"SHINGLES: Pharmacy Perspective"

January 2016

Shingles (Herpes Zoster) is a nerve infection caused by the varicella-zoster virus. It is this same virus that causes chicken pox. This is a common public health issue that seems to becoming more and more common. Pharmacy practitioners are in a unique place to provide critical information to patients. In this lesson we discuss the significance of therapies.

Pharmacists will be able to:

1. Discuss the relationship between shingles & chicken pox.
2. List the risk factors for developing shingles.
3. Describe the degree of shingles prevalence.
4. Comment upon the methods used to diagnose shingles.
5. Discuss immunization against shingles as well as the vaccine used for this purpose.
6. List the names of the antivirals used in the treatment of shingles as well as their efficacies.
7. Relate the causes & treatment of PHN.

Technicians will be able to:

1. Discuss the relationship between shingles & chicken pox.
2. List the names of the antivirals used for treating shingles as well as their efficacies.
3. Relate the causes & treatment of PHN.

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Shingles

Shingles (Herpes Zoster) is a nerve infection caused by the varicella-zoster virus which is the same virus that causes chickenpox. Its hallmark is the appearance of a painful rash anywhere on the body. Shingles is an extremely common viral infection. To acquire shingles a patient must have previously been infected with chickenpox. Following recovery from chickenpox the virus remains in sensory ganglia via the cutaneous endings of the sensory nerves and lies there (sometimes for years) until it is reactivated and emerges as a cutaneous rash that is characteristic of shingles. Reactivation may be triggered by: a decrease in the immune system of the body; intake of immunosuppressive drugs; malignancy; local irradiation; and surgery. The rash often appears as a single stripe. It rarely appears over a wide area as in chickenpox. Systemic symptoms such as fever, malaise, headache, and pain may occur. In most cases the rash provokes local reactions ranging from itching, numbness, and tingling to excruciating pain due to nerve involvement. Even though the infection and rash disappear after the patient has fully recovered, about 20 to 30% of the cases experience pain that may persist for months, years and even for life. This pain is known as post herpetic neuralgia (PHN), which will be discussed later in this lesson.

Shingles can occur at any age, but it is infrequent among the young. The incidence increases with age. It peaks at age 50 and over. Irritation and flu-like symptoms may occur prior to the appearance of the rash. Itching, tingling, and pain may come next. The rash first appears as red maculopapules that may become a cluster of vesicles filled with serous exudate. Newly formed vesicles may continue to appear for several days, after which the rash, if secondarily complicated by bacterial infection, becomes pustules and later on turns to scabs. In severe cases the rash leaves scars and skin discoloration. The rash or blisters appear in a unilateral, dermatomal pattern following the innervation of sensory nerves. Parts of the body that are usually affected are the trunk, cervical and lumbar areas. The trigeminal nerve is often involved, in particular that of the ophthalmic branch. This can lead to keratoconjunctivitis and disruption of motor activity, including weakness of the eye muscles and mydriasis (dilation of the pupil). Ophthalmic shingles refers to cases that affect the eye and the surrounding tissues and may result in immediate or delayed vision impairment. Facial and auditory nerves may be involved resulting in the appearance of vesicles in the external ear and in facial paralysis known as Ramsey Hunt Syndrome. This may lead to hearing impairment and imbalance. Involvement of the cervical ganglia may result in elevation of protein level in the cerebrospinal fluid. The infection usually subsides in two to three weeks.

Risk factors of developing shingles are: a family history of having the disease in the past. Close relatives who acquired the infection are at higher risk of developing the disease than those with no family history of the infection or PHN. Complications of shingles are PHN, secondary bacterial infection at the rash site and addiction to opioids which often are used to treat severe pain caused by PHN, especially if used in long-term (over a year) treatment. Diminished quality of life may lead to depression. Prognosis ranges from good to poor depending on the general health of the patient, age, status of the immune system, the time when treatment with antivirals was initiated, duration of infection, and previous shingles vaccination. While shingles is not a life-threatening disease, it can be debilitating. Zoster sine herpete (ZSH) is a type of shingles that is characterized by symptoms similar to regular shingles except the rash is absent. It exhibits pain, tingling and itching but no rash at any point during the course of the infection. The incidence of ZSH is rare.

DIAGNOSIS

Shingles can be diagnosed clinically once the distinctive and recognizable rash appears. ZSH cannot be diagnosed clinically due to the absence of rash. However, both ordinary shingles and ZSH may be diagnosed through laboratory testing. The rash must be distinguished from that caused by herpes simplex, contact dermatitis, urticaria and drug eruptions. Direct fluorescent antibody staining of cells from fluid extracted from blisters or from scrapings from the base of a lesion is used to diagnose shingles with rash. This method is rapid and specific but is not as sensitive as polymerase chain reaction (PCR). Viral cultures which are performed on liquid from blisters give more accurate results. Tzanck smear, which can be performed at bedside, consists of placing material from blisters or scrapings on a glass slide for microscopic viral identification. The test is inexpensive, quick, but has only 50 - 70% accuracy. Because the body provides antibodies during the course of the infection, antibody titers (ELISA) can give the amount of antibodies produced. The test has 85% accuracy. PCR is as accurate as viral culture, but gives quicker results and is more expensive.

PREVALENCE

Shingles is among the most common viral infections. Incidence of shingles has been on the rise over recent years not only in the U.S. but worldwide. It has been estimated that between 1992 and 2010 the rate of increase was in individuals 65 years of age and older. It has been theorized that the reason for this increase is due to vaccination of children against chickenpox. However, this assumption was refuted. In a CDC study using data from 1992 to 2010 it was revealed that in patients 65 years of age and older shingles cases were rising even before chickenpox vaccinebecame available. Furthermore, there was no increase in the rate of shingles after the vaccine use became widespread. About 33% of adults in the U.S. will acquire shingles during their lifetime. Most patients who acquire shingles rarely get the disease for a second or third time. The annual number of new cases ranges from 1.2 – 3.4 per 1000 to 3.9 – 11.8 per 1000 in individuals over 65 years of age. About 95% of patients 85 years and older will have at least one shingles attack, while 5% will have more than one occurrence. About 1% - 4% of shingles patients require hospitalization due to complications. About 30% of those who are hospitalized are patients whose immune system has been weakened as a result of diseases or because they take immunosuppressant drugs. Death as a direct result of shingles is rare. It is estimated that about 96 persons die annually in the U.S. from shingles. Practically all fatalities occur in the elderly or in those whose immune system has been compromised. These patients include those with cancer, in particular leukemia and lymphoma, HIV, those who undergo organ transplantation, and those who use immunosuppressants such as corticosteroids and drugs for prevention of transplant rejection. Though shingles can be acquired by both men and women, it seems more common in women. Explanation of this observation has not been determined. Some studies have concluded that shingles is less common among blacks by about 50%. About 1 million cases of shingles occur in the U.S. annually. Approximately 2.1 million physician visits by patients who suffer from shingles or its complications occur every year in the U.S., costing over $500 per patient. Those older than 65 years of age are 7 times more likely to develop shingles than younger patients.

IMMUNITY AND VACCINATION

Immunity is the state of providing protection from infectious diseases. Once a person develops immunity to a specific infection, exposure to the microorganisms will not result in infection. In order to stimulate the immune system of the body against a particular disease, a vaccine can be administered, usually by injection, but it could be given orally or by spraying in the nose, depending on the disease in question. The process of administering a vaccine is known as vaccination, whereas protection against a disease by administering the vaccine is termed immunization. Once the vaccination is given, it stimulates the immune system to produce antibodies that are specific for fighting a particular disease.

A vaccine against shingles has been available since 2006 and is approved for patients over age 50. The vaccine reduces the risk of acquiring shingles. Some vaccinated patients may still get shingles. If that happens, the course of the infection is usually much shorter and milder than in those who have not been vaccinated. Furthermore, development of post herpetic neuralgia will be less intense. It is estimated that only 1 in 5 adults in the U.S. are vaccinated.

Not all individuals should be vaccinated. Those who should not receive the vaccine are:

1. Experiencing weakened immune system due to a disease state or intake of immunosuppressants. The vaccine, which consists of live attenuated varicella-zoster virus, may result in a dissemination of shingles,
2. Undergoing chemotherapy and radiation treatment,
3. Suffering from leukemia, lymphoma, or tuberculosis,
4. Allergic to any of components of the vaccine, in particular gelatin and neomycin,
5. Pregnant. Women who plan to become pregnant should postpone becoming pregnant until 3 months have elapsed after receiving the vaccine.

It is estimated that 99% of Americans aged 40 and older have had chickenpox. Many do not recall the encounter. Elderly patients should be vaccinated even if they do not remember having had chickenpox. There is no maximum age for getting the vaccine. Individuals who suffered from shingles during their lifetime should be vaccinated in order to reduce the risk of future recurrences of shingles. There is no waiting period between having shingles and getting vaccinated. It is recommended that in such cases a health provider should be consulted to determine the risks and the benefits. It has been estimated that protection from shingles vaccine lasts for five years.

SHINGLES VACCINE

Zostavax

Zostavax is a shingle vaccine that consists of lyophilized live attenuated herpes zoster virus. It is available as a single 0.65 ml suspension to be injected subcutaneously in the deltoid region of the upper arm. It is contraindicated in individuals with history of anaphylactic reaction to gelatin, neomycin or any of the constituents of the vaccine. Zostavax is stored frozen and must be reconstituted immediately after its removal from the freezer. A sterile diluent is provided for reconstitution. The reconstitution process calls for injecting the diluent into the vial that contains the lyophilized virus followed by gentle shaking to ensure complete mixing and

avoidance of foaming. The reconstituted vaccine contained in the vial should be withdrawn and the entire contents immediately injected subcutaneously in order to maintain potency of the vaccine. Any reconstituted vaccine should be discarded if not used within 30 minutes. The reconstituted vaccine has a white to pale yellow, cloudy to translucent appearance. Some people have experienced hypersensitivity reactions including anaphylaxis following injection. The vaccine should not be administered to anyone who is sensitive to any of the components of the vaccine. The vaccine has been shown to reduce the incidence of shingles. It also reduces the incidence of PHN, and the pain associated with shingles rash. Adverse effects of Zostavax include: pain, swelling, pruritus and redness around the injection site as well as headache. Hypersensitivity reactions have occurred following injection with Zostavax.

TREATMENT

There is no cure for shingles. The objectives of treatment are: to relieve pain, shorten duration of the infection, enhance healing, and reduce the risk of complications. It is important to realize that preventative treatment through vaccination is an essential measure for reducing risk of developing shingles as well as reducing the long-term pain caused by PHN. To optimize results, treatment must begin immediately after the rash appears. Patients who suspect that they have shingles affecting the eyes, nose or face should seek medical care promptly. Antiviral medications are mostly effective once given in the very early stages. Initiation of treatment within 72 hours following rash appearance will significantly reduce the chance for developing later complications. The main options used in treating shingles are:

1. Antivirals
2. Analgesics
3. Topical Corticosteroids

Others include topical medications such as antibiotics; local anesthetics and astringents (such as calamine lotion and burrows solution).

ANTIVIRALS

The most commonly used antivirals in the treatment of shingles are: acyclovir, famciclovir and valacyclovir.

ACYCLOVIR

This was approved by the FDA in the 1980s. It is a guanosine analogue antiviral drug that exerts its action via intracellular conversion to acyclovir triphosphate, which is the pharmacologically active form of the drug. Non-phosphorylated acyclovir, such as acyclovir monophosphate and diphosphate, has little or no effect on the virus activity. The drug is poorly soluble in water and has only 15% - 30% bioavailability after oral administration. If there is a need for a rapid and high blood concentration, the drug should be administered intravenously. Percutaneous absorption, following application to intact skin results in minimal or no absorption. Following absorption from the GI tract it is well distributed in the body and has protein binding affinity ranging from 9% - 33%. It is excreted through the kidneys by glomerular filtration and tubular secretion. The intake of 800 mgs of acyclovir 5 times daily for 10 days has shortened the time for rash formation of scabs, enhanced healing, reduced pain and reduced formation of new crops of blisters. Administration of the antiviral within 48 hours of rash onset gives best results. The onset of treatment should commence immediately upon the appearance of symptoms such as itching, tingling, pain, burning and rash. It can be taken with or without food but with

a full glass of water. Taking the drug with food may reduce stomach upset. Throughout the duration of therapy, the patient should drink plenty of water to keep the kidneys functioning properly. Acyclovir, like other antivirals, does not cure shingles, but is capable of slowing the breakout of the rash and the spread of virus in the body. It can pass into breast milk and may produce adverse effects in infants. The entire quantity of medications prescribed should be taken for the entire period specified in the prescription even if symptoms improve.

Acyclovir is available in 499-800 mg tablets, 200 mg capsules, 50 mg/ml injection and 200 mgs/mo suspensions. The injections are used to prevent recurrent outbreaks of infection, especially in patients with weak immune systems. The medication can be taken with or without food in a dose of 800 mg every 4 hours a day for 7-10 days. The dose depends on severity of the infection as well as response to treatment. The drug is available generically from several manufacturers. Research indicates that acyclovir is becoming less effective over time to certain herpes strains. Adverse effects of acyclovir include nausea, diarrhea, weakness, appetite loss and headache.

FAMCICLOVIR

This drug was approved by the FDA in 1994. It is a guanosine analogue and is considered a prodrug of penciclovir. It has been available generically since 2007. It comes in 125 mg, 250 mg and 500 mg tablets. The usual adult dose is 500 mgs three times daily for a week. The drug is inactive directly against the virus, but once in the body it is converted to penciclovir which is active against the virus. Famciclovir has pharmacological activity and side effects similar to acyclovir, except it has a longer duration of action. Common adverse effects include nausea, diarrhea, and appetite loss.

VALACYCLOVIR

This is another example of a guanosine analogue. It was approved in 1995. It mimics one of the building blocks of DNA. Like acyclovir, it interferes with replication of viral DNA. It is a prodrug that is inactive as such, but when taken it is converted to acyclovirin and ultimately to acyclovir. Its action is similar to acyclovir except it has longer duration of action. The regular adult dose is 1 g three times daily for 7 days. It is available in tablets containing 500 mgs and 1000 mgs.

ANALGESICS

Drugs such as ibuprofen, acetaminophen, and opioids such as codeine and hydrocodone may be used to help reduce severe pain.

CORTICOSTEROIDS

These may be used in severe cases for a short time together with the antivirals. However, it has been shown that the use of corticosteroids does not change the course of the infection any more than using antivirals alone.

POSTHERPETIC NEURALGIA (PHN)

About 25% of shingles patients will develop complications. The most common are secondary bacterial infection, formation of scars, and risk of vision impairment when the rash appears around the eyes. However, the most serious complication is the long-term pain that occurs after the disappearance of the rash. This is termed postherpetic neuralgia (PHN). As indicated earlier, activation of the dormant virus located in the body will invade the nerve tissue and

slowly makes its way to the surface of the skin causing shingles with the characteristic rash. In some cases, between the time of virus reactivation and disappearance of the rash, damage to the nerves may occur as a result of the virus invasion. Frequently, after the rash disappears, pain will flare up. This pain is termed postherpetic neuralgia (PHN). Thus PHN may be defined as a chronic nerve pain that persists after resolution of the shingles rash. It can last for years. PHN also includes pain that resolves with the disappearance of the rash but returns at a later date. About 10% - 15% of patients develop PHN one month after the onset of shingles, 5% after three months. At one year 3% of the patients will continue to have severe pain. About 60% of patients 60 years of age and older and 75% of patients 70 years of age and older develop PHN. The pain is intense and characterized by burning, stabbing, sharp, and deep. The area becomes so sensitive that pain is felt even upon light pressure.

TREATMENT OF PHN

Treatment of PHN is individualized depending on the severity of the symptoms and general health of the patient. One or more of the following medications may be used:

1. Topical medications such as lidocaine patches, and capsaicin skin patches.
2. Anticonvulsants
3. Opioids alone or in combination with NSAIDs
4. Antidepressants

TOPICAL TREATMENT

These may contain 5% lidocaine and should be applied to intact skin to avoid absorption from broken or exposed skin. They should be used with caution in patients who are allergic to lidocaine or to para-aminobenzoic acid derivatives such as, tetracaine and benzocaine. A lidocaine patch was approved by the FDA in 1999.

CAPSAICIN SKIN PATCH

This contains the active ingredients in chili peppers and is a local irritant that relieves pain.

ANTICONVULSANTS

In addition to their use to manage seizures, anticonvulsants such as carbamazepine, gabapentin, and pregabalin are used to reduce pain caused by PHN. Both carbamazepine and gabapentin are used to control epilepsy and neuropathic pain such as PHN. Pregabalin is used in the management of seizures, anxiety disorders and neuralgia that is caused by PHN, diabetes and fibromyalgia.

OPIOIDS

These are narcotic analgesics that can be used alone or in combination with ibuprofen or acetaminophen.

ANTIDEPRESSANTS

Drugs like nortriptyline can provide analgesic action in addition to their antidepressant activity.

SUMMARY

Shingles is a common infection caused by the varicella-zoster virus. It is characterized by an outbreak of a very painful rash anywhere on the body. It is common among the elderly and affects men and women. The disease is not life-threatening but it is debilitating. One of the complications is the possible development of chronic pain that arises after the resolution of the rash (PHN). Shingles vaccine is available. It reduces the incidence by over 51%.

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1. Does the program meet the learning objectives?

Relationship between shingles & chickenpox	YES NO
Risk factors for developing shingles	YES NO
Methods for diagnosing shingles	YES NO
Vaccine for shingles	YES NO
Names of antivirals for treating shingles	YES NO
Causes & treatment of PHN	YES NO

2. Was the program independent & non-commercial YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____

5. What did you like least about this lesson?_____

Please Mark the Correct Answer(s)

1. **Which of these is true about shingles?**
   A. Caused by same virus as chickenpox
   B. Following chickenpox, the virus remains in body for 2 months
   C. Most common in patients under 45 y/o
   D. Rash can appear all over body except around eyes

2. **About 10,000 people die annually in the U.S. as a result of shingles.**
   A. True B. False

3. **Shingles vaccine:**
   A. Only for patients 75 y/o & older
   B. Not given to patients allergic to gelatin & neomycin
   C. May be given during pregnancy
   D. Given IV

4. **One in 5 adults in the U.S. are vaccinated against shingles.**
   A. True B. False

5. **Shingles treatment must begin immediately upon appearance of rash.**
   A. True B. False

6. **Which of these is NOT an adverse effect of Zostavax?**
   A. Swelling at site of injection
   B. Headache
   C. Blood pressure elevation
   D. Pain around injection site

7. **Which of these is FASLE?**
   A. Acyclovir is a prodrug
   B. Acyclovir shortens rash time
   C. Acyclovir has protein binding ability
   D. Acyclovir cures shingles

8. **Fanciclovir is given only by injection.**
   A. True B. False

9. **PHN is characterized by pain after resolution of rash.**
   A. True B. False

10. **Which of these is used in the reduction of pain caused by PHN?**
    A. Hydrocodone
    B. Capsaicin
    C. Pregabalin
    D. All of these

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