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The Spice of Life: Synthetic Cannabinoids and the Chaos They Create

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Introduction:

Synthetic cannabinoids (SC), are often marketed to the lay public as "safe alternatives" to natural cannabinoids, like marijuana. However, since they first became available for purchase in the United States in 2008, SC have posed a serious public health risk. In 2015 alone, there were over 7,000 cases of adverse events related to SC use reported to poison control centers across the county.[1] In Alabama, between March and May of the same year, there were 1,019 suspected cases of SC toxicity presenting to emergency departments; 246 of these cases required hospitalization and five resulted in death.[2] Regardless of their high potential for harm, SC are used among patients of all backgrounds, ages, and races, and serve as an unforgiving substitute for natural cannabinoids.[3,4]

These agents were originally developed to research the structure and function of cannabinoid receptors, CB1 and CB2. This research led to the eventual synthesis and production of SC for commercial purposes. Generated as a liquid to be vaporized in e-cigarettes for inhalation, or applied to random plant matter to be smoked or brewed into tea, SCs are packaged as legal substitutes for marijuana under a variety of trade names (Figure 1).[3,5]

In 2012, the Drug Enforcement Administration passed the Synthetic Drug Abuse Prevention Act, classifying synthetic cannabinoids and their isomers as Schedule I, prompting manufacturers to modify the chemical structures of their products to create new isomers not prohibited under the law, and allowing them to remain legally available.[6,7] These structural changes led to significant variability in potency, duration, and physiologic effects, making management of SC-associated toxicities considerably more challenging.[6]

IN THIS ISSUE:

Figure 1. Synthetic Cannabinoid Products[3,5]

- Angry Birds
- Bhang
- Black Mamba
- Bombay Bang
- Dr. Feel Good
- Gangsta
- K2
- Killa Gorilla
- Kush
- Kronic
- Mojo
- Moon Rocks
- Mr. Nice Guy
- Ninja
- Outer Space
- Scooby Snax
- Sexy Monkey
- Skunk
- Smacked
- Smoking Santa
- Spice
- Spice XX
- Tomcat
- WANTED
- Yucatan

Mechanistically, SCs were designed to mimic the effects of tetrahydrocannabinol (THC), which agonize cannabinoid receptors in the central nervous system to induce its associated effects, such as altered mental status, decreased coordination, perceptual changes, and sensory alterations.[8] SCs and, in some cases, their active metabolites tend to have a higher potency, greater receptor stimulation, and longer duration of action compared to THC, making their effects more extreme and less predictable. Additionally, due to their potency there is an increased risk for withdrawal symptoms seen with continued use of SCs; this is not the case for natural cannabinoids.[3,6] Although there are structural similarities to THC, SCs do not react on a routine urine drug screen, making them desirable to those who wish to avoid the risk of detection.[6] Thus, identifying patients who have consumed these substances becomes exceedingly difficult. Clinicians must rely on a potential barrage of symptoms and non-specific laboratory parameters to determine the etiology of a patient's clinical presentation, which can be as variable as the SCs themselves.

Clinical Evidence

In 2015, the largest recorded US outbreak of adverse drug reactions attributed to SC occurred in Mississippi, prompting the Center for Disease Control and Prevention (CDC) to aid in the investigation and response. The CDC evaluated 1,243 ED admissions that were suspected to be SC related, examining patient characteristics and clinical presentation. Demographically, 83% were male between 18 to 39 years old; however, the overall ages ranged from 12 to 72 years old. Common symptoms included agitation, violent or aggressive behavior, confusion, and somnolence, while common clinical findings were tachycardia and hypertension.[4] Out of 119 patients treated at the University of Mississippi Medical Center (UMMC), thirty-eight required hospitalization, with 12 being admitted to the intensive care unit.[9] Similar demographics and adverse events were observed in a German case series of 29 patients. Additional symptoms noted in this case series included minor hypokalemia necessitating supplementation, and nausea and vomiting requiring antiemetics.[10] Other case reports observed a wide range of clinical presentations and outcomes including severe psychosis. Tachycardia is the most common symptom seen with SC use, and typically occurs secondary to SC-associated agitation (Table 1).[11] Other clinical findings include respiratory depression, cardiac arrest, catatonia, nephrotoxity, rhabdomyolysis, and seizures, all varying in severity.[11] Management of these toxicities should be individualized to the scope and severity of each patient's clinical manifestations.

Table 1. Clinical Manifestations of Synthetic Cannabinoid Toxicity[11]

Common	Less Common	Additional Clinical Findings
- **Altered mental status**	- Seizures	- Tachycardia
- **Lethargy**	- Catatonia	- Hypertension
- **Agitation/Aggression**	- Self-inflicted trauma	- Hypokalemia
- **Emesis**	- Rhabdomyolysis	- Elevated Serum Creatinine
- **Hallucinations**	- Acute kidney injury	- Elevated Creatinine kinase
- **Anxiety**	- Respiratory depression	- Elevated BUN/SCr ratio
		- Negative Urine Drug Screen

Treatment

There are no direct pharmacologic treatments for SC toxicity; thus, current therapy is primarily focused on supportive care. Intravenous fluids are often required to manage fluid disturbances and electrolyte imbalances related to emesis and dehydration (Table 2).[11] Duration of SC effects can vary, lasting anywhere from hours to months. For patients suffering from new onset psychosis, antipsychotics may be required with or without inpatient care. In the more severe psychiatric manifestations, neuroleptics and/or hospitalization may be required. Patients presenting with anxiety, agitation, irritability, or seizures often require benzodiazepines, along with airway stabilization and sedation in patients with significant seizure activity.[6,11] For patients who use SCs routinely, withdrawal is often seen. Typically, headache, agitation, diaphoresis, nausea/vomiting, and insomnia are symptoms seen in SC withdrawal. For those who require treatment, quetiapine has demonstrated some benefit when benzodiazepines fail to manage their symptoms.[11,12] The best route for managing SC-related toxicities, is likely preventing their initial use.

Table 2. Treatment of Synthetic Toxicity[11]

Presentation	Management Options Reported in Case Studies/Series	Duration of Treatment
Acute kidney injury	Fluids Dialysis Corticosteroids	Not reported
Anxiety/Agitation	Benzodiazepines (lorazepam, midazolam, diazepam)	Hours to 4 weeks
Catatonia	Diphenhydramine Benzodiazepines	<1 day
Emesis	Antiemetics (ondansetron, promethazine) Diphenhydramine IV fluid resuscitation hot showers	Hours to 3 days
Hypokalemia	Potassium replacement	<1day
Psychosis	Hospitalization Neuroleptics (risperidone, haloperidol, aripiprazole clozapine, olanzapine)	Hours to 120 days*
Seizures	Benzodiazepines Intubation	1 to 4 days

***Some psychotic symptoms persisted for up to 6 months in otherwise healthy patients**

Conclusion

Looking forward, pharmacists play a pivotal role in educating the public about these agents. The unpredictability of the contents and effects of the SC should be highlighted for those who use them under the assumption that they are harmless. Synthetic cannabinoids are not an innocent alternative to marijuana. They are dangerous, creating much chaos for healthcare systems when trying to treat patients with suspected SC consumption.

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Update on the Pharmacological Management of High Blood Pressure in Pediatrics

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Introduction:

Because of interest in pediatric hypertension, the American Academy of Pediatrics (AAP) recently released clinical practice guidelines to update screening and management recommendations for pediatric hypertension from the 2004 publication, Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[1] The updated guidelines provide a more inclusive look at pediatric hypertension, including more broad-based weight based dosing for children compared to previous guidelines, which only outlined treatment for overweight or obese children. There has been an association of elevated BP in adolescents with hypertension in early adulthood.[2] For this reason, it is important that pharmacists recognize and appropriately manage elevated blood pressure (BP) in the pediatric population and attempt to negate the consequences of hypertension later in life.

Diagnosis and Screening

The AAP now recommends that the treatment target for pediatric hypertension be a blood pressure less than the 90th percentile for children ages 1-13 years old or a BP less than 130/80 mmHg for children 13 years and older. A table can be found in the guidelines that further define blood pressure categories and stages by percentile.[3] Some non-pharmacologic strategies for lowering blood pressure include implementation of the Dietary Approaches to Stop Hypertension (DASH) diet, 30 to 60 minutes of vigorous activity 3 to 5 times a week, weight loss if obesity is a contributing factor to the patient's hypertension, and stress reduction through meditation.[4]

Table 1: Dosing Information for Individual Agents Used in the Treatment of Pediatric Hypertension.[4]

Drug Class	Drug	Dosing Range	Formulations
Angiotensin-converting enzyme (ACE) Inhibitors	Benazepril	**≥6 y:** 0.2 – 0.6 mg/kg/day (up to 40 mg/day) given once daily	Tablet, 2 mg/mL EOS[a]
	Captopril	**Infants:** 0.05 – 6 mg/kg/dose given once daily to four times daily **Children:** 0.5 – 6 mg/kg/dose given three times daily	Tablet, 1 mg/mL EOS[a]
	Enalapril	**≥ 1 mo:** 0.08 – 0.6 mg/kg/day (up to 40 mg/day) given daily to twice daily	Tablet, 1 mg/mL oral solution, 0.1 mg/mL and 1 mg/mL EOS[a]
	Fosinopril	**≥ 6 y, < 50 kg:** 0.1 mg mg/kg/day – 40 mg/day given once daily **≥ 6 y, ≥ 50 kg:** 5 – 40 mg/day given once daily	Tablet
	Lisinopril	**≥ 6 y:** 0.07 – 0.6 mg/kg/day (up to 40 mg/day) given once daily	Tablet, 1 mg/mL oral solution, 1 mg/mL EOS[a], 2 mg/mL EOS[a]
	Ramipril	1.6 – 6 mg/m^2/day given once daily	Capsule
	Quinapril	5 – 80 mg/day given once daily	Tablet, 1 mg/mL EOS[a]
Angiotensin II Receptor Blockers (ARB)	Candesartan	**1-5 y:** 0.02 – 0.4 mg/kg/day (up to 16 mg/day) given once daily to twice daily **≥ 6 y, < 50 kg:** 4 – 16 mg/day given once daily **≥ 6 y, ≥ 50 kg:** 8 – 32 mg/day given once daily	Tablet, EOS[a] ranging from 0.1 to 2 mg/mL
	Irbesartan	**6-12 y:** 75 – 150 mg/day given once daily **≥ 13 y:** 150 – 300 mg/day given once daily	Tablet
	Losartan	**≥ 6 y:** 0.7 – 1.4 mg/kg (up to 100 mg) given once daily	Tablet, 2.5 mg/mL EOS[a]
	Olmesartan	**≥ 6 y, < 35 kg:** 10 – 20 mg given once daily **≥ 6 y, ≥ 35 kg:** 20 – 40 mg given once daily	Tablet, 2 mg/mL EOS[a]
	Valsartan	**≥ 6 y:** 1.3 – 2.7 mg/kg (up to 160 mg) given once daily	Tablet, 4 mg/mL EOS[a]
Thiazide diuretics	Chlorthalidone	0.3 – 2 mg/kg (up to 50 mg) given once daily	Tablet
	Chlorothiazide	10 – 20 mg/kg/day (up to 375 mg/day) given once daily to twice daily	Tablet, oral suspension, solution for injection, 50 mg/mL EOS[a]
	Hydrochlorothiazide	1 – 2 mg/kg/day (up to 37.5 mg/day) given daily to twice daily	Tablet, oral capsule
Calcium Channel Blockers (CCB)	Amlodipine	**1-5 y:** 0.1 – 0.6 mg/kg/day (up to 5 mg/day) given once daily **≥ 6 y:** 2.5 – 10 mg given once daily	Tablet, 1 mg/ml oral suspension, 1 mg/mL EOS[a]
	Felodipine	**≥ 6 y:** 2.5 – 10 mg given once daily	Tablet
	Isradipine	0.05 – 0.6 mg/kg (up to 10 mg/day) given twice daily to three times daily in capsule form and once daily in ER tab	ER Tablet, Capsule, 1 mg/mL EOS[a]
	Nifedipine extended release	0.2 – 3 mg/kg/day (up to 120 mg/day) given once daily to twice daily	ER Tablet

EOS = Extemporaneously prepared oral solution

Treatment

If non-pharmacologic therapies alone fail to achieve the blood pressure goal, pharmacologic agents may be initiated in addition to continued lifestyle modification efforts. Drug classes used for initiation of pharmacologic treatment of pediatric HTN include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), long-acting calcium channel blockers (CCBs), or thiazide diuretics. In most patients, there is no evidence to support use of one of these classes over the other for initiation of treatment, except in African-American patients. African-American patients have been observed to have less of a response to ACE inhibitors.[5,6] These patients may need to be started on a higher dose of an ACE inhibitor or it may be preferred to initiate therapy with either a long-acting CCB or thiazide diuretic. Extrapolating from research conducted in the adult population, β-blockers are not recommended for initiation of treatment due to higher potential for adverse effects and lack of evidence for efficacy. It is important to note for adolescents of childbearing age that ACE inhibitors and ARBs are contraindicated in pregnancy. An ACE inhibitor or ARB is preferred for initiation in a pediatric patient with HTN who also has chronic kidney disease, proteinuria, or diabetes. Information regarding dosing for individual agents used in the treatment of pediatric HTN can be found in Table 1.[4]

Table 2: Common Adverse Effects Associated with Anti-hypertensives[4]

Class	Common Adverse Effects	Severe Adverse Effects
ACE inhibitors	Cough, headache, dizziness, asthenia	Hyperkalemia, acute kidney injury, angioedema, fetal toxicity
ARBs	Headache, dizziness	Hyperkalemia, acute kidney injury, fetal toxicity
Thiazide diuretics	Dizziness, hypokalemia	Dysrhythmias, cholestatic jaundice, new onset diabetes mellitus, pancreatitis
Calcium Channel blockers	Flushing, peripheral edema, dizziness	Angioedema

Monitoring

Following initiation of pharmacologic treatment for pediatric HTN, frequent monitoring and treatment adjustment (dose adjustments and/or addition of a second or third agent) is essential until the blood pressure goal is met. A patient should be seen every 4-6 weeks until the goal is met, and then every 3-4 months once the goal is achieved. In addition to monitoring blood pressure and ensuring the patient is at goal, patients should also be assessed for adherence to therapy and screened for adverse effects at each follow-up visit. Common adverse effects in pediatric patients associated with anti-hypertensives can be found in Table 2.[4]

Discussion

As is the case for many pediatric disease states, treatment evidence for hypertension in pediatric populations is limited compared to the extensive literature available on the treatment and management of hypertension in adults. It has therefore been necessary to analyze evidence generated from other study designs to assess and update practice guidelines and it is important to note potential evidence gaps that exist in the management of pediatric hypertension. The most notable gap in information surrounds the long-term implications of pediatric hypertension on the presence of disease (HTN and/or cardiovascular disease) in adulthood. Evidence gaps create opportunity for future research into the long-term outcomes of hypertension in childhood and adolescence. Two promising studies already in progress are the Childhood Cardiovascular Cohort Consortium and the Adult Hypertension Onset in Youth study. The aims of these studies are to evaluate the effects on elevated blood pressure in childhood and adolescence on target organ damage and development of cardiovascular complications in adulthood.[7,8]

Conclusion

Pediatric hypertension is a complex disease state that warrants further exploration into treatment and management options. As such, the AAP recommends reevaluation of these clinical guidelines with consideration of any new published evidence every 5 years. It is through this kind of diligent research and reassessment of current clinical practices that optimum care can be provided for pediatric patients.

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Addressing Common Errors with Insulin Therapy

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Clinical Case Scenario 1: *JB is a 57-year-old African-American male who presents to your clinic after recently being diagnosed with type 2 diabetes mellitus (T2DM) for his initial diabetes education session complaining that his "insulin just isn't working." At his previous visit, he was prescribed Lantus (insulin glargine) Solostar 10 units subcutaneously daily. He explains that although he has taken the injections as prescribed, his blood sugars have still been high. After talking further with JB, he tells you that he stores both the unopened box of insulin pens, as well as the box of insulin pens that he is currently using, in his nightstand drawer so that it is easily accessible. Upon showing you how he uses his insulin, you notice once he gives the injection, he immediately pulls the syringe out. JB asks you to help him address the issue with his insulin therapy.*

Background:
Diabetes is a chronic condition in which the body either cannot produce insulin or it cannot adequately use the insulin it produces.[1] In 2015, roughly 23 million people ages 18 or above in the United States had been diagnosed with diabetes.[2] Diabetes can be managed through lifestyle modifications and drug therapy, although one very common therapy is insulin itself. Insulin has been associated with high rates of medication errors.[3] For this reason, education to patients and other healthcare providers is a crucial piece to prevent adverse outcomes and hospitalizations.

Clinical Evidence and Rationale: JB's first error discovered is improper storage of his insulin. While it is okay to store in-use vials and pens for a certain amount of time at room temperature, unopened packages should be stored in the refrigerator.[4] As shown in Table 1 below, insulin storage instructions vary, so it is essential to make sure patients know how long they can safely keep their insulin at room temperature. It is also important that patients know not to freeze their insulin, or leave it in excessive heat, such as in a hot car. JB also has issues with his technique. Instead of giving the injection and pulling the needle out immediately, the needle should be left in the skin for 5-10 seconds after injecting to

prevent the insulin from leaking back out.[4] Should leaking occur despite prolonging the injection, the patient can also try pinching up on the skin before pressing the plunger or inserting the needle at a 45-degree angle rather than 90 degrees.[4]

Table 1: Proper Insulin Storage Based Upon Place and Time[5]

Proper Insulin Storage		
Insulin Type	**At Room Temperature**	**In the Refrigerator (all insulins)**
Inhaled insulin (Afreeza)	Unopened Blister Card: within 10 days Opened Strips: within 3 days Inhaler: replace after 15 days	Until the expiration date printed on the package so long as the package has not been opened nor punctured
Rapid Acting -Aspart (Novolog), -Glulisine (Apidra),-Lispro (Humalog)	Vial and Pen: up to 28 days	
Regular	Novolin R Vial: up to 42 days Humulin R Vial: up to 31 days	
NPH	Novolin N Vial: up to 42 days Humulin N Vial: up to 31 days Humulin N Pen: up to 14 days	
Long-Acting -Detemir (Levemir)	Vial and Pen: up to 42 days	
-Glargine (Lantus, Toujeo)	Lantus Pen and Vial, Basglar[6] Pen: up to 28 days Toujeo Pen: up to 42 days	
-Degludec (Tresiba)	Pen: up to 56 days	

Table 2: Other Insulin Errors Involving Administration and Technique

- Reusing needles
  - Patients should never reuse needles or syringes because they can become dull and not penetrate the skin as easily.[7]
  - Patients should never share needles due to potential exposure to blood-borne pathogens.[7]
- Timing of injection
  - Patients should be counseled on the specific timing of injections.[8]
  - Rapid acting insulins are typically given within 15 minutes of a meal. Longer acting agents can be given any time during the day as long as the injection is given at the same time each day.[3]
- Giving the wrong type of insulin
  - Because patients on different kinds of insulin have the potential to confuse them, patients should mark their different insulins to keep them straight.[9] Patients can also request pens for one type of insulin and use the other in vial with syringe form to avoid this error.[9]
- Giving the injection in the same place
  - The risk of lipohypertrophy is present when patients inject into the same site multiple times.[7] Patients should be told to rotate sites of injection and avoid giving in the same spot twice. Also, clinicians should teach patients how to identify damaged tissue. Correct self-inspection of injection sites can help prevent lipohypertrophy.[10]
- Failing to check the pen
  - Patients should be encouraged to double check the dose of insulin they are injecting.[7] They are also encouraged to check the expiration date as well.[7] Patients should be aware of the signs and symptoms of hypoglycemia and be educated on what to do should they inject the incorrect dose or type of insulin.
- Not inverting or rolling insulin pens to properly mix insulin
  - Certain insulins require inversion or gently rolling the pen or vials to properly mix the components in the injection.[7] Failure to do so may result in variable blood glucose readings and adverse events.[7] Generally, intermediate and premixed insulins are the ones which need to be mixed, but the patient should be encouraged to ask if they are unsure.[7]
- Not priming the pen
  - New pens should be primed prior to use.[7] This is accomplished by pointing the needle straight up, dialing two units of insulin into the pen, and pressing the plunger while continuing to hold the needle straight up.[7] Repeat this step until a drop appears, at which point, the pen is ready for use.[7]
- Failing to correctly remove outer and inner needle covers
  - Insulin pens are now developed with protective coverings to prevent accidental needlesticks. This new technology hides the needle so that it is never actually shown, which can be confusing to patients who are switched to standard insulin pens.[11] Be sure patients are aware that they will see the needle when using standard insulin pens and that these pens have two covers (an outer cover and a needle shield) that must both be removed in order to properly give the insulin injection.[11]

Clinical Case Scenario 2: *CJ is a one-day old white female infant admitted to the neonatal intensive care unit (NICU) at your hospital due to complications at birth. The patient had shown some progression during her time on the unit; however, 3 days into her stay, she was hyperglycemic and needed to receive insulin. The pharmacy department had delivered a supply of undiluted adult insulin to the floor earlier on day 3 of CJ's stay. CJ's nurse drew up the correct amount of insulin, not realizing it was undiluted. She administered the dose without having another nurse check behind her. As a result, CJ received an overdose of insulin.*

Clinical Evidence and Rationale: This example insulin error represents several failures of critical checkpoints at which the error could have been prevented. The first error is that pharmacy delivered undiluted adult insulin to NICU. American Society of Health-System Pharmacists (ASHP) recommends that hospital standards should be developed to determine what concentrations will be stored in patient care areas and ensure that they are stored away from other medications to prevent mixing them up accidentally.[8] For adult patients, they recommend storing only U-100 concentrations of insulin vials and pens.[8] If the nurse had another nurse check behind her, the error might have been avoided altogether. For this reason, high-alert medications, such as insulin, always deserve to be double checked.

Table 3: Insulin Recommendations Related to Hospitalizations

- Timing of insulin administration
  - Often, patients will receive insulin too far in advance from their meals.[12] Hospitals should prospectively monitor blood glucose in patients on insulin, coordinating their injections with meals and testing their sugar.[8] Protocols should be in place to manage hypoglycemia and hyperglycemia.[8]
- Discontinuation of antidiabetic medications
  - It is recommended to discontinue antidiabetic medications due to potential interactions and adverse effects that are more regularly seen in the hospital, such as in a patient with acute renal insufficiency.[12]
- Basal-bolus regimens are preferred to sliding-scale
  - The American Diabetes Association (ADA) strongly discourages the use of sliding scale insulin.[13] Several reasons support this recommendation including the absence of basal insulin. A more physiologic option of 'basal-bolus' which provides coverage of blood glucoses throughout the day is ideal.[12]

Hyperglycemia is similarly important, since leaving it untreated can result in negative outcomes and it is often involved in medication errors in hospitalized patients.[12] The 2018 ADA Guidelines define hyperglycemia as blood glucose ≥ 140 mg/dl, yet decisions regarding treatment are generally specific to the institution and the reason for hospitalization.[13] There can be many different causes of increased blood sugar in hospitalized patients, and selecting the optimal regimen is often difficult.[12] Sicker patients often require more insulin, especially if they were on insulin as an outpatient.[12] Also, using fluids with dextrose, being given parenteral or enteral nutrition, or being prescribed certain medications can all cause fluctuations in blood glucose and can be cause for increased insulin.[12]

Conclusion:

Since insulin is considered a high-alert medication, special care must be taken to prevent negative consequences from insulin therapy. Education continues to play an integral role in preventing insulin errors in both the outpatient and inpatient settings. As skills and technology continue to advance, it is hopeful that insulin errors will permanently decline.

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Use of Extended Infusion Piperacillin/Tazobactam in Pediatric Patients

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Introduction:

Piperacillin/tazobactam (TZP) is a widely used antimicrobial in both pediatric and adult patients to treat Gram negative infections. However, due to the increasing incidence of antimicrobial resistance it is paramount that clinicians use optimal dosing strategies to effectively treat these infections. Due to the time dependent nature of TZP, the non-protein bound (fT) concentration of the drug must exceed the minimum inhibitory concentration (MIC) of the organism at the site of infection (fT>MIC) for the most efficacious bactericidal activity.[1] Therefore, unlike aminoglycosides, an increase in TZP concentration does not have additional antimicrobial effect. For TZP, the unbound drug must exceed the MIC for greater than 50% of the dosing interval to ensure maximum bactericidal effects. One method to increase the amount of time above MIC is extended-infusion dosing. By extending the length of the drug infusion, the concentration remains above the MIC longer than it would for traditional intermittent dosing.1 In addition to improving patient outcomes, increasing the fT>MIC via extended-infusion dosing has other potential benefits including reductions in both cost and bacterial resistance.[1, 2]

There have been numerous studies published demonstrating the benefits of using extended-infusion TZP in adults to achieve pharmacodynamic targets more easily and providing better clinical outcomes compared to the standard TZP infusion. However, this data cannot always be extrapolated to pediatric patients due to differences in pharmacokinetic parameters in adults versus children. Therefore, data in pediatric patients have

InPharmative, page 10

been limited to results from population-based pharmacokinetic and pharmacodynamic modeling studies.[4] These studies have yielded theoretical results based on Monte-Carlo simulations to extrapolate data gathered from plasma concentrations obtained from 0.5 hour infusions following the first dose of TZP. In one study, optimal results were defined as the probability of target attainment (PTA) ≥ 90% for MICs 4 - 128 mg/L. TZP doses ranged from 50-130 mg/kg/dose not to exceed the recommended maximum dose of 400 mg/day. Dosing intervals were every 4, 6, or 8 hours with infusion durations of 0.5, 2, 3, or 4 hours. Results from this study demonstrated that standard infusions of 0.5 hours were inadequate for MICs of ≥ 8 mg/L and ≥ 4 mg/L for patients 2 - 6 months old and 6 months to 6 years old, respectively.[5] Another study, using samples from critically ill pediatric patients showed similar results. For patients 9 months to 11 years old, to obtain PTA greater than 90% for MIC > 8 mg/L, a dose of 100 mg/kg q8h over 4 hour infusion was required.[4] Although these modeling studies have been able to guide dosing recommendations thus far, they have not been able to prove positive clinical outcomes of extended-infusion dosing.

Clinical Evidence:

Knoderer et al conducted a study to determine if the use of extended-infusion TZP (4 hours duration) is a safe and effective alternative to traditional intermittent infusion (30 minutes duration) in a pediatric population. The trial was a one year, single-centered, retrospective case series of children who received TZP every 8 hours and infused over 4 hours. Since this has not been previously studied in a pediatric population, researchers used Monte Carlo simulations involving PK data derived from traditional intermittent TZP dosing (administered over 30 minutes) to determine the extended-infusion dose of TZP for the study. Patients were included if they were between 1 month and 17 years old, had a documented Gram negative infection and received extended infusion TZP for ≥ 48 hours. Exclusion criteria included if the patients received >1 dose of an additional agent for a Gram negative infection (except for double coverage with an aminoglycoside or fluoroquinolone), received multiple TZP dosing regimens, were inadequately treated for a Gram positive or fungal infection, cared for in the neonatal intensive care unit, received any type of renal replacement therapy, or patients with cystic fibrosis.[4] The primary outcome of the study was clinical cure at 21 days after initiation of extended infusion TZP. Clinical cure was defined as the patient being afebrile, complete symptomatic resolution, normalized white blood cell (WBC) count, and had negative follow-up cultures when cultures were available. Secondary endpoints included length of stay, duration of TZP treatment, 30 day readmission, and 30 day mortality.[6]

Of the 1004 patients screened, 39 children (19 males and 20 females) were included into the study. The most common reason for exclusion was no documentation of a Gram negative infection. Additionally, 11 patients had CF and therefore were also excluded. Interquartile ranges of demographic data showed a median age of 5 (2-9) years, a weight of 19.5 (11.5-36) kg, TZP dose 111.4 (100-112.5) mg/kg. The duration of therapy was 4 days with a minimum and maximum of 2 and 16 days, respectively.[6]

The most common organism found was E. coli and K. pneumoniae, with blood and wound as the most common culture sites. All follow-up cultures resulted in no growth. Overall, 74% of patients met the predefined criteria for 21-day clinical cure. The main reason for not reaching clinical cure was due to ongoing infection related symptoms. Although not all the differences met statistical significance, patients that did not meet clinical cure were generally younger, longer hospital stay (23 vs. 11 days; p=0.037), and in the intensive care unit (ICU) (50% vs. 17.2%; p=0.087). No deaths were reported and no adverse reactions occurred.[6]

Conclusion:

Due to the limited amount of research on newer antibiotics and innovative administration regimens in children, it is important to understand relevant adult data, and its applicability to the pediatric population. Utilizing these optimal dosing regimens proven beneficial in adults can also minimize negative clinical outcomes and bacterial resistance2. As stated before, many adult studies have shown positive outcomes with extended-infusion TZP and many children have been successfully treated with similar regimens. However, as always, more research needs to be done to determine the optimal dose and conditions to use this regimen routinely in pediatric patients.

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