University HOSPITAL
Newark, NJ

Pharmacy News

First Quarter 2022
Vol. XV, Issue 1

Special Points of Interest:

- P&T Update-Formulary Additions/Deletions
- Neonatal IV Infusion Drips Standardization
- Tenecteplase Medication Guide
- Hazardous Wastes and Safe Medication Disposal
- Gilbert Syndrome

P&T Update

Formulary Additions

1. ***Papaverine/Phentolamine 30mg/1mg/ml (Bimix)***
   Papaverine/Phentolamine/Prostaglandin E1 30mg/1mg/10mcg/ml (Trimix)
   Phenylephrine 0.1% Intra-cavernosal injection

   REQUESTED INDICATIONS (NOT FDA-APPROVED): Erectile dysfunction
   Approved for Formulary Addition (Will need to order from EmpowerRx Compounding pharmacy)

   Bimix has been studied as an intra-cavernosal injection medication used for ED treatment in men. It has been approved for formulary addition with need to order from EmpowerRx Compounding Pharmacy.

2. ***Cefpodoxime***
   INDICATIONS (FDA-APPROVED): CAP, UTI, STI
   Approved for Formulary Addition – No restrictions

   Cefpodoxime is a third-generation cephalosporin (ceftriaxone comparable) with broad activity which maintains stability in certain beta lactamases. The most commonly prescribed dose is 200mg Q12H.

Formulary Deletions

1. ***Alprostadil (Edex®) intra-cavernosal injection***
   Manufacturer Discontinued. Formulary deletion approved.

2. ***Ethyl alcohol 99% 5mL***
   Papaverine/Phentolamine 30 mg/1mg/ml (Bimix), Papaverine/Phentolamine Alprostadil 30 mg/1mg/10 mcg/ml (Trimix), phenylephrine 0.1% Intra-cavernosal injection was added to formulary for use and Alprostadil was deleted – Deletion approved

Formulary Restriction Modification

None.

Policies & Procedures/Floor stocks

1. Accountability of Controlled Substances

   Policy defining the responsibility of paramedics and registered nurses for the controlled medications under their control during their shift and compliance with all accountability processes. – Approved

Adult Anti-Infective Dosing Adjustment Guideline

1. Updated dosing guidelines – Approved

   Adult Antiretroviral Dosing Adjustment Guideline
   Updated dosing guidelines – Approved

Clinical/Medication Guidelines

1. Tenectaplase Medication Guideline

   Presented medication guideline on Tenectaplase - **Informational**

University Hospital Formulary Additions and Deletions from January 2021 to December 2021

Generic Name	Brand Name	P&T Date	Approved	Denied	Deleted	Reason/Comments/ Criteria
Tretinoin		Jan-21	X			Oral, restricted to oncology services/home medication restricted to second sign
Cardioplegia Solution		Jan-21			X	
Methacholine Kit		Jan-21	X			Line Extension
Methacholine 100mg Vial		Jan-21			X	Deletion due to ready to use Kit
Methylene Blue 0.5%		Jan-21	X			Line extension due to 1% on back order for years
Sodium Zirconium Cyclosilicate	Lokelma	Feb-21	X			Approved for restriction status changed to being unrestricted
Insulin Lispro aabc 100 unit/mL kwikpen and multidose vial	Lyumjev	Feb-21	X			Medication sample addition to the ACC clinical F level
Dextromethorphan		Mar-21	X			Approved for Formulary addition with 48 hour duration limit for Use in Perioperative Pain Management
Capsaicin Cream		Mar-21	X			
Cabotegravir-Rilpivirine ER	Cabenuva	Apr-21	X			ID clinic will determine optimal patient selection
Glucose Oral Gel 40%	Sweet Cheek	Apr-21	X			Line Extension

Daratumumab	Darzalex	May-21	X			Approved for Formulary Addition with Restriction for use to Oncology Service
Diclofenac 1% Gel	Voltaren	May-21	X			
Fentanyl 10 mcg/mL Syringe		May-21	X			Line Extension
Tenecteplase	TNKase	Jun-21	X			
Doxylamine	Unisome	Jun-21	X			
Biotin 300mcg		Jun-21			X	Manufacturer Discontinued
Remimazolam	Byfavo	Jul-21	X			Six-month approval limited to those with procedural credentials within the GI suite.
Collagenase clostridium histolyticum	Xiaflex	Jul-21	X			Specialty pharmacy purchasing/WHITE-BAG process or ensuring cost coverage prior to initiating therapy
Sodium Tetradecyl Sulfate	Sotradecol	Oct-21	X			
Artesunate		Oct-21	X			ID consult service
Sodium citrate 4%		Oct-21	X			Patients with heparin allergies or HIT (or suspected HIT) for dialysis catheter locks
Alprostadil Intracavernosal injection		Nov-21	X			Urology clinic use only
Ethyl alcohol 98% 5mL		Nov-21			X	Patients with heparin allergies or HIT (or suspected HIT) for dialysis catheter locks

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University Hospital Formulary Additions and Deletions from January 2021 to December 2021

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Ethyl alcohol 99% 5mL		Nov-21	X			Line extension
Papaverine/Phentolamine 30 mg/1mg/ml	Bimix	Dec 2021	X			Will need to order from EmpowerRx Compounding Pharmacy
Papaverine/Phentolamine/Prostaglandin E1 30 mg/1mg/10 mcg/ml	Trimix	Dec 2021	X			Will need to order from EmpowerRx Compounding Pharmacy
Phenylephrine 0.1% intra-cavernosal injection		Dec 2021	X			Will need to order from EmpowerRx Compounding Pharmacy
Alprostadil intra-cavernosal injection	Edex	Dec 2021			X	Deletion due to alternatives approved

Contributed by:
Saeid Bayoumi, Pharm.D. Candidate 2022, Fairleigh Dickinson University, School of Pharmacy

Quality Assurance-Performance Improvement (QA-PI) Project Neonatal IV Infusion Drips Standardization

Background:
A collaborative effort by the Neonatology division, PCS and Pharmacy was undertaken to overhaul the neonatal intravenous medication drips including the standardization of the concentrations, volumes, diluents dosages, Epic build/Alaris pump library update, revision of the IV compounding area workflow and the staff education.

The **objective** was to enhance the neonatal patient safety and simplify the administration logistics by providing the drips in small volume syringes rather than bags which resulted in extra volumes/long tubing/wastage.

Operationalization:

1. ***Determining standard concentrations of the neonatal IV drips***
   a. Multidisciplinary collaboration with the Neonatologists, Pharmacy dept., and PCS to review the existing IV drip concentrations and updating them based on the standard references was undertaken.

b. The standard diluent was updated to dextrose 5 % and standard volume to 50 ml to enable dispensing in the syringes.
c. The standard IV drip concentration policy (707-500-115) was updated consequently and approved by the Pharmacy & Therapeutics Committee.
d. The sample update is outlined in the table below:

Neonatal Standardized Continuous Intravenous Infusion Drug Concentrations 2020-21

Notes: The neonatal IV drips dispensation should be in syringes (preferred).
D5W should be the preferred diluent unless specified otherwise or stability issues.

Generic Name	Brand Name	Standard Mix (optional mix)	Concentration (Optional conc.)	Diluents (Notes)
Alprostadil		500 mcg/50 mL	10 mcg/mL	D5W or NS
Amiodarone	Cordarone®	90 mg/50 mL	1.8 mg/mL	D5W (premix) or NS
DOBUTamine	Dobutrex®	100 mg/50 mL	2 mg/mL	D5W (premix) or NS
DOPamine		80 mg/ 50 mL 80-160 mg/50 mL	1.6 mg/ml 1.6 mg-3.2 mg/mL	D5W (premix) or NS
Epinephrine	Adrenalin®	3 mg/ 50 ml 1-3 mg/50 mL	0.06 mg/mL 0.02-0.06 mg/mL	D5W or NS
Esmolol	Brevibloc®	500 mg/50 mL	10 mg/mL	NS premix or D5W
Fentanyl		500 mcg/ 50 ml 100-1000 mcg/50 mL	10 mcg/ml 2-20 mcg/mL	D5W or NS
Heparin		500 unit/ 50 mL	10 units/mL	D5W or NS
Insulin		25 unit/50 ml 5-25 units /50 mL	0.5 units/mL 0.1-0.5 unit/mL	NS or D5W
Midazolam		25 mg/ 50 ml 5-25 mg/50 mL	0.5 mg/mL 0.1-0.5 mg/mL	D5W or NS
Milrinone		10 mg/50 mL	0.2 mg/mL	D5W(premix)
Morphine		10 mg/ 50 mL 5 mg/50 mL	0.2 mg/mL 0.1 mg/mL	D5W or NS
Norepinephrine	Levophed®	1.6 mg/ 50 mL 0.8 – 5 mg/ 50 mL	0.032 mg/ ml 0.016-0.1 mg/mL	D5W or NS
Vasopressin	Pitressin®	0.5 units/50 mL 2.5 units/50 mL	0.01 units/mL 0.05 units/mL	D5W or NS
Vecuronium	Norcuron®	10 mg/50 mL	0.2 mg/mL	D5W or NS

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Quality Assurance-Performance Improvement (QA-PI) Project – Neonatal IV Infusion Drips Standardization

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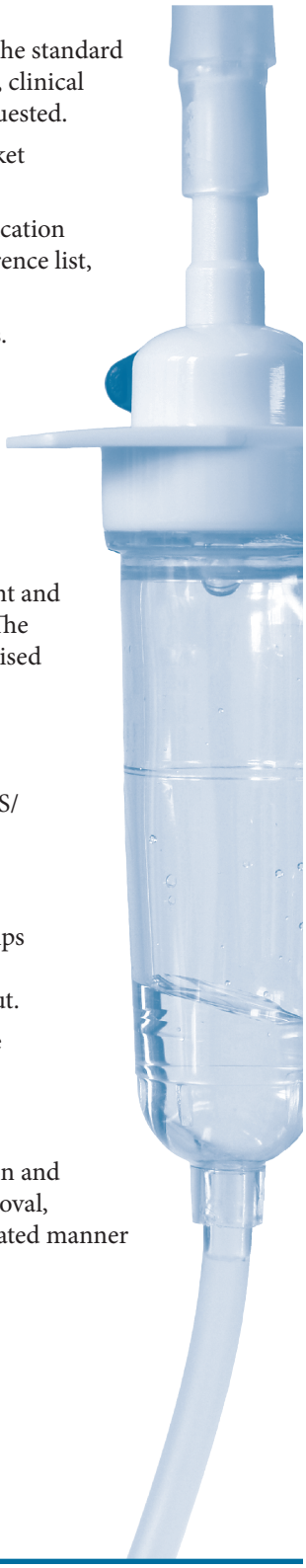
2. ***Heat ticket Submission for the IST update***
   a. A heat ticket for the EPIC build/update pertaining to the neonatal drips was submitted outlining the standard concentrations, alternative concentrations, volume, dosage, frequency, routes (central/peripheral), clinical advisory as applicable and any other pertinent areas. The Alaris pump library update also was requested.
   b. Comprehensive medication record building in the Epic testing environment based on the heat ticket submitted were undertaken by the IST.
   c. Validation ensued in the EPIC testing environment with the multidisciplinary group of each medication record with regards to only approved standardized concentrations available on the provider preference list, while ensuring that the correct diluent/syringe dispensation.
   d. Pump library update was undertaken and verified against the revised standardized concentrations.

3. ***Staff Education/Go live***
   a. Once all the components were validated/ready in the EPIC testing environment and pump, a go live date was selected.
   b. Staff education on the PCS/Pharmacy/Provider end ensued on the upcoming changes.
   c. Updated Alaris pump library was pushed out on the evening before the go live date.
   d. On the go live date, the IST moved the revised medication records in the EPIC PROD environment and replaced all the existing old records from EPIC/ preference lists/order sets with the revised ones. The pharmacy worked with the neonatology residents to reorder all the existing IV drips using the revised records.
   e. The IV room in the pharmacy dispensed these IV drips using syringes, in the new volume/ concentrations/diluent as ordered.
   f. The RNs administered the IV infusion drips using the syringe pumps with assistance from the PCS/ Pharmacy readily available in case of any issues.

4. ***Post Go live Assessment/Staff Feedback***
   a. No issues were encountered in any of steps with the go live: ordering/migration of the updated drips build in EPIC was without any glitches, IV room compounding/hook up assembly was seamless, administration to the patients was immaculate and communication to the staff was well carried out.
   b. Staff Nurse Feedback: The administration of the updated drips went smoothly. It was touted as the easiest transition the nurses had seen.



Concluding Remarks:

Overall, it was a project of tremendous undertaking to enhance safety of our vulnerable neonatal population and improve the logistics of medication ordering/compounding/administration. The planning, committee approval, execution, education and assessment were impeccably carried out by a multidisciplinary team in a coordinated manner and thanks to all for making it a success.

Contributed by: Neonatology Providers, Neonatology PCS, Pharmacy Department, IST, QA/PI
Submitted by: Dr. Nishat Faruqui/Pharm. D., BCPS

Tenecteplase Medication Guide

Indications/Dosing:

Indication	Tenecteplase Dose
Acute Ischemic Stroke (AIS) within 4.5 hours of last known well – *off label*	0.25 mg/kg, maximum 25 mg
Massive pulmonary embolism – *off label*	30 mg for <60 kg 35 mg for 60-69 kg 40 mg for 70-79 kg 45 mg for 80-89 kg 50 mg for ≥ 90 kg
Cardiac arrest secondary to pulmonary embolism – *off label*	
STEMI	

Mechanism of Action/Kinetics:

Tenecteplase binds to fibrin and converts plasminogen to plasmin. Tenecteplase is essentially alteplase with the exception of 3 point mutations and is more fibrin specific, more resistant to plasminogen activator inhibitor -1 (PAI-1), with a longer duration of action compared to alteplase

Comparison of Thrombolytic Agents

Thrombolytic	Infusion time	Generation	Direct plasminogen activator?	Half-life, min	Fibrin selectivity	PAI resistance*	FDA Indication	Formulary?
Alteplase	120 min (PE), 60 min (stroke), 1 min (cardiac arrest)	Second	Yes	4-8	++	++	PE, AIS, STEMI	Yes
Tenecteplase	5-10 seconds	Third	Yes	20-24 (initial), 90-130 (terminal)	+++	+++	STEMI	Yes

**PAI is a 52-kDa circulating glycoprotein that is the primary native of plasminogen-activating enzymes, and greater PAI resistance confers a longer duration of fibrinolysis*

Preparation & Administration (see page 3)

- Remove the tenecteplase 50mg/10mL kit after the order is placed in Epic
- Remove shield assembly from supplied 10 mL syringe
- Withdraw 10 mL of Sterile Water for Injection (SWFI) from the supplied diluent vial. Note: Do not use Bacteriostatic Water for Injection
- Inject 10 mL of SWFI into the tenecteplase vial directing the diluent stream into the powder, slight foaming is common
- Gently swirl until contents are completely dissolved (usually ~ 1 minute), DO NOT SHAKE
    - **Reconstituted preparation contains tenecteplase 5 mg/mL**
- Inspect the solution for particulate matter or discoloration (should be a colorless to pale yellow solution)
- Withdraw the appropriate volume of solution
- Administer as an IV bolus over 5 to 10 seconds using a peripheral vein
- Flush a dextrose-containing line with a saline-containing solution prior to and following administration (precipitation may occur when tenecteplase is administered in an IV line containing dextrose).

Contraindications:

- Overall, tenecteplase has similar contraindications to other thrombolytics, and should be used with caution in patients who are at high risk of bleeding. See Stroke Toolkit on UH Clinical Links site for more detailed list of contraindications.

Monitoring:

- For stroke patients, please utilize the green sheet, located in the Emergency Department, as a monitoring aid
    - A neuro assessment and vital signs (BP, HR, RR, SpO2) should be documented for 24 hours from the time thrombolysis is given: every 15 minutes for 2 hours (8 times), every 30 minutes for 6 hour (12 times), every 60 minutes for 16 hours (16 times), for a total of 24 hours.

Reversal Recommendations:

- See UH Anticoagulation Reversal Guidelines for recommendations

Contributed by: ED Clinical Pharmacists, Emergency Department, Neurology Department
Submitted by: Dr. Jaclyn Scalgione, PharmD., BCPS

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Pharmacy News

Ischemic Stroke Thrombolysis

Patient deemed thrombolysis candidate by Neurology

Contraindication to fibrinolysis?
(See *Stroke Toolkit* on clinical links for more detailed list of contraindications)

this list of contraindications is a guideline and a physician experienced in the treatment of acute stroke may modify the list on a case by case basis

Exclusion Criteria

- Current or history of intracranial hemorrhage
- Ischemic stroke within 3 months
- Symptoms suggestive of SAH
- Arterial puncture in non-compressible site within 7 days
- Intracranial or spinal surgery within 3 months
- Recent significant head trauma within 3 months
- Known structural intracranial cerebrovascular disease
- Known malignant intracranial neoplasm
- Blood pressure SBP > 185 mmHg or DBP > 110 mmHg
- Active internal bleeding
- Bleeding diathesis: platelets <100,000 mm3, aPTT> 40s, PT > 15 s, INR >1.7
- Anticoagulation contraindications (last dose within):
  - Apixiban (Eliquis®) within 48 hours**
  - Dabigatran (Pradaxa®) within 72 hours**
  - Enoxaparin (Lovenox®) therapeutic dose within 24 hours**
  - Heparin therapeutic dose and aPTT > ULN**
  - Rivaroxaban (Xarelto®) within 48 hours**
  - Warfarin (Coumadin®) and INR> 1.7

  ** for patients with normal renal function, activity may be prolonged in patients with renal impairment
- Blood glucose <50 mg/dL or > 400 mg/dL
- CT shows frank hypo-density or extensive hypo-attenuation
- Symptoms consistent with infective endocarditis
- Known or suspected aortic arch dissection
- Gastrointestinal hemorrhage within previous 21 days
- Gastrointestinal malignancy

Additional Exclusion Criteria for Onset 3-4.5 Hours

- Imaging evidence of ischemic injury involving more than 1/3 middle cerebral artery territory

Relative Exclusion Criteria

- Major surgery/serious trauma within previous 14 days
- Lumbar or arterial puncture in previous 7 days
- Recent or active menorrhagia
- Pregnancy or post-partum (<14 days)
- Hemorrhagic ophthalmic condition
- Acute myocardial infarction within 3 months
- Other cardiac condition: acute pericarditis, known LV thrombus, cardiac myxoma, papillary fibroelastoma
- Intracranial arterial dissection
- Large burden of cerebral micro-bleed on MRI
- Current systemic malignancy

Consider risk vs. benefit:

- Only minor, non-disabling symptoms; or rapidly improving stroke symptoms (clearing spontaneously)
- Seizure at onset of symptoms, only if residual symptoms are thought to be post-ictal etiology

Relative Exclusion Criteria for Onset 3-4.5 hours

- NIHSS score > 25

Consider risk vs. benefit:

- Oral anticoagulant use
- History of prior stroke AND diabetes mellitus

No Contraindication to fibrinolysis

Contraindication to fibrinolysis

Refer to Stroke Team or Emergency Medicine team for alternative therapy

Wake-up stroke

Refer to Neurology for thrombolytic recommendation
Although rare, in the setting of wake-up stoke, ***alteplase*** *[0.9 mg/kg (max 90 mg), 10% bolus (max 9 mg) over 1 min, remaining infusion (max 81 mg) over 60 min]* can be considered
Bolus to be administered by Neurology MD

Last known well within 4.5 hours

Time out by neuro MD to review patient criteria, inclusion/exclusion criteria, and dosing

Tenecteplase (TNK): 0.25 mg/kg (max 25 mg/5ml)
Administration: single IV push over 5-10 seconds given by Neurology MD, refer to page 3 for preparation instructions

Endovascular intervention if applicable

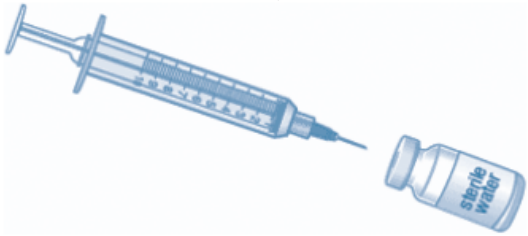
This tip sheet is intended to be flexible. They serve as reference points or recommendations, not rigid criteria. Guidelines should be followed in most cases, but there is an understanding that, depending on the patient, setting, circumstances or factors, guidelines can and should be tailored to fit individual needs. February 2022

Preparation for Tenecteplase Administration

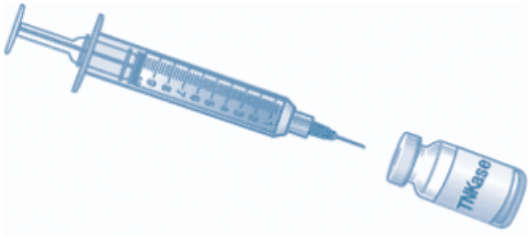
Preparation for Tenecteplase Administration
Full instructions on reconstitution and administration
Fullon video dosing and administration

Step 1: Remove the shield assembly from the supplied B-D 10 mL syringe with TwinPak™ Dual Cannula Device.

Step 2: Aseptically WITHDRAW 10 mL of Sterile Water for Injection, USP, using the B- D 10 mL syringe with TwinPak™ Dual Cannula Device included in the kit. Do not use Bacteriostatic Water for Injection, USP.



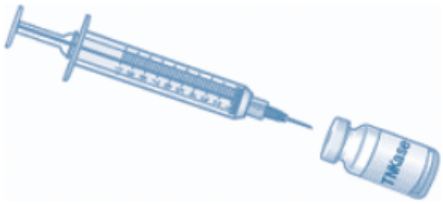
Step 3: INJECT entire contents (10 mL) into the TNKase vial, directing the diluent into the powder. Slight foaming upon reconstitution is not unusual; any large bubbles will dissipate if the product is allowed to stand undisturbed for several minutes. **Final concentration is 50 mg/10 mL (5mg/mL)**



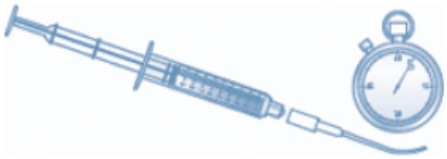
Step 4: GENTLY SWIRL until contents are completely dissolved. DO NOT SHAKE. Solution should be colorless or pale yellow and transparent. Once the appropriate dose of TNKase is drawn into the syringe, stand the shield vertically and recap the red tab cannula.

Step 5: Determine the correct dose of TNKase based on patient weight. TNKase is for IV administration only.

Step 6: WITHDRAW the appropriate volume of solution based on patient weight. **The recommended total dose should not exceed 25 mg for stroke, 50 mg for all other indications.** Discard solution remaining in the vial.



Step 7: FLUSH a dextrose-containing line with a saline-containing solution prior to and following administration (precipitation may occur when TNKase is administered in an IV line containing dextrose). **ADMINISTER as an IV BOLUS over 5 seconds.**



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Pharmacy News

Hazardous Wastes and Safe Medication Disposal

One ongoing public health issue is the rise of prescription drug abuse and misuse in people of all ages.[1] Drug abuse ranges from using a family member's prescription for personal use to taking unauthorized drugs by the federal government.[1] A common misconception about prescription drug use is that prescription drugs are less harmful than illicit narcotic drugs, and therefore, these can often become inappropriately used.[1] A well-established method of eliminating the chances of abuse is the proper disposal of medications or the rendering of medications inactive. This method is not only a way to tackle substance abuse, but it also addresses another public health issue: environmental damage. In the inpatient setting, medication disposal is an implemented and effective process throughout all institutions, especially in the pharmacy department. There are different methods to dispose prescription medications depending on the drugs' characteristics.

Defined by the Resource Conservation and Recovery Act (RCRA), pharmaceutical wastes fall into three different categories: P-listed, U-listed, and characteristic hazardous wastes.[2] The environmental protection agency (EPA) has identified about 400 chemicals that can be classified in the first two categories combined.[3] P-listed wastes are substances that are harmful in small quantities, requiring stringent regulations when disposing.[3] Compared to U-listed wastes, P-listed wastes are more acutely toxic, but both are considered hazardous and have their own list of chemicals.[3] Therefore, the handling of P-listed wastes and their containers has stricter requirements.[4] For a waste to be classified as a P-listed or U-listed, it must meet the following criteria: (1) pharmaceutical containing a substance I the P-listed/U-listed waste list, (2) chemical component must be unused, and (3) chemical component must be 100% pure, technical grade, or as a single entity.[2] Characteristic hazardous wastes are a type of chemical that have properties that can cause harm to people or the environment.[2] The EPA has defined four chemical properties that can cause a drug to be classified as a characteristic hazardous waste: ignitability, corrosivity, reactivity, and toxicity.[2] Due to the nature of the drugs from all three categories, the EPA restricted the handling of these wastes to healthcare facilities and reserved distributors. The drugs from these classes are discarded separately from non-RCRA drugs.[2]

Non-RCRA drugs are those that do not fall in the hazardous categories defined by the RCRA. Although they are not identified by the RCRA, these substances need to be handled and disposed of properly. Common disposal methods are via the trash or the toilet, but these disposal methods are not recommended for most pharmaceuticals due to their ability to be retrieved or cause environmental damage unless they are discarded in a specific way suggested by the FDA.[5] To combat the problem, there are multiple disposal methods available to safely discard unwanted pharmaceuticals. Products such as DisposeRx, Deterra, Rx Destroyer, Drug Buster, and Pill Catcher utilize various methods to make unwanted products undesirable. Additionally, federally supported National Drug Take Back Days, held twice annually, provide communities the opportunity to discard medications safely.[5]

The proper disposal of pharmaceuticals has a major impact on both social and environmental levels as it may contribute to unnecessary drug exposure to the most vulnerable populations which contributes to the opioid epidemic. The need to educate the community about proper disposal is especially important in a society where prescription drug misuse and abuse is a serious concern. A way to spread understanding regarding this issue is by ensuring that pharmacists are knowledgeable about medication disposal regulations and by utilizing pharmacists to provide patient education to their communities.[6] Understanding the magnitude of the problem caused by improper drug disposal will help mitigate future damage from improper/illicit use of medications.

References:

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Contributed by:
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Gilbert Syndrome

What is Gilbert's Syndrome?

Gilbert Syndrome (GS) is a genetic disorder (also known as Meulengracht disease) which affects bilirubin conjugation in the liver.[1,2,3] The decreased glucuronidation leads to recurrent jaundice episodes caused by intermittent unconjugated bilirubin level elevation.[1,2] GS often has an autosomal recessive pattern of inheritance, and it affects the gene UGT1A1 that codes uridine diphosphonate (UDP) glucanosyltransferase. As a result of the genetic mutation, there is a 60-70% decrease in phase II hepatic clearance of bilirubin. In Asian populations, GS with a UGT1A1 missense mutation is generally inherited in an autosomal dominant manner.[1] This syndrome affects 3-7% of the US population with higher levels around 10% in Western Europe.[3] In around 33% of cases, patients are asymptomatic and remain undiagnosed due to the benign nature of the GS.[1]

Diagnosis and Management

Patients with GS may often present with mildly elevated total bilirubin levels with normal levels of liver transaminases, biliary damage markers, and RBC counts.[4] The normal range of total bilirubin is 0.1 to 1.2 mg/dL (1.71 to 20.5 µmol/L), and jaundice may become evident at levels of 2.0 mg/dl.[5] The total bilirubin levels in GS patients may vary, but usually do not exceed 85µmol/L. Patients with GS are typically asymptomatic but yellowing of the sclera, skin and mucous membranes may be noted upon clinical examination.[1,6] This mild jaundice may be exacerbated during periods of stress, illness, and fasting.[1,5] Consequently, patients should be educated on these precipitating factors and the short duration of the mild jaundice. Nevertheless, if episodes are prolonged, severe, or accompanied by abdominal pain, changes in urine or stool color, further investigation may be needed. It would be recommended to contact a medical professional.[1,5,6]

In neonates, GS generally may cause an elevation in unconjugated bilirubin, but not to the extent of causing kernicterus. Conversely, when there is a comorbid hemolytic disorder, neonatal jaundice may worsen to kernicterus.[2] GS does not require any monitoring, dietary restrictions, or lifestyle modifications. However, it is recommended that patients with GS notify healthcare workers of their diagnosis to prevent needless testing. In patients with comorbid disorders leading to increased bilirubin, phenobarbital can be given.[1,2,7] Phenobarbital can normalize bilirubin clearance in the liver and the serum.

GS is often diagnosed by excluding other potential diagnoses. Conditions such as hemolysis, anemia, glucose-6-phosphate dehydrogenase deficiency (G6PD), and prosthetic heart valve placement can cause increases in unconjugated hyperbilirubinemia. Moreover, genetic disorders such as Crigler-Najjar syndrome often can be mistaken for GS. Medications such as rifampin, acetaminophen, sulfasalazine, erythromycin, and estrogens can elevate bilirubin levels. Hyperthyroidism can also reduce glucanosyltransferase activity.[1]

Interestingly, GS may have potential benefits for patients. Bilirubin itself has antioxidant properties and has beneficial effects on the cardiovascular system. Studies have shown decreased incidence of diseases such as ischemic heart disease and various cancers. When compared to the general population, patients with GS had a lower rate of all-cause mortality.[2,8] Studies in patients with type 2 diabetes have shown slower progression of proteinuria and neuropathy independently associated with elevated bilirubin levels. Despite the promising results, more studies are required to elucidate the protective effects of bilirubin in this population.

Potential Drug Interactions

Due to altered drug metabolism in patients with GS, interactions with certain medications may arise. For instance, medications such as rifampin and contrast agents can inhibit the reuptake of bilirubin, leading to hyperbilirubinemia. However, this can be resolved by the discontinuation of such medications.[7] Acetaminophen, a known hepatotoxic agent, is typically metabolized through glucuronidation.

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Gilbert Syndrome

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In some patients with GS, drug metabolism is shifted to oxidative pathway, leading to the accumulation of toxic metabolites, but there is not enough data to provide a recommendation regarding dose changes. Gemfibrozil, when used with lipophilic statins, can theoretically cause an increased risk of myopathy in patients with GS.[1] As such, these medications should be used with caution when used in combination in a patient with GS.

Pharmacogenomics

Patients with GS typically have 10-35% of the normal UGT1A1 activity which can potentially affect the effectiveness of treatments. Irinotecan is metabolized through UGT1A1 to form a toxic metabolite, SN-38. Studies have found that patients with the TA7 allele had an increased risk for neutropenia. Similarly, sorafenib, a tyrosine kinase inhibitor (TKI), should be used in caution with patients who are heterozygous for the UGT1A1*28 allele, because its use can worsen hyperbilirubinemia.[1] Another potential interaction comes from antiretroviral protease inhibitors which can have an effect on unconjugated bilirubin levels in the blood.[1,7] Clearly, knowing and understanding the effects of these genes is important in determining treatment for patients and potential adverse events.

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