derived from pharmacokinetic studies conducted in non-SOT patients or healthy volunteers.

Prednisone and methylprednisolone are the two most commonly used synthetic corticosteroids in SOT recipients [2]. While structurally similar, differences exist. Prednisone is an inactive prodrug, converted through first pass metabolism to the active drug, prednisolone. While methylprednisolone is active, it differs from prednisolone by the presence of a methyl group at the 6α position and a hydrogen-bond donor at position C-11. These minor structural modifications enhances its P-gp affinity and cellular efflux, increasing its susceptibility to pharmacokinetic drug–drug interactions [23,30].

Anti-Fungal Agents

Most pharmacokinetic interactions with steroids have been reported with the use of azole antifungals, which can effect endogenous cortisol production.

Fluconazole

Although pharmacokinetic confirmation is lacking, an Addisonian crisis has been reported after discontinuation of prophylactic fluconazole in a liver transplant patient taking prednisone [31]. One large tertiary care hospital investigated the clinical impact of combination of fluconazole with prednisone. The study found 70.3% (n=2,941) of patients prescribed an azole experienced a potential drug interaction. The most common potential interaction was of fluconazole with prednisone (n=745) [32]. No steroid related adverse events were noted by chart review, with 47 patients administered fluconazole with prednisone, suggesting little clinical significance of this interaction at commonly prescribed doses; however, monitoring for signs and symptoms of an interaction when initiating or discontinuing fluconazole in the setting of a steroid is warranted.

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Ketoconazole

One study reported that six healthy participants who were given ketoconazole 200 mg/day for six days had decreased intravenous (IV) methylprednisolone clearance by 60% and increased the AUC by 135%, leading to a reduced 24-hour cortisol AUC [33]. In a follow-up study, eight healthy participants were given IV methylprednisolone (15 or 30 mg) alone, then they were given ketoconazole 200 mg daily for seven days, and showed oral methylprednisolone clearance decreased by 46% with the administration of ketoconazole, leading to recommendations for a 50% reduction in methylprednisolone dose when used in conjunction with ketoconazole [34].

In a similar study involving four healthy participants, ketoconazole 200 mg/day for six days did not significantly alter prednisolone pharmacokinetics after administration of oral prednisone at 20 mg. No significant changes were noted in renal excretion of prednisone or prednisolone. In addition, 24 hour cortisol AUC ratios (with prednisone: baseline) were not significantly altered with ketoconazole administration [35]. This was confirmed in a subsequent study evaluating six healthy volunteers receiving IV prednisolone (14.8 mg) after six days of ketoconazole 200 mg daily [36].

In contrast, Zurcher et al. evaluated 10 healthy participants receiving ketoconazole at 200 mg/day for seven days with oral prednisone (0.8 mg/kg) and IV prednisolone (0.8 mg/kg) on separate occasions, and showed a two-fold decrease in urinary excretion of 6-beta-OH-prednisolone in all participants suggesting ketoconazole inhibits 6-beta-hydroxylase, a major metabolism pathway of prednisolone. In addition, the ratio of 6-beta-OH-cortisol/17-OH-corticosteroids declined by more than 50%. However, AUC ratios of prednisolone/prednisone after oral prednisone and IV prednisolone were found to be independent of ketoconazole suggesting the conversion of prednisone to prednisolone is not affected by ketoconazole. Therefore, it was concluded that ketoconazole increases exposure to prednisolone [37]. There is insufficient evidence for empiric dose reduction with concomitant use of ketoconazole and prednisone or prednisolone. Clinicians should monitor for steroid-related adverse effects.

Itraconazole

Being a potent CYP3A4 inhibitor, itraconazole has been shown to inhibit metabolism of both oral and IV methylprednisolone. In a double-blind, placebo-controlled crossover study, 10 healthy individuals received itraconazole at 200 mg (or placebo) orally for four days, then 16 mg of oral methylprednisolone. Oral methylprednisolone AUC increased 3.9-fold, Cmax 1.9-fold, and half-life 2.4-fold following itraconazole when compared to placebo. This led to mean cortisol plasma levels of only 13% when compared to methylprednisolone alone [38]. In a similar study design, itraconazole increased IV methylprednisolone total AUC 2.6-fold, 12–24 hour AUC 12.2-fold, half-life from 2.1 to 4.8 hours and decreased clearance by 60%. This led to morning cortisol level reduction by 91% when compared to methylprednisolone alone [39]. This interaction was again confirmed in a study of 14 healthy males receiving oral methylprednisolone at 48 mg, then prednisone at 60 mg after a washout period with and without four days of itraconazole (400 mg on day one, then 200 mg daily for three days). The study showed itraconazole increased methylprednisolone 24 hour AUC, Cmax, and half-life by 2.5, 1.6, and 1.7-fold, respectively [40]. Furthering this point, the effect of itraconazole at 200 mg twice daily on methylprednisolone (12 mg orally) pharmacokinetics resulted in case reports of patient harm [41]. A dose reduction of 50% in methylprednisolone should be considered when starting itraconazole.

In a similar study design, only small changes in measured prednisolone AUC, Cmax, or half-life were observed following prednisone administration with or without itraconazole [40]. Contradictory to these findings, Varis et al. evaluated itraconazole at 200 mg daily for four days on 20 mg of oral prednisolone pharmacokinetics in 10 healthy participants in a double-blind placebo-controlled crossover study. Itraconazole statistically significantly increased prednisolone total AUC by 24% and half-life by 29% compared to placebo. This related to a statistically significant decrease in mean morning cortisol concentrations by 27% compared to placebo. The study authors concluded that though statistically different, these relatively small changes in prednisolone pharmacokinetics may not be clinically relevant [42]. Taken together, the effect of itraconazole on prednisolone pharmacokinetics may be less pronounced than the effect of methylprednisolone.

In a double-blind crossover study of eight health patients, itraconazole 200 mg daily for four days increased oral dexamethasone AUC, Cmax, and half-life by 3.7 fold, 1.7 fold, and 2.8 fold, respectively. Intravenous dexamethasone AUC and half-life increased by 3.3 fold and 3.2 fold, respectively; whereas, systemic clearance decreased by 68% when given with itraconazole. Morning cortisol concentrations where significantly lower at 47 hours and 71 hours after both oral and IV dexamethasone administration with itraconazole compared to the same dose of dexamethasone and four days of placebo [43]. The combination of dexamethasone and itraconazole may result in prolonged steroid-related adrenal suppression.

Administration of voriconazole and posaconazole may result in similar drug interactions since inhibition of similar CYP enzymes are expected. Monitoring for steroid related side-effects is warranted when using these combinations.

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Isavuconazole

A prospective pharmacokinetic interaction study of 20 patients evaluated interactions between isavuconazole at 200 mg three times daily for two days followed by 200 mg daily, and prednisone at 20 mg once on day 9, found no clinically significant changes in prednisolone mean $AUC_{0-\infty}$ or C_{max} [28]. The C_{max} of isavuconazole was increased by approximately 26% and the AUC_{τ} was unchanged. No dose adjustments for prednisone or isavuconazole are anticipated with concomitant use based on this study.

Anti-Tubercular Agents

Rifampin increases the metabolism of cortisol, thereby [44] lowering prednisolone AUC by 66% and increasing clearance by 45% [45]. In another study, rifampin significantly decreased the plasma half-life and bioavailability of prednisolone in patients with asthma. Even with dose increases of 93% of prednisolone, asthma control remained inferior. One patient was withdrawn from the study due to poor asthma control after a five-fold increase in prednisolone dose [46].

Other case reports of harm occurring due to loss of steroid efficacy with rifampin range in diseases such as nephrotic syndrome, giant cell arteritis, immunosuppression for renal transplant, and asthma [47–50]. A pharmacokinetic study of two patients with giant cell arteritis treated with prednisone and rifampin found that prednisolone clearance increased by greater than 200% and half-life decreased by 40% to 60% compared to prednisolone administration without rifampin. Authors suggest a doubling of prednisone dose when used with rifampin [48]. Though not as well characterized, a similar interaction between rifampin and methylprednisolone would be expected. In a case of a methylprednisolone dependent asthmatic patient, asthma control was lost after rifampin was added, leading to an ineffective switch to prednisone. Only discontinuation of rifampin restored good asthma control [51]. Monitoring for signs of steroid failure when rifampin is added to medication regimens of patients with steroid dependent conditions is necessary, with the potential for development of rejection and graft failure if immunosuppressive doses are not adequately adjusted. Though an alternative agent such as rifabutin may also interact with steroids, reports of specific drug–drug interactions are lacking.

In one study of single dose prednisolone and weekly dose isoniazid, prednisolone was shown to significantly decrease isoniazid plasma concentrations in slow and rapid acetylators by 25% and 40%, respectively, as increased renal clearance of isoniazid after prednisolone administration was observed in both groups [52].

Macrolides

Given the frequent combination of macrolide and steroid use in asthma, much of the data regarding macrolide interaction with steroids comes from the asthma literature. Macrolides are considered to be “steroid-sparing” agents in patients with asthma due, in part, to their inhibition of P-gp and CYP3A4 [53]. In six patients with asthma, oral erythromycin significantly decreased mean IV methylprednisolone clearance by 46% ($p<0.01$) and increased half-life by 51% ($p<0.01$) [54]. Similarly, clarithromycin decreased mean oral methylprednisolone clearance by 65% ($p=0.004$) and significantly increased methylprednisolone plasma concentrations and half-life by more than two-fold [55]. In patients receiving prednisone, clarithromycin had no effect on measured prednisolone pharmacokinetics. Thus, in cases where prolonged macrolide therapy is warranted, prednisone may be considered over methylprednisolone [53–55]. The azalide, azithromycin, is less likely to interact with methylprednisolone and prednisone, and is often a suitable alternative to a macrolide.

Antivirals

Ritonavir

Ritonavir is commonly utilized in combination for the treatment of HCV and human immunodeficiency virus (HIV). Although ritonavir has antiviral activity, it is often utilized as a “booster” for other medications contained within the treatment regimen [9,56]. Ritonavir exhibits this effect through inhibition of CYP enzymes increasing the area under the cure for the active antiviral agents. There have been greater than 30 cases of Cushing’s syndrome and/or secondary adrenal insufficiency secondary to administration of orally or nasally inhaled fluticasone in combination with ritonavir utilized for HIV or HCV treatment [57–59]. In a study of 18 healthy individuals who received fluticasone propionate nasal spray (200 mcg daily) and ritonavir (100 mg twice daily) for seven day increased the fluticasone AUC by 350-fold and increased the C_{max} by 25-fold compared to baseline. These pharmacokinetic effects resulted in an 86% reduction in plasma cortisol AUC levels [56]. Cushing’s syndrome and/or secondary adrenal insufficiency has also been observed in patients who have received intra-articular, intramuscular, and epidural triamcinolone injections [60–64].

The pharmacokinetic effects of ritonavir (200 mg twice daily) on prednisone (20 mg once) were evaluated in 10 healthy individuals at day 4 and day 14. The AUC for the active metabolite prednisolone increased from baseline by 37% on day 4 and 28% on day 14. The half-life was increased by approximately one hour and there were no differences between C_{max} and T_{max} observed [65]. A pharmacokinetic evaluation of inhaled beclomethasone (160 mcg twice daily) and ritonavir (100 mg twice

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daily) in 20 healthy individuals demonstrated a statically significant increase of 223% in the AUC of 17-monopropionate, beclomethasone's active metabolite. Despite this significant increase, there was not a significant reduction in serum cortisol levels seen [66]. There is sufficient evidence to recommend the avoidance of use of corticosteroids with significant CYP3A4 metabolism, such as fluticasone and triamcinolone, in combination with ritonavir due to the risk of Cushing's syndrome and adrenal suppression. Alternative steroids, such as beclomethasone and prednisone, should be utilized and a reduction of 25% should be considered for long-term therapy. While other protease inhibitors (e.g., boceprevir, simeprevir, and telaprevir) pharmacokinetic and dynamic effects on corticosteroids have not specifically been evaluated, many possess CYP3A4 inhibitory properties and signs and symptoms of Cushing's syndrome and adrenal suppression should be evaluated in these patients.

Cobicistat

Cobicistat is a potent CYP3A4 inhibitor utilized as a "booster" in the management of HIV. A case report of a 39-year-old man utilizing fluticasone nasal drops (800 mcg twice daily) initiated on HIV therapy containing cobicistat, demonstrated adrenal suppression and morning cortisol < 50 nmol/L. The nasal drops were transitioned to beclomethasone nasal spray and the man's morning cortisol levels rebounded to 149 nmol/L six weeks later [67]. This is currently the only case report of adrenal suppression with cobicistat. Due to cobicistat's pharmacologic properties intended to create advantageous pharmacokinetic interactions, similar recommendations to avoid corticosteroids metabolized by CYP3A4 and dose reduce or monitor for side effects, similar to ritonavir, should be followed when using corticosteroids.

Conclusions

Interactions of immunosuppressants with specific antimicrobials agents may result in high levels of immunosuppressants leading to toxicity, or sub-therapeutic levels leading to graft rejection. Many untoward interactions can be prevented by substitution of alternative anti-infective agents or by judicious adjustments in immunosuppressant dosing after considering known effects of anti-infective agents. There are two keys to success in this approach: cognizance by all clinicians caring for the SOT recipient and continued education of the patient regarding the potential for drug interactions that may affect their overall immunosuppression.

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