

# Pediatric Pharmacotherapy

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## **Drug-induced Photosensitivity (Our Read-it-at-the Beach Issue!)**

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As summer approaches, many of your patients and their families will be taking vacations, and some will likely be heading for the beach. This is an excellent time to provide additional counseling on the risks of medication-induced photosensitivity reactions. This brief article will discuss those agents known to cause photosensitivity and advice for patients and careproviders.

### Definitions

Photosensitivity is a relatively general term used to describe any cutaneous reactions to light. Photosensitivity reactions may be more specifically categorized as phototoxic or photoallergic in nature. Phototoxicity is much more common than photoallergic reactions. The term phototoxicity encompasses both sunburn and reactions caused by chemical photosensitizers, such as medications. These reactions are typically manifested by a delayed erythema and edema, followed by hyperpigmentation and desquamation. Phototoxicity may occur after first exposure to a drug and is not immunologically mediated.<sup>1-5</sup>

True photoallergic reactions are much less common. These reactions are a variation of contact dermatitis and are believed to result from a type of hypersensitivity, in which the drug forms an immunogenic complex with cutaneous proteins in the presence of light energy. Photoallergic reactions tend to be mild with initial treatment and become more pronounced with repeat exposures.<sup>1-5</sup>

### Topical Photosensitizers

Photosensitizing medications applied to the skin surface may result in significant cutaneous damage after only minimal sun exposure. While the reactions to some medications are well Table 1. Photosensitizing Medications<sup>1,2,6,7</sup>

established, such as the topical use of sulfonamides and tetracyclines for acne, there are many ingredients in topical preparations and cosmetics for which the risk of photosensitivity is unknown.

Most consumers are unaware of the potential photoallergic reactions caused by use of over-the-counter antibacterial products containing halogenated salicylanilides. While many of these products were removed from the market in the late 1970's, some first-aid creams, acne preparations, and deodorant soaps are still in use.<sup>1,4</sup>

It should be remembered that photosensitization can also have beneficial effects. For example, psoralens and coal tar products are applied to the skin specifically to induce photosensitization and increase cell turn-over following exposure to visible or ultraviolet light.<sup>1</sup>

### Systemic Photosensitizers

The majority of medications causing skin damage are systemic photosensitizers. They range in intensity, from the potent inducers of phototoxic reactions like amiodarone, sulfonamides and tetracyclines, thiazide diuretics, and sulfonylurea antidiabetic agents to weak photosensitizers like diphenhydramine. The damage induced by these agents, however, is related not only to their potency, but also the dose and duration of therapy, the number of sun exposures, and the length of time in the sun at each exposure.<sup>1-7</sup>

Table 1 includes medications that have been reported as causing photosensitivity reactions. In nearly all of these cases, the reaction is phototoxic in nature, rather than photoallergic.<sup>1,2,6,7</sup>

acetazolamide	diphenhydramine	methotrexate	quinidine
acetoexamide	doxepin	methoxsalen	quinine
alprazolam	doxycycline	methyclothiazide	risperidone
amantadine	enoxacin	methyldopa	salicylates
amiodarone	estrogen/progestin	methyldopate	saquinavir
amitriptyline	felbamate	metolazone	secobarbital
amobarbital	fleroxacin	minocycline	selegiline
amoxapine	floxuridine	mirtazapine	sertraline
azithromycin	flucytosine	nabumetone	silver sulfadiazine
benzocaine	fluorouracil	nalidixic acid	sparfloxacin
benzthiazide	fluphenazine	naproxen	sulfamethoxazole
butabarbital	flutamide	nifedipine	sulfasalazine
captopril	fluvoxamine	norfloxacin	sulfisoxazole
carbamazepine	furosemide	nortriptyline	tetracycline
carbinoxamine	ganciclovir	ofloxacin	thiethylperazine
carprofen	glipizide	olsalazine	thioridazine
chlordiazepoxide	glyburide	omeprazole	thiothixene
chloroquine	gold salts	paramethadione	tolazamide
chlorothiazide	griseofulvin	paroxetine	tolbutamide
chlorpromazine	haloperidol	pentobarbital	trazodone
chlorpropamine	hydrochlorothiazide	perphenazine	tretinoin
chlorthalidone	hydroflumethiazide	phenelzine	triamterene
ciprofloxacin	ibuprofen	phenobarbital	trichlormethiazide
clofazimine	imipramine	phenylbutazone	trifluoperazine
clomipramine	indapamide	phenytoin	triflupromazine
clozapine	interferon beta	piroxicam	trimethadione
co-trimoxazole	isoniazid	polythiazide	trimethoprim
cyproheptadine	isotretinoin	porfimer	tripelennamine
dacarbazine	ketoprofen	procaine	valproic acid
danazol	leuprolide	prochlorperazine	vinblastine
dantrolene	lincomycin	promazine	
dapsone	losartan	promethazine	
demeclocycline	loxapine	protriptyline	
desipramine	maprotiline	pyrazinamide	
dichlorophenamide	methazolamide	pyridoxine	
diflunisal	methdilazine	pyrimethamine	

### Prevention

The key to preventing phototoxicity reactions is to avoid prolonged sun exposure in susceptible patients. The following questions may be useful for evaluating the degree of risk to the patient and the need for counseling.

1. Is this specific medication necessary? If the patient's typical activities require a significant amount of time out of doors, the use of an alternative therapy should be considered.<sup>4</sup>
2. How will the medication be used? Short-term courses may require only temporary limitations

on activities, while chronic therapy may mean considerable alterations in daily activities.

3. How likely is the reaction? While the exact degree of phototoxicity cannot be predicted for an individual patient, the relative risk associated with the medication, the dose used, and the patient's likelihood to suffer skin damage (e.g. fair skin, freckles) should be considered.<sup>3</sup>

Once these factors have been considered, the patient and his/her family should be instructed on methods to reduce sun damage. These methods are the same as those used to prevent a sunburn: avoidance of sun exposure, wearing protective clothing (including hats), and the appropriate use of sunscreen products. All patients, especially

adolescents, should also be cautioned to avoid using tanning beds.<sup>4</sup>

In addition, parents need to know what signs and symptoms indicate that their child should be brought to medical attention. Phototoxicity reactions are often delayed and can reach peak damage up to 72 hours after sun exposure.<sup>3</sup>

### Summary

Photosensitivity is a relatively common adverse reaction to medications. Educating families about the need to protect the skin from damage can prevent severe reactions. Restriction of the amount of time spent in direct sunlight and proper use of protective clothing and sunscreens are needed to avoid phototoxicity.

### **References**

1. Epstein JH. Actinic manifestations: Cutaneous diseases induced by the sun. *Clin Pharmacol Ther* 1974;16:959-63.
2. Jarratt M. Drug photosensitization. *Int J Dermatol* 1976;15:317-23.
3. Blaylock WK. Common drug reactions: Their mechanisms and management. *Virginia Medical* 1981;108:529-33.
4. Todd B. Photosensitizing medications. *Geriatr Nurs* 1984;5:263.
5. Kaplan AP. Drug-induced skin disease. *J Allergy Clin Immunol* 1984;74:573-9.
6. Reentz S. ed. *Clinical Pharmacology*. Tampa: Gold Standard Multimedia, Inc., 1997.
7. Gelman CR, Rumack BH, Hutchison TA, eds. *DRUGDEX<sup>®</sup> System*. MICROMEDEX, Inc., Englewood, Colorado 1998.

### **Pharmacology Literature Review**

#### Aggression Associated with Gabapentin Use

This article reviews 12 cases of gabapentin-induced aggression involving children. As gabapentin use in children increases for both seizure prophylaxis and analgesia, the reports of this adverse effect have increased. The onset of aggression in the cases reviewed was often preceded by a period of subtle behavioral changes including moodiness, agitation, and isolation. The aggressive behavior was manifested by a variety of symptoms, ranging from hyperactivity to fighting and cruelty towards others. While the authors caution that a definitive causal relationship between gabapentin and aggression has not been established, they suggest that patients and their families be counseled regarding this potential adverse drug effect. Pressler KL, Rose DF, Phelps SJ. Gabapentin and aggression in pediatric patients: A review of the literature. ***J Pediatr Pharm Pract* 1998;3:100-5.**

#### Ifosfamide Metabolites

Ifosfamide must undergo hydroxylation prior to developing cytotoxic activity. In addition to this desired metabolic pathway; however, ifosfamide may also undergo dealkylation to the cytostatically inactive compounds which have been associated with CNS and renal toxicity. Some investigators have suggested that the production of these toxic metabolites is related to the method of ifosfamide administration.

The authors of this paper investigated the production of metabolites in children receiving ifosfamide by continuous infusion versus short-term (1 hr) intermittent therapy over a 2 to 5 day period. Urinary metabolites were studied during 23 cycles of therapy in 22 children. The study revealed no significant differences in the pattern of metabolite formation or the quantity of potentially toxic byproducts between the two different administration techniques. As a result, the authors concluded that method of administration is not likely to play a role in the development of ifosfamide-induced toxicity. Blaschke HS, Hohenlocher B, Rossi R, et al. Excretion kinetics of ifosfamide side-chain metabolites in children on continuous and short-term infusion. ***Inter J Clin Pharmacol Ther* 1998;36:246-52.**

#### Metabolic Changes During the Menstrual Cycle

This review describes some of the recent research into the effects of physiologic variables on pharmacokinetics and pharmacodynamics. The authors focus on the effects of a typical menstrual cycle on physiologic variations in organ system function, potential effects on chronic illnesses, and on the absorption, distribution, metabolism, and elimination of medications. Considerable attention is given to changes in the cytochrome P450 enzyme system. The authors use this review to call attention to both the limited research in this area and the need to include pre-menopausal women in clinical trials. Kashuba ADM, Nafziger AN. Physiologic changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. ***Clin Pharmacokinet* 1998;34:203-18.**

#### Tobramycin after Lung Transplant

A case of a 12 year old male who received tobramycin prior to and following a living-related, bilateral lung transplant is presented.

Pharmacokinetic parameters were altered throughout his postoperative course. Initially following surgery, he experienced a period of delayed tobramycin elimination, likely the result of acute renal failure and the use of multiple nephrotoxic medications. After the patient's renal function had returned to baseline (normal) values, he was placed once again on tobramycin at post-operative day 38. Despite normal serum creatinine and urine output values, he continued to have impaired drug clearance. The authors describe their management of this case and the potential role of continued cyclosporine use in altering tobramycin pharmacokinetics. Hollar KD, Scott CS, Dupruis RE. Tobramycin pharmacokinetics in a pediatric patient with cystic fibrosis following lung transplantation. **J Pediatr Pharm Pract 1998;3:110-4.**

#### Top 200 for 1997

The yearly analysis of the ranking pharmaceuticals in the United States has been released by IMS America. The top 20 pharmaceutical products in 1997, ranked by sales, were (listed by brand name): Prilosec, Prozac, Zocor, Epogen, Zolof, Zantac, Paxil, Norvasc, Claritin, Vasotec, Premarin, Augmentin, Imitrex, Procardia XL, Pravachol, Biaxin, Lupron Depot, Cipro, Cardizem CD, and Pepcid. These 20 products alone accounted for more than \$20 million in sales. The 20 most frequently prescribed products were Premarin, Synthroid, Trimox, Lanoxin, Watson Lab's generic hydrocodone/acetaminophen, Prozac, Warrick's generic albuterol, Prilosec, Vasotec, Norvasc, Coumadin, Zolof, Claritin, Zocor, Paxil, Procardia XL, Zantac, Zestril, Mylan's generic furosemide, and Cardizem CD. The article provides other rankings in addition to these two. This information is not only an interesting reflection of prescribing practices in the United States, but also a means of predicting future expenditures in health care settings. Anon. Top 200 Drugs of 1997: IMS analysis describes major market shifts. **Pharm Times 1998;64(4):31-49.**

#### Treatment of Pediatric SVT

This brief review focuses on the benefits and risks associated with the treatment of pediatric supraventricular tachycardia. For short-term therapy, adenosine, verapamil, propafenone, flecainide, and procainamide are addressed. For

long-term therapy, the discussion includes digoxin, beta-adrenergic blocking agents, flecainide, propafenone, sotalol, and amiodarone. Curative treatment with ablation is also covered. Based on their review, the authors propose several treatment protocols. Ofammatter J, Bauersfeld U. Safety issues in the treatment of p(a)ediatric supraventricular tachycardias. **Drug Safety 1998;18:345-56.**

#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/22/98:

1. Montelukast (Singulair<sup>®</sup>), a leukotriene receptor antagonist, was added to the formulary for the management of asthma in adults and children 6 years of age and older. The recommended dose in patients 6 to 14 years of age is one 5 mg chewable tablet daily in the evening. Patients over the age of 14 should begin therapy with one 10 mg tablet daily in the evening. Montelukast is the first agent of this class to gain FDA approval in young children.
2. Clopidogrel (Plavix<sup>®</sup>) was also added to the formulary. This antiplatelet agent is used to reduce the risk of atherosclerotic events in patients with established peripheral arterial disease or following recent stroke or myocardial infarction. Use of clopidogrel is restricted to those patients unable to tolerate ticlopidine.
3. Polifeprosan 20 with carmustine implant (Gliadel wafer<sup>®</sup>) was rejected.

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