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Pradaxa® for Pediatric Venous Thromboembolism

By: Antonietta Paneccasio, Pharm.D.

Background: Pediatric venous thromboembolism (VTE) is a serious condition associated with increased mortality and significant complications including pulmonary embolism, cerebrovascular events, and postthrombotic syndrome.[1] The incidence of VTE in children in the general population is relatively low at 0.07 to 0.14 per 10,000. However, the rate increases in hospitalized pediatric patients by 100- to 1000-fold to ≥58 per 10,000 admissions due to the increase in VTE risk factors with central access devices being the single most common contributing factor. The standard of care (SOC) for treatment and secondary prevention of VTE in children has historically been limited to the use of low-molecular-weight heparin (LWMH), unfractionated heparin (UFH) or oral vitamin K antagonists (VKAs).[1,2] Current guidelines do not include recommendations for direct oral anticoagulants for VTE in children.[3] However in June of 2021, dabigatran (Pradaxa®; Boehringer Ingelheim Pharmaceuticals) received approval from the Food and Drug Administration for treatment of VTE in pediatric patients 8 to <18 years of age following administration of a parenteral anticoagulant for at least 5 days, and for recurrence prevention of VTE in those who have received previous treatment.[4]

Mechanism of Action: Dabigatran is an oral direct thrombin inhibitor that reversibly inhibits free and fibrin-bound thrombin.[4,5] Since thrombin enables the conversion of fibrinogen to fibrin in the coagulation cascade and promotes platelet aggregation, its inhibition prevents thrombus formation.[4]

Clinical Trials: The pediatric indications for dabigatran were based on two clinical trials.[2,6] The use of dabigatran for VTE in pediatric patients was evalu-

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Mifepristone and Misoprostol for Early Pregnancy Loss

By: Elizabeth Ridgway, Pharm.D.

Background: Mifepristone is a synthetic steroid derivative, which binds competitively to the progesterone receptor.[1] It is approved by the Food and Drug Administration (FDA) for the medical termination of intrauterine pregnancy, also called medical abortion, up until the 70th day of gestation. Misoprostol (Cytotec®; Pfizer), a prostaglandin E_1 analog, promotes the activation of a positive feedback cycle leading to uterine contractions.[2,3] The American College of Obstetricians and Gynecologists (ACOG) 2018 Practice Bulletin recommends using mifepristone in combination with misoprostol to manage early pregnancy loss or miscarriage.[4] This combination is recommended specifically for a subset of miscarriages called "missed" miscarriages in which the gestational sac containing the nonviable fetus remains fully or partially intact in the uterus. Misoprostol and mifepristone work in synergy to facilitate vigorous uterine contractions which expel the gestational sac.[5] Mifepristone "primes" the uterus increasing

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ated in a multi-center, randomized, controlled, open-label, phase 2b/3, non-inferiority study (DIVERSITY).[2] A pediatric age-adjusted and weight-adjusted dosing regimen of dabigatran was compared to SOC which included LMWH, UFH, VKAs, or fondaparinux. A dosing nomogram was used to calculate the dose, utilizing the patient's age and weight. The study included patients <18 years of age with an acute VTE who were initially treated with parenteral anticoagulation and required anticoagulation for at least 3 months. Patients were randomized 1:2 to receive either SOC (n=90) or dabigatran (n=177) and were stratified by age. The three stratified age groups were as follows: ages 12 to <18 years, 2 to <12 years, and birth to <2 years. Dabigatran capsules were used in patients ages 8 to <18 years, pellets were used in patients <8 years, and the oral solution was available for patients ages birth to <12 months. The primary composite outcome was the proportion of children with complete thrombus resolution and freedom from recurrent VTE and VTE-related death. Select secondary outcomes included freedom from major bleeding and pharmacokinetic/pharmacodynamic (PK/PD) assessments at time intervals outlined in the study criteria. The primary composite outcome of complete thrombus resolution, freedom from recurrent VTE and VTE-related death was met by 38 (42%) of children treated with SOC and by 81 (46%) of children treated with dabigatran ($p<0.0001$ for non-inferiority). The incidence of major bleeding events among the SOC and dabigatran groups was similar ($p=0.96$). The pediatric PK/PD profile was similar to the adult PK/PD profile. The authors concluded that dabigatran was non-inferior to SOC for treatment of acute VTE in pediatric patients <18 years of age with similar PK/PD parameters as in adults and could be considered as an alternative to SOC. The use of dabigatran for secondary prevention of VTE in children was evaluated in an open-label, single-arm, prospective cohort safety study following the DIVERSITY study.[6] Pediatric patients (>3 months to < 18 years of age) treated for VTE for ≥3 months with SOC, or who completed dabigatran or SOC treatment in the DIVERSITY study and had unresolved clinical thrombosis risk factors requiring further anticoagulation were included to receive dabigatran for up to 12 months. The primary endpoints were VTE recurrence, bleeding events, and mortality at 6 and 12 months. Of the 203 children who received dabigatran, two (1%) experienced on-treatment VTE and three (1.5%) experienced major bleeding. No on-treatment deaths were reported. The authors found that dabigatran showed a favorable safety profile for secondary VTE prevention in children >3 months to <18 years of age.

Safety: Dabigatran was associated with headache (10%), vomiting (8%), and abdominal pain (5%) as reported in the DIVERSITY trial.[2] Similar adverse effects were reported in the secondary prevention trial.[6]

Dosing and Administration: Dabigatran is given orally twice daily; the dosing interval should be as close to every 12 hours as possible at about the same times each day.[4] The recommended dose of dabigatran for pediatric patients ages 8 to <18 years is based on the patient's actual body weight. Weight-based dosing recommendations are listed in the package insert. Dabigatran should not be used in pediatric patients with an eGFR <50 mL/min/1.73 m^2. The dose should be administered with a full glass of water without regard to meals. The capsules should be swallowed whole without breaking, opening, or chewing.

Cost and Availability: Dabigatran is currently available as capsules in three different strengths: 75 mg (NDC 00597-0355-09), 110 mg (NDC 00597-0108-54), and 150 mg (NDC 00597-0360-55).[4] Dabigatran oral pellets were FDA-approved in June 2021, but are not yet available.[5] The average wholesale price for any strength of dabigatran is $9.54 per capsule. The average annual cost is approximately $6965, based on the typical dose for patients weighing 26 to 41 kg.

Formulary Status: Dabigatran is on the Pediatric CCHS Formulary restricted for initiation of therapy to the Departments of Pediatric Hematology and Oncology and Pediatric Cardiology for the treatment of active VTE. Continuation of therapy is not restricted. It is also on the Adult CCHS Formulary without restrictions.

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the rate of gestational sac expulsion associated with misoprostol from approximately 84% to 97%.[5-8]

Clinical Trials: Several recent trials have demonstrated that the use of mifepristone and misoprostol resulted in higher rates of successful medical management of missed miscarriage and lower rates of surgical intervention than mifepristone alone.[3,5] The MifeMiso trial, one of the largest of those investigations, was a parallel-group, double-blind, randomized, placebo-controlled, multi-center study conducted at 28 centers in the United Kingdom.[3] The primary endpoint was failure to pass the gestational sac within 7 days after randomization and the secondary endpoint was the need for surgical intervention before discharge. Women (N=711) diagnosed with missed miscarriage via ultrasound in the first 14 weeks of gestation were randomized to receive either mifepristone (n=357) or a matched-placebo (n=354) followed 48 hours later by misoprostol. Failure to pass the gestational sac with medical management was observed in significantly fewer women who received mifepristone and misoprostol than those who received misoprostol alone (17% vs. 24%, respectively; 95% confidence interval (CI) 0.54-0.99; p=0.043). Additionally, significantly fewer women in the active treatment group than the placebo group required surgical intervention (17% vs. 25%, respectively; CI 0.53-0.95; p=0.021). The incidence of adverse effects and the need for blood transfusion were similar between groups. The authors concluded that treatment with mifepristone plus misoprostol was more effective than misoprostol alone for managing missed miscarriages.

Dosing for Early Pregnancy Loss: Mifepristone is administered as a 200 mg oral tablet given once to manage early pregnancy loss, 24 hours before misoprostol use.[1] For the management of missed miscarriage, misoprostol 800 mcg (four 200 mcg tablets) is self-administered vaginally for two doses at least 24 hours apart.[4] Patients should follow-up with their healthcare providers within 7 to 14 days to confirm passage of the gestational sac.[2] If complete expulsion has not occurred, another dose of misoprostol 800 mcg may be administered or surgical management strategies should be considered.

REMS Requirements: Despite ACOG 2018 recommendations, the use of mifepristone is still relatively limited, partially due to a Risk Evaluation and Mitigation Strategy (REMS) program which restricts the use of mifepristone to specific care settings and providers.[9] For mifepristone, Elements to Assure Safe Use (ETSU) include Prescriber and Patient Agreement Forms. Mifepristone is available as Mifeprex® (Danco Laboratories) and generic mifepristone (GemBioPro) and each product has its own Prescriber Agreement Form. Only authorized providers, working under the supervision of a Designated Provider, can order mifepristone. Providers must ensure that appropriate patient education is conducted, consent has been obtained, and the serial number associated with mifepristone is documented in the medication administration record (MAR). Pharmacists must ensure that consent has been obtained before administration and that the mifepristone serial number has been documented within the MAR.

Cleveland Clinic Health-System Care Path: Mifepristone is available at the Cleveland Clinic Health-System (CCHS).[10] Consultation with providers in the Obstetrics, Gynecology, and the Women's Health Institutes is recommended for any patient who may be a candidate for mifepristone. The current Care Path associated with mifepristone is consistent with the ACOG 2018 Practice Bulletin, in which mifepristone is used for the management of missed miscarriage in combination with vaginally administered misoprostol.

Formulary Status: Mifepristone is currently on both the Adult and Pediatric CCHS Formularies restricted to Obstetrics/Gynecology providers who are REMS certified.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Anifrolumab (Saphnelo®)	Monoclonal Antibody	SLE	Restricted to the Department of Rheumatology for outpatient use only in patients with active, moderate-to-severe SLE not controlled on current therapy
Avalglucosidase Alfa (Nexviazyme®)	Enzyme	Pompe Disease	Restricted to Geneticists and the Department of Hematology/Oncology for outpatient use only
Tisotumab Vedotin (Tivdak®)	Monoclonal Antibody	Recurrent or Metastatic Cervical Cancer	Restricted to the Department of Hematology/ Oncology for outpatient use only

SLE=Systemic Lupus Erythematosus

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Cangrelor (Kengreal®)	Antiplatelet Agent	Bridging Prior to Cardiac Surgery	Modified restrictions to include use by Staff Physicians from Neuroendovascular
Chemotherapy Agents	Anticancer Agents	Various Cancers	Modified restrictions for oral and parenteral chemotherapeutic agents to allow qualified pharmacists to order subsequent doses of chemotherapy in the inpatient and outpatient settings
Olanzapine (Zyprexa®) Intramuscular	Antipsychotic Agent	Agitation/Aggression	Modified restrictions to include use in Code Violet (Ohio)/Code Grey (Florida) with or without Psychiatric consult

Denials and Removal from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Insulin Detemir (Levemir®)	Insulin	Diabetes	Due to low usage, insulin detemir will be removed from the CCHS Formulary and have an automatic therapeutic interchange to insulin glargine (Lantus®)*
Mirabegron (Myrbetriq®)	Beta Agonist	OAB	Due to the higher cost, a decision was made to convert all mirabegron orders to trospium via a therapeutic interchange*
Vibegron (Gemtasa®)	Beta Agonist	OAB	Due to the higher cost, a decision was made to convert all vibegron orders to trospium via a therapeutic interchange*

*Details are in Lexicomp
OAB=Overactive Bladder

Product Standardization and Process Change to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Pegfilgrastim (Neulasta®)	Colony Stimulating Factor	Neutropenia	Orders for pegfilgrastim (Neulasta®) injection/syringe will be converted to the biosimiliar pegfilgrastim-jmdb (Fuphila®). Note: The preferred onbody injector product will remain Neulasta® OnPro
Zolpidem (Ambien®)	Hypnotic Agent	Catatonia	A new order set for zolpidem for catatonia will be created.

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Avalglucosidase Alfa (Nexviazyme®)	Enzyme	Pompe Disease	Restricted to Geneticists and the Department of Pediatric Hematology and Oncology for outpatient use only
Brivaracetam (Briviact®) (Oral Formulations)	Antiepileptic Agent	Partial Onset Seizures	Restricted to continuation of therapy from home
Epoprostenol (Flolan®, Veletri®) Inhaled	Prostacyclin	Respiratory Distress	Restricted to ICU Staff Physicians with Pediatric Cardiology Consultation or Pediatric Cardiology Staff Physicians Administration will be restricted to the PICU (M-43), CC Laboratory, and M-40 Cardiac OR Suite*
Olanzapine (Zyprexa®) Intramuscular	Antipsychotic Agent	Agitation/Aggression	Restricted to the Departments of Emergency Medicine and Child and Adolescent Psychiatry
Siltuximab (Sylvant®)	Monoclonal Antibody	CRS Management	Restricted to the Department of Pediatric Hematology and Oncology and Blood and Bone Marrow Transplantation for the management of CRS following CAR modified T-cell therapy or blinatumomab therapy, as an alternative to tocilizumab

*For use in patients >10 kg. Intend to initially use in only the Cardiac Catheterization Laboratory with plans to expand to the other areas listed. A standard operating procedure for use is currently being developed.
ICU=Intensive Care Unit PICU=Pediatric Intensive Care Unit CC=Cardiac Catheterization OR=Operating Room
CRS=Cytokine-release syndrome CAR=Chimeric Antigen Receptor

Process and Procedural Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Intravenous Immune Globulin (IVIG)	Immune Globulin	Various Indications	Doses of IVIG will be automatically rounded to the nearest 5 grams as long as the dose remains within 10% of the originally ordered dose
Kcentra® (Prothrombin Complex Concentrate, Human)	Blood Product Derivative	Various Indications	Doses of Kcentra® will be automatically rounded to the nearest vial (500 units) for patients > 40 kg
Pediatric Anticoagulant Reversal Protocols	Anticoagulant Reversal Agents	Anticoagulant Reversal	The following pediatric anticoagulant reversal protocols have been approved: Warfarin-Induced Life Threatening Bleeds Associated with Cardiac Surgery and DOAC Anticoagulant Hemorrhage Reversal*

*The protocols have been reviewed and approved by physicians from Pediatric Heart Failure, Neurology, Anesthesia, Cardiothoracic Surgery, Emergency Medicine, and Hematology. Use of protocols will be limited to ICUs, ORs, and EDs throughout the enterprise.
DOAC=Direct Oral Anticoagulant