A 9-year-old male patient developed thrombocytopenia (platelet count: $94 \times 10^3/\mu L$) approximately three months after starting cholestyramine for hypercholesterolemia. During the period of thrombocytopenia, no episodes of bleeding were noted. Post drug discontinuation, platelet counts returned to baseline values. Rechallenge, performed twice on separate occasions, resulted in thrombocytopenia recurrence within the first month after reinitiation of the drug. Because a log-normal curve of volume distribution could not be generated via the automatic particle counters, a stained blood smeared analysis was performed, revealing large and giant platelets but no alterations in other cells. Platelet aggregation was within normal limits. Both parents had normal cell counts, ruling out the possibility of an inherited giant platelet disorder.

The authors concluded that this case strongly suggested drug-induced platelet gigantism, primarily based on the temporal relationship between drug and event and in the absence of a familial history of platelet disorders. They stated that this was the first report of cholestyramine-induced gigantism and noted that this reaction may be missed by automatic particle counters and lead to a misdiagnosis of thrombocytopenia.

Cholestyramine ["Questran"]
ANTIBIOTICS  
Agranulocytosis  

In a prospective cohort study over a 15-year period, 102 cases of drug-induced agranulocytosis were reported, of which 21 were antibiotic related. The antibiotic agents included sulfamethoxazole (9), amoxicillin (3), imipenem (2), cefotaxime (2), ceftriaxone (1), ceftazidime (1), piperacillin (1), vancomycin (1), and tinidazole (1). The mean duration of antibiotic therapy was 12 days, but ranged from three to 29 days. The median age of the patients was 68 years; all the patients were adults. In all patients, normal blood cell counts were established prior to antibiotic therapy and the diagnosis of drug-induced agranulocytosis was confirmed via myelogram. Five patients were treated with granulocyte colony stimulating factor (300 mcg/day). All but one patient recovered. The mean duration of recovery was 9.3 days in all patients and 7.8 days in patients treated with granulocyte colony stimulating factor.

The authors concluded that antibiotics represent approximately 20% of the causative drugs in nonchemotherapy-induced agranulocytosis. The two major antibiotic groups responsible for this reaction in this study were sulfamethoxazole and beta-lactams. They also noted that recovery was enhanced in patients who were treated with granulocyte colony stimulating factor.

Antibiotics  

VIGABATRIN  
Retinal Dysfunction  

In a prospective study, 21 children with epilepsy who had taken vigabatrin for more than six months were monitored for retinal changes. Patients received a mean dose of 55.8 mg/kg/day (range: 25-114 mg/kg/day) for a mean duration of 35.7 months (range: 6-85 months). Of these patients, only three were receiving the drug as monotherapy. Four children (19%) with vigabatrin as add-on therapy developed eye changes including retinal pigmentation, hypopigmented retinal spots, and optic atrophy. The doses used in three children with pigment disturbances ranged from 25 to 50 mg/kg/day. In the child with optic atrophy, vigabatrin doses were 50 mg/kg/day. The duration of therapy in all these children ranged from 33 to 81 months. Visual-evoked potentials (VEPs), performed in all 21 patients, revealed normal-evoked potentials in five patients and abnormal-evoked potentials in 16 patients.

The authors concluded that vigabatrin can cause ocular damage and should be used with caution. The authors noted that most young children may not be able to communicate about their eye problems. They also recommended that prior to drug initiation, patients undergo baseline VEPs, regular eye examinations, and electroretinography every three to six months.

Vigabatrin [“Sabril,” “Sabrilan”]
Koul R et al (Dept Child Health, Div Paediatric Neurology, Sultan Qaboos Univ Hosp, Al Khod, PO Box 38, Zip Code 123, Sultanate of Oman; e-mail: rkoul@omantel.net.com) Vigabatrin associated retinal dysfunction in children with epilepsy. Arch Dis Child 83:469–473 (Dec) 2001
NIMESULIDE
Overdose: Hypoglycemia, Hypothermia

A 20-month-old boy developed mild acidosis shortly after accidentally ingesting eight times the daily recommended dosage of nimesulide (40 mg/kg). Treatment upon hospitalization included gastric lavage with activated charcoal, intravenous 0.3% normal saline, and intravenous ranitidine. At eight hours post admission, the patient developed hypoglycemia (3.44 mmol/L) and hypothermia (35°C). Systolic blood pressure decreased to 60 mmHg. Treatment included a warming blanket and increased fluids to 2000 mL/m²/day. Six hours later, the serum glucose was documented at 4.44 mmol/L with a rise in body temperature. At 20 hours post admission, blood pressure, body temperature, and mild acidosis normalized. The patient was discharged after 48 hours.

The authors concluded that the development of hypotension and hypothermia in this patient was a result of nimesulide overdose. A potential mechanism of action was not identified. The authors suggested that frequent monitoring of vital signs is essential in managing acute nimesulide overdoses.

Nimesulide ["Sulide," "Sulimed," "Teonim"]
Yapacki E et al (Dept Pediatrics, Hacettepe Univ Sch Med, Hacettepe Univ, Ihsan Doramac Çocuk Hastanesi, Gastroenteroloji Ünitesi, 06100 Ankara, Turkey; e-mail: haozen@hacettepe.edu.tr) Hypoglycaemia and hypothermia due to nimesulide overdose. Arch Dis Child 85:510 (Dec) 2001

TOPIRAMATE
Angle Closure Glaucoma, Myopia

A 43-year-old female patient developed blurred vision and headache approximately one day after starting topiramate (dosage not provided). The only other medication taken at the time was paroxetine. The medication was stopped after three doses. An initial ocular examination revealed a visual acuity of 20/20. However, the examination also revealed narrow angles and an increased ocular pressure of 29 mmHg in the right eye and 30 mmHg in the left eye. Treatment included 0.5% timolol maleate in both eyes. At five days after topiramate was discontinued, visual acuity was 20/20 in both eyes and the intraocular pressure was 12 mmHg in the right eye and 16 mmHg in the left eye. A high-frequency B-scan revealed a narrow anterior chamber, forwarded displacement of the lens, and swollen ciliary processes in both eyes. Timolol eye drops were continued. At 12 days after topiramate was discontinued, visual acuity, intraocular pressure, and anterior chamber depth normalized to baseline values.

The authors concluded that this patient experienced ciliary body swelling and angle closure glaucoma induced by topiramate therapy. Possible causes of ciliary swelling may be related to edema formation within the ciliary body or a drug-induced elevated prostaglandin. They recommended that clinicians be aware of this possible adverse event related to topiramate therapy.

Topiramate ["Topamax"]
A 49-year-old female patient developed diarrhea shortly after atorvastatin therapy (10 mg daily) was substituted for gemfibrozil (600 mg twice daily). Concurrent medications also included metformin (850 mg three times daily for five years), insulin 70/30 (36 units in the morning and 34 units in the evening), and lisinopril (10 mg daily). Taking atorvastatin with food and using loperamide as needed did not ease the diarrhea symptoms. At a two-month follow-up, the diarrhea had worsened to three to four episodes daily accompanied by nausea and abdominal cramping. Cerivastatin was substituted for atorvastatin at 0.3 mg daily. Although the diarrhea initially improved, it recurred after two weeks of therapy, requiring discontinuation of all lipid treatments. Laboratory screenings for infectious etiologies were negative. A colonoscopy also revealed no abnormalities. Treatment with cholestyramine was unsuccessful in reversing symptoms. At this point, the patient had diarrhea for five months and metformin was discontinued. Within three days after the discontinuation of metformin, the diarrhea resolved completely. No recurrent episodes were evident during a seven-month follow-up period. The patient also revealed that a short lapse in metformin therapy for about five days early in therapy reduced the diarrhea, which restarted when she restarted the drug.

The authors concluded that this patient experienced late-onset metformin-induced diarrhea. Possible mechanisms included increased intestinal motility and malabsorption. The authors suggested that metformin be considered as a possible cause of diarrhea in patients, even if they have been stabilized on a dose for prolonged therapy.

Metformin [“Glucophage”]
Foss MT & Clement KD (Univ Wyoming Family Practice Residency Program, 821 East 18th St, Cheyenne, WY 82001) Metformin as a cause of late-onset chronic diarrhea. Pharmacotherapy 21:1422–1424 (Nov) 2001

A 74-year-old diabetic female patient developed seizures and cardiocirculatory collapse immediately after receiving an injection of 8% phenol in glycerine solution at the lumbar (L2 and L4) site. Immediate treatment included cardiopulmonary resuscitation, intubation, and epinephrine (11 mg). Mean arterial blood pressures remained reduced despite repeated administration of vasoactive drugs. There was no indication of hypersensitivity reactions or bleeding. Intravenous infusions included epinephrine, norepinephrine, and dobutamine. The left ventricular ejection fraction was less than 10%. Urinary excretion of total phenol was increased (366 mg). The mean arterial blood pressure stabilized, and the patient was weaned from mechanical ventilation after 24 hours. Intravenous infusions were stopped within 72 hours. The patient was discharged from the intensive care setting after five days.

The authors concluded that this patient suffered a severe, temporary myocardial depression after receiving percutaneous phenol lumbar sympathectomy. They suggested that systemic toxicity occurred as a result of massive local resorption or accidental intravascular injection of phenol.

Phenol
Bulpoa PA et al (Dept Intensive Care, Mont-Godinne Univ Hosp, Univ Catholique de Louvain, 5530 Yvoir, Belgium; e-mail: pierre.bulpoa@rean.ucl.ac.be) Acute cardiogenic shock after lumbar sympathectomy by phenol injection. Intensive Care Med 27 (Nov 23) http://link.springer.de/link/service/journals/00134/contents/01/01152/
CISATRACURIUM
Anaphylactoid Reactions

Six cases of anaphylactoid reactions related to cisatracurium administration were reviewed. The patients were all adults (age range: 25-60 years) undergoing various operations. The cisatracurium dose administered ranged from 12 mcg/kg to 167 mcg/kg. Symptoms occurred within two minutes to 20 minutes after the induction of anesthesia and included wheezing (3), increased airway pressure (3), arterial hypotension (5), tachycardia (3), bradycardia (1), brachial block (1), urticaria (1), and flushing (1). The duration of symptoms lasted from 30 minutes to approximately 24 hours. No systemic reactions were observed. Skin testing was positive in two patients at concentrations of 1:1000 and in four patients at concentrations of 1:100.

The authors concluded that cisatracurium was clearly identified as the trigger substance in six patients who exhibited anaphylactoid symptoms after anesthesia induction. They cautioned clinicians to be aware that the anaphylactoid incidence may be higher than initially considered.

Cisatracurium ["Nimbex"]

AMIODARONE
Acute Pulmonary Toxicity

A 72-year-old male inpatient developed a low-grade fever and dyspnea approximately five days after starting amiodarone for post operative onset of atrial fibrillation. Surgery was for coronary artery bypass grafting. Initial amiodarone loading dose was 400 mg twice daily for four days followed by 400 mg daily. Other concurrent medications were not provided. Additional symptoms included supplemental oxygen to keep oxygen saturation at 90%, an increased white blood cell count (15,000), and bilateral lower lobe infiltrates. A sputum culture was negative for infectious etiology. However, a computed tomography scan of the chest revealed lower lobe infiltrates without pulmonary emboli. Amiodarone therapy was suspected, and the drug was stopped after a total of eight days of therapy and cumulative dose of 7.2 g. Despite discontinuation of the drug, pulmonary function continued to decline and the patient required prednisone therapy (40 mg three times daily). His condition continued to deteriorate, and he was intubated on the 25th post operative day, requiring 100% fraction of inspired oxygen. Additional treatment included intravenous diltiazem for atrial fibrillation. A percutaneous tracheostomy was performed on post operative day 55. Approximately 60 days after stopping the amiodarone, the patient was weaned from the respirator. Follow-up over the next 18 months was uneventful.

The authors concluded that this patient developed acute pulmonary toxicity after a short course of amiodarone. Possible mechanisms of action included impaired lipid metabolism leading to increased cellular and phospholipid content, resulting in damage to the pulmonary endothelium. Amiodarone is also known to promote the release of toxic oxidants when exposed to high oxygen concentrations, leading to capillary leak syndrome and adult respiratory distress syndrome.

Amiodarone ["Cordarone"]
Kaushik S et al (Lazar HL: Dept Cardiothoracic Surgery, Boston Med Center, 88 E Newton St, B404, Boston, MA 02118; e-mail: harold.lazar@bmc.org) Acute pulmonary toxicity after low dose amiodarone toxicity. *Ann Thoracic Surg* 72:1760–1762 (Nov) 2001
ORLISTAT AND ANTIHYPERTENSIVES

Interaction: Lack of Hypertension Control

Three cases of uncontrolled hypertension occurred in patients who started orlistat therapy and had been previously stabilized on antihypertensive therapy.

Patient 1. A 47-year-old male patient was hospitalized with a hypertensive crisis (260/140 mmHg) within one week after orlistat was added to his regimen. Antihypertensive regimen consisted of atenolol (100 mg daily), losartan (100 mg daily), and hydrochlorothiazide (12.5 mg daily). Once the orlistat was discontinued, the hypertensive crisis was successfully controlled and returned to baseline values. Rechallenge 20 days later resulted in similar diastolic blood pressure increases (100 to 110 mmHg). Blood pressure normalized within three days after orlistat was withdrawn.

Patient 2. A 58-year-old male patient developed hypertension (160/100 mmHg) and an intracranial bleed within one week after starting orlistat. Additional antihypertensive medications included enalapril (20 mg daily) and losartan (50 mg daily). Once the orlistat was discontinued, the hypertension was controlled with clonidine and nifedipine (dosages not provided).

Patient 3. A 48-year-old female patient developed hypertensive episodes (180/120 mmHg) within two months after starting orlistat treatment. The antihypertensives enalapril and amlodipine were switched to losartan and hydrochlorothiazide. Orlistat was continued and blood pressure normalized. However, hypertensive episodes recurred 20 days later. Hypertension was successfully controlled within 48 hours after orlistat was finally withdrawn.

The authors suggested that the failure of hypertension control in these patients resulted from a possible interaction between orlistat and the antihypertensive medications. A possible mechanism of action was a decrease in absorption of concurrent medications as a result of increased gastrointestinal motility and defecation, or diarrhea. In addition, orlistat increases the proportion of fat in the chyme.

Orlistat ["Xenical"]
Antihypertensives

Valscecia ME et al (Dept Pharmacology, Facultad de Med, Univ Nacional del Nordeste, Reg Pharmacovigilance Centre Northeast Argentina, Moreno 1240 3400-Corrientes, Argentina; e-mail: mvalscecia@med.unne.edu.ar) Interaction between orlistat and antihypertensive drugs. Ann Pharmacother 35:1496–1497 (Nov) 2001

ZAFIRLUKAST

Severe Hepatotoxicity

A 55-year-old female patient developed severe hepatitis within five months after starting zafirlukast (20 mg twice daily) for asthma. The only concurrent medication was albuterol sulfate nasal spray. Upon admission, abnormal laboratory values included aspartate aminotransferase (655 U/L), alanine aminotransferase (1213 U/L), and gamma glutamyl transferase (12.15 ukat/L). Prior to the initiation of zafirlukast, baseline liver function tests were normal. Laboratory screenings for infectious etiologies were negative. In addition, ultrasound tests of the abdominal and liver areas were within normal limits. A liver biopsy revealed submassive hepatic necrosis with eosinophilic infiltrates. Once zafirlukast was discontinued, the patient’s symptoms quickly improved, and liver function tests normalized within two months.

The authors concluded that zafirlukast was responsible for hepatic injury in this patient. A mechanism of action was not provided.

Zafirlukast ["Accolate"]

LACTULOSE
Pneumatosis Intestinalis, Pneumoperitoneum

A 57-year-old male patient with cryptogenic cirrhosis was admitted for mental status changes and abdominal pain. Medications upon admission included neomycin (2 g daily) and lactulose (30 mL orally, three times daily). Upon admission, the lactulose dose was increased to 45 mL four times daily with the addition of lactulose enemas. Because the patient only experienced bowel movements after enemas, the lactulose dose was increased to 60 mL four times daily and bisacodyl tablets every evening. A computed tomography scan of the abdomen revealed free air and pneumatosis intestinalis. At this time, oral lactulose was stopped and daily lactulose enemas and antibiotics were started. A repeat x-ray of the abdomen three days after oral lactulose was stopped revealed resolution of peritoneal symptoms. No obstructions or tears were noted throughout the remainder of the hospital stay.

The authors concluded that pneumatosis intestinalis and free air developed in this patient secondary to lactulose therapy. The authors suggested that the lactulose interacted with colonic bacteria to produce gas in the intestinal lumen. The accumulated gas was able to penetrate the intestinal walls via microdefects, thus creating free air in the peritoneum. The authors suggested that clinicians be aware of this possible but unusual reaction associated with lactulose.

Lactulose [“Cephulac,” “Chronulac”]
Goodman RA & Riley TR (Hershey Med Center, PO Box 850, Mail Code H045, Hershey, PA 17033)

GEMFIBROZIL AND GLIMEPIRIDE
Interaction: Increased Plasma Concentrations

In a randomized, two-phase crossover study, 10 healthy adult volunteers were treated with gemfibrozil, placebo, and glimepiride. The mean age of the subjects was 23 years, and eight were women. All the women were taking concurrent oral contraceptives during the study. During phase one of the study subjects received gemfibrozil (600 mg) or placebo twice daily for three days. On the third day, one dose of glimepiride (0.5 mg) was administered with 150 mL of water. A two-week washout period separated the study phases. Gemfibrozil significantly increased the mean area under the curve of glimepiride by 23% (137.9 vs 169.9 ng.hr/mL) when compared to placebo. The mean half-life was only slightly but significantly prolonged (2.1-2.3 hours). A nonsignificant increase (14%) was also observed in peak serum concentrations of glimepiride when administered with gemfibrozil (31.3 vs 35.6 ng/mL).

The authors concluded that gemfibrozil moderately increased the plasma concentrations of glimepiride, possibly related to inhibition of cytochrome P450 2C9.

Gemfibrozil [“Lopid”]
Glimepiride [“Amaryl”]
Niemi M et al (Kivisto KT, Dept Clin Pharmacology, Helsinki Univ Central Hosp, PO Box 340, FIN-00029 HUS, Finland; e-mail: kari.kivisto@hus.fi) Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of glimepiride. Clin Pharmacol Ther 70:439–445 (Nov) 2001
NELFINAVIR AND ATORVASTATIN, SIMVASTATIN

Interaction: Increased Plasma Concentrations of Statins

In an open-labeled, sequential, multiple-dose study, 32 healthy volunteers received atorvastatin and simvastatin with nelfinavir. The subjects were divided into two groups. Group one received atorvastatin (10 mg once daily) for the first two weeks and received atorvastatin and nelfinavir (1250 mg twice daily) for an additional two weeks. Group two received simvastatin in the morning (20 mg daily) for two weeks and received simvastatin with nelfinavir (1250 mg twice daily) for an additional two weeks. Mean peak serum concentrations and area under the curve (AUC) at 24 hours of atorvastatin were increased by 122% (16.4 vs 7.4 ng-eq/mL) and 74% (134 vs 77 ng-eq-hr/mL) after the addition of nelfinavir. Time to peak concentrations were not affected (5 hours). Larger increases were also noted with simvastatin for peak plasma concentrations with a 517% increase (45.7 vs 7.4 ng-eq/mL) and a 505% increase in AUC (255 vs 42 ng-eq-hr/mL). Time to peak concentrations increased by a mean of one hour (3-4 hours) after the addition of nelfinavir to simvastatin therapy. Nelfinavir in combination with atorvastatin and simvastatin was reported as well tolerated, with 27 subjects reporting a total of 64 adverse events. A total of 38 of these events were considered treatment related. The most frequently reported events included diarrhea (17), rash, and headache.

The authors concluded that the administration of nelfinavir increases the steady-state simvastatin concentrations extensively and increases atorvastatin concentrations moderately. A suggested mechanism of action was inhibition of P450 enzyme 3A4 metabolism of the statins by nelfinavir. The authors recommended that coadministration of simvastatin with nelfinavir be avoided and that concomitant atorvastatin and nelfinavir be used with caution.

Nelfinavir ["Viracept"]
Atorvastatin ["Lipitor"]
Simvastatin ["Zocor"]


STIBOGLUCONATE

Bone Marrow Dyserythropoiesis

A 37-year-old male AIDS inpatient developed severe anemia within three weeks after starting intravenous sodium stibogluconate (850 mg daily) for the treatment of a Leishmania infection. Hemoglobin was reduced to 6.9 g/dL, requiring a red blood cell transfusion. Concurrent therapy included triple antiretroviral therapy and secondary prophylaxis therapy with cotrimoxazole. A bone marrow aspirate performed at this time revealed karyorrhexis in most of the nuclear red cell progenitors but no evidence of Leishmania spp. Stibogluconate therapy was discontinued. A repeat myelogram four weeks later revealed normal characteristics. During a one-year follow-up, there was no recurrence of either visceral leishmaniasis or anemia.

The authors concluded that this patient experienced stibogluconate-induced bone marrow damage. No mechanism of action was provided.

Stibogluconate ["Pentostam"]

Hernandez JA et al (Servico de Hematologia Hosp de Mataro, Carretera de Cirera s/n, 08304 Mataro, Barcelona, Spain; e-mail: jahernandez@csm.scs.es) Acute toxicity in erythroid bone marrow progenitors after antimonial therapy. Haematologia 86:1319 (Nov) 2001
MIRTAZAPINE
Peripheral Edema

A 60-year-old male outpatient developed peripheral edema and shortness of breath within one month after starting mirtazapine (45 mg at bedtime) for depression and anxiety. Other concurrent medications included aspirin (325 mg once daily), atenolol (75 mg daily), gabapentin (300 mg three times daily), naproxen (500 mg twice daily), and lorazepam (0.5 mg twice daily). Additional symptoms included a 9 kg weight gain during a one-month period. Within four days after discontinuing mirtazapine, the patient experienced significant reduction in peripheral edema. No rechallenge was performed, and the patient was started on paroxetine without edema recurrence during a four-month follow-up period.

The authors concluded that edema was possibly caused by mirtazapine in this patient, based on the temporal relationship between the drug administration and appearance of symptoms. Other possible causes may have been a change in medical status or blood pressure.

Mirtazapine [“Remeron”]
Kutscher EC et al (Coll Pharmacy, Univ Iowa, S443 Pharmacy Bldg, Iowa City, IA 52242-1112; e-mail: brian-lund@uiowa.edu) Peripheral edema associated with mirtazapine. Ann Pharmacother 35:1494–1495 (Nov) 2001

CHLOROQUINE
Retinopathy

A 55-year-old female patient was hospitalized with high fever, headache, and visual symptoms during chronic chloroquine prophylaxis therapy for malaria. Chloroquine was taken as 150 mg base product twice weekly for eight years. The total cumulative dose was 125 g. Visual symptoms included blurred distance vision, difficulty in reading, blind spots, and photophobia. Malaria was confirmed and treated with mefloquine. Symptoms of fever and headache resolved, but ocular symptoms persisted. A fundus examination revealed macular hyperpigmentation and depigmentation around the macula. Visual acuity was impaired but color vision was normal. The patient had taken no other drugs known to cause retinopathy and had no familial or personal history of macular dystrophy or retinal degeneration. Chloroquine prophylaxis was discontinued. Two years later, an ophthalmologic examination revealed the persistence of maculopathy.

The authors concluded that this patient experienced retinopathy after malaria prophylaxis with chloroquine for eight years. Possible mechanisms include chloroquine’s effect on the retinal pigment epithelium, occasionally progressing to a bull’s-eye maculopathy. The authors suggested that patients taking chloroquine undergo early eye examinations with follow-up exams every six months. They noted that a precise threshold cumulative dose for chloroquine retinal toxicity has not been established.

Chloroquine [“Aralen”]
Seven cases of increased INRs were noted with concurrent warfarin and rofecoxib or celecoxib.

**Patient 1.** A 55-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (3.5) within one week after starting celecoxib (100 mg once daily). Chronic medications included hydroxyzine, nefazodone, ranitidine, levothyroxine, cyclobenzaprine, and calcium with cholecalciferol. Despite withholding the warfarin dose for one day, the INR remained high (4.0). Celecoxib was discontinued after 18 days of therapy because of hematuria. INRs reduced to 2.3 at next testing approximately one month later.

**Patient 2.** A 74-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (4.1) within one month after starting rofecoxib (12.5 mg once daily). Chronic concurrent medications included aspirin, amitriptyline, atenolol, diltiazem, isosorbide dinitrate, simvastatin, ranitidine, alendronate, theophylline elixir, guaifenesin, calcium, triamcinolone, and sublingual nitroglycerin. The warfarin dose was reduced from 31.5 mg to 28 mg weekly, resulting in reduction of the INR to 2.7.

**Patient 3.** A 77-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (4.6) within two days after starting rofecoxib (12.5 mg once daily). Chronic medications included lisinopril, metoprolol, simvastatin, and ranitidine. A reduction in warfarin dosage from 24.5 mg to 17.5 mg weekly resulted in reduced INRs (1.8 to 2.8).

**Patient 4.** A 69-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (3.4) within two weeks after starting celecoxib (200 mg once daily). Other chronic concurrent medications included aspirin, trazodone, digoxin, terazosin, amlodipine, simvastatin, furosemide, potassium chloride, lisinopril, allopurinol, colchicine, theophylline, and albuterol inhaler. Within two weeks after celecoxib was discontinued, INRs reduced to 2.2. Two rechallenges of celecoxib resulted in INR increases to 4.7 and 4.4, respectively. Discontinuation again resulted in INR reductions to previous values.

**Patient 5.** A 75-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed bruising within three days after starting celecoxib (100 mg twice daily). Concurrent medications included amitriptyline and vitamin B complex with C. Rechallenge with celecoxib resulted in increased INR (4.1) within one week. Warfarin dosage reduction from 17.5 mg to 14 mg weekly brought INR values within previous ranges.

**Patient 6.** A 75-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (4.6) within two weeks after starting celecoxib (100 mg twice daily). Chronic concurrent medications included aspirin, digoxin, allopurinol, diltiazem, simvastatin, furosemide, lisinopril, and isosorbide dinitrate. Warfarin dosage reduction from 21 mg to 19.25 mg weekly resulted in reduced INRs (1.8 to 2.9). After celecoxib was stopped, warfarin dosages were increased to maintain therapeutic INRs.

**Patient 7.** A 79-year-old male patient, previously stabilized on warfarin with therapeutic INRs, developed increased INRs (3.4) within one week after taking celecoxib. Concurrent medications included digoxin, triamcinolone, salmeterol, albuterol, verapamil, and losartan. Warfarin dosage reduction from 38.5 mg to 31.5 mg weekly resulted in therapeutic INRs.

The authors concluded that previously stabilized patients experienced increased INRs after the initiation with rofecoxib or celecoxib. Possible inhibition of CYP2C9 metabolism or protein-binding interference was suggested. The authors recommended weekly INR monitoring during concomitant therapy until the INR is determined to be stable.

Rofecoxib ["Vioxx"]
Celecoxib ["Celebrex"]
Warfarin ["Coumadin"]

Stading JA et al (Sch Pharmacy Allied Health Professions, 2500 California Plaza, Omaha, NE 68178; e-mail: pharmdoc@radiks.net) Seven cases of interaction between warfarin and cyclooxygenase-2 inhibitors. *Am J Health Syst Pharmaco* 58:2076–2080 (Nov 1) 2001
CARVEDILOL
Hepatotoxicity

A 40-year-old male patient was admitted for pruritis and jaundice approximately six months after starting carvedilol therapy for hypertension. The dosage of carvedilol had been titrated to 50 mg twice daily over a six-month period prior to admission. The only other concurrent medication included lisinopril (20 mg daily) for the previous three years. Physical examination revealed no remarkable features with the exception of slight skin yellowing, dark urine, and proteinuria. Abnormal laboratory values included serum sodium (133 mEq/mL), alkaline phosphatase (202 U/L), lactate dehydrogenase (480 U/L), gamma glutamyl transferase (391 U/L), aspartate transaminase (204 U/L), and alanine transaminase (312 U/L). Serological screenings for infectious etiologies were negative. Treatment included intramuscular hydroxyzine (50 mg) and the discontinuation of carvedilol. Within three weeks, the liver function tests had normalized. One year later, the patient developed pruritic symptoms 10 days after starting metoprolol (12.5 mg twice daily). Liver function tests at that time were normal. Pruritus resolved after the metoprolol was stopped.

The authors concluded that this patient developed a rare case of hepatotoxicity related to carvedilol therapy. They recommended that patients taking carvedilol be monitored for signs and symptoms of hepatotoxicity.

Carvedilol [Coreg]
Hagmeyer KO & Stein J (Coll Pharmacy, Univ Toledo, 2801 W Bancroft St, Toledo, OH 43606; e-mail: Khagmey@unet.utohledo.edu) Hepatotoxicity associated with carvedilol. Ann Pharmacother 35:1364–1366 (Nov) 2001

SERTRALINE
Hypoglycemia

An 82-year-old female patient was admitted to the emergency room for hypoglycemia (32 to 76 mg/dL) approximately 25 days after starting sertraline (50 mg once daily) for mild depression. Concurrent medications included oral furosemide (20 mg daily), ramipril (5 mg daily), clopidogrel (75 mg daily), and a nitroglycerin patch (0.4 mg/hr for 12 hours). She also used lorazepam intermittently for anxiety (1 mg as needed). A physical examination upon admission revealed diaphoresis and slight confusion. Abnormal laboratory values, other than blood glucose, were low potassium (3.2 mEq/L). Glucose levels stabilized at 77 mg/dL, and the patient was discharged with instructions to stop both sertraline and furosemide. Three hours later, she was re-admitted with blood glucose of 29 mg/dL. Treatment included intravenous 50% dextrose and water. During a four-day hospital stay, no further episodes of hypoglycemia occurred. Serum concentrations of sertraline and its metabolite were not abnormally elevated but demonstrated prolonged half-lives. The patient was discharged. No further episodes of hypoglycemia occurred during a six-month follow-up period.

The authors concluded that sertraline was possibly related to this patient’s hypoglycemic episodes. Suggested mechanisms of action included direct effects of serotonin on serum glucose concentrations, increased insulin output, reduced gluconeogenesis, and increased insulin receptor sensitivity.

Sertraline ["Zoloft"]
Pollak PT et al (Suite 409, Bethune Bldg, Queen Elizabeth II Health Sci Centre, Victoria Gen Site, Halifax, Nova Scotia B3H 2Y9, Canada; e-mail: amioikinetics@hotmail.com) Sertraline induced hypoglycemia. Ann Pharmacother 35:1371–1374 (Nov) 2001
HERBAL REMEDY
Nicotine Intoxication (First Report*)

A healthy eight-year-old boy was hospitalized shortly after being treated with a topical herbal remedy for eczema. The product was applied to mild and moderate eczematous areas on the upper and lower limbs. Symptoms developed within 30 minutes and included dizziness, unsteadiness, and labored breathing. After taking a bath to wash the paste off, the child vomited and became unarousable. During ambulance transportation to the hospital, he vomited and regained consciousness intermittently. A physical examination upon hospitalization revealed dilated pupils, sweating, and bradycardia. Treatment included a single intravenous atropine dose (20 mcg/kg). Other laboratory and hematological parameters were within normal ranges. Because acute meningitis was suspected, broad-spectrum antibiotic therapy was initiated and the patient was admitted to an intensive care setting. Upon further investigation, it was revealed that the paste had been made from a ground mixture of tobacco leaves, lime, and freeze-dried coffee. Serum and urine sampling approximately 12 hours post symptom onset revealed a serum concentration of 89 mcg/L and 1430 mcg/L of nicotine and cotinine, respectively. In addition, urine concentrations were 1120 mcg/L and 6960 mcg/L, respectively. A diagnosis of nicotine intoxication was determined.

The authors concluded that this was the first report of acute nicotine toxicity resulting from dermal absorption of an herbal remedy. They recommended accurate history taking during hospital admissions for unexplained reasons.

Herbal Remedy
Davies P et al (Dept Paediatrics, Luton & Dunstable Hosp, Lewsey Rd, Luton LU4 ODZ, UK; e-mail: daviespatrick@hotmail.com) Acute nicotine poisoning associated with a traditional remedy for eczema. Arch Dis Child 85:500–502 (Dec) 2001

ENALAPRIL
Fatal Hepatotoxicity (First Report*)

A 80-year-old female patient was hospitalized with jaundice approximately one month after starting enalapril (5 mg daily) for the treatment of hypertension and mild heart failure. No other concurrent medications were mentioned. Enalapril was stopped on admission. Elevated laboratory values included conjugated bilirubin (17 mg/dL), alkaline phosphatase (1999 U/L), aspartate aminotransferase (585 U/L), alanine aminotransferase (244 U/L), and gamma glutamyl transferase (487 U/L). Serological screening for infectious etiologies was negative. The patient declined liver biopsy. Nine days post admission, the conjugated bilirubin increased to 46 mg/dL. A second abdominal ultrasound appeared unchanged and normal. Twenty days post admission, the patient developed grade III encephalopathy and severe coagulation disorders. Death occurred on hospital day 30. No autopsy was performed.

The authors concluded that this was the first case report of fatal hepatotoxicity related to enalapril therapy. A causality assessment via the Naranjo scale determined the likelihood for this adverse effect as probable. A specific mechanism of action was not provided.

Enalapril [*Vasotec*]
Gonzalez MA et al (Serv Internal Med, Hosp Univ Virgen del Rocío, c/San Salvador, 5, 41013 Sevilla, Spain; e-mail: magpuente@nacom.es) Fatal hepatotoxicity associated with enalapril. Ann Pharmacother 35:1492 (Nov) 2001 (letter)
<table>
<thead>
<tr>
<th>A.</th>
<th>ANNUAL INDEX</th>
</tr>
</thead>
</table>
| ACECLOFENAC | ANTIHYPERTENSIVES AND ORLISTAT  
  Loss of hypertension control, 330 |
| ACENOCOUMAROL | ANTIPSYCHOTICS  
  Thrombocytosis (neonatal), 128 |
| ACETAMINOPHEN | ANTIRETROVIRALS  
  Hepatotoxicity in pregnancy*, 320 |
| ACYCLOVIR AND VALACYCLOVIR | ARISTOLOCHIC ACIDS  
  FDA safety alert, 172  
  Nephropathy, 300  
  Product recall, 172 |
| ADVERSE DRUG REACTIONS | ARSenic TRiOXiDe  
  FDA alert, 96  
  QT prolongation, 2  
  Sudden death, 194  
  Torsades de pointes, 95  
  Ventricular tachycardia, 2 |
| ALATROVAFLOXACIN | ATORvASTATIN AND NELFINAVIr  
  Increased statin concentrations, 334 |
| ALENDRONATE AND NAPROXEN | AZATHIOPRiNE  
  Hypersensitivity, 162 |
| ALOSETRON | AZITHROMYCIN  
  Anaphylaxis*, 98 |
| AMANTADINE |  |
| AMIODARONE |  |
| AMOXICILLIN CLAVULANIC ACID |  |
| ANESTHESIA |  |
| ANTHRACYCLINES |  |
| ANTIBIOTICS |  |
| ANTICONVULSANTS |  |
| ANTIHYPERTENSIVES |  |
|  |  |

* = first reports
C.

CAFFEINE
Arrhythmia (fatal), 147
Hypokalemia in pregnancy, 311
Seizures, 139

CALCIUM GLUCONATE
Calcinosi cutis, 133

CAPECITABINE
Onycholysis, 260
Onychomadesis, 260

CARBAMAZEPINE
Cutaneous pseudolymphoma*, 205
Hypersensitivity syndrome (children), 143

CARBAMAZEPINE AND RITONAVIR
Interaction: carbamazepine concentrations increased, 38

CARVEDILOL
Hepatotoxicity, 339

CEFODIZIME AND VANCOMYCIN
Renal failure, 286

CELECOXIB
Cardiovascular events, 238
Gastrointestinal ulcersations, 173
Hepatitis (cholestatic), 48, 195, 207
Pleural effusion recurrence, 182
Renal failure, 200
Visual disturbances, 14

CELECOXIB AND WARFARIN
Increased INRs, 338

CEPHALEXIN
Allergic reaction: legal action, 116

CERIVASTATIN
FDA safety alert, 186, 225
Market withdrawal, 225

CETIRIZINE
Hepatitis*, 215

CHLORAMBUCL AND PREDNISONE
Seizures, 152

CHLORDIAZEPoxide
Undeclared ingredients in herbals, 69

CHLORDIAZEPoxide/CIDINIUM
Thrombocytopenic purpura, 222

CHLOROQUINE
Cardiac toxicity, 67
Retinopathy, 337

CHOLESTYRAMINE
Platelet gigantism*, 321

CIPROFLOXACIN AND METHADONE
Interaction: sedation, respiratory depression*, 7

CISAPRIDE
Contraindicated use, 19
QT prolongation in neonates, 170

CISATRACURIUM
Anaphylaxis, 328

CISPLATIN
Bradycardia, 142

CLARITHROMYCIN AND SIMVASTATIN
Rhabdomyolysis, 41

CLONAPAM
Burning mouth syndrome*, 224

CLOPIDOGREL
Aplastic anemia* 42

CLOZAPINE
Cardiomyopathy, 233
Pseudopheochromocytoma, 150
Pulmonary embolus, 82
Weight gain, 136

CLOZAPINE AND LAMOTRIGINE
Increased clozapine concentrations, 308

CLOZAPINE AND LISINOPRIL
Increased clozapine concentrations*, 180

CLOZAPINE AND QUETIAPINE
Granulocytopenia, 108

COCAINE
Ventricular dysfunction, 157

COLCHICINE
Rhabdomyolysis, 74

COLISTIN
Bronchoconstriction, 124

CONTRACEPTIVES (ORAL) AND FLUCONAZOLE
Interaction: increased estradiol concentrations, 246

CORTICOSTEROIDS
ADRs in COPD patients, 102
Avascular hip necrosis: legal action, 105
Fracture risk, 25

COUGH/COLD MEDICATIONS
Toxicity, 245

CYCLOPHOSPHAMIDE
Bladder carcinoma, 185

CYCLOSPORINE AND ST JOHN’S WORT
Decreased cyclosporine concentrations, 304

* = first reports
D.

DALTEPARIN
Alopecia, 117
Retroperitoneal bleeding, 50

DESIPRAMINE
Legal action, 78
Overprescription, 78

DESMPRESSIN
Cerebral edema, 65
Hyponatremia, 174

DEXAMETHASONE
ADRs in low birth weight infants, 24
Cardiac changes (fatal), 208
Cerebral tissue growth reduction (neonates), 55
Medication error: legal action, 106

DIAZEPAM
Prolonged sedation in neonates, 161

DICLOFENAC
Hemolytic anemia (fatal), 214
Hyperkalemic paralysis, 20

DIDANOSINE
Hepatic failure, 243

DIDANOSINE AND HYDROXYUREA
Pancreatitis, 26

DIGOXIN
Legal action, 3
Medication error, 3

DIGOXIN AND ITRACONAZOLE
Interaction: digoxin concentrations increased, 81

DILTIAZEM
Hyperpigmentation (photodistributed)*, 57

DIPHLHYDRAMINE
Cognitive ADRs in hospital elderly, 272

DIPHTHERIA, PERTUSSIS, POLIO VACCINE
Myopericarditis*, 235

DIRITHROMYCIN
Sudden death, 83

DOCETAXEL
Nail changes, 103

DOTHIEPIN
Increased risk of ischemic heart disease, 275

DOXEPI (TOPICAL)
Systemic ADRs, 112

DOXYCYCLINE AND WARFARIN
Bleeding, 145, 163

E.

ECSTASY
Myocardial infarction, 149

ENALAPRIL
Eosinophilic gastroenteritis*, 242
Hepatotoxicity (fatal)*, 342
Hyperkalemic paralysis, 39

ENOXAPARIN
Anticoagulation (excessive) 114
Fat necrosis, 18
Hepatic transaminases elevation, 28

ENTERAL FEEDING AND WARFARIN
Interaction: warfarin resistance, 290

EPHEDRA
Seizures, 139

ERGOTAMINE
Death: legal action, 107

ERYTHROPOIETIN
Alopecia, 9
FDA advisory, 59
Product tampering, 59

ESTROGENS AND FLUOXETINE
Galactorrhea, 77
Hyperprolactinemia, 77

ETANERCEPT
Injection site reactions, 218

F.

FAMCICLOVIR
Choreiform movements in dialysis patients*, 204

FENFLURAMINE
Aortic valve regurgitation, 11
Legal action, 11
Valvular heart progression, 68

FENOFLURABE
Liver fibrosis, 262
Serum creatinine elevations*, 256

FENOFIBRATE
Increased INRs, 201

FENTANYL
Coughing*, 168
Patch overdose due to surgical warming blanket*, 267
Urinary retention in infants*, 276

FILGRASTIM
FDA advisory, 59
Product tampering, 59

* = first reports
FLECAINIDE
ST segment elevation, 22

FLUCONAZOLE
Adrenal failure (acute), 111
Torsades de pointes, 110

FLUCONAZOLE AND CONTRACEPTIVES (ORAL)
Interaction: increased estradiol concentrations, 246

FLUCONAZOLE, RITONAVIR, AND MAPROTLINE
Interaction: overdose, cardiac conduction disorder, 282

FLUDARABINE
Autoimmune thrombocytopenia, 276

FLUOROURACIL
Mortality rate increase, 148
Photosensitivity, 49

FLUOXETINE AND ESTROGENS
Galactorrhea, 77
Hyperprolactinemia, 77

FLUTICASONE
Intracranial hypertension*, 123

G.

GATIFLOXACIN
Seizures, 280

GEMCITABINE
Alveolar hemorrhage (fatal)*, 270

GEMFIBROZIL AND GLIMEPIRIDE
Increased plasma concentrations, 333

GEMFIBROZIL AND SIMVASTATIN
Rhabdomyolysis (fatal), 295

GINKGO BILOBA
Cerebral hemorrhage, 27

GINSENG
Mania, 293

GLIMEPIRIDE AND GEMFIBROZIL
Increased plasma concentrations, 333

GLUCAGON
Hyponatremia, 97

GLYBURIDE AND IBUPROFEN
Hypoglycemia*, 61

GOLD
Keratitis, 309
Pneumonitis, 178

GREEN TEA
Reduced dietary iron absorption, 80

H.

HALOFANTRINE
Sudden death, 83

HALOPERIDOL
QT prolongation, 165

HALOPERIDOL AND OLANZAPINE
Neuroleptic malignant syndrome, 104

HENNA
Contact dermatitis, 37
Hemolysis in GP6D deficiency, 306

HEPARIN
Thrombocytopenia, 126, 229

HERBAL REMEDY
Arsenic poisoning, 199
Contamination, hypoglycemia, 283
Nicotine intoxication*, 341

HORMONE REPLACEMENT
Dry-eye syndrome, 318

HYALURONATE
Acute arthritis, 121, 167

HYDROCHLOROTHIAZIDE
Hyponatremic encephalopathy, 227

HYDROCORTISONE
Fatal candidiasis (neonates), 316

HYDROXYUREA AND DIDANOSINE
Pancreatitis, 26

I.

IBUPROFEN AND GLYBURIDE
Hypoglycemia*, 61

IMMUNE GLOBULIN (IV)
Hyponatremia, 118

INDINAVIR
Renal complications, 259

INFLIXIMAB
FDA safety alert, 297, 298
Heart failure risk, 298
Hepatitis (cholestatic), 54
Mortality, 273
Pulmonary aspergillosis*, 100
Tuberculosis, 278, 297

INSULIN
Legal action, 155
Medication error (fatal), 155

INTERFERON ALFA
Pulmonary hypertension*, 153
Rheumatoid arthritis, 220

* = first reports
INTERFERON BETA
BOOP*, 93
INTERFERON-RIBAVIRIN
Homicidal ideation*, 212
INTERLEUKIN-2
Hemolytic anemia, 254
INTOXICATIONS
Hospitalizations, 284
IOVERSOL
Sialadenitis, 319
IRINOTECAN
Mortality rate increase, 148
IRON DEXTRAN
ADRs in hemodialysis patients, 115
ISOTRETINOIN
Depression, 47
Ocular ADRs, 274
Suicide, 47
ITRACONAZOLE
Cardiac ADRs, 135
Congestive heart failure, 166
FDA safety alert, 135
Hepatic ADRs, 135
ITRACONAZOLE AND DIGOXIN
Interaction: digoxin concentrations increased, 81
KAVA
Hepatitis, 36, 198
Liver transplantation, 36
KETOROLAC
Anaphylaxis in NSAID-tolerant patient*, 87
LACTULOSE
Pneumatosis intestinalis, 332
LAMOTRIGINE AND CLOZAPINE
Increased clozapine concentrations, 308
LATANOPROST
Angina exacerbation*, 291
Migraines*, 70
LATEX
Anaphylaxis rates, 29
LETOZOLE
Hyperlipidemia*, 271
LEUCOVORIN
Mortality rate increase, 148
LEVODOPA
Sleep attacks, 158
LEVOFLOXACIN AND WARFARIN
Increased INRs*, 191
LEVOMETHADYL
Cardiac ADRs, 141
FDA safety alert, 141
LIDOCAINE
Conduction disturbances, 30
Seizures, legal action, 119
LINEZOLID
FDA alert, 72
Myelosuppression, 72, 299
LISINOPRIL AND CLOZAPINE
Increased clozapine concentrations*, 180
LITHIUM
Stuttering exacerbation*, 228
LORAZEPAM
Death, 76
Legal action, 76
Propylene glycol toxicity, 252
Respiratory arrest, 76
LOSARTAN
Mannitol toxicity, 91
M.

MAPROTILine AND RITONAVIR,
FLUCONAZOLE
Interaction: overdose, cardiac conduction disorder, 282
MEDICATION ERRORS
Rates in adult ICU patients, 302
Rates in pediatric hospitals, 11, 131
Rates in US hospitals, 253
MEFLOQUINE
Sudden death, 83
MELOXICAM
Ischemic colitis*, 71
MEPERIDINE
Medication error: legal action, 109
MESALAMINE
Bronchiolitis obliterans, 312
METFORMIN
Diarrhea, 326
METHADONE AND CIPROFLOXACIN
Interaction: sedation, respiratory depression*, 7
METHOTREXATE
Medication error: fatal bone marrow suppression, 223

*= first reports
Pancytopenia (single dose)*, 234
Stress fracture, 206

**METHYLPHENIDATE**
Esophageal lodging, 314

**METHYLPREDNISOLONE**
Hip necrosis, 202

**METHYLTESTOSTERONE**
Behavioral changes, 66

**METOCLOPRAMIDE**
Hemoglobinemia (fatal), 177

**MICONAZOLE (VAGINAL) AND WARFARIN**
Interaction: anticoagulation potentiation, 73

**MINOCYCLINE**
Pseudotumor cerebri, 226
Serum sickness, 46

**MIRTAZAPINE**
Bone marrow suppression, 255
Peripheral edema, 336

**MISOPROSTOL**
Uterine rupture, 317

**MMR VACCINE**
Allergic reactions, 56
ITP, 58

**MONENSIN**
Rhabdomyolysis (fatal)*, 303

**MONTELUKAST**
Churg Strauss syndrome, 151

**MOXIFLOXACIN**
Tachycardia, 16

**N.**

**NALBUPHINE**
Psychosis, 221

**NAPROXEN**
Interstitial nephritis, 130
Postop bleeding, legal action, 120

**NAPROXEN AND ALENDRONATE**
Gastric ulcers, 17

**NELFINAVIR AND ATORVASTATIN**
Increased statin concentrations, 334

**NELFINAVIR AND SIMVASTATIN**
Increased statin concentrations, 334

**NEVIRAPINE**
DRESS syndrome, 315

**NIFLUMIC ACID**
Cutaneous reactions (pediatrics), 127

**NIMESULIDE**
Hypoglycemia, 324
Hypothermia, 324

**NITROFURANTOIN**
BOOP, 43

**NSAIDs**
Gastrointestinal reactions, 31
Miscarriage risk, 53

**O.**

**OFLOXACIN**
Diabetes insipidus, 251

**OLANZAPINE**
Diabetes mellitus, 154
Hyperlipidemia, 248
Hypoglycemia, 85
Somnambulism*, 188
Writer’s cramp, 159

**OLANZAPINE AND HALOPERIDOL**
Neuroleptic malignant syndrome, 104

**ONDANSETRON**
Anaphylaxis, 281

**ORLISTAT AND ANTIHYPERTENSIVES**
Loss of hypertension control, 330

**OXYBENZONE**
Anaphylaxis, 90

**OXYCODONE**
FDA safety alert, 209

**P.**

**PANTOTHENIC ACID AND BIOTIN**
Eosinophilic pleuropericardial effusion*, 113

**PAROXETINE**
Cutaneous vasculitis*, 84
Decreased awareness of hypoglycemia, 305
Withdrawal syndrome, 64

**PEMOLINE**
Hepatotoxicity, 203

**PERGOLIDE**
Pleuropulmonary disease, 216

**PHENOL**
Cardiogenic shock, 327

**PHENYTOIN AND PHENOBARBITAL**
Hypersensitivity syndrome, 32, 143

**PHYTOESTROGENS**
Endometrial cancer, 307

**PILSICAINIDE**
ST segment elevation, 22

**PRANLUKAST**
Eosinophilic endomyocarditis*, 247

**PRAVASTATIN**
Liver fibrosis, 262

* = first reports
PREDNISONE AND CHLORAMBUCIL
Seizures, 152
PROCHLORPERAZINE
Photosensitivity, 49
PROPOFOL
Cough, persistent*, 285
FDA safety alert, 129
Increased mortality (pediatrics), 129
Keratitis, 289
Legal action: overdose and death, 217
PROTEASE INHIBITORS
Lipodystrophy, 79
PYRAZINAMIDE AND RIFAMPIN
Hepatitis (fatal)*, 125, 244
PYRIDOXINE
Metabolic acidosis, 197
QUETIAPINE
Cataracts*, 190
Hyperlipidemia, 248
Leukopenia*, 137
Tardive dyskinesia, 263
QUETIAPINE AND CLOZAPINE
Granulocytopenia, 108
RADIOCONTRAST MEDIA
Extravasation, 13
Legal action, 13
RAPACURONIUM
Market withdrawal: FDA alert, 88
RIFAMPIN AND PYRAZINAMIDE
Hepatitis (fatal)*, 125
RISPERIDONE
Retrograde ejaculation, 101
Tardive dyskinesia, 23
RISPERIDONE AND VALPROIC ACID
Interaction: valproic acid concentrations increased, 249
RITONAVIR AND CARBAMAZEPINE
Interaction: carbamazepine concentrations increased, 38
RITONAVIR, FLUCONAZOLE, AND MAPROTIline
Interaction: overdose, cardiac conduction disorder, 282
RITUXIMAB
CMV infection reactivation (fatal), 265
ROFECOXIB
Cardiovascular events, 238, 310
Nephritis, 181
ROFECOXIB AND WARFARIN
Increased INRs, 338
ROSIGLITAZONE
Pulmonary edema, 34
ROTAVIRUS VACCINE
Infantile intussusception, 62, 169
SEDATIVES
Legal action, 144
Respiratory failure, 144
SELEGILINE
Hypertensive crisis*, 187
SENSIDES
Dermatitis mimicking abusive burns*, 6
SERTALINE
Decreased awareness of hypoglycemia, 305
SERTRALINE
Hypoglycemia, 340
Migraines*, 301
SILDENAFIL
Cardiovascular ADRs, 99
SIMVASTATIN
Liver fibrosis, 262
Memory loss*, 175
SIMVASTATIN AND CLARITHROMYCIN
Rhabdomyolysis, 41
SIMVASTATIN AND GEMFIBROZIL
Rhabdomyolysis (fatal), 295
SIMVASTATIN AND NELFINAVIR
Increased statin concentrations, 334
SIROLIMUS
Osteonecrosis, 269
SPIRONOLACTONE
ADRs in CHF patients, 92
STAR FRUIT
Oxalate nephropathy, 45
STIBOGLUCONATE
Bone marrow damage, 335
ST JOHN’S WORT AND CYCLOSPORINE
Decreased cyclosporine concentrations, 304
SULFADIAZINE
Crystalluria, 288

* = first reports
**SULFONYLUREAS AND SULFONAMIDES**  
Cross-hypersensitivity, 60

**T.**

**TATTOOING**  
Bacterial endocarditis*, 4

**TERBINAFINE**  
Cutaneous lupus, 277  
FDA safety alert, 134  
Hepatic ADRs, 134, 258  
Pancytopenia, 258

**THALIDOMIDE**  
Deep-vein thrombosis, 236  
Insomnia, 122

**THEOPHYLLINE**  
Hyponatremia, 52

**THIORIDAZINE**  
Visual loss (acute)*, 140

**TICLOPIDINE**  
Colitis, 184  
Pulmonary disease, 184

**TOPIRAMATE**  
Depression, 264  
FDA Alert, 266  
Glaucoma, 219, 325  
Myopia (acute)*, 146, 266  
Suicidal ideation, 264

**TRAMADOL**  
Dependence, 183

**TRETINOIN**  
Photosensitivity, 49

**TRIAMCINOLONE**  
Hip necrosis, 202

**TRIMETHOPRIM**  
Hyponatremia, 52

**TRIMETHOPRIM/SULFAMETHOXAZOLE**  
Interstitial nephritis (acute) in renal transplant patient*, 33

**TROGLITAZONE**  
Pulmonary edema, 34

**V.**

**VACCINATIONS**  
Seizure risk, 237

**VALACYCLOVIR**  
Choreiform movements in dialysis patients*, 204

**VALACYCLOVIR AND ACYCLOVIR**  
Cross-sensitivity, 250

**VALPROATE**  
Cutaneous pseudolymphoma*, 205  
Thrombocytopenia, 1

**VALPROIC ACID AND RISPERIDONE**  
Interaction: valproic acid concentrations increased, 249

**VANCOMYCIN**  
Confusion, 138  
Lactic acidosis, 138

**VANCOMYCIN AND CEFODIZIME**  
Renal failure, 286

**VENLAFAXINE**  
Hair loss*, 176

**VERAPAMIL**  
Legal action, 8  
Medication error, 8  
Toxicity after product substitution, 86

**VERTEPORFIN**  
Syncope, coma, 44

**VIGABATRIN**  
Retinal dysfunction, 323

**VITAMIN D3**  
Hypercalcemia, 192

**W.**

**WARFARIN AND CAPECITABINE**  
FDA alert, 294  
Increased INRs, 294

**WARFARIN AND CELECOXIB**  
Increased INRs, 338

**WARFARIN AND DOXYCYCLINE**  
Bleeding, 145, 163

**WARFARIN AND ENTERAL FEEDING**  
Interaction: warfarin resistance, 290

**WARFARIN AND FENOFIBRATE**  
Increased INRs, 201

**WARFARIN AND LEVOFLOXACIN**  
Increased INRs*, 191

**WARFARIN AND MICONAZOLE (VAGINAL)**  
Interaction: anticoagulation potentiation, 73

**WARFARIN AND ROFECOXIB**  
Increased INRs, 338

**Z.**

**ZAFIRLUKAST**  
Hepatic dysfunction, 21, 331

**ZIDOVUDINE**  
Hepatic failure, 243

**ZINC SULFATE**  
Increased ADRs in elderly, 257

* = first reports