Common Adverse Drug-Drug Interactions in Dermatology: Oral Therapies

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ABSTRACT

Drug-drug interactions between systemic oral therapies in dermatology can result in preventable iatrogenic causes of patient morbidity and mortality. Most of these interactions are due to cytochrome P450 or renal excretion interactions. We review here a number of drugs and drug-drug interactions seen in general dermatology, including methotrexate, bexarotene, macrolides, cyclosporine, epinephrine, isotretinoin, spirinolactone, allopurinol, and oral contraceptives.

INTRODUCTION

Pharmacotherapy in dermatology can be especially complex and challenging: the wide array of comorbidities that patients present to care with and the spectrum of systemic oral therapies that are commonly prescribed in a standard dermatology practice increase the likelihood of adverse drug-drug interactions. Such interactions can range from neutralized drug efficacy to fatal adverse effects and are most commonly due to the potentiation or antagonism of cytochrome P450 metabolism or competitive renal excretion by an offending drug to affect the pharmacokinetics of concurrently dosed drugs. Drug-drug interactions can contribute to up to 60% of adverse drug reactions seen in the inpatient or immediate discharge setting, representing a potentially significant iatrogenic source of preventable healthcare costs, morbidity, and mortality in patient care.[1,2] We review here the most common systemic treatments causing drug-drug interactions in standard dermatology practice.

METHOTREXATE

Methotrexate (MTX) acts through inhibition of dihydrofolate reductase and thymidylate synthetase, reducing folate formation and impairing DNA synthesis/repair, respectively. It is used at high doses in standard chemotherapy regimens and at low doses in psoriasis, Crohn disease, rheumatoid arthritis, and other autoimmune conditions. Toxicities, which can occur at all doses, include myelosuppression, hepatotoxicity, renal impairment, and pneumonitis. A near total reliance on renal excretion without production of inactive metabolites makes MTX vulnerable to drug-drug interactions when kidney function is affected.[3] In fact, MTX represents the highest severity of drug-drug interactions of all medications prescribed in the outpatient setting.[4]

Trimethoprim-sulfamethoxazole (TMP-SMX), which also inhibits folate synthesis, can interact with MTX to severe systemic adverse events through multi-fold proposed mechanisms: 1) potentiated inhibition of dihydrofolate reductase impairs folate production and causes myelosuppression 2) sulfamethoxazole and MTX are both nephrotoxic and can cause a positive feedback loop of impaired kidney excretion, leading to further elevated levels of both drugs. In a systemic analysis of 1 case-control study and 17 case reports, concurrent MTX and TMP-SMX was a risk factor for pancytopenia, occurring notably at low doses (5 to 15 mg per week) of MTX.[5] There were no consistent hepatic, renal, or pulmonary findings across the literature but the authors advised caution in patients with preexisting kidney conditions. The link between increased nephrotoxicity and concurrent MTX and TMP-SMX use still remains to be definitively investigated, even at high dose MTX.[6]

The interaction between NSAIDs and MTX has long been investigated, with at least 30 cases and studies in the literature.[5] The proposed mechanism is competitive renal tubular excretion, thereby increasing serum MTX levels. High-dose MTX has well-documented interaction with NSAIDs, causing myelosuppression, transaminitis, and acute kidney injury. Overall, indomethacin, diclofenac, ibuprofen, and high-dose aspirin has shown propensity to interact with MTX while incidences involving naproxen, probenecid, flurbiprofen, piroxicam, ketoprofen, metamizole, and low-dose aspirin were rare.[5] This is in contrast to the interaction between low-dose MTX with NSAIDs, which exhibits pharmacokinetic interaction but with minimal clinical significance.[7] A Cochrane review of inflammatory arthritis patients concluded the relatively safe concurrent use of NSAIDs (including etodolac, celecoxib, and etoricoxib) with MTX in this clinical setting, except for high-dose aspirin, which can precipitate hepatic and renal problems.[8]

ACITRETIN

Acitretin replaced etretinate in the treatment of keratinizing disorders due to high lipophilicity of etretinate and its subsequent presence in adipose tissue after cessation for up to 3 years.[9] With a significantly shorter half-life[10], acitretin is the preferred therapeutic option given the teratogenic potential of both compounds and a shorter recommended contraception period after treatment cessation of acitretin. However, alcohol can cause ethyl esterification of acitetretin to etretinate, likely related to ethanol metabolism to acetyl coenzyme A, an activator of etretinate production from acitretin.[11] In patients with concomitant alcohol use of 150 to 200 g or more during acitretin treatment, etretinate was detectable in a dose-dependent manner with alcohol intake for up to 57 days after acitretin discontinuation, compared to no etretinate found in patients without alcohol consumption.[11,12] As a result of this interaction and the widespread use and presence of alcohol in consumer products, the recommended contraceptive and pregnancy avoidance period after acitretin treatment is now extended to 3 years in the US. Patients should further be cautioned to maintain alcohol abstinence during therapy and for at least 2 months after stopping acitretin.

BEXAROTENE

Bexarotene, a selective retinoid X receptor agonist used in cutaneous T cell lymphoma,

is metabolized by cytochrome P450 3A4 (CYP3A4) and is, thus, susceptible to interactions with drugs that induce or inhibit CYP3A4. Because of the high incidence of hypertriglyceridemia and risk of pancreatitis, patients on bexarotene are typically started on lipid-lowering agents. Fibrates are first-line therapy in this context to specifically target triglyceride levels. Gemfibrozil is the only fibrate contraindicated with concurrent bexarotene use due its potent inhibition of CYP3A4, increasing serum levels of bexarotene and causing extreme hypertriglyceridemia. In a study of 54 patients receiving bexarotene, 2 of 3 patients taking concurrent gemfibrozil had incidences of hypertriglyceridemia-related pancreatitis while patients taking other lipid-lowering agents had no incidences of pancreatitis.[13]

MACROLIDES

Macrolide antibiotics can interact, to varying degrees, with numerous common drugs due to its inhibition of the CYP3A4 metabolic pathway and a pro-motile effect that may enhance the enteric absorption of drugs.[14] The three most commonly prescribed macrolides exhibit varying propensities to inhibit CYP3A4 and cause drug interactions: erythromycin most strongly, clarithromycin less so, and azithromycin has no effect on CYP3A4.[14] For example, erythromycin and clarithromycin, but not azithromycin, interact with statins to increase the relative risk of rhabdomyolysis and acute kidney injury by two-fold.[15] Other medications that can interact with macrolides, particularly erythromycin, include triazolam, pimozide, cisapride, quinidine, warfarin, cyclosporine, theophylline, carbamazepine, and antihistamines.[16] Interactions involving erythromycin should be avoided due to risk of precipitation of QT prolongation, torsades de pointes, and other fatal arrhythmias. Patients using erythromycin and concurrent CYP3A4 inhibitors had 5 times the rate of sudden deaths from cardiac causes compared to patients taking erythromycin without concurrent CYP3A4 inhibitors.[17] The association between azithromycin and cardiovascular death remains controversial and further studies, particularly in the context of specific drug interactions, are necessary before any conclusions can be made.[18.19]

CYCLOSPORINE

Cyclosporine has as extensive a list of side effects, which include nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, hyperlipidemia, hypertrichosis, and lymphoproliferative disease, as interacting drugs, owing to its inhibition of multiple metabolic players, including CYP3A4, organic anion transporting polypeptides (OATP), multidrug resistance-associated protein 2 (MRP2), and multidrug resistance protein 1 (MDR1).[20.21] Aminoglycosides, erythromycin, TMP-SMX, calcium channel blockers, antifungals, cimetidine, ranitidine, carbamazepine, phenytoin, rifampin, and phenobarbital, all CYP3A4-metabolized, should be used concurrently with caution.

Statins are frequently used for cyclosporine-induced hyperlipidemia. Statins undergo discrete metabolic pathways: lovastatin, simvastatin, and atorvastatin are primarily oxidized by CYP3A4, while pravastatin, fluvastatin, rosuvastatin, and pitavastatin are affected by perturbation of OATP and other transporters.[22-24] Due to the widespread effects of cyclosporine on multiple metabolizing proteins, it has a uniquely observed pharmacokinetic impact on all statins, increasing area

under concentration-time curve (AUC) by 2 to 20-fold, though the clinical significance is not to be overstated.[24] While the concurrent use of cyclosporine and statins can lead to myopathy and rhabdomyolysis, statins at low doses may be safely used with cyclosporine.[24] Further, statins do not appear to pharmacokinetically perturb plasma concentrations of cyclosporine.[25]

EPINEPHRINE

The potentially fatal interaction between epinephrine-based local anesthetic and beta-blockers was described in a case series of 6 patients on daily propranolol who exhibited hypertensive crises and subsequent bradycardia after in-office administration of 1:100,000 or 1:200,000 of epinephrine.[26] The mechanism underlying this interaction rests on epinephrine's effect as both a vasoconstrictor and vasodilator due to its agonism of α_1 (vasoconstriction of skin and mucous blood vessels), β_1 (increases heart rate and contractility), and β_2 receptors (vasodilation of skeletal muscle blood vessels). Concurrent epinephrine and beta-blockers, particularly non-selective beta-blockers, can precipitate potent alpha-receptor effects, leading to hypertension and reflex bradycardia. Levonordefrin and norepinephrine have significantly decreased or no β_2 receptor activity, and thus have higher risk of this interaction, as evidenced in the literature.[27,28]

The non-selective blockers propranolol and pindolol have demonstrated propensity to interact with epinephrine, while cardio-selective blockers (β_1 only) do not induce hypertension with concomitant epinephrine.[28-30] This interaction appears to occur in a dose-dependent manner with epinephrine levels.[30] Many of these aforementioned cases and studies took place in the plastic or dental surgery context, which require large amounts of epinephrine compared to dermatologic procedures. It is likely that the doses of epinephrine used in the dermatologic and Mohs setting is insufficient to induce hypertensive episodes, though use should be optimally minimized in patients on daily non-selective beta-blockers.[31]

ISOTRETINOIN

Oral isotretinoin is a vitamin A analogue primarily used in the treatment of severe acne vulgaris. Common side effects include cheilitis, xerosis, and increased photosensitivity while rare and serious side effects include myalgia, depression, and pseudotumor cerebri.[32] Due to well-known teratogenic properties, isotretinoin must be accompanied by effective contraception when used in females of reproductive age.

Because tetracycline antibiotics, particularly doxycycline and minocycline, are also used to treat acne vulgaris, their interaction with isotretinoin is of vital importance in dermatologic practice. Pseudotumor cerebri, a condition in which intracranial hypertension may mimic signs and symptoms of a brain mass such as papilledema, visual disturbances, nausea, vomiting, headaches, and tinnitus, can be caused by concurrent tetracycline and isotretinoin use.[33] If left unrecognized and untreated, this can lead to permanent vision loss. It is thought that this occurs due to effects on cyclic adenosine monophosphate, causing decreased cerebrospinal fluid outflow at the arachnoid villi level.[34]

This interaction can induce pseudotumor cerebri in as few as 3 weeks.[35] Therefore, combination therapy with these agents is not recommended. Fortunately, a history of prior use of oral tetracyclines in the majority of patients who begin oral isotretinoin do not appear at risk of

developing intracranial hypertension.[36] In fact, there is evidence that oral isotretinoin can safely be used in patients who have developed pseudotumor cerebri while on tetracyclines in the past.[37] Nonetheless, it is important to monitor these patients for signs and symptoms of increased intracranial pressure, as early intervention greatly improves the prognosis of this condition.

SPIRONOLACTONE

Spironolactone is a potassium-sparing diuretic used in dermatology for the treatment of hormonal acne.[38] It achieves its diuretic and hormonal effects through androgen and mineralocorticoid receptor antagonism, the latter of which inhibits aldosterone and decreases potassium excretion in the cortical collecting duct of the nephron. While its "potassium-sparing" effect is sometimes desired, it also increases the risk of hyperkalemia, which can be precipitated or exacerbated by the addition of other medications, particularly TMX-SMP and renin-angiotensin inhibitors.

TMX-SMP is known to increase the risk of hyperkalemia in patients taking spironolactone, resulting in up to a 12-fold increased risk of hospital admission for patients on this combination.[39] The mechanism by which this occurs is impaired potassium secretion due to an amiloride-like inhibition of sodium channels in the luminal membrane of the distal tubule. A population-based, nested case-control study of 328 Canadian patients on spironolactone found an increased risk of sudden death among those who received trimethoprim-sulfamethoxazole versus ampicillin.[40] A similar pattern of hyperkalemia has been observed in older adults on a combination of spironolactone and a renin-angiotensin axis inhibitor (ACE inhibitors or angiotensin receptor blockers). This is likely has the same mechanism and is more commonly seen in real-life practice than in clinical trials.[41]

It is crucial to note that all of these studies focused on older adults. The majority of patients prescribed spironolactone by a dermatologist are otherwise healthy, pre-menopausal women. The necessity of potassium monitoring in this population is questionable, as recent evidence suggests that the rate of hyperkalemia in healthy young women taking spironolactone is equal to the baseline rate of hyperkalemia in this population.[42] Nevertheless, when clinically appropriate, alternative antibiotics and antihypertensive agents should be chosen for these patients.

ALLOPURINOL

Allopurinol, a xanthine oxidase inhibitor used in maintenance of gout, has extensive interactions with other drugs, the most serious of which are with azathioprine and 6-mercaptopurine. These two medications are metabolized by xanthine oxidase, and co-administration with allopurinol without dose adjustment can cause potentially fatal pancytopenia.[43] However, azathioprine and allopurinol combination therapy at reduced doses has proven to be a safe and effective treatment option for patients with inflammatory bowel disease.[44]

Allopurinol has other important interactions, including several with dermatologic manifestations. Ampicillin is thought to cause more frequent drug rashes when taken alongside allopurinol, evidenced from the Boston Collaborative Drug Surveillance Program, established in 1966.[45,46] Since then, no large-scale confirmatory studies have been performed. However, a recent report showed hypersensitivity symptoms, including an extensive, erythematous, papular eruption, with amoxicillin, a related penicillin-derivative,

in a patient with previous adverse reaction to allopurinol.[47] The authors attribute this to a possible co-sensitization. It is therefore best to avoid these two antibiotics whenever possible in patients taking allopurinol, particularly in patients with a history of adverse dermatologic reaction to allopurinol.

ORAL CONTRACEPTIVES

The concurrent use of oral contraceptives (OCs) and oral antibiotics remain in a long-standing debate over the extent of clinically significant interaction. It is known that rifampin increases the metabolism of OCs, leading to sub-contraceptive concentrations of OC steroids.[49] Anecdotal reports of pregnancy occurring on antibiotics used in dermatologic practice suggested that low-dose tetracyclines may have a similar effect.[50] However, no pharmacokinetic studies have detected a change in plasma levels of OCs with tetracycline antibiotics.[51] Additionally, a large case-crossover study demonstrated that antibiotic use in dermatologic practice does not increase the risk of accidental pregnancy on OCs.[52] The authors did find that a few individual patients showed significant decreases in OC concentration while taking tetracyclines. Because there is currently no way to predict which individuals will exhibit this effect, it is still appropriate to use caution when prescribing OCs and oral antibiotics simultaneously and recommend a second or alternate form of birth control, such as condoms or intra-uterine devices, in patients who do not desire pregnancy.

CONCLUSION

Interactions involving MTX, acitretin, bexarotene, macrolides, cyclosporine, epinephrine, isotretinoin, spirinolactone, allopurinol, and OCs may be commonly seen in dermatology practice and can lead to severe systemic effects. Thorough medication reconciliation and cautious use of interacting drugs are important to avoid these preventable drug-drug interactions.

Conflict of Interest Disclosures: none.

Funding: none.

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