Dermatotoxicology

Eighth Edition

Edited by
Klaus-Peter Wilhelm
Hongbo Zhai
Howard I Maibach

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Published by Informa Healthcare, 119 Farringdon Road, London EC1R 3DA, UK.

Simultaneously published in the USA by Informa Healthcare, 52 Vanderbilt Avenue, 7th Floor, New York, NY 10017, USA.
Informa Healthcare is a trading division of Informa UK Ltd, Registered Office: Informa House, 30–32 Mortimer Street, London W1W 7RE, UK. Registered in England and Wales number 1072954.

A CIP record for this book is available from the British Library
Library of Congress Cataloging-in-Publication Data available on application

ISBN: 978-1-84184-855-6
eISBN: 978-1-84184-857-0

Orders may be sent to: Informa Healthcare, Sheepen Place, Colchester, Essex CO3 3LP, UK
Telephone: +44 (0)20 7017 6682
Email: Books@Informa.com
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Typeset by Exeter Premedia Services, Chennai, India
Printed and bound in the UK

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1 Pharmacogenetics and dermatology

Tsippora Shainhouse, Ernest Lee, and Howard I. Maibach

INTRODUCTION

Pharmacogenetics, Adverse Drug Reactions, and Personalized Medicine

Pharmacogenetics is the study of the role that inheritance plays in the individual variation in drug response. The response spectrum of a drug may range from life-threatening adverse drug reactions (ADRs) to inadequate therapeutic effects. For the clinician, this concept is relevant when asking why a drug is expectedly efficacious in one segment of the population, ineffective for another, and toxic or even fatal for a third. Identification of genetic variations that result in differences in drug bioavailability, biotransformation and, ultimately, clinical response is the key to the new era of "personalized medicine." Personalized medicine promises to deliver safer, more effective therapies to patients by down-playing the one-drug-fits-all theory, in exchange for recognizing the impact of a person's specific genetic make-up on the pharmacodynamics (PD) and pharmacokinetics (PK) of a specific drug, and integrating this information to develop a personalized therapeutic plan (1).

PK describes what the body does to a drug to make it available for use. A drug's PK properties are determined by genes that direct the disposition [absorption, distribution, metabolism, excretion (ADME)] of a drug in the body (2). Drug-metabolizing enzymes, specifically those of the cytochrome p450 family, and drug transporter proteins, such as P-glycoprotein (P-gp) transporters, play a key role in this process. These particular enzymes are governed by allelic variations within both similar and ethnically diverse populations. The most common functional consequence of these variations is concentration-related toxicity, either due to the accumulation of prodrug (consider an azathioprine patient with nonfunctional ThiopurineS-methyltransferase (TMPT) alleles will have debilitating myelosuppression) or increased, adverse clinical effect in rapid metabolizers (ultra-rapid codeine-converting mothers with a specific CYP2D6*2 $\times$ 2 allele can inadvertently kill their breastfed infants by overdosing them with the morphine endproduct).

PD describes what a drug does to the body, that is, the clinical impact. For example, variation in the intrinsic amount of VKORC1 gene product (vitamin K epoxide reductase) that an individual has will impact the effect that warfarin has on bleeding tendency. Certain alleles/haplotypes are more common in specific ethnic populations. Haplotype-specific guidelines have been published to determine the ideal starting dose to attain and maintain a therapeutic International Normalized Ratio (INR).

In children, we must consider not only differences in genotype, but to some degree, variation in gene expression during growth and development (3). Although TMPT enzyme activity is most likely present at birth, and CYP2D6 and CYP3A4 are acquired in the first few weeks of life, delayed maturation of other drug-metabolizing enzymes can contribute to concentration-dependent toxicities, and altered concentrations of circulating plasma proteins can affect drug distribution (cephalosporins in neonates).

More than 2 million cases of ADRs, including 100,000 deaths, are reported annually in the United States (4,5). They account for 2.4–12% of hospital admissions, 4.6% of deaths in hospitalized patients, and have been reported to be the 4th leading cause of death in hospitalized patients (6). This costs the US over $177 billion annually (7).

In situations in which genetic risk factors can accurately predict risks for serious ADRs, either idiosyncratic or dose-related, drug-specific pharmacogenomic biomarkers are invaluable in the prevention of these ADRs and in tailoring clinical treatment decisions.

However, to be successful clinical tools, biomarkers should have high positive and negative predictive values, be simple to perform and interpret, be easy to repeat, sourced from easily accessible body fluids or tissue, and be cost-effective (8).

The US Food and Drug Administration (US FDA) has already approved labels on various drugs to include information associated with human genomic biomarkers. In specific cases, recommendations are made for pharmacogenetic testing before initiating treatment (warfarin, thiopurines, carbamazepine in Asian patients, abacavir), and in others, dose selections are offered (7,9).

ANTIMETABOLITES

Azathioprine and 6-Mercaptopurine

Thiopurine drugs, including 6-mercaptopurine (6-MP) and azathioprine, a prodrug that is converted to 6-MP in vivo, are cytotoxic and immunosuppressant medications used in the management of autoimmune connective tissue disease, immune-bullous skin disease, atopic dermatitis, neutrophilic dermatoses, photodermatoses, and as an antirejection drug in organ transplant patients. These drugs have a narrow therapeutic window with the potential for life-threatening myelosuppression (10).

Once azathioprine is absorbed and converted to 6-MP in the red blood cell (RBC), it can undergo one of three competing processes. Therapeutically, it is intended to be anabolized by the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to its active form, the purine nucleotide analog, 6-thioguanine (6-TGN). 6-TGN can then be incorporated into DNA strands, thus suppressing DNA replication and new cell formation. The other two pathways halt this process and create inactive metabolites by one of two processes: oxidation by xanthine oxidase (which will be discussed further in the following section); or methylation by

TABLE 1.1
Frequency of Thiopurine S-Methyltransferase Alleles by Race (%) (9)

Allele	Caucasian	African American	Asian
TPMT*2	0.2	0.4	0
TPMT*3A	3–5	0.4–0.8	0
TPMT*3C	0.2	2–7	2–5

thiopurine S-methyltransferase (TPMT), a cytosolic drug-metabolizing enzyme. In fact, the level of measured TPMT in RBCs is inversely proportional to the concentration of 6-TGN in RBCs. Genetic polymorphisms of TPMT are associated with TPMT activity. Thus, patients with a genetic predisposition for high enzyme activity may be chronically underdosed, whereas patients with low TPMT activity are prone to developing toxic levels of 6-TGN and are at high risk for severe leukopenia, and even death from standard dosing. An 89% of the population has clinically normal TPMT activity, associated with inheritance of at least one wild-type allele, TPMT*1. An 11% of the population has intermediate levels of TPMT activity, and 1/300 of people inherit low or absent TPMT activity, as an autosomal recessive trait. Among the low-activity population, three alleles account for 95% of these inherited cases: TPMT*3A, the most common variant in Caucasians, TPMT*3C, the most common variant in East Asians and African Americans, and TPMT*2. TPMT*3A and *3C alleles result in virtually no enzyme activity, whereas *3B and *2 yield significantly decreased enzyme activity (Table 1.1) (9,11).

Patients who are homozygous for alleles that result in low or no enzyme activity must be treated with 1/10–1/15 the standard doses of 6-MP and azathioprine, and they must be monitored carefully with serial complete blood counts throughout the treatment (11). TPMT phenotyping is more common than genotyping, and considered to be more reliable in predicting and averting thiopurine toxicity and myelosuppression (12). Six separate economic evaluations of TPMT testing for patients prescribed thiopurine drugs recommended that TPMT is a cost-effective preventative measure (13). As such, TPMT enzyme testing must be determined before initiating treatment, to avoid both underdosing and toxicity.

Allopurinol

Decreased activity of xanthine oxidase is not related to genetic variability but rather to drug interactions. Allopurinol inhibits xanthine oxidase in the 6-MP metabolic process, thus shunting more substrate through the HGPRT pathway, yielding increased, immunosuppressive levels of 6-TGN that can lead to significant myelosuppression. If a patient requires both allopurinol and azathioprine, the azathioprine dose must be reduced by 75% (14).

Interestingly, allopurinol is the most common cause of toxic epidermal necrolysis (TEN) in Europe and Israel (15). Carriers of the HLA-B*5801 allele have an increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, Stevens–Johnson syndrome (SJS) and TEN (16). This is most notable in Han Chinese patients in Taiwan, as well as Japanese and Thai patients (17), and it is suggested that this biomarker be tested before initiating treatment in Asian patients, in particular (18).

Methotrexate

Methotrexate is an anti-inflammatory and immunosuppressive drug that is commonly used in the management of psoriasis, as well as other immunobullous and autoimmune connective tissue dermatoses. It acts as a competitive antagonist of the enzyme dihydrofolate reductase, thus preventing the conversion of dihydrofolate to tetrahydrofolate, a co-factor in the production of purine nucleotides for DNA and RNA synthesis. By inhibiting DNA synthesis in competent lymphocytes, it acts as an immunosuppressive agent.

Allelic variations in the gene for 5,10-methylene-tetrahydrofolate reductase (MTHFR) enzyme, specifically at the 677 codon, can be used to predict lymphocyte sensitivity to methotrexate. Studies have demonstrated that lymphocytes heterozygous for the mutant allele MTHFR 667T are significantly more sensitive to methotrexate than those carrying the homozygous wild-type allele MTHFR 667C, suggesting that this pharmacogenetic biomarker may be considered in the calculation of methotrexate dosing (19). The impact of a second MTHFR polymorphism at codon 1298 (C is more sensitive than A) is not as strong as the 667 locus; however, the combined heterozygous state (677CT/1298AC) in patients who do not receive folate supplementation together with their methotrexate, yields a lower rate of hepatotoxicity (20).

A recent review of eight different polymorphisms in five of the enzymes involved in folate, purine, and pyrimidine metabolism in psoriatic patients being treated with methotrexate revealed some relevant biomarkers, with an even more clinically relevant intervention strategy (20). Patients with the reduce folate carrier (RFC) 80A allele (wild type is G) have no therapeutic response to methotrexate, and have such a high incidence of adverse side effects, and tend to self-select by discontinuing treatment. Similarly, patients with the 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC) 347G polymorphism in the ATIC gene have more severe side effects that leave patient self-selecting to discontinue therapy. Polymorphisms in the thymidylate synthase (TS) 5-UTR gene not only demonstrate poor therapeutic response, but significant adverse drug events. Psoriatic patients with the TS 5-UTR 3R allele have a very poor therapeutic response to methotrexate, if they have palmoplanatar psoriasis, but all patients with this allele receiving methotrexate without folic acid supplementation have a 12–15× increase in ADRs, including a 13× incidence of hepatotoxicity. Similarly, psoriatics with the TS 5-UTR 6bp del allele have an 8× increased risk for a significantly elevated alanine transaminase with unsupplemented methotrexate treatment. As such, the impact of many polymorphism-related ADRs in psoriatic patients on methotrexate therapy can be reduced or eliminated with folic acid supplementation.

5-Fluorouracil

TS catalyzes the conversion of deoxyuridylate and 5,10-methylenetetrahydrofolate (CH_2H_4 folate) to deoxythymidine monophosphate (dTMP) and 7,8-dihydrofolate. This reaction is the sole de novo biosynthesis of thymine in DNA, and therefore inhibition of TS blocks DNA synthesis, thereby causing cell death.

5-Fluorouracil (5-FU) is a fluorinated pyrimidine analog (the prodrug of 5-fluoro-2-deoxyuridine monophosphate (FdUMP) that covalently binds to TS, thus inactivating the anabolic enzyme complex and preventing the conversion of deoxyuridine monophosphate

to dTMP, which is required for DNA synthesis. 5-FU also incorporates itself into RNA strands as an abnormal base pair, thus inhibiting cell growth. Clinical data have suggested that response to 5-FU-based chemotherapy regimens is inversely associated with intratumoral TS mRNA and protein expression (21). There are three functional gene polymorphisms that regulate TS expression, help prognosticate disease-free and overall survival, as well as predict therapeutic benefit of 5-FU (1).

5-FU is currently one of the most widely administered chemotherapeutic agents used for the treatment of epithelial cancers. Systemic 5-FU (intravenous administration) is poorly absorbed; 20% is anabolized to the active metabolite, whereas 80% is quickly catabolized by the liver and excreted in the urine. Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the catabolism and clearance of 5-FU. Expression of DPD has been related to tolerance and response to 5-FU-based therapy. Low expression or absence of DPD is associated with 5-FU accumulation and increased risk of severe toxicity; high expression of DPD is associated with poor response to 5-FU therapy. Molecular studies have suggested that there is a relationship between allelic variants in the DPYD gene (the gene that encodes DPD), found on chromosome 1p22, and a deficiency in DPD activity, thus providing a potential pharmacogenetic basis for 5-FU toxicity. A 3–5% of the population has low or no DPD activity. Four allelic variants have been demonstrated to have clinical relevance. The c1905 + 1 G > A (otherwise known as IVS14 + 1G > A or DPD*2A) is a splice variant leading to zero enzyme activity. However, this phenotype is not clinically apparent in the presence of a second wild-type allele. The c1679 T > G mutation (isoleucine to serine at codon 560) and c2846 A > T (aspartic acid to valine at codon 949) produce low enzymatic activity. A deep intronic (noncoding) slicing mutation (c1129–5923 C > G) is relevant in the European population (22).

Some studies have correlated tumoral DPD activity with 5-FU response, suggesting it may be a useful pharmacogenomic marker of patient response to 5-FU-based chemotherapy (23). It is possible that tumor DPD activity may predict the clinical severity of a patient's response to topical 5-FU application in the treatment of nonmelanoma skin cancers (NMSCs), including erythema, swelling, and treatment efficacy.

ANTICONVULSANTS

Carbamazepine

Human leukocyte antigen (HLA) allelic biomarkers can be helpful in predicting ADRs, particularly in patients at risk for severe hypersensitivity reactions. Symptoms of these systemic events include rash (often macular–papular exanthems), fever, malaise, nausea, headache, and myalgias, and usually develop within 6 weeks of starting a given medication. Discontinuation of the medication leads to symptom resolution, but re-introduction of the same medication can produce an immediate-type hypersensitivity reaction that results in severe hypotension, respiratory failure, and even death.

Carbamazepine, a firstline agent in seizure management, and now used off-label in the treatment of headache, chronic pain, trigeminal neuralgia and mood disorders can cause SJS and TEN. Other anticonvulsants are associated with similar ADRs. In 2007, the US FDA added a blackbox warning to the drug's label, recommending that Asian patients be tested for the HLA-B*1502 allele, a demonstrated biomarker for carbamazepine-associated SJS–TEN, before initiating therapy (9,24). Asians and patients with Asian ancestry have a 98% incidence of carbamazepine-induced SJS–TEN if they carry the HLA-B*1502 allele. The frequency of this allele is highest in South Asians (Han and Hong Kong Chinese, Taiwanese, Thai, Indians; 8–11%) *versus* North Asians (Beijing Chinese, Japanese, Koreans; 1–2%) (25). Interestingly, other races carrying this allele do not have the increased risk of developing SJS–TEN (26,27).

A new allelic variant HLA-A*3101 has been determined to be a biomarker for carbamazepine-induced hypersensitivity in Caucasians of European descent. The skin findings may range from maculopapular exanthems to severe blistering reactions. With a 5–10% prevalence of carbamazepine-associated hypersensitivity in Europeans, investigators have suggested that recommendation to screen for this second, important biomarker be added to the drug's US FDA labeling (28).

Dilantin + Fluconazole/Rifampin

Dilantin (valproic acid) is considered to be one of the safer antiepileptic drugs, less likely to induce a hypersensitivity-type reaction at standard doses. Metabolized by the p450 enzyme, CYP2C9, serum concentration of valproic acid will be affected by drug–drug interactions with common dermatology drugs, which may inhibit (e.g., fluconazole) or induce (e.g., rifampin) the CYP2C9 enzyme.

ANTIRETROVIRALS

Human immunodeficiency virus (HIV) is an increasingly difficult virus to treat because it is continually mutating. Most patients require a cocktail of medications to attempt to halt viral replication at various steps in its life cycle. Interestingly, patients who are homozygous for null alleles in the chemokine receptor (CCR)-5 gene are resistant to HIV infection and do not contract the disease (29). Other patients carry gene polymorphisms that predispose them to severe adverse reactions to specific antiretroviral drugs.

Abacavir

Abacavir is a nucleoside analog inhibitor of HIV-1 reverse transcriptase that is used in combination with other antiretrovirals (usually lamivudine and ritonavir) as an effective means of retarding susceptible HIV strains. Approximately 4.3% of patients (Caucasian > African American) have developed a severe drug hypersensitivity reaction to this medication, presenting with fever, rash, malaise, headache, acute respiratory symptoms, and even life-threatening hypotension and cardiovascular collapse, if the medication is not discontinued. It typically appears within the first six weeks of initiating treatment (median time of onset is 11 days) (30). The HLA B*5701 allele was identified as a risk factor for abacavir hypersensitivity. Because a second exposure to the drug yields an immediate-type hypersensitivity reaction, which can lead to angioedema and death, cutaneous patch testing was used to corroborate and increase the specificity of the clinical diagnosis (31,32). Recent studies have since demonstrated the cost-effectiveness of HLA B*5701 genotyping to screening patients prior to initiating abacavir therapy (33,34). HLA-DR7 and HLA-DQ3 have also been associated with abacavir hypersensitivity.

Neveripine

Cutaneous reactions are common in patients being treated with non–nucleoside reverse transcriptase inhibitors (NNRTIs). Rashes develop in about 15% of patients on neviripine, 1.5% of which are severe; it is associated with a 0.301% incidence of SJS (1). The rash is usually noted within the first 2–4 weeks of initiating treatment, and is not expected to develop beyond the first three months. Drug-induced hypersensitivity syndrome (DRESS) has been associated with the HLA-DRB*0101 polymorphism. It occurs more commonly in women and in patients with higher CD4 counts at the initiation of therapy (>250 cells/mm^3 in women or >400 cells/mm^3 in men). Hepatotoxicity is an even more common adverse effect of neviripine therapy. The incidence of neviripine-induced hepatotoxicity may actually be decreased in patients with the MDR1 *3434T allele (1). Neviripine is metabolized in the liver by CYP3A4 and CYP2D6 enzymes. Neviripine levels may be increased or decreased in patients taking concomitant medications that utilize these same enzymes. This in turn would lead to changes in efficacy as well as the frequency and intensity of adverse side effects.

Efavirenz

Efavirenz, one of the most potent NNRTIs (14), is metabolized in the liver by CYP3A4 and CYP2B6 enzymes. It is well tolerated, but is often associated with rashes. Forty percent of pediatric HIV patients have presented with rash during treatment, but only 1% have developed SJS (1). Unlike neviripine treatment, it is not necessary to discontinue this drug for mild-to-moderate rashes, as they tend to resolve with time. However, concomitant medications that induce CYP3A4 and CYP2B6 enzymes can reduce the levels of efavirenz, thus reducing its efficacy (14).

ANTIFUNGALS

Warfarin interaction

The azole drugs interfere with CYP 2C9 (fluconazole is a potent inhibitor) and CYP 3A4 (ketoconazole and itraconazole are potent inhibitors). Any drug using these pathways may have its metabolism altered when given concomitantly with an azole antifungal agent (35). Excessive anticoagulation can occur with a significant increase in INR values when fluconazole, (36) ketoconazole, (37), or itraconazole (38) are taken with warfarin.

Simvastatin myopathy

Rhabdomyolysis is described as an adverse event of simvastatin therapy either by itself or in combination with other medications. The antifungal ketoconazole increases the possibility of rhabdomyolysis developing from the use of simvastatin (39). Ketoconazole is an antifungal sterol synthetic inhibitor of the azole group. Azole antifungals inhibit the CYP3A4-mediated metabolism of simvastatin resulting in increased serum levels and effects of simvastatin.

Co-administration of simvastatin with itraconazole in healthy volunteers has led to rises of over 10-fold in the area under the curve) and C_{max} (maximum concentration) of simvastatin (40). Case reports also document rhabdomyolysis with concurrent use of fluconazole (41). Lowest possible doses of statins should be used if co-administration of the azoles cannot be avoided. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness.

Voriconazole

Voriconazole is a broad spectrum triazole antifungal agent available as both an oral and intravenous formulation. It has potent in vitro as well as in vivo activity against a broad spectrum of pathogens, including *Aspergillus*, *Candida*, and *Cryotococcus* (42). Voriconazole metabolism is highly affected by the CYP2C19 enzymes. CYP2C19 is the least expressed CYP2C isozyme in the liver. Despite this, its polymorphisms can affect the metabolism of several classes of drugs, including antipsychotics, antidepressants, and proton pump inhibitors (43). Carriers of two null alleles display the poor metabolizer (PM) phenotype, whereas extensive metabolizers (EMs) carry at least one functional allele. Heterozygous EMs are sometimes referred to as intermediate metabolizers (IMs) (44). Approximately 20% of Asians but only 3–5% of Caucasians and Africans are PMs. The two most common defective alleles are CYP2C19*2 and CYP2C19*3, the latter occurring primarily in Asians. By contrast the CYP2C19*4 allele is more common in Caucasian (frequency = 0.6%) and accounts for at least 5% of the PMs in Caucasians (45). Most recently, CYP2C19*17 was detected; it is associated with increased CYP2C19 activity due to increased gene transcription. It is rare in Asians but quite common in Africans and Europeans (46). Because voriconazole is primarily metabolized by the CYP2C19 isozyme, genotyping may have clinical utility, particularly because voriconazole has a somewhat narrow therapeutic index (47).

ANTIBIOTICS

Antibiotic use in dermatology can be affected by the genetic polymorphisms that alter metabolism of these medications. Some of the pertinent pathways for metabolism of dermatologic drugs include (*i*) *N*-acetylation and (*ii*) CYP enzymes.

Metabolism by *N*-Acetylation

Individuals who are rapid acetylators excrete the target drugs rapidly, and therefore experience higher than expected rates of treatment failure (48). In addition, rapid acetylators require higher doses of medication for clinical effect. Individuals who are slow acetylators are more likely to develop side effects from medications: these include neuropathy from isoniazid; drug-induced lupus from procainamide and hydralazine; and TEN from sulfonamides (49). Individual differences in metabolism may predispose patients to idiosyncratic reactions from antibiotics metabolized by this pathway.

Sulfonamides

Sulfonamides are metabolized by *N*-acetylation (mediated by a genetically polymorphic enzyme) and oxidation to potentially toxic metabolites. Those who are slow acetylators appear to be most at risk (50). In particular, the slow acetylator phenotype is a risk factor for SJS/TEN. Wolkenstein et al., looked at 32 inpatients admitted for sulfonamide- or anticonvulsant-induced SJS/TEN as well as a control group of 20 healthy volunteers; 17/18 patients with sulfonamide-induced SJS/TEN were slow acetylators compared with 8/14 patients with anticonvulsant-induced SJS/TEN *versus* 10/20 healthy volunteers (51).

Isoniazid

In the 1950s, a high variation in individual rates of excretion of isoniazid was observed among people being treated for tuberculosis (52).

Following a single oral dose of isoniazid, a bimodal pattern of plasma isoniazid levels was demonstrated, leading to the concept of rapid and slow eliminators of this drug. The genetic basis for this variation arose from the observation that monozygotic and dizygotic twins had a high concordance rate for excretion rates. Further investigation revealed that the enzyme responsible for the metabolism of isoniazid was *N*-acetyltransferase (NAT). This enzyme is central in the metabolism of a wide variety of drugs, all of which contain an arylamine or hydrazine group. The genetic basis for variability in the action of this enzyme results from polymorphisms at the *NAT2* gene locus. Fifteen variant alleles for *NAT2* have been identified. Several of the alleles have been associated with the rapid acetylator phenotype (*NAT2*4*, *NAT2*12*, and *NAT2*13*), whereas others have been associated with slow acetylation (*NAT2*5*, *NAT2*6*, *NAT2*7*, and *NAT2*14S*) (53). In particular, there appears to be an association of the slow-acetylator phenotype and drug-induced liver injury (54).

Rifampin

Potential adverse drug interactions between antibiotics and oral contraceptives are of great relevance in dermatologic practice. The enterohepatic circulation of contraceptive steroids can be interfered with by antibiotic effects on bacterial flora in the bowel, and lower serum levels of the contraceptives can result. Some have suggested increasing the estrogen component of the pill to 50 µg or adding other forms of birth control for the duration of antibiotic therapy (55). However in practice, the failure of oral contraceptives with oral antibiotics is low (56). In fact, a recent review of the literature suggests that there is little convincing evidence to show a systematic interaction between antibiotics and oral contraceptives other than rifampin (57). Rifampin, an antibiotic used in treating diseases, such as tuberculosis, is a known CYP3A4 and CYP2C9 inducer in vivo (58,59). It has also been suggested that rifampin is an inducer of CYP1A2, CYP2C8, and CYP2C19 (60–63).

Doxycycline

Doxycycline is a CYP3A4 substrate, and hence its metabolism has the potential to be altered depending on the individual genetic profile. Tetracyclines as a group interfere directly with CYP isoforms, and thus influence the metabolism of medications that utilize this pathway. (Please see Ashourian and Cohen for a comprehensive list of possible drug interactions with the tetracyclines (64).) The most relevant dermatologic interactions include (*i*) increasing the level of methotrexate, (*ii*) increasing risk of pseudotumor cerebri with concomitant isotretinoin use, and (*iii*) interference with bactericidal activity of the penicillins, which depend on bacterial wall synthesis for efficacy.

Sirolimus (Formerly Known As Rapamycin)

Rapamycin and its derivatives are immunosuppressive macrolides that block mammalian target of rapamycin (mTOR) function and yield antiproliferative activity against a variety of malignancies (65). Topical rapamycin has shown efficacy in the treatment of angiofibromas in tuberous sclerosis (66). Regarding sirolimus/rapamycin, results from different studies have demonstrated that there is a significant association between sirolimus concentration/dose ratio and CYP3As polymorphisms (67–69). A lower sirolimus concentration/dose ratio was observed in the CYP3A5*1 carriers (*1/*3 or *1/*1) than in the CYP3A5*3/*3 carriers, suggesting that CYP3A5 nonexpressors require lower sirolimus dose to achieve therapeutic concentrations. There is also an association between the CYP3A4*1B polymorphism and higher sirolimus requirement (70–72).

ANTICOAGULANTS

Warfarin (Coumadin)

Warfarin is a racemic, oral anticoagulant prescribed most commonly for the treatment and prevention of thromboembolic events. While usually seen in patients presenting to dermatology with a history of myocardial infarction, stroke and pulmonary emboli, and deep vein thrombosis, it is sometimes necessary to prescribe it for autoimmune, dermatologic-associated diseases, including antiphospholipid syndrome. However, more relevant is the interaction of concomitant dermatology medications that interact with warfarin-metabolizing enzymes.

S-warfarin, which is 3–5 times more potent than R-warfarin, is primarily metabolized by CYP2C9 (9). Polymorphisms in the gene influence drug metabolism and efficacy. The CYP2C9*2 −430 C > T base pair change encodes an arginine to cysteine amino acid change at codon 144, that results in a 30–40% reduction in enzyme activity for S-warfarin metabolism (IM) (73), compared with patients with the wild-type CYP2C9*1/*1 genotype. A second polymorphism of the same gene is the CYP2C9*3 −1075A > C base pair change. This alteration of isoleucine to leucine at the 359 codon, yields an almost complete loss of function of the enzyme (PM), and negligible S-warfarin metabolism. CYP2C9*2, *3 alleles are seen in 8–12% of Caucasians, 1–3% of African Americans, and in <1% of Asians (4). Clinically, these patients require a significantly lower warfarin dose to maintain therapeutic INR levels and to prevent dangerous bleeding events (74). As CYP2C9 enzymes metabolize 10% of all drugs (14), warfarin metabolism can be affected by co-administration of other medications. Antifungals, fluconazole in particular, is a potent CYP2C9 inhibitor; concomitant therapy can result in a markedly elevated level of warfarin.

A third genetic polymorphism that affects warfarin metabolism involves the VKORC1 (vitamin K 2, 3-epoxide reductase complex, subunit 1) gene, the target enzyme of warfarin. The VKORC1–1639 G > A base pair substitution yields an increased level of warfarin active metabolite. The AA genotype is seen in up to 80% of Chinese patients and 14% of Caucasians (4). It is important to lower the initial dose in these patients. New warfarin dosing tables for achieving optimal INR levels, which incorporate both clinical and pharmacogenetic data, have been developed (75). The WRAPID algorithm demonstrates similar time to achieve first therapeutic response and time to stable anticoagulation, which is independent of CYP2C9 or VKORC1 genotype (76).

Clopidogrel (Plavix)

Antiplatelet therapy is a key in the prevention of atherothrombotic disease processes. Dual therapy with clopidogrel and aspirin is most common. Aspirin is discussed in the following section. Clopidogrel is a prodrug that is converted by CYP2C19 enzymes to an active compound that inhibits adenosine diphosphate (ADP)-induced platelet aggregation. Many patients on this treatment regimen continue to develop recurrent thromboembolic and ischemic

events. Genetic polymorphisms in this CYP enzyme explain some of the variability in clopidogrel efficacy (77). Clopidogrel-treated patients with the loss-of-function CYP2C19*2 allele exhibit reduced platelet inhibition compared with those with the wild-type CYP2C19*1 allele, and experience a higher rate of cardiovascular events (78) (this is important because estimates suggest that up to 25% of whites, 30% of blacks, and 50% of Asians carry the loss-of-function allele, which would render them resistant to clopidogrel (79,80). Even patients with reduced-function CYP2C19*3, *4, or *5 alleles may derive less benefit from clopidogrel than those with the full-function CYP2C19*1 allele. Concomitant administration of clopidogrel and proton pump inhibitors, specifically omeprazole, which is often co-administered to prevent gastrointestinal side effect, and is an inhibitor of CYP2C19, produces a small reduction in the inhibitory effects of clopidogrel on ADP-induced platelet aggregation (81). This interaction does not appear to increase the risk of cardiovascular events.

Acetylsalicylic Acid-induced Urticaria

Aspirin [acetylsalicylic acid (ASA)] is an anti-inflammatory drug that acts by acetylating the enzymes in platelets that synthesize thromboxane A2 (TXA2), and at higher levels, prostaglandin inhibitor 2 (PGI2). TXA2 inhibition prevents platelet aggregation, activation, inflammation, and fever reaction. PGI2 inhibition prevents platelet aggregation induced by endogenous vessel wall enzymes, as well as vasodilation. Most patients presenting to the dermatologist are taking low-dose aspirin for the prevention of stroke and myocardial infarction. These patients tend to have ecchymoses in the skin, and bleed easily and longer with cutaneous surgical procedures. However, ASA has numerous off-label dermatologic uses, including, but not exclusive to, erythema nodosum, postherpetic neuralgia, vitiligo, antiphospholipid antibody syndrome, Degos' disease, necrobiosis lipoidica diabeticorum, erythromelalgia, and mastocytosis (14).

However, aspirin-exacerbated respiratory disease (AERD) and aspirin-induced/intolerant urticaria (AIU) are immune-mediated reactions, associated with mast cell activation, degranulation, and histamine release that can result in severe angioedema and cardiovascular collapse. More commonly seen in women, it is important to consider this reaction when initiating ASA therapy. Recent studies have investigated the TXA2 receptor, as well as the CRTH2 genes in both of these conditions. In women with AERD, the frequency of the CC/CT genotype of TXA2R −+ 795T > C locus is significantly more prevalent, as is the TT genotype of CRTH2 −466T > C locus (82). Patients with a diagnosis of chronic urticaria (CU) did not have a particular genotype at the CRTH2 −466T > C locus, but CU patients with the TT genotype required a significantly higher dose of oral antihistamines to control their clinical symptoms (83). AIU patients demonstrate a higher frequency of the TT genotype at the TXA2R −4684T > C locus, which may be associated with lower TXA2R expression, potentially contributing to the AIU phenotype (84). Finally, a significant association has also been demonstrated in AIU patients and the C haplotype at that IL18 −607A > C gene locus (85).

ANTIHISTAMINES

Antihistamines are used to relieve itch. In dermatology, they are used for the management of atopy, allergic rhinitis, allergic contact dermatitis, and acute urticaria and CU. Histamine, which is produced and stored in mast cells, is mediated by H1 histamine receptors to produce allergic-type itch. First-generation antihistamines (diphenhydramine, hydroxyzine, chlorpheniramine, cyproheptadine, promethazine are very effective, but because they are lipophilic, they cross the blood–brain barrier and can be overly sedating. Other side effects (weight gain, atropine-like effects, including xerostomatitis, blurred vision, constipation, and dysuria) make it difficult to use them for a long term or at increased doses. Second-generation antihistamines (loratidine, cetirizine, fenofexadine, desloratadine) have similar efficacy, but are much less sedating. This group of newer medications have prodrugs and active drug compounds. Most of the antihistamines are metabolized in the liver by the CYP3A4 enzyme system. Patients with liver disease or who are taking concomitant CYP3A4 inhibitors may have longer plasma half-life and a higher serum concentration of the drug, leading to prolonged side effects. Common CYP3A4 inhibitors used in dermatology include erythromycin, ketoconazole, and itraconazole. Because some of the antihistamines, in turn, can act as CYP3A4 inducers or inhibitors, they, too, can increase (or decrease) the serum concentration of other co-administered medications, leading to potentially serious adverse reactions. Terfenidine, a first-generation H1 blocker and astimazole, a second-generation H1 blocker, when taken with other CYP3A4 inhibitors have the potential to cause life-threatening ventricular arrhythmias, such as torsade de pointes. These two antihistamines are no longer on the market in the United States.

Medications that block type 2 histamine receptors (H2) have not shown efficacy in the management of H1-mediated itch. They are generally prescribed for the treatment of gastric histamine release. Some physicians still use them as adjuvant therapy for urticaria. As they are p450 enzyme inhibitors, they have the potential to increase the serum concentration of other medications with narrow therapeutic ranges (and great side effect profiles), including warfarin, phenytoin, theophylline, and imipramine.

IMMUNOSUPPRESSANTS

Cyclosporin

Cyclosporin (CsA) is an immunosuppressant that is commonly used in the treatment of rheumatoid arthritis and psoriasis, as well as prophylaxis to prevent transplant organ rejection. Unlike many other oral immunosuppressants, it is not cytotoxic, does not suppress bone marrow, and it is not teratogenic (14). It is metabolized by hepatic CYP3A4 enzymes and is excreted through bile and feces; dosage reduction is required in patients with liver insufficiency, whereas it is not required in patients with renal failure or on hemodialysis. CsA prevents inflammation by inhibiting IL-2 production by activated CD4+ T cells. CsA binds to cyclophilin, which inhibits calcineurin binding, thus preventing nuclear factor of activated T cells (NFAT-1) from transcribing cytokines, including IL-2. Gene polymorphisms in CYP3A4 have not shown significant alterations in cyclosporine metabolism, per se, however, co-administration with CYP3A4 inhibitors (including ketoconazole, erythromycin, diltiazem, and progesterone) will significantly increase the serum concentration of CsA, leading to increased immunosuppression and increased risk of side effects. Similarly, CYP3A4 inducers (isoniazid, rifampin, clotrimazole, griseofulvin, dexamethasone, carbamazepine, phenobarbital, and phenytoin) have been shown to reduce serum CsA concentration, requiring higher doses for clinical efficacy (86,87).

The ABCB1 gene (a.k.a. multidrug resistance, MDR-1 gene) encodes a P-gp that both metabolizes and is induced by CsA. In adults, there are no significant clinical differences reported in CsA oral bioavailability, with respect to particular polymorphisms in either the ABCB1 gene or the CYP3A genes (88). However, there is strong linkage disequilibrium between particular polymorphisms, creating common haplotypes consisting of 3435C > T and either 2677G/T or 1236C > T (1). Studies in pediatric patients with endstage renal disease have demonstrated an association between CsA oral bioavailability and specific haplotypes of the ABCB1 gene, including 1236C > T and 2677G > T polymorphisms, as well as the related alleles 1199G > C, 1236C > T and 3435C > T, but only in older than eight years of age (89). Carriers of the variant alleles had a CsA oral bioavailability that was 1.5-times higher than patients with wild-type alleles, suggesting that the PK of CsA is related to age or developmental stage (89). It is not yet determined whether or not it is necessary to test for these ABCB1 allelic variants before initiating CsA therapy, to determine optimal dosing in children over eight years of age.

Interestingly, and importantly, an association has been reported between the donor ABCB1 genotype and CsA nephrotoxicity. Donors with the genotype ABCB1 3435 TT have significantly reduced P-gp activity, and standard CsA dosing was strongly associated with CsA nephrotoxicity (90).

Dapsone

Dapsone [4,4-diaminodiphenylsulfone (DDS)] is an antibiotic/antiprotozoic, used in the treatment of leprosy, malaria, and AIDS-related pneumocystis carinii pneumonia. It acts like other sulfonamides, by inhibiting the synthesis of dihydrofolic acid by competitively binding to the active site of dihydropteroate synthetase. While less understood, dapsone also acts as an anti-inflammatory with antineutrophilic effects, used definitively in the management of dermatitis herpetiformis. Other dermatologic applications have included acne (oral and now, topical formulations), Behcet's disease, bullous, and cicatricial pemphigoid, epidermolysis bullosa acquisita, lupus, pyoderma gangrenosum, subcorneal pustular dermatoses, leukoclastic vasculitis and even spider bites (91). Dapsone is absorbed rapidly from the gastrointestinal tract and metabolized in the liver by either *N*-acetylation or *N*-hydroxylation. In the former, primary metabolic pathway, dapsone is acetylated in the liver by *N*-acetyl transferase (NAT2) to monoacetyl dapsone, which then undergoes glucouronidation to produce water-soluble metabolism for renal excretion. There is significant allelic variability in the NAT2 gene. Patients with NAT2*5 (341T > C; amino acid change of Ile114 > Thr), *6 (590G > A; amino acid change of Arg197 > Gln), *7 (857G > A; amino acid change of Gly286 > Glu), and *14 (191G > A; amino acid change of Arg64 > Gln) polymorphisms tend to be PMs/slow acetylators (92). Patients with the slow acetylator phenotype (approximately 40–80% of Caucasians and 10–30% of Asians) exhibit reduced presystemic extraction (i.e, higher bioavailability) and slower elimination of dapsone, but, for this drug, it does not appear to be particularly relevant in its clinical utility, including dosing or increased risk for side effects, including the hepatotoxicity associated with other NAT2-metablized drugs, including isoniazid.

However, patients with mutations in the hydroxylation pathway are at increased risk of significant toxicity, including methemoglobinemia and hemolytic anemia. *N*-hydroxylation of dapsone into the active metabolite, dapsone hydroxylamine, which is a strong oxidant, causes RBC cell membrane damage and subsequent hemolysis. Also, dapsone hydroxylamine reacts with oxyhemoglobin (Fe2+) to form methemoglobin (Fe3+) and nitrosoarene, which gets reduced to another hydroxylamine by NADPH reductase or glutathione in the RBC. While all patients taking dapsone develop a 15% methemoglobinemia, it is not problematic. Patients with levels below 20% are rarely symptomatic. Side effects include nausea, dyspnea, and tachycardia with levels of 30%, lethargy and loss of consciousness with levels of 55% and death at 70% (93). Glucose-6-phosphate dehydrogenase (G6PD) is an antioxidant enzyme that oxidizes and effectively reduces the serum concentration of dapsone hydroxylamine, thus reducing the risk of adverse events. *N*-hydroxylation occurs via various p450 enzymes, including CYP2C9. The PM phenotype is associated with CYP2C9 *2, *3, *5, *6, *8, and *11, and is seen in 1–6% of Blacks, <1% of Asians, and in 2–6% of Caucasians (92). In PMs, dapsone metabolism is shifted significantly to the *N*-acetylation pathway, significantly increasing the amount of bioavailable dapsone and increasing risk of hepatotoxicity.

Co-administration of dapsone with other p450-metabolized medications can alter dapsone levels and impact risk of adverse events. When concurrently prescribed with rifampin, a CYP2C9 inducer, in the treatment of leprosy, it can result in and 7- to 10-fold decrease in dapsone serum levels. While dosing may require adjustment for the treatment of pneumocystis carinii pneumonia, it does not for leprosy, because dapsone levels still reach the minimum inhibitory concentration (94).

Patients with a genetic mutation associated with G6PD deficiency (usually Blacks, Asians, and patients of Mediterranean descent) have an increased buildup of dapsone hydroxylamine, leading to increased RBC hemolysis and a potentially severe anemia. It is recommended that G6PD level and complete blood count be checked before initiating therapy.

Other adverse events associated with dapsone include agranulocytosis and dapsone hypersensitivity syndrome. Agranulocytosis is an idiosyncratic, unpredictable reaction that is most common in patients with dermatitis herpetiformis, with a 25-fold increased risk compared with other patients being treated with dapsone (95). Dapsone-associated drug hypersensitivity syndrome (fever, rash, eosinophilia, and liver and lymph node involvement) is unpredictable, but is most likely to be related to sulfonamide sensitivity. Risk of sulfonamide hypersensitivity increases for patients who are slow acetylators, possibly because of the slow metabolism of the drug. However, polymorphisms in the genes that encode the drug-metabolizing enzymes have not demonstrated an increase in sulfonamide hypersensitivity (96).

Glutathione deficiency has been hypothesized as related to sulfonamide reactions, particularly in HIV-seropositive individuals. Reactive sulfa metabolites can cause direct cell injury and death in vitro in cells infected with HIV. Glutathione helps protect these cells by preventing the oxidation of hydroxylamine and in the formation of more potentially toxic metabolites. However, a prospective study failed to demonstrate glutathione deficiency in HIV-infected patients who develop hypersensitivity (97).

Interestingly, topical dapsone is not associated with methemoglobinemia, and drug hypersensitivity has not been reported.

Tacrolimus (Protopic)

Tacrolimus ointment is a nonsteroidal anti-inflammatory topical therapy, which is indicated for the treatment of atopic dermatitis in