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Drug-induced Thrombocytopenia: Pediatric Cases from the Medical Literature

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Drug-induced thrombocytopenia (DITP) is a rare, but potentially serious adverse medication reaction. Over 100 drugs have been linked with DITP, many commonly used in children. It often goes unrecognized, attributed to sepsis or mistaken for immune thrombocytopenic purpura (ITP).[1-5] This issue of *Pediatric Pharmacotherapy* provides a brief overview of mechanisms underlying DITP, describes recent reports of this adverse effect in children reported in the medical literature, and provides additional resources for patient evaluation and management.

Definition and Proposed Mechanisms

Drug-induced thrombocytopenia occurs when drug exposure leads to an accelerated clearance of platelets through the reticuloendothelial system. It is not associated with suppression of platelet production. Patients typically present with petechiae and bruising, often accompanied with flu-like symptoms (fever, chills, nausea, and vomiting). A small number of cases will progress to severe thrombocytopenia (a platelet count < 20,000/mm^3) and serious bleeding. In rare cases, DITP has been fatal.

There are currently six different mechanisms proposed for the development of ITP. Most cases of DITP result from production of drug-dependent antibodies that bind to specific epitopes on platelet surface glycoproteins. Sensitizing drugs are believed to bind to both the antibody and the platelet surface, forming tight bonds at glycoprotein IIb/IIIa or Ib/V/IX complexes, the primary receptors for fibrinogen and von Willibrand factor. Drug-dependent antibodies usually develop after 5-14 days of exposure to the drug, but may occur at longer intervals in drugs given intermittently. Symptoms generally begin to resolve within days of drug discontinuation, and platelet counts typically return to baseline within a week. Although drug-dependent antibodies may persist for months to years, thrombocytopenia will not recur unless the drug is reintroduced.[1-5]

Diagnosis

In 1998, George and colleagues devised a set of criteria for assessing reports of DITP and levels of evidence for establishing a particular drug as the cause of thrombocytopenia in an individual patient.[2] In order to meet the definition of DITP, drug administration must have preceded the development of thrombocytopenia (defined as a platelet count less than 100,000/mm^3), and discontinuation must have produced complete resolution. In addition, alternative causes must have been excluded. Other drugs used during the period in question must have been continued or re-introduced after resolution of the thrombocytopenia to rule out their role. Lastly, any re-introduction of the drug must have produced recurrent thrombocytopenia. While developed for analyzing published cases, these criteria are also useful for establishing the diagnosis of DITP in the clinical setting and for determining the need for drug discontinuation.

In addition to clinical assessment, the relationship between the drug and the development of DITP may be confirmed through documentation of drug-dependent anti-platelet antibodies. A number of techniques exist for detecting the presence of antibodies. Although identification of heparin-induced antibodies is fairly routine, laboratory testing for antibodies associated with other drugs may take several days for completion and may not be available at all institutions. While a positive test is useful for establishing the need for avoiding the drug in the future, negative results do not definitively exclude DITP, since antibody titers may be too low to detect.[1-4]

Drugs Associated with DITP

Aster, George, and their colleagues from the University of Wisconsin and the University of Oklahoma have written extensively on the

diagnosis and management of DITP for more than a decade.[1-4] They completed their first systematic review of DITP cases in 1998 and have published several updates since that time. Based on these reviews, the authors have compiled a list of drugs commonly associated with DITP in adults (Table).[1]

Table. Drugs Most Frequently Linked to DITP[1]

Abciximab	Interferon-α
Acetaminophen	Linezolid
Carbamazepine	LMW heparins*
Chlorothiazide	Methyldopa
Chlorpropamide	Nalidixic acid
Cimetidine	Naproxen
Cyclosporine	Oxaliplatin
D-penicillamine	Phenytoin
Danazol	Procainamide
Diazepam	Quinidine
Diclofenac	Quinine
Efalizumab	Ranitidine
Eptifibatide	Rifampin
Fludarabine	Tirofiban
Gold salts	Trimethoprim/ sulfamethoxazole
Heparin	Valproic acid
Hydrochlorothiazide	Vancomycin
Ibuprofen	
Infliximab	

* LMW, low-molecular-weight

In addition to their systematic reviews, these investigators have created a very useful resource, Platelets on the Web, available at www.ouhsc.edu/platelets (accessed 8/10/10). The site contains lists of drugs associated with DITP, both in single case reports and larger case series, as well as a list of potential foods, beverages, complementary and alternative medicines, dietary supplements, and herbal products that may produce DITP. Links to recent articles on diagnosis and testing methods are also provided, as well as a patient's description of his experience having DITP.

Pediatric Case Reports and Series

Although it appears to occur less frequently in children than adults, DITP should always be included in the differential diagnosis of acute thrombocytopenia. Many cases of DITP in children are initially misdiagnosed as ITP. This was illustrated in a recent report from Biner and colleagues, who described a 6-year-old girl admitted with a platelet count of 24,000/mm^3 who was diagnosed with ITP.[6] A bone marrow aspiration revealed increased megakaryocytes, indicating response to on-going platelet destruction. She received corticosteroids and intravenous immune globulin for 6 months without improvement. At a follow-up visit, it was noted that the patient had been receiving isoniazid and rifampin for pulmonary tuberculosis throughout the previous 8 months. Both drugs were discontinued, and the patient's platelet count rose to normal values in a week.

In an attempt to assess the incidence of pediatric DITP, Bertuola and colleagues (sponsored by the Italian National Institute of Health) conducted a multi-center prospective study of medication use in children admitted with a diagnosis of thrombocytopenia or bleeding over an 8-year period.[7] During admission, a careful medication history was obtained for each child to identify medication exposure within the previous 3 weeks or vaccine administration within the previous 6 weeks. A total of 387 cases of thrombocytopenia were identified and compared to 1,924 controls. The drugs identified in this study are similar to those reported by Aster's group. Use of antibiotics was associated with a 2-fold increase in the risk for thrombocytopenia (OR 2.4, 95% CI 1.8, 3.1). Mucolytics, non-steroidal anti-inflammatory agents, acetaminophen, and the measles, mumps, rubella (MMR) vaccine were also associated with an increased risk.

Heparin

Immune-mediated heparin-induced thrombocytopenia (HIT) is the most commonly reported cause of DITP. Unlike other DITP cases, HIT rarely produces bleeding and can result in thrombosis. The diagnosis of HIT should be considered in any patient with more than a 30-50% decline in platelet count after approximately 5-14 days of treatment. Onset may be much more rapid (1-2 days) in patients with previous heparin exposures. The mechanism underlying the development of HIT is complex. Heparin-dependent antibodies bind to the complexes formed by heparin and platelet factor 4, activating platelets through FcγIIa receptors. The activated platelets release microparticles which cause thrombin generation. Diagnosis may be confirmed through either immunoassays to detect antibody or functional assays to evaluate the degree of platelet activation.[4-6]

It is estimated that 5% of adults given heparin will develop HIT.[5,8] The incidence in pediatric patients is estimated to be only 0.5-1.5%.[8,9] There are relatively few reports of pediatric HIT in the literature, but this may reflect under-reporting as much as a true difference between children and adults. In 2008, Schmitz and colleagues described HIT in a 15-year-old boy with dilated cardiomyopathy receiving heparin

for prevention of intracardiac thrombosis.[10] After 4 weeks of treatment, the patient experienced a sudden drop in platelet count by approximately 50%. While awaiting immunoassay confirmation of the HIT diagnosis, the patient's condition deteriorated to the point at which implantation of a left ventricular assist device (LVAD) was required. Heparin was continued during LVAD placement, but replaced with argatroban when the assay results were reported as positive. The patient was later successfully transitioned to warfarin. Heparin was later used during cardiac transplantation without further complications.

Last year, Maurer and colleagues reported HIT in an obese 11-year-old girl receiving heparin followed by enoxaparin for deep vein thrombosis (DVT) that developed when she was hospitalized for lobar pneumonia.[11] On treatment day 16, she developed acute thrombocytopenia and recurrent DVT in both legs, and bilateral pulmonary emboli. Immunoassay testing for HIT was positive. The patient was placed on bivalrudin, then later warfarin and fondaparinux. She continued to develop thromboses until she was stabilized on argatroban and warfarin. She successfully transitioned to warfarin alone and was discharged on hospital day 141.

Antiepileptic Drugs

Several antiepileptic drugs have been associated with DITP. Valproic acid is one of the more frequently reported causes. In 2008, Nasreddine and Beydoun conducted a prospective, multi-center, double-blinded trial to evaluate the effect of high versus low trough valproic acid concentrations on platelet count.[12] They assessed a total of 851 valproic acid concentrations and concomitant platelet counts from 265 patients between 10 and 75 years of age. Seventeen percent of the patients experienced at least one period of thrombocytopenia. The probability of developing thrombocytopenia was strongly correlated with trough values. None of the patients experienced severe bleeding, but 5% withdrew due to thrombocytopenia. All patients recovered after discontinuation or dose reduction. The dose-response relationship and the ability of some patients to tolerate resuming treatment suggest that this may not be an immune-mediated form of DITP.

Although previously reported in only a few adults, levetiracetam-induced thrombocytopenia was recently described in a 6-year-old child.[13] The patient had been placed on levetiracetam for seizures associated with a cerebral venous thrombosis. Five weeks after starting therapy, he developed petechiae on the skin and mucosa. Other than thrombocytopenia, laboratory studies were unremarkable. Bone marrow aspiration revealed only increased megakaryocytes. As no other causative agents appeared likely, levetiracetam was discontinued. Within days, the platelet count began to increase and normalized 4 weeks after discontinuation.

Vancomycin

Dilli and colleagues recently described a case of DITP associated with vancomycin use in a premature infant born at 32 weeks gestation.[14] Vancomycin was started on day of life 25 and continued once a blood culture grew coagulase-negative staphylococcus. After 7 days of treatment, the patient's platelet count dropped to 47,000/mm^3. Coagulation studies and interleukin-6 levels were normal. The diagnosis of DITP was made and vancomycin was discontinued, despite the inability to detect vancomycin-dependent antiplatelet antibodies. The platelet count began to rise 3 days later, reaching 337,000/mm^3 within 10 days.

Imipramine

In 2009, Aksoy and colleagues reported an unusual case of immune-mediated DITP caused by imipramine.[15] The patient, a 5-year-old boy was being treated for attention-deficit-hyperactivity disorder with imipramine 10 mg daily. At his one week follow-up, he was noted to have petechiae on both legs. A platelet count obtained at that time was 18,000/mm^3. There were no other abnormalities. Increased megakaryocytes were noted on the bone marrow aspiration smear. Imipramine was discontinued and the patient was treated with methylprednisolone. Within a week, his platelet count had risen to 391,000/mm^3. He recovered without sequelae.

Pantoprazole

Several case reports of proton pump inhibitor-associated thrombocytopenia in adults have been published, but Miller and colleagues have recently reported the first pediatric case.[16] They describe a 9-day-old female born at 38 weeks gestation. She was diagnosed with hypoplastic left heart and underwent a Norwood procedure. Her postoperative course was complicated by sepsis and disseminated intravascular coagulation. During her recovery, she was placed on pantoprazole for stress ulcer prophylaxis. Following a bi-directional Glenn procedure on hospital day 75, the dose of pantoprazole was doubled to 1 mg/kg every 12

hours. Six days later, her platelet count dropped to 37,000/mm^3. No other laboratory values were abnormal. Other potential drug causes were ruled out. Pantoprazole was discontinued and replaced with omeprazole 1 mg/kg/day. Her platelet count began to rise within 4 days. Although a causal relationship could not be firmly established, the authors suggest that clinicians be aware of the potential for thrombocytopenia in patients receiving pantoprazole.

Management of DITP

Patients with mild petechial hemorrhages and bruising rarely require any treatment beyond discontinuation of the causative agent. Those with severe thrombocytopenia may require transfusion to avoid progression to intracranial or pulmonary hemorrhage. Corticosteroids, intravenous immune globulin, and exchange transfusions have been used in the management of DITP, but there are no adequate studies to demonstrate clear benefit from these therapies. Once the causative drug has been identified, the patient and/or family should be aware of the need to avoid this drug in the future. Information about the drug reaction should be included in the patient's medical record and reported through the Food and Drug Administration's MedWatch Adverse Event Reporting System at www.accessdata.fda.gov/scripts/medwatch/ (accessed 8/14/10).[1-4]

Summary

Although not as commonly reported in children as it has been in adults, DITP can lead to serious complications. The potential for DITP should be considered in any patient who develops unexpected thrombocytopenia.

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