Intro

CB: Welcome back to the Med Thread! We are cluing up our series of episodes that involve our students, their questions and evidence-based practice, and this one certainly showcases a mix of topics.

MC: Most definitely! We have four today and first off, the students will discuss options for Shingles vaccination and what to do if a patient has recently been infected with the shingles virus. Should they get vaccinated and if so, when?

CB: We will also touch on reflux and heartburn in pregnancy, what do we recommend if ranitidine is not effective?

MC: Next, which agent is better for treatment of diarrhea as a result of chemotherapy, Lomotil or Imodium?

CB: And lastly, do inhaled corticosteroids for asthma affect a child's growth?

MC: We will be back as a duo next month where we discuss a topic that bombards us in practice, those ever so frequent warnings about QT prolongation. How, and why, do so many medications have this warning? What is the risk exactly? And in whom might we be concerned?

CB: So sit back, relax and enjoy the last episode of this series featuring our students!

Shingles Vaccination

A: Hi everyone! I'm Adam, and I'm a third year student at MUN's School of Pharmacy. Thanks for tuning into today's MedThread. Myself and fellow classmates are here today to discuss the Herpes Zoster infection, also known as shingles, and appropriate vaccination guidelines. Here with me today we have Olivia, Kristie, and Rebecca. Rebecca, did you want to start us off?

R: Sure. Hi everyone. Today we will be looking to see if it is safe for an elderly person to get the shingles vaccine if they have recently been diagnosed with shingles. Furthermore, we will do a thorough investigation as to which vaccine they should receive and when it is safe for them to receive it with respect to their latest herpes zoster infection.

A: That seems to be a popular topic of conversation these days. Where would you go as a healthcare professional if you wanted to look up some information for your patient?

R: Well, we began our search using all available resources but quickly learned that there were many guidelines that were different between American and Canadian references. We had to adapt our search strategy early-on to account for the discrepancies, which meant limiting what information we took from UptoDate, DynaMed, CDC and many American-based guidelines.

We also learned early-on that primary resources were harder to find on this topic compared to summary guidelines due to how new this area is with the Shingrix vaccine coming to market pretty recently, in 2017. But, we used Health Canada guidelines and NACI (National Advisory

Committee on Immunization) a lot, and The Pharmacist's Letter had some great articles comparing the vaccines.

A: Rebecca, could you also give our listeners an overview of what shingles is?

R: Sure. Shingles is the reactivation of the varicella zoster virus which lies dormant in the dorsal root ganglia after prior exposure to varicella. This prior exposure can either be from having chicken pox or having received the chickenpox vaccine. Shingles presents a painful rash that usually develops on one side of the body. The rash consists of blisters that typically scab over in 7 to 10 days and clears up within 2 to 4 weeks. For some people, the pain can last for months or even years after the rash goes away. This long-lasting pain is called postherpetic neuralgia, and it is the most common complication of shingles.

A: We get a lot of questions asking if shingles is contagious; could you elaborate on this?

R: Of course. So basically, you cannot catch shingles from someone with shingles and you cannot catch shingles from someone with chickenpox. In order to get shingles, you have to have prior exposure to varicella. However, if you have never had chickenpox, you can get chickenpox from someone with an active shingles blister. This information can be found on CDC website. Actually, I have even heard people say that they heard that if you get the shingles vaccine you can give chickenpox to your unvaccinated grandchildren. However, the transmission of the vaccine virus has not been reported in clinical trials, as per Health Canada.
(CDC, https://www.cdc.gov/shingles/about/transmission.html)

A: Great, I am glad we addressed this. As we know, there are two different vaccinations for herpes zoster; did you want to talk a bit about this Kristie?

K: Sure. So, Zostavax was the first shingles vaccine and came out in 2006, and the second version came out in 2008. Shingrix consists of two doses given intramuscularly at 0 and then 2-6 months later and Zostavax is a single subcutaneous injection. Just to note, there are more injection site side effects with the administration of Shingrix as compared to Zostavax.

A: So is there anyone that can't have these vaccinations?

K: Both vaccines are options in patients 50 and older that are immunocompetent. Shingrix is safe to use in patients who are immunocompromised as well but Zostavax cannot be used in immunocompromised patients. People who have an allergy to any component of the vaccine should not receive the vaccine. Also, people with current herpes zoster infections should not be vaccinated.

A: Interesting! So how does the efficacy between both of these vaccines compare?

K: Vaccine efficacy decreases with age and time more quickly with Zostavax than with Shingrix. In fact, the incidence of herpes zoster three years post-immunization appears to be double in those vaccinated with Zostavax as compared to Shingrix. Essentially, there is significant waning of protection one-year post immunization with Zostavax. The lasting effect associated with Shingrix is due to the adjuvant, which induces a high cellular immune response to help address the natural age-related decline in immunity.
(Baxter, 2017)

A: Is there any clinical evidence to support this difference?

K: I did find a clinical trial completed in Belgium. It was a small study with only 90 people aged 50-70. In the study, 45 patients received the two doses of Shingrix two months apart and the other group received the Zostavax vaccine. Results from the trial showed that the CD4+ T cell and humoral responses were higher with Shingrix and remained elevated for 42 months. From this trial we can conclude that Shingrix is the preferred vaccination; it results in a greater immune response and is as equally safe as Zostavax.
(Leroux-Roels, 2012)

A: So now we will turn to Olivia. So once someone has shingles, should they eventually get the vaccination?

O: Yes they should. Vaccination is recommended regardless of shingles history, so patients who have already had shingles should still get the vaccine to prevent a second infection. Different safety concerns are not expected in persons with a history of shingles. The Canadian Immunization guide recommends to wait at least 1 year after the latest shingles episode before starting the 2 dose series of Shingrix, and that persons with active herpes zoster should not be immunized with herpes zoster vaccine. The NACI concludes that there is fair evidence to recommend immunization (Grade B evidence), and the stated time frame of at least one year after the HZ episode is a discretionary NACI recommendation, based on expert opinion. NACI concludes that there is insufficient evidence to recommend an interval between a previous episode of HZ and vaccination with RZV (Shingrix).
(Health Canada, https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-8-herpes-zoster-(shingles)-vaccine.html)

A: So what about those lucky few who did not get chickenpox as a child and have not been exposed to the varicella zoster virus?

O: Shingrix is indicated, regardless of varicella infection history. Almost all Canadians eligible for herpes zoster immunization will have had prior varicella exposure, even if they cannot remember. Otherwise, there is no known safety risk associated with immunization of healthy individuals who are susceptible to varicella. Serologic testing is not recommended before or after receiving herpes zoster vaccine. However, if in the rare circumstance that an adult aged 50 years and older is known to be susceptible to varicella, based on previous serological testing for another reason, the individual should be vaccinated with two doses of univalent varicella vaccine rather than the herpes zoster vaccine. That's because, Shingrix has not been evaluated in persons who are seronegative to varicella, and it is not indicated for the prevention of varicella.

A: Very interesting. So what about those people that received Zostavax between the time Zostavax was put to market and when Shingrix was released?

O: Shingrix is the preferred shingles vaccine, and is recommended even in patients that have previously been vaccinated with Zostavax or Zostavax II. NACI recommends that those 50 years of age and over who have already been immunized with Zostavax be re-immunized with 2 doses of Shingrix at least one year after Zostavax (Evidence level C). Again, this is a discretionary NACI

recommendation that is based on expert opinion, and the NACI concludes that there is insufficient evidence to recommend an interval between Zostavax and Shingrix - Grade I evidence. According to the CDC (an American resource), you should wait at least 8 weeks after a patient received Zostavax to administer Shingrix (Evidence Level C). They also say to administer Shingrix especially if it has been more than five years since Zostavax or Zostavax II was given, as most of the protection is lost by then.

A: So is there a consensus worldwide about when you should get the vaccine after a shingles infection?

R: Everyone seems to agree that you should receive the shingles vaccine, but there seems to be no agreement about how soon after an active infection you can get the vaccine. UptoDate is an American reference and they recommend that you wait 3 years to get the vaccination after an active infection, but there was also a FDA guideline on Dynamed that recommended that you only needed to wait until acute illness resolves to give the vaccination. Health Canada guidelines recommend to wait a minimum of 1 year between a herpes zoster infection and beginning the vaccine series. As you can see there is conflicting evidence.
(Mills, 2010)

A: So what should we take from this?

R: Since we are practicing here in Canada, we will err on the side of caution and go with the Health Canada guideline and recommend that those who have had a previous shingles infection are still eligible to receive the vaccine, but there should be a minimum of 1 year between a herpes zoster infection and beginning the vaccine series. Shingrix is the preferred vaccine for optimal shingles protection, receiving 2 doses at 0 and 2-6 months.

A: Thanks for the talk today, folks. It was interesting to see what recommendations are in place for those 50 and older, and when they can actually get the herpes zoster vaccine after a current infection. There is definitely a lot of useful information to take home today. Thanks for listening.

Pregnancy and GERD

G: Hi everyone, my name is Gina

M: I'm Megan,

E: I'm Emily,

H: And I'm and Hayley.

G: We are all currently in our third year of pharmacy school here at Memorial University. We are here with you today to discuss gastroesophageal reflux disease commonly known as GERD specifically with respect to treatment in pregnant women.

Today in our podcast we are going to look at a specific patient, JR and address the safety and efficacy of pharmacological treatment options in our patient. To complete this assessment we followed an evidence based practice approach which included a thorough exploration into

available databases such as PubMed and Drugs in Pregnancy and Lactation. Both databases contained relevant studies pertaining to the GERD treatment in pregnancy.

To start, we would like to provide some background information about GERD. GERD is a digestive disorder classified as "troublesome or frequent acid regurgitation or heartburn." It can include signs and symptoms such as a burning sensation in the stomach, chest pain, and frequent belching. As healthcare professionals we know that GERD pathophysiology is multifactorial. However, there are a few pathophysiological reasons resulting in an increased incidence in pregnancy. The first being increased intra-abdominal pressure as a result of added pressure due to the developing fetus. This causes stomach contents to be pushed upward resulting in the presentation of signs and symptoms pertaining to GERD. Reduced tone in the lower esophageal sphincter can also occur during pregnancy. This is mediated by progesterone levels. Finally, alterations of gastrointestinal motility can occur in pregnancy and may decrease gastric emptying promoting signs and symptoms of GERD.

To add on that, many studies have found an increase in the incidence of GERD symptoms during pregnancy; one longitudinal study stated that 30-80% of pregnant women will experience and complain of heartburn. With a high rate of occurrence, it is even considered by obstetricians to be normal in a healthy pregnancy. With this being said, we believe with so many other changes occurring during the pregnancy, it is important to relieve the mother of extra stressors that come from experiencing GERD, in order to enhance the overall experience of pregnancy and impending motherhood.

To supplement our discussion here today we will next look into a patient scenario: JR is a 30 year old female who is in her second trimester of pregnancy. When she was 8 weeks pregnant, she started to experience symptoms of GERD including a burning sensation in her chest, chest pain and frequent burping. JR was prescribed ranitidine 150mg twice daily from her family doctor, but it has not provided her with any relief of her symptoms. She has no known drug allergies and her current medications include prenatal vitamins and ranitidine as previously mentioned. She has no other medical conditions or past history. JR is now looking for another recommendation of something that she could take to help relieve her symptoms. Thus, based on the given scenario our ultimate research question was concluded to be: In a 30 year old pregnant female, are PPIs (proton pump inhiitors) safe and effective in the treatment of GERD who is currently taking ranitidine with no relief of symptoms?

Upon conducting a critical appraisal research process to provide optimal care for our patient, we started with searching PubMed for relevant studies. In particular we were looking for Case Control studies to determine outcomes of pregnant women taking PPIs such as omeprazole. We also looked into retrospective cohort studies to look at adverse effects of the medication. So our search terms: PPIs or proton pump inhibitors, Pregnancy , Safety, Efficacy, and GERD.

The Safety of Fetal Exposure to Proton Pump Inhibitors During Pregnancy was the first study we looked at in from the Drugs in Pregnancy and Lactation resource. This was a large retrospective cohort study in which pregnant women had been exposed to a PPI (lansoprazole, omeprazole or pantoprazole) during the first trimester of pregnancy. It was concluded from this study that exposure to PPIs during the first trimester was not associated with an increased risk of major defects and further the study revealed that exposure during the third trimester was not

associated with increased risk of perinatal mortality, premature delivery, or low birth weight. *(Matok, 2012)*

The second study, The Safety of Proton Pump Inhibitors in Pregnancy found using PubMed was a prospective controlled cohort study that compared pregnant women in the first trimester exposed to omeprazole, lansoprazole or pantoprazole. It was concluded from the results that PPIs do not represent a major teratogenic risk in humans and they are not associated with an increased risk for major congenital birth defects, spontaneous abortions or preterm delivery. *(Diav-Citrin, 2005)*

The third and final study we will discuss today, is the Use of Proton Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects which we found on Pubmed. This was a large cohort study and it was used to assess the association between exposure to PPIs during pregnancy and the risk of major birth defects among all infants born alive. The exposure period was from 4 weeks prior to conception through 12 weeks of gestation. It was concluded that the exposure to PPIs during the first trimester of pregnancy was not associated with a significantly increased risk of major birth defects.
(Pasternak, 2010)

The studies that we have just mentioned are considered to be reputable as we have critically appraised all studies that were referenced. Initially, we were expecting to find information based on specific guidelines that outlined the treatment of GERD in women who are pregnant. This was something that was not found after our in depth search through various studies and resources. There were many cohort studies found as expected due to the fact that randomized controlled trials would not be safe for use in the pregnant population, but no specific guidelines were solidified. As well, it was quite difficult to try and find specific information on specific therapies that were both effective and safe in the various trimesters. Although there were plenty of resources and studies out there with good and credible information, there is definitely room for conducting further studies and presenting concrete information.

Based on our findings, we recommended our patient, JR to be prescribed omeprazole 20mg once daily, taken half an hour before breakfast. Omeprazole specifically is a PPI that is listed as one of the drugs of choice for GERD in pregnancy for refractory cases after patients have tried non-pharmacological choices or lifestyle modifications plus treatment with other drug classes with no success. The dosing range of omeprazole is 20-40 mg, but we chose the lower end of the range as it is recommended to start on a lower dose of a PPI initially as the higher dose may not be necessary. JR should continue this treatment for 4 weeks and then return for further assessment to ensure the medication prescribed is effective and tolerable. Although determined to be safe in terms of proper fetal development, we would assess safety in our patient in terms of adverse effects or reactions to the medication.

Along with the treatment recommendation, we also recommend JR continue to try other methods in attempt to reduce symptoms of GERD. Such methods include, avoid eating up to 3 hours before bedtime, avoid lying down after meals, avoid tight clothing, and elevating the head of the bed by 10-20cm. As well, JR should modify her diet; eliminating irritating foods that may be spicy or high in fat, and choosing to eat small meals more often instead of large meals at once.

Just to ease the minds of mothers moving forward, we also assessed information regarding the use of omeprazole while breastfeeding. Any small passage of proton pump inhibitors, such as omeprazole, into breast milk is likely destroyed in the neonate's stomach through acid hydrolysis. Data is limited, however, it has been concluded that omeprazole and pantoprazole specifically are transferred into the breast milk in small quantities. As well, lansoprazole and omeprazole are used for the treatment of GERD in neonates and pediatrics further implying safety in newborns.

Thank you for taking the time to follow along with our discussion today. We hope this was educational and will hopefully be implemented into your practice. With the high incidence of GERD in pregnancy, it is important to feel confident in treating patients in this situation but effectively and safely.

Diarrhea in chemotherapy

S: Hi Guys, this is Tad, Andrew, Satpyul and Jennifer with you today to discuss chemotherapy induced diarrhea and the options we have for take home antidiarrheal medication. Many cancer patients are experiencing diarrhea due to the side effect of chemotherapy. For the treatment of chemotherapy-induced diarrhea, there are some discussions about the comparison of efficacy between Lomotil and Imodium. Let us discuss more about this issue with the scenario.

T: In this scenario an elderly woman is experiencing adverse effects from chemotherapy. Specifically, she is suffering from grade 2 diarrhea (4-6 bowel movements per day) for which Imodium has been prescribed. However, the Imodium fails to restore regular bowel movements and the physician elects a course of Lomotil as an alternative option. The Lomotil therapy proves effective as after 2 days bowel movements return to normal levels.

The patient has recently finished the 3 rounds of FOLFOX which is a chemotherapy regimen used to treat stage 2 colon cancer. The components of FOLFOX include folinic acid, fluorouracil, oxaliplatin. At present the main concern is hypokalemia as low levels of potassium can lead to serious cardiac events including heart failure. Diarrhea can induce hypokalemia due to impaired absorption of potassium from food. There are no other medical conditions of note and the patient is not taking any other current medications besides FOLFOX and Imodium.

Our specific clinical question for this study is: In patients receiving Folfox chemotherapy for colon cancer, is Lomotil more effective than Imodium as a take home anti diarrheal? In order to design this question we utilized the PICO format to clearly identify the population (patients receiving chemotherapy), intervention (Lomotil), comparison (Imodium), and the outcome (relief of diarrhea). The question was of interest to us as according to established treatment guidelines for diarrhea in chemotherapy as Lomotil is not the first line option but rather Imodium.

J: Here is some background information on the medications that we are comparing in our clinical question. Lomotil is a combination medication composed of diphenoxylate and atropine, diphenoxylate is an anti diarrheal and atropine is an anticholinergic used to discourage substance abuse. The way Lomotil works to stop diarrhea in patients is by slowing down the intestinal motility by acting directly on the smooth muscle of the GI tract. We see Lomotil used alone or in combination with other antidiarrheals for the management of diarrhea in patients

older than 12 years old. Some common adverse effects that are caused by using Lomotil are; nausea, skin flushing, dizziness, sedation, and headache.

Imodium is an antidiarrheal medication called loperamide, it stops diarrhea by binding to receptors in the intestine, slowing GI transit time and allowing for more water absorption back into the body. We see Imodium being used in practice in both specific and non specific causes of diarrhea and is the recommended first line agent in patients over the age of 2 years, experiencing diarrhea. Some common adverse effects of Imodium are, dizziness, nausea, constipation and abdominal cramps.

A: Diarrhea is a common side effect many patients receiving chemotherapy experience. This adverse effect is estimated to be as high as 45% with chemotherapeutic agents like irinotecan or 5-fluorouracil. In the patient situation we have presented, they were receiving the FOLFOX chemotherapy regimen which includes 5-fluorouracil, and is likely the cause of their diarrhea.

When a patient taking chemotherapy presents with diarrhea, there are 3 key things that we must do. First, we have to rule out other causes of the diarrhea, such as the presence of an acute bacterial infection, an unusual food they ate, or something more serious than simply the side effect of the chemotherapy. Secondly, we would look at their diet, and help them modify it in the short term so that diarrhea can be minimized. There are certain things we eat that can aggravate diarrhea, such as spicy foods, excessive fatty foods, and coffee, so it can be beneficial to recommend limiting these agents when possible. Finally, we look at medications that are used to treat chemotherapy induced diarrhea. The three medications we use are loperamide, Lomotil (which is a combination of diphenoxylate and atropine) and octreotide. The current guidelines stated by BC Cancer are that loperamide is used for grade 1 diarrhea that persists for more than 12-24 hours, or for moderate grade 2 diarrhea. This medication is first used at a lower dose of 4 mg to start, followed by 2 mg every 4 hours or after each unformed stool to a maximum of 16 mg per day, but can be increased to 4 mg to start followed by 2 mg every 2 hours if needed. The next medication, Lomotil is said to be used “at the discretion of the treating physician” and can be used in addition to loperamide for grade 1 or 2 diarrhea, according to BC Cancer. The final medication octreotide is often used in more severe situations where patients generally require hospitalization. This medication is given as a subcutaneous injection three times per day, and is used for grade 1 or 2 diarrhea that persists longer than 24 hours despite the used of high dose loperamide with or without Lomotil. Octreotide can also be used for patients experiencing grade 3 or 4 diarrhea.
(http://www.bccancer.bc.ca/nursing-site/Documents/GuidelinesforManagementofCID.pdf)

S: We searched through UptoDate, Micromedex, Dynamed, CMAs CPG Database, and Pubmed. We found the medication monographs of Lomotil and Imodium in CPS, and basic clinical information through the article titled “Management of Side Effects of Cancer Therapy and Radiation Therapy” in CTC. UptoDate and Micromedex suggest their clinical recommendation that Imodium is a better agent for this case. We searched the primary research through PubMed, and found some articles related this clinical question. However, we figured out that most articles found through PubMed cited the original study of a collection of papers published from 1970’s and 80’s. We found the original study and explored the information regarding the comparison of the efficacy between Imodium and Lomotil.

When we were searching the primary research through PubMed, we do not have any date

restrictions on our search, and we evaluated articles in English only. We don't include any animal and pediatric studies. The search terms were "chemotherapy induced diarrhea", "loperamide", "Lomotil", "diphenoxylate", and "Imodium". We reviewed abstracts of the articles for relevance, and then, we read the full contents of the relevant articles for appropriate judgement.
(Dom, 1974; Palmer, 1980)

T: From Uptodate, under management of chemotherapy induced diarrhea, it is stated that there are no available studies that directly compare the efficacy of Lomotil and Imodium in the setting of chemotherapy for colon cancer. However, the authors do provide a list of references that examine a number of comparative studies of Lomotil and Imodium in acute and chronic cases. Although these studies are not directly what we wanted for our case they do provide some data in regards to the differential efficacy of these two anti-diarrheals. Of note the majority of these studies were conducted several decades ago from 1974-1981 which made us question why further studies were not conducted beyond this point. The studies, in accordance with guidelines used today, demonstrated that Imodium was more effective in controlling diarrhea than Lomotil and was associated with a more favorable safety profile unlike Lomotil which is associated with CNS effects. We attempted to locate a meta-analysis evaluating the strength of the papers but were unable to identify any such study. Based on available research it appears that resolution of diarrhea with Lomotil rather than Imodium is an atypical outcome which gives the case the potential to serve as a case report thereby leading to additional studies.

J: What our team recommended for MS, given that Lomotil is effective in restoring normal bowel movements in MS, we recommend that she utilize this drug again should she experience diarrhea brought on by future chemotherapy treatments. Although Imodium is recommended as first line in chemotherapy induced diarrhea it is important to consider that patients do not have uniform responses to drugs and so alternatives may prove more effective in controlling disease in certain individuals. Given that Lomotil is associated with adverse effects we also recommend monitoring MS for nausea, confusion, dizziness, and drowsiness.

A: This was a very interesting case, and despite not finding much clinical evidence regarding the use of Lomotil over loperamide, it is a great example of how certain medications can be beneficial to specific patients despite a lack of strong evidence highlighting the use of evidenced-based medicine vs clinical experience. We believe that guidelines should always be followed, and evidenced based practice is strongly recommended; however, once all options have been exhausted, the trial of other medication that could potentially treat the patient, where the benefit outweighs the risks of the medication, can sometimes provide a solution.

ICS and growth

E: Good afternoon everyone, welcome to our evidence based practice podcast. This is Emily Bisson, Monica White and Dani Banham, and we are 3rd year pharmacy students at Memorial University School of Pharmacy. Today our topic will address the question of whether low dose inhaled corticosteroids suppress normal growth in preadolescents with mild to moderate asthma as compared to treatment without corticosteroids.

M: In community pharmacy, inhalers are dispensed frequently to people of all ages. It is common that when a parent drops off a new prescription for an inhaled corticosteroid for their child that

questions start to be asked. For several years, questions have been raised about whether inhaled corticosteroids affect a child's growth. We can understand how concerning it would be to hear that your child's growth could be reduced if they use their prescribed steroid inhalers. For that reason, today we will shed light on what the evidence actually says about the use of inhaled corticosteroids and the effect on growth in children to clarify any misconceptions around this topic.

D: In order to bring light to this topic we came up with a case that exemplifies what a health care professional could see in practice: The mother of an 8-year-old boy recently diagnosed with asthma comes into the pharmacy to drop off a new prescription for Flovent HFA 50 mcg, 1 puff twice a day. After speaking to the mother, you determine that she is hesitant to give her son an inhaled corticosteroid because she read online that steroids can stunt the growth of a child. She is wondering if her son's growth will be affected by using the steroid inhaler.

E: In order to answer this question we started our research by looking in the product monographs in the Health Canada Drug Product Database to see if this issue was addressed, and what was mentioned about it. What we found under the Systemic Effects in the Warnings and Precautions subsection of the Flovent HFA monograph is that growth retardation has been reported as a systemic effect of fluticasone. It also states that a reduction in growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases. Just to compare with other inhaled corticosteroids, we looked up the budesonide monograph which stated the same information as the Flovent monograph with the addition of a double-blind study in children and adolescents treated with budesonide. This study showed that their adult height was 1.2cm shorter than those randomized to placebo. We will talk about this study further on in the podcast.

M: I think the first misconception that patients have about inhaled corticosteroids is when they hear the word steroids. When people think of "steroids" they tend to associate that with prednisone, or anabolic steroids which are usually given systemically, affecting almost all the organ systems in the body. These drugs tend to have nasty side effects like osteoporosis, growth suppression, hyperglycemia, and hypertension, to name a few. Inhaled corticosteroids are different because they work locally and they are rarely systemically absorbed. This is a key message to highlight to parents since the likelihood of steroid effects are much reduced when taken by inhalation versus oral administration.

D: From here, we wanted to dig a little deeper to see where this evidence was coming from. So, we consulted more comprehensive databases like DynaMed, PubMed, Embase and Up-to-date. In these references we found very similar evidence. Slight differences were mostly due to the fact that the drugs and doses compared differed depending on the study. Some studies focused on comparing the effects on growth of specific inhaled corticosteroids like budesonide, fluticasone or beclomethasone against each other or to placebo, while many other studies focused on the overall effect of inhaled corticosteroids on growth, using high and low dose.

E: In addition, while reviewing the literature we determined that there are really two primary endpoints that were being studied in these trials. The first being growth velocity which is the rate at which a child grows to reach their final adult height and the second being overall height reduction which is a reduction in adult height. In terms of a reduction in growth velocity, studies showed that inhaled budesonide, beclomethasone, and fluticasone had a greater effect on

growth velocity and overall height after the first year of treatment compared to placebo, with budesonide being the only ICS associated with significant reduction at two years. It was also noted that the effects on adult height did not appear to be progressive or cumulative. There is some evidence to suggest that higher doses of ICS may cause a greater reduction in growth velocity that with lower doses of ICS. It was indicated in two trials that there was a reduction in growth velocity of 0.2 and 0.48 cm/year for the high dose ICS compared to the low dose.
(Loke, 2015; Pruteanu, 2014)

M: Now in terms of a reduction in overall adult height, we found the double blind study mentioned in the Flovent HFA product monograph was actually pulled from the CAMP trial. This was a two-part study and was the first big prospective study that followed children using ICS into adulthood, where children aged 5 to 12 years old were treated for 4 to 6 years with budesonide, nedocromil or placebo. At the end of the study, a 1.1 cm mean difference in height was measured. When the patients were followed up again in adulthood through the "Effects of Inhaled Glucocorticoids in Childhood on Adult Height" study, a 1.2 cm mean difference in their adult height was measured where the differences in adult height were deemed not significant. This evidence was further emphasized in a second trial titled "Impact of Inhaled Corticosteroids on Growth in Children with Asthma: Systematic Review and Meta-Analysis," where similar results were concluded.
(Kelly, 2012)

D: After gathering all this information, we concluded that there was limited evidence pertaining to the effects of fluticasone compared to placebo, as most of the evidence found was with budesonide.

E: While it is noted that ICS do reduce growth velocity and overall height in the first year of treatment, there is no significant reduction in overall adult height with the use of ICS in childhood compared to placebo. The potential systemic effect of growth reduction can even be minimized by titrating to the lowest ICS dose at which effective control of asthma is maintained.

M: It is also important to weigh the risks and benefits of starting an ICS with the possibility of systemic effects and the potential effects of uncontrolled asthma, because as we mentioned earlier uncontrolled asthma can also affect a child's growth.

D: Therefore, in response to our case we have come to the conclusion that at low doses of fluticasone such as 50 mcg in this case, it is unlikely that the child would experience a decrease in growth velocity or overall growth reductions. It would be best to treat the child's asthma with a low dose ICS to prevent effects of uncontrolled asthma such as growth reduction and frequent exacerbations.

CB: Thanks again for listening to the Med Thread. You can reach us with your comments, and topics you want to hear about by email at medthread@mun.ca or by connecting with us through the School of Pharmacy on Facebook.

See you next month!

References

Baxter R, Bartlett J, Fireman B, Marks M, Hansen J, Lewis E, Aukes L, Chen Y, Klein NP, Saddier P. Long-term effectiveness of the live zoster vaccine in preventing shingles: a cohort study. American journal of epidemiology. 2017 Jun 21;187(1):161-9.

Bergman L, Djärv L. A comparative study of loperamide and diphenoxylate in the treatment of chronic diarrhoea caused by intestinal resection. Ann Clin Res 1981; 13:402.

Bharucha T, Ming D, Breuer J. A critical appraisal of'Shingrix', a novel herpes zoster subunit vaccine (HZ/Su or GSK1437173A) for varicella zoster virus. Human Vaccines & Immunotherapeutics. 2017;13(8):1789-97.

Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, Van Tonningen MR, Clementi M, De Santis M, Robert-Gnansia E, Valti E, Malm H, Ornoy A. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Alimentary pharmacology & therapeutics. 2005 Feb;21(3):269-75.

Dom J, Leyman R, Schuermans V, Brugmans J. Loperamide (R 18 553), a novel type of antidiarrheal agent. Part 8: Clinical investigation. Use of a flexible dosage schedule in a double-blind comparison of loperamide with diphenoxylate in 614 patients suffering from acute diarrhea. Arzneimittelforschung 1974; 24:1660.

Guilbert TW, Mauger DT, Allen DB, Zeiger RS, Lemanske RF Jr, Szefler SJ, Strunk RC, Bacharier LB, Covar R, Sorkness CA, Taussig LM, Martinez FD, Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. J Allergy Clin Immunol. 2011 Nov;128(5):956-63.e1-7. Epub 2011 Aug 4.

Jaffé G. A comparison of lomotil and imodium in acute non-specific diarrhoea. J Int Med Res 1977; 5:195.

Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC. Effect of inhaled glucocorticoids in childhood on adult height. New England Journal of Medicine. 2012 Sep 6;367(10):904-12.

Leroux-Roels I, Leroux-Roels G, Clement F, Vandepapelière P, Vassilev V, Ledent E, Heineman TC. A phase 1/2 clinical trial evaluating safety and immunogenicity of a varicella zoster glycoprotein e subunit vaccine candidate in young and older adults. The Journal of infectious diseases. 2012 Aug 7;206(8):1280-90.

Loke Y, Blanco P, Thavarajah M, Wilson A. Impact of Inhaled Corticosteroids on Growth in Children with Asthma: Systematic Review and Meta-Analysis. PLOS ONE. 2015;10(7):e0133428

Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Digestive diseases and sciences. 2012 Mar 1;57(3):699-705.

Mills R, Tyring SK, Levin MJ, Parrino J, Li X, Coll KE, Stek JE, Schlienger K, Chan IS, Silber JL. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine. 2010 Jun 7;28(25):4204-9.

Palmer KR, Corbett CL, Holdsworth CD. Double-blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhea. Gastroenterology 1980; 79:1272.

Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. New England Journal of Medicine. 2010 Nov 25;363(22):2114-23.

Pelemans W, Vantrappen F. A double blind crossover comparison of loperamide with diphenoxylate in the symptomatic treatment of chronic diarrhea. Gastroenterology 1976; 70:1030.

Pruteanu A, Chauhan B, Zhang L, Prietsch S, Ducharme F. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Cochrane Database of Systematic Reviews. 2014;.