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Herpes Zoster

(Diploma Thesis)

Mentor of Diploma thesis

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ABSTRAKT

Tato diplomová práce se zabývá častým onemocněním Herpes Zoster, které se týká většiny lidí ve všech věkových kategoriích. Práce poskytuje celkový pohled na konkrétní choroby a jejich diagnózy. Pozornost je zaměřena na samotnou léčbu jednotlivých onemocnění, tedy na léky a dávkování.

Analýze jsou podrobeny epidemiologické aspekty a nežádoucí účinky onemocnění Herpes Zoster. Práce dále odkazuje na rizikové faktory, které vedou ke vzniku onemocnění, a popisuje způsoby, které pomáhají předcházet a zvládat komplikace při Herpes Zoster. Věnuje se též způsobům zabránění přenosu tohoto onemocnění a možnostem snížení rizika postherpetické neuralgie a chronické bolesti.

ABSTRACT

This thesis is about Herpes Zoster, a common disease that touches most of people at all ages. In this paper, we are going to give a general view of the specific disease and in the diagnosis of this disease. As well in the disease's treatments, means drugs and doses.

Epidemiological aspects of Herpes Zoster are analyzed as also the adverse reactions on the human. Furthermore, we refer to the risk factors that lead to the disease.

Ways that help to prevent and manage the complications of Herpes Zoster, ways to prevent the transmission of Zoster and ways reduce or prevent post-herpetic neuralgia and chronic pain.

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1. Introduction

The virus is a microorganism and parasitic pathogen that causes various infectious diseases in plants, animals and people. With the passage of time made possible the observation of the viruses from the electric microscope and so observed that the virus has RNA or DNA and they multiply in living cells (against host cell) because they lack enzyme system. The virus is inactive when is outside of the cell and the size of the virus varies. The dermatitis may be due to the infectious viruses causing rashes during childhood, such as measles and chickenpox.

Specific, one known virus is the Herpes virus (herpes simplex) known also as Human Herpes Virus 1 belongs to a class of virus that can cause the Varicella Zoster Virus (VZV) and Herpes zoster (Konstantinos I. Kanitakis, 2005).

The Herpes zoster virus has 130-170nm and is pathogenic for the skin, eyes, nervous system and mucous membranes. There are two types of Herpes virus, the Herpes virus 1 that causes the facial herpes and the Herpes virus 2 that causes the herpes genital. This diploma analyzed the herpes virus 1.

Herpes virus 1 or Herpes zoster is caused by the chickenpox virus, and can be considered as a painful disease, and there is a formation of rashes, which then disappear. Every person who has had chickenpox can develop shingles at some point in his life. Individuals who get one of the two viruses (chickenpox or herpes zoster) have immunity against the other and this called cross-immunity (Konstantinos I. Kanitakis, 2005).

For the treatment of herpes zoster are used antiviral (virostatics) drugs that are nucleoside or nucleotide analogues. There are used drugs like Acyclovir (Zovirax) or Valacyclovir (Valtrex), corticosteroids, NSAID's and some more combinations of drugs that analyzed later on.

2. Definition of Herpes zoster

Herpes zoster because ‘encloses’ one side of the body gets the name from the Latin name cingulus and from the Greek language zostrix that means belt or girdle (Ramos T. A., et al 2006). Herpes zoster or shingles is a lupus vesicular skin disease and is a painful

situation because blisters are created across the nerves (see Figure 1). Herpes is directly related to the varicella virus because this is caused by. The varicella virus usually occurs in childhood with symptoms such as high fever, characteristic rashes, has the ability to remain dormant for decades in the nerve cells of the sensory dorsal root ganglion and can be reactivated when finding opportunity. The cause of this reactivation is unknown but usually is related with a transient failure of the immune system and the age. The greater age one has the greater chances has to develop blisters. Herpes zoster usually affects the lumbosacral, the cervical, and the cranial dermatomes (Buchbinder SP., et al 1992). The chickenpox virus transmitted through the respiratory tract and can be transferred to and infect other people. The incubation time is 14 days and after this period the infected cells penetrate the capillaries, reach the skin that infect it and then the characteristics rashes shown (Arvin A.M., 1996).

The rashes appear for few days and the patient may feel pain even no rashes are shown. This is known as zoster sine herpette (Gilden DH., et al 1994). In immunocompromised patient, the dermatomal distribution of the virus is low and the total duration of the disease is usually 7-10 days, but the skin to return to its normal state may need 2-4 weeks. In elderly, the duration is 6 weeks maybe and more. The pain, however, can remain for years and is one of the complications of zoster that is called Postherpetic neuralgia (PHN) and occurs more in elderly > 50 years old (Taylor LP., et al 2002). Initially, the rash begins as small red dots (plaques) on the face, scalp and upper arms and legs. After 10– 12 hours these red dots become into small blisters and pustules followed by the formation of scabs.

The localization of herpes zoster in dermatomes requires special attention because herpes zoster with dermatological distribution is an infection of the healthy adult and there is a high risk of virus reactivation in the immunosuppressed patients (HI, leukemia). For this reason, caution should be given and look clinically the patient but also to ask for the personal of medical history.

Shingles is a self-limiting disease and can be treating with antiviral agents (Acyclovir, famciclovir and valaciclovir) that are used in the whole Europe. These drugs can be given orally in the first 48-72 hours of the appearance of the rash so to decrease the symptoms like pain. These drugs blocks virus replication and inhibit its spread. For the pain, can be used also analgesics or local anesthetics (Dworkin RH., et al 2003).



Figure 1: Painful shingles are created across the nerves

Source: http://www.aidsmeds.com/articles/Shingles_6798.shtml, accessed at 25.06.2013

3. Pathophysiology of Herpes zoster

The Herpes Zoster is caused by the chickenpox (Varicella zoster virus-VZV) comprising from a double-stranded DNA virus and is a contagious virus. The primary infection of chickenpox appears during the childhood and then the virus entry and remains dormant in the sensory dorsal root ganglia for decades (Strauss SE., 1994). Therefore, herpes zoster occurs only in persons that have been infected in the past by the chickenpox virus. The cause of the reactivation is unknown but usually is due to low immune system, low cell-mediated immunity that are responsible for the activation of T-lymphocytes, stress, age, fatigue, trauma and some other factors (Thomas SL., et al 2004). The varicella zoster virus after reactivation travels in the nerve cells and then the intact virions are able to penetrate the epidermis because travel through the axons of the skin. Therefore, virions cause skin infection by forming blisters and pain (Post herpetic neuralgia-PHN). This pain may appear some time to years. After studies performed have shown that the PHN destroy with the passage of time the nerves of the dorsal root ganglia and of spinal cord (Bowsher D., 1995).

4. Clinical manifestation of Herpes zoster

Herpes zoster is a dermatomal disease and most often, the characteristic rashes occur at the lumbar or thoracic nerve part or in the chest spinal nerves (see Figure 2). The signs and the symptoms occur on the one side of the body and usually in one dermatome.

Herpes commonly begins with the prodrome phase and this is the first stage of symptoms before the rash onset and usually lasts 3 days but sometimes can last 2 weeks. During this prodromal phase, constitutional symptoms like burning, itching, hyperesthesia or pruritus can appear three or more weeks before rash onset in the dermatomes, which will become affected (Stankus SJ., et al 2000). Usually, during the appearance of this prodrome there are chances to confuse the symptoms of Herpes zoster with gastrointestinal disorders, cardiac problems, gynecological and various others.

After the prodromal phase, the characteristic rash of Herpes zoster, localized pain and an erythematous vesicular rash is developed which followed by dermatomal distribution. The most characteristic symptoms of the rash are the headache, the photosensitivity but the most important symptom is the pain, which described like burning, stabbing and can also lead to the most important complication the post-herpetic neuralgia (Goh L., et al 1997). Usually the rash affects the ophthalmic dermatome in the trigeminal nerve, which may lead to blindness. Shingles form blisters approximately in 7-10 days but to return to its normal phase may need 2-4 weeks (Wilson JF., 2011).

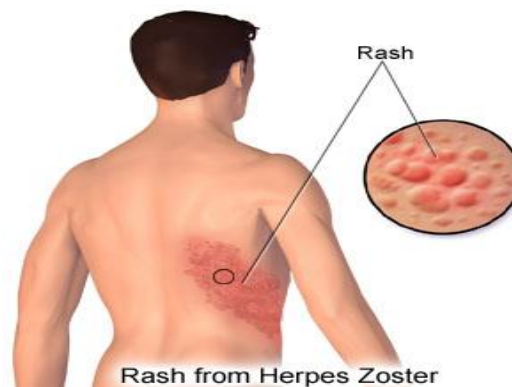


Figure 2: The characteristic rash of Herpes zoster

Source: <http://www.drugs.com/cg/herpes-zoster.html> , accessed at 28.06.2013

5. Diagnosis of Herpes zoster

Herpes zoster can be diagnosed clinically because is enough for the healthcare providers to understand it when there are developed skin lesions. Patient with herpes zoster will have localized pain, which appear a few days to weeks and a characteristic erythematous vesicular rash that leads to a dermatomal allocation. First red spots are

formed which then are converting to small vesicles. The inflammations of the skin can be motley or accumulated. Most patients describe the zoster with a burning sensation or dysesthesias.

In cases where there is absence of the rash or in immunosuppressed patients in which the pattern of the blisters and location of the rash are atypical there are laboratory and physical methods for diagnosis (Beers, et al 2004):

- ✓ Tzanck test: In this test, a smear is taken from the blister and the cells that have been infected with herpes will be sizable and will have nuclei.
- ✓ Viral culture of the rashes: Because the virus is growing slowly is not used very frequent for practical objectives.
- ✓ Immunoglobulin (IgM) antibody test: In this situation IgM antibody appears in the blood only when the herpes virus is reactivated (Arvin AM., 1996)
- ✓ Direct immunofluorescent test: Is rapid and low cost test
- ✓ PCR test
- ✓ Monoclonal antibody test

6. Causes and risk factors

VZV consists of a double-stranded deoxyribonucleic acid and is infectious. So only those who have been infected with chickenpox can develop herpes zoster sometime in their life. This is happening because the chickenpox virus remains dormant for decades in the sensory dorsal ganglia and can be reactivated when finding opportunity. Investigations have shown that the one-third of the population will show herpes zoster especially those with age older than 60 years (Harpaz R., et al 2008).

These that are in higher risk to develop herpes zoster are the immunosuppressed people like those with HIV, with malignancies and reduced immune system. Some recent trials have demonstrated that the existence of herpes zoster is increasing but we cannot give the explanation. However, the sure is that after decades, the incidence of HZ will change because science is constantly evolving and there will be changes in the therapy of malignant, of HIV and possibly because of the result of childhood vaccination (Seward J., 2000).

Shingles occur only in those persons that had been infected in the past with chickenpox. There are specific risk factors that involved and increase the appearance of herpes zoster:

6.1 Infection with VZV

The primary factor and the most important role for the appearance of Herpes zoster is the re-activation of Varicella zoster virus, which is in latent phase. The first infection with the VZV appears as chickenpox and since then as herpes (shingles). The age at which the person experienced chickenpox associated with the age at which zoster occurs. However, the people at risk for pediatric zoster are those who in the early childhood gain an intrauterine infection with VZV (Kilgore PE., et al 2003 and Brunell PA., et al 1981).

6.2 Aging

The aging is the most basic and the most important risk factor for the appearance of herpes zoster. First of all after many investigations that have been conducted around the world for the relationship between the age and the chickenpox have shown that the incidence of herpes zoster is directly connected with the age. Specific studies showed that the older age one has, the greater chances to develop herpes zoster. The sure is that the total number of cases with herpes zoster will rise because the generation of the babies getting old. The older persons or the immunosuppressed patients are at high risk to develop herpes zoster because the cell-mediated immunity activates less T-lymphocyte, which secretes cytokines. (Hope-Simpson RE., 1965 and Thomas SL., et al 2004).

The age also has a direct relationship with the development of Post herpetic neuralgia (PHN). The risk of PHN increases after the age of 50 years old. This relationship has proven in a survey was done and the results showed that people >50 years old have a percentage 80-85% more chances to develop Post herpetic neuralgia (Choo PW., et al 1997).

6.3 Immunosuppressant individuals and emotional stress

People suffering from HIV, AIDS and bone or marrow transplantations are at risk to develop herpes zoster. Also at risk are those with childhood cancer because all those have weak immune system (Buchbinder SP., et al 1992). The patients with Hodgkin's disease and lymphoma are at risk. Some more risk factors are the exhibition to immunotoxins and the psychological stress, which will result in appearance of herpes after 6 months of the

event (Gatti A., et al 2010). Immunosuppressed have 20 times more chances to develop herpes than immunocompetent patients.

6.4 Certain drugs

Some certain drugs decrease the immune system and contribute in the development of shingles. Such drugs are used from patients with organ transplantations, HIV, diabetes, lupus erythematosus and others. Some of these drugs are the infliximab, cyclosporine, ezathioprine, adalimumab.

6.5 Female sex

Studies reported that the incidence of herpes zoster in women is more common than in men. The percentage for the women's herpes is around 11%. Generally if be included all the risk factors together there is a percentage of 35% for women appearance and specific for those with age over 50 years. In addition, the developing of PHN is more in women than in men. Of course, others believe that sex does not play a role in the incidence of herpes zoster (Thomas SL., et al 2004).

6.6 Ethnicity

Some investigations made in US support that the white race develops more often herpes zoster than the black one (Tseng HF., et al 2011).

6.7 Seasons

Studies have been reported that the reactivation of VZV is more common in the summer and this because of the ultraviolet irradiation and because the skin is exposed. However, some other scholars believe that there is no relationship (Arvin AM., 1996).

7. Complications of Herpes zoster

Herpes zoster is a self-limiting disease and is caused when varicella zoster virus, which belongs to the alpha herpes virus of human, reactivated (Abendroth A., et al 2010). Clinically this reactivation is important because of the various complications that causes. These complications can affect the neurological, the ocular and others systems (Volpi A., 2007). For the good management of the complications the treatment must begin quickly in order to decrease the severity. Some of these complications are:

7.1 Pain

Herpes zoster when is active creates a discomfort pain which is the primary and the most common complication. The pain can occur with three ways:

- It can be a constant pain
- It can be periodic
- It can occur like electric shock-spasm

The pain can be defined also as allodynia or hyperalgesia, two complications that are more potent. The feeling of pain change with the temperature and at night is more severe. This complication is important because affects everyday life of the patient and the quality of life. However, pain does not appear on a daily basis (James WD., et al 2006).

7.2 Post herpetic neuralgia (PHN)

Post herpetic neuralgia occurs in older people with age older than 50 years. Is the most common and the most severe complication, which exists for more than one month, maybe for years. The pain is described as burning, gnawing and allodynia (Dworkin RH., et al 1996). The pain affects the nerves of the spinal cord. Do not develop all the patients post herpetic neuralgia. This depends from the age, gender and from the kind of the shingles. Sometimes if the pain is persistent and not treated effectively may lead to the depression of the patients (Straus SE., et al 2008).

7.3 Secondary infection

There are chances for bacterial infections, *Staphylococcus aureus* or *Streptococcus*, when the blisters did not covered and clean well.

7.4 Ramsay Hunt syndrome

The symptoms of this syndrome are loss of taste, vomiting, dizziness, hearing of loss, ringing and severe pain in the ear. This syndrome occurs when herpes affect the cranial nerves. This lead to facial paralysis, and rash is noticed in the ear. Facial paralysis can be intermittent and the loss of hearing may be total or partial (Kim JH., et al 2007).

7.5 Effects on the brain

The effects on the brain can be for example meningitis and encephalitis. In immunocompetent people, these complications are mild but in immunosuppressed are severe and may lead even to the death (Grann Jw Jr., 2002).

7.6 Ocular infection

When herpes infect the eye, herpes zoster ophthalmicus envelop. In this case, the herpes affect the trigeminal nerve and shingles appear in the face. This means that the eyes are at high risk and when are involved the treatment is difficult. Herpes zoster also causes glaucoma, keratitis, retinitis (James WD., et al 2006 and Tugal-Tutkum I., et al 2010).

7.7 Urinary tract infections

The effects of herpes in the urinary tract are not so frequent but when it is happening cause urinary retention, hematuria and erectile dysfunction (Erol B., et al 2009).

8. Prevent the transmission of Herpes

Shingles can be transmitted from one patient to another through the contact with the fluid of the rash. The varicella zoster virus and the herpes zoster can be transmitted and infect even people who have never been infected in the past with chickenpox. Therefore, these persons can develop only chickenpox and no herpes zoster.

Shingles can be transmitted less than varicella zoster virus. The patient should cover the rash because will be less dangerous and less risky to spread. In addition, should not scrape the rash, should keep it covered and it is necessary to wash the hands systematically in order to avoid the transmission of the virus.

In order to avoid the transmission of the zoster individuals that have herpes zoster must avoid going to the work or in places with people so to avoid come in contact with sensitive persons. Individuals should be avoided at people with herpes are primarily pregnant women, newborns and older people. All of us should know the symptoms of zoster so to can dodge as people with herpes (Bolyard E.A., et al 1998).

9. Treatment of Herpes zoster

The existence of an effective treatment requires a very good education of the patients around herpes zoster. Patients should know what is happening with herpes zoster, the symptoms, the risk factors and the complications. They should be prepared to face herpes when it will appear the chronic pain that causes and they should know how to use right the drugs. It is important to know that for better confrontation of pain patients should start the therapy in the first 24 hours.

All the future patients with herpes must know how to protect the others from the virus in order to prevent the transmission. For this reason, those with active herpes should avoid to contact with others, especially with those that did not affected in the past with VZV, pregnant women, immunosuppressed people, infants and young children. Therefore, it is better to placed infected patients alone.

9.1 Antiviral agents

Antiviral drugs reduce the healing time of the skin lesions, the acute pain, the severity of symptoms and the formation of new lesions (Schmader K., 1995). However, to have these results the patients must take the drug in the first 72 hours after the appearance of the rash. Also is important to know that the antiviral drugs do not affect all the patients with herpes zoster but more those who are older than 50 years, have severe rash or they have not any trunked involvement.

After many studies that have been conducted on whether the antiviral reduce the post herpetic neuralgia are contestable. However, studies have shown that acyclovir and valacyclovir can reduce a little the post herpetic neuralgia (Crooks RJ., et al 1991), with the condition that the therapy begins in the first 72 hours or better 48 hours. Because if the therapy starts after 72 hours there will be adverse effects in elderly like ophthalmic problems and severe pain.

In this group, there are two most known antiviral drugs, the acyclovir and the valacyclovir. Both of these are safe, give good benefits and reduce the risks. Some clinical trials shown that valacyclovir have greater efficacy and greater bioavailability after oral administration than acyclovir (Degreef H., 1994).

It is recommended the administration of these drugs to start in the first 72 hours in order to avoid the formation of new vesicles and motor, ocular or neurologic complications (Katz J., et al 2004). The patients who still form vesicles after 7 days of antiviral therapy are recommended to continue for more days the therapy. However, attention must be given in those that have done mistaken diagnosis.

- *Acyclovir*

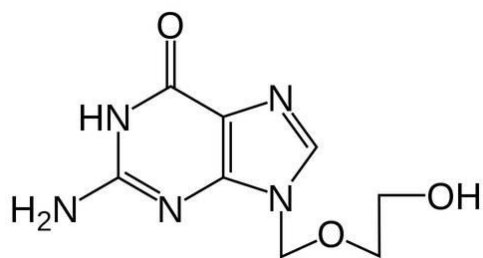


Figure 3: Chemical structure of acyclovir

Source: <http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---A/Acyclovir.htm> , accessed at 08.07.2013

Acyclovir is an anhydrous basis as is showing in the Figure 3. Acyclovir is an antiviral and the prototype drug, which is used against herpes zoster. This drug reduces the duration of the virus, decreases the formation of new vesicles, the pain and the time of healing (Huff JC., et al 1988 and McKendrick MW., et al 1986).

The acyclovir is a nucleoside analogue and can be administered per oral or intravenously. Immunosuppressed patients and these which are not able to take drug orally, it is preferred the intravenously administration.

According to the pharmacology, acyclovir is converted by thymidine kinase to acyclo-guanosine monophosphate and then through phosphorylation is converted to triphosphate by kinases. This acyclo-guanosine triphosphate inhibit the replication of the herpes DNA and this completed by inhibiting the DNA polymerase, by terminating the viral DNA growth and by inactivating the viral DNA polymerase (American journal of Medicine, 1982). Acyclovir general has poor oral bioavailability and the peak concentration of

plasma appears after 1-2 hours. The elimination half-life is about 3 hours and is excreted by glomerular filtration, tubular and renal secretion.

Acyclovir is administered per oral, in the form of capsules, tablets and suspensions. The brand name of acyclovir is Zovirax and each capsule or tablet contains 200mg, 400mg or 800mg and the excipients, like lactose, providone and others.

In adults, the dosage can be 800mg, five times per day for 7-10 days. It is important the patient to be consistent, compliance and to start the therapy in the first 72 hours of the rash onset. The patient should not exceed the recommended dose because there will be nephrotoxic problems and adequate hydration especially in those with renal failure. In patients with renal failure is recommended the intravenously administration.

Others adverse effects are the fever, headache, pain and peripheral edema. In the nervous system can be observed par aesthesia, ataxia, tremor, coma and psychotic symptoms. In addition, the adverse effects can be diarrhea, nausea, gastrointestinal tract complications, visual problems, alopecia, Stevens-Johnson syndrome and pruritus. In hepatobiliary tract and in pancreas can be observed jaundice and hepatitis. Last can be observed myoskeletal complications like myalgia and urogenital complications like blood in the urine.

The precautions of acyclovir is that the patient must inform the doctor if he/she has allergies or is allergic to this specific active substance (acyclovir) or in any excipient. For this reason, in order to avoid any complication is important the doctor to know the personal medical history of each patient. When the patient is taking acyclovir is recommended not drinking and not driving because acyclovir can cause drowsy (<http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681045.html>, accessed at 08.07.2013).

Is someone forgot to take a dose can take it as soon as he/she remember it and to continue with the next proper dose. However, in cases of over dosage, there will be observed the adverse effects like nausea, vomiting, headache, gastrointestinal tract problems and others. In order to remove the unabsorbed drug is recommended the patient to take charcoal. Hemodialysis is one method, which helps also to remove unabsorbed acyclovir in the case of overdosage, toxicity, renal failure and anusia

(<http://www.rxlist.com/zovirax-drug/overdosage-contraindications.htm>, accessed at 08.07.2013).

- *Valacyclovir*

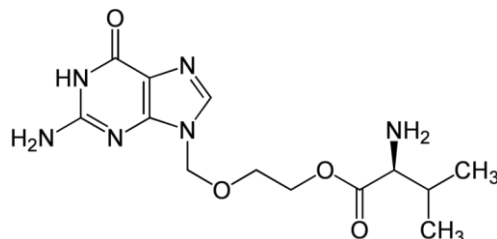


Figure 4: Chemical structure of valacyclovir

Source:

http://es.m.wikipedia.org/wiki/Archivo:Valacyclovir_Structural_Formulae.png,

accessed at 08.07.2013

Valacyclovir (see Figure 4) is an antiviral drug and nucleoside analogue, which is used against herpes simplex 1 and 2 and chickenpox. The brand name of valacyclovir is Valtrex and is used against shingles, genital herpes, herpes zoster and cold sores. Valacyclovir has long bioavailability after oral administration than acyclovir and the action of valacyclovir lasts longer.

Mechanism of action:

Valacyclovir hydrochloride is converted to acyclovir by esterases and has antiviral activity against herpes zoster 1 and 2 and against chickenpox. Then the thymidine kinase, which is more active than cellular thymidine kinase, converts the acyclovir to acyclovir monophosphate which then is converted to triphosphate by cellular enzymes. Acyclovir triphosphate inhibits the replication of the viral DNA of herpes and this completed by inhibiting the DNA polymerase, by terminating the viral DNA growth and by inactivating the viral DNA polymerase. The Figure 5 shows schematically the mechanism of action of valacyclovir:

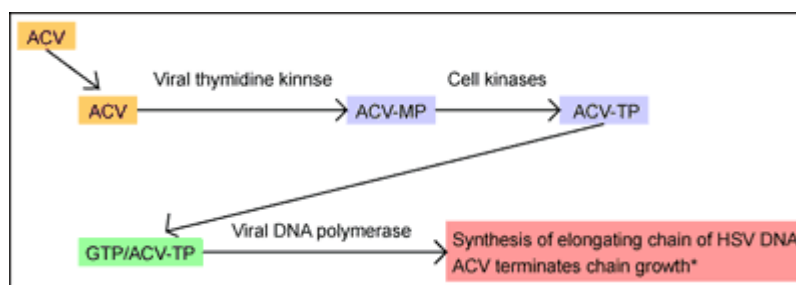


Figure 5: The mechanism of action of valacyclovir. Primary is converted to acyclovir by esterases, then to acyclovir monophosphate by thymidine kinase and final to acyclovir triphosphate, which inhibits the replication of the viral DNA of herpes.

Source: <http://www.medscriptspharmacy.com/valtrex.htm>, accessed at 08.07.2013

Valacyclovir is in the form of caplets, which are blue and administered per oral before or after food. Each caplet contains 500mg or 1gr of the active substance valacyclovir and the excipients like dioxide, providone, colloidal silicon dioxide and others. The dosage for the orofacial herpes is 2gr of valacyclovir, two times daily for only one day because of the high dose. For the treatment of herpes zoster the dosage of valacyclovir is 1gr, three times daily for 7 days.

The therapy is recommended to start in the first 48 hours of the rash onset. The treatment of the intermittent herpes is the usage of 500mg valacyclovir, two times daily for 5 days. General careful should be given in patients with renal failure and the dosage is recommended to reduce. Valacyclovir interacts with cimetidine, NSAID's and probenecid. These interactions lead to change the action of the main drug valacyclovir and to cause several adverse effects. In addition, this can lead to an increase of valacyclovir concentration in the blood.

Attention should be given when the doctor makes diagnosis and prescribed medicines because the patient is important to inform the doctor if he/she has allergy in some active substances or excipients. For this reason is basic the doctor to know the personal medical history of each patient. Valacyclovir because can cause drowsy the patient should avoid to drive and not to drink. Also is recommended the patient to avoid the close contact with others because the herpes is transmitted easy.

For this reason, avoid kissing the others and especially the immunosuppressed patients (<http://www.medicinenet.com/valacyclovir/article.htm>, accessed at 09.07.2013).

If a woman is pregnant, the usage of valacyclovir should be used in special cases. However, studies have not accurate results about how much the uses of acyclovir or valacyclovir affect the pregnant woman.

Some of the adverse effects of valacyclovir are the headache, nausea, vomiting and pain in the lower back and in stomach. The most serious adverse effect is the thrombotic thrombocytopenic purpura (TTP), which is observed in HIV patients, in patients with bone or renal transplantations. The death can be caused from thrombotic thrombocytopenic purpura and when there are problems with the kidneys or the medication affects the cells of the blood. In addition, an important complication is the renal impairment, which is related to patients with renal disease. This is caused because some patients take more dose than the recommended. Attention should be given in elderly patients in which should be given low dosages in order to avoid renal impairment. Although can be observed complications in the central nervous system like mood changes, hallucinations, confusion and problems in concentrating. In cases of over dosage unabsorbed valacyclovir can be observed in renal tubules when the solubility of the intratubular fluid is higher. The method to remove the precipitated valacyclovir is the hemodialysis (<http://www.drugs.com/sfx/valacyclovir-side-effects.html>, accessed at 09.07.2013).

Patients with ocular herpes zoster should be treated immediately because the infection of trigeminal nerve by herpes can leads to blindness, iritis and keratopathy especially in elderly 50 years old (Cobo M., et al 1987). Antiviral therapy should be administered in these patients like acyclovir or valacyclovir and may be combined with corticosteroids. It is important to reduce the mortality and morbidity of herpes and for this reason is necessary a safe treatment to start early from the first symptoms. Usually the patients develop once herpes in their life after the activation on chickenpox, of the varicella zoster virus.

9.2 Corticosteroids

Corticosteroids are administered orally and help to decrease the pain, the post herpetic neuralgia, the process of the clinical treatment, the complications and to procure analgesia.

The most known corticosteroid that is used for the treatment of herpes is the prednisolone (see Figure 6). This can be administered together with acyclovir so to decrease the feeling of pain and this is achieved because decrease the inflammation of the affected nerves (Whitley RJ., et al 1996). Some studies that have been conducted have shown that the usage of prednisolone can prevent the post herpetic neuralgia but some other studies have shown that there is no relationship (Whitley RJ., et al 1996 and Esmann V., et al 1982). The dosage is 40mg or 60m once a day, usually in the morning, for 7-10 days.

Some studies examined the evaluation of the usage of corticosteroids together with acyclovir and he results were that this combination succeeds the reduction of neuritis (Whitley RJ., et al 1996 and Wood MJ., et al 1998). Also another study show that the combination of injected steroids, local anesthetics, antivirals and analgesics reduce the pain which is caused by herpes for 1 month (van Wijck AJ.,et al 2006).

In severe cases of herpes pain, in cases of facial paralysis and complications in the central nervous system, the usage of corticosteroids should be reduced.

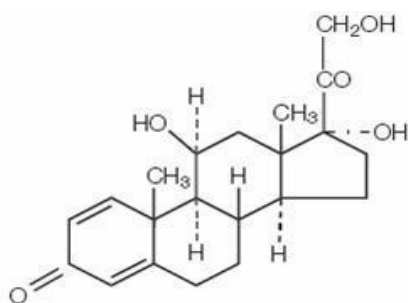


Figure 6: Chemical structure of prednisolone

Source: <http://www.drugs.com/pro/prednisolone-tablets.html> , accessed at 10.07.2013

The patients who use drugs that decrease the immune system are more sensitive than the immunocompetent. Herpes zoster can be a serious problem and can cause the death in immunosuppressant patients and mainly in elderly patients. It is important in elderly and

persons who had not been infected by chickenpox to not exposure in the virus and to caution by infected patients. The varicella zoster immune globulin can prevent and protect those who exposed to chickenpox. The corticosteroids heal the rashes of the herpes but the prolonged use of corticosteroids is not recommended because can cause glaucoma, damage to the nerves of the eye and other diseases. The immunosuppressant patients who use corticosteroids should avoid coming in contact with patients that have chickenpox or zoster. In cases that have been exposed must start the medical treatment as soon as possible. Patients with hypothyroidism or these patients that have ocular herpes the corticosteroids should be used with moderation and caution (<http://www.drugs.com/pro/prednisolone-tablets.html>, accessed at 10.07.2013).

Some adverse effects of corticosteroids and prednisolone can be musculoskeletal like loss of muscle mass, weak muscles, osteoarthritis and neurological like vertigo, nausea, vomiting and headache. Also in gastrointestinal tract can be observed some complications like pancreatitis and peptic ulcer.

According to the pharmacology prednisolone is agonist of alpha and beta glucocorticoid receptor and can reduce the inflammation. This anti-inflammatory action achieved by inhibiting the transcription of COX-2, T-cells and cytokines. Also inhibits the phospholipase A2 and with the cytotoxic actions reduce the mediated immune reactions of cells and antibodies.

9.3 Analgesics

Patients with limited skin involvement can have severe pain and for this reason is important to check it. If the diagnosis is made early, there are many possibilities to decrease the risk for post herpetic neuralgia except the acute pain. Therefore, the quality of patient life will be better especially in elderly, which have more possibilities to develop post herpetic neuralgia. Analgesics are administered per oral within 72 hours of the rash onset. Analgesics, for example ibuprofen (see Figure 7) and naproxen (see Figure 8) may be administered in patients during herpes with acute and chronic neuralgic pain. Also together with analgesics can be added anticonvulsant agents for example gabapentin, or the tricyclic antidepressants like amitriptyline, so to reduce the prevalence and severity of pain. Many analgesics can be used for the treatment of herpes:

- *Ibuprofen*

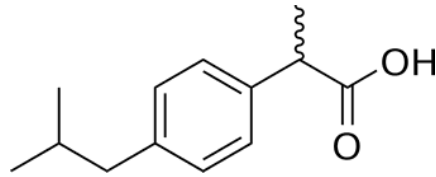


Figure 7: Chemical structure of ibuprofen

Source: <http://www.galinos.gr/web/drugs/main/substances/ibuprofen>, accessed at 11.07.2013

Ibuprofen is NSAID's, is derivative of propanoic acid and is used to relief the pain and fever. Ibuprofen inhibits the enzyme-COX, which converts arachidonic acid to prostaglandin H₂. Also can reduce the pain but simultaneously can cause several adverse effects like diarrhea, hypertension, heart failure, renal impairment and hyperkalemia (Rossi S., 2004)

The duration of ibuprofen is around 4-8 hours. Ibuprofen is in the form of tablets and the maximum amount for adults is 3.200 mg. But general the doses for all patients depends on the body mass (<http://www.drugs.com/ibuprofen.html>, accessed at 11.07.2013)

- *Naproxen*

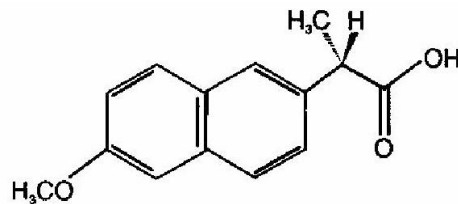


Figure 8: Chemical structure of naproxen

Source: <http://www.medicineonline.com/drugs/n/4266/NAPROXEN-DELAYED-RELEASE-TABLETS.html>, accessed at 11.07.2013

Naproxen is NSAID's and reduces the hormones that cause the feeling of pain in the body by inhibiting the enzymes COX-1 and COX-2. Naproxen is used for several diseases like fever, arthritis, gout, tendinitis, migraine and dysmenorrhoea (French L., 2005). Patients that have allergy to this must not use this active substance. There are many risks when someone takes naproxen, like heart attack, chest pain, weakness muscles, vision

problems, shortness of breath and many others. For this reason is important the patient to inform the doctor if he/she has liver disease, heart disease, history of heart attack, high blood pressure and blood clotting.

Also can be used the capsaicin that contains chili pepper and can treat the post herpetic neuralgia (Lee PJ., et al 1998). The capsaicin when is putted on the skin in the affected nerves three times daily, release the substance P that is a neuropeptide and can relief the pain. Patches also can be used that contain lidocaine in order to reduce post herpetic neuralgia.

10. Treatment of herpes zoster and Postherpetic neuralgia

Postherpetic neuralgia is pain in the nerves because of varicella zoster virus. Usually the pain occurs in one dermatome in which then is developing herpes zoster. This pain may be appear for months even and years and is more common in elderly older than 50 years. These that are at risk are the immunosuppressant patients, people suffering from HIV, AIDS and transplantations. Also at risk are these with cancer, with Hodgkin disease, the female sex and the white race.

The symptoms for postherpetic neuralgia are the pain, which is severe, appears for more than 3 months, and is likened as burning. Post herpetic neuralgia is a difficult situation as well as and the treatment is. First, the patient with PHN should be addressed to the physician, to the doctor in order to administer him/her one drug of these groups:

10.1 Tricyclic antidepressants

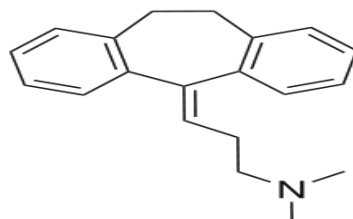


Figure 9: General chemical structure of tricyclic antidepressants

Source: http://en.wikipedia.org/wiki/Tricyclic_antidepressant, accessed at 12.07.2013

Tricyclic antidepressants (TCA) are heterocyclic and contain three rings (see Figure 9). Similar to these are the tetracyclic antidepressants. In TCA belong the

selective-serotonin-reuptake inhibitors (SSRI), the norepinephrine reuptake inhibitors (NRI) and the serotonin-norepinephrine-reuptake inhibitors (SNRI) antidepressants.

The tricyclic antidepressant except their benefit in the treatment of postherpetic neuralgia is used also for the treatment of dysthymia, anorexia, panic disorder, mood disorder and in many others. The tricyclic antidepressants can reduce the postherpetic neuralgia by inhibiting the serotonin and norepinephrine reuptake or by blocking the sodium channels (Ardid D., et al 1992). Some tricyclic antidepressant drugs are nortriptyline, desipramine, imipramine and amitriptyline.

For better results is recommended to start the use of TCA after one year of the symptoms appearance, but the time in order to understand the effectiveness of these drugs takes weeks (MacFarlane BV., et al 1997). The tricyclic antidepressants have many side effects, like dry mouth, urinary retention, akathisia, tachycardia, muscle weakness and especially in patients older than 50 years old (Gelder, et al 2005).

Tricyclic antidepressants interact with cimetidine, antipsychotics, fluoxetine and calcium channel blockers, so with these drugs that inhibit cytochrome P450. This happens because the metabolism of TCA takes place in cytochrome P450. Usually for the therapy of post herpetic neuralgia in elderly nortriptyline is used and the dosage is 10-25mg in the night for two weeks or can be administered for one day only in higher doses, 75-150mg.

Selective-norepinephrine-reuptake inhibitors antidepressants like venlafaxine or duloxetine are used for the treatment of postherpetic neuralgia, for diabetic neuropathy, for social anxiety disorder and in many other diseases. The dosage of SNRI antidepressants for the relief of postherpetic neuralgia is 60-120mg, which is taking separated into two doses (Cymbalta, 2011).

10.2 Opioids

Opioids are psychoactive and bind to opioid receptors. These drugs are used to the treatment of pain like post herpetic neuralgia, cancer pain and rheumatoid arthritis (Alexander GC., et al 2012). Also is used in patients in whom the tricyclic antidepressants have no effect. Opioids administered per oral or through patches. The usage of opioids is usually the second choice for the treatment of postherpetic neuralgia. There are many adverse effects like vomiting, dry mouth, constipation, hypothermia, orthostatic

hypotension and hallucinations (Doyle D., et al 2004). Caution should be given in this group because one of the most serious adverse effect is the tolerance and when is happens in order to alleviate it zinc, NMDA antagonists or calcium-channel blockers is used (Kollars JP., et al 2005).

Opioid analgesics help to the quality and the comfort of patient's life and this because decrease the acute pain in patients with herpes zoster through the several mechanisms of actions in the Central nervous system and in Peripheral nervous system. Analgesic opioids usually used together with weak analgesics like acetaminophen or with non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen. However, these combinations have not been studied if there are effective in patients with HZ or chronic neuropathic pain. The most know drug that is used for the treatment of postherpetic neuralgia is the:

- *Oxycodone*

This drug is narcotic opioid and is used to control the severe pain especially in patients with herpes zoster. Oxycodone should not be given in the patients that have a history of drug addiction and is recommended do not drink during the therapy with oxycodone. There are several side effects like dyspnea, respiratory arrest, nausea, constipation, anxiety, pain in the abdominal, bradycardia even and death. Also the risk of using oxycodone is that the patient has many possibilities to be addicted to this drug (<http://www.drugs.com/dosage/oxycodone.html>, accessed at 13.07.2013).

Oxycodone is administered per oral 10-30mg six times daily. The mechanism of action of this drug is the action on κ -opioid receptor but has effects similar to morphine that acts on μ -receptor and this because the metabolism of oxycodone takes place in the liver (Kalso E, 2007)

- *Tramadol*

Tramadol can relief the pain, and it has properties similar to opioids and is a weak agonist of μ -opioid receptor. Tramadol inhibit serotonin and nor-epinephrine release and the maximum dose is 400mg/d. Not severe adverse effects can cause in gastrointestinal tract (Boureau F., et al 2003).

- *Tapentadol*

Also can relief the pain, is a weak agonist of μ -opioid receptor and inhibits more the release of nor-epinephrine. The maximum dose of tapentadol is 600mg/d.

10.3 Anticonvulsants

Anticonvulsant or antiepileptic drugs are used for the treatment of epileptic seizures but also for the therapy of neuropathic pain and postherpetic neuralgia. The anticonvulsant drugs suppress the excited nerves that are responsible for the feeling of pain and for postherpetic neuralgia. The drugs that are used more usually are the gabapentin and the pregabalin. Studies have shown that are effective to treat PHN (Rowbotham M, et al 1998).

- *Gabapentin*

Gabapentin is the most common drug used for the treatment of postherpetic neuralgia. The dosage, which should be administered, is 400mg, three times daily for few weeks. Gabapentin has good benefits in the quality of patient's life and in the relief of postherpetic neuralgia. This drug can be administered together with antiviral drugs, like acyclovir or valacyclovir, in order to decrease the acute pain.

In the most patients have noted no serious adverse effects and for this the patients can take larger amount of dose. This does not mean that no one will do not have adverse effects for example memory disturbances, liver toxicity, dizziness, agitation, stomach pain and many other complications. However, in elderly the usage of gabapentin is safer than tricyclic antidepressants (MacFarlane BV., et al 1997).

- *Pregabalin*

Pregabalin is similar to gabapentin and the dosage ranges between 150-300mg per day. The dose depends on the tolerance of the body and how it response. Pregabalin can be used in combination with analgesics, antivirals or antidepressants because in order to treat the postherpetic neuralgia requires several approaches (<http://www.anesthesia-analgesia.org/content/105/6/1805.full.pdf+html>, accessed at 06.07.2013).

10.4 Patches

- *Lidocaine*

Lidocaine is anesthetic drug and is used for the treatment and relief of postherpetic neuralgia. There are small patches placed on the skin in the affected area. This patch has low adverse effects and can be used together with other oral medications. Lidocaine has the possibility to bilge into the skin and is recommended as the first choice for the treatment of postherpetic neuralgia (Kanazi GE., et al 2000).

- *Capsaicine*

Capsaicine contain chilli pepper, which can reduce the nerve pain caused by postherpetic neuralgia. Capsaicine can be found in the form of patch and cream, but studies have shown that cream is not so effective. It is preferred in the form of patch because contains higher amount of capsaicine than cream. It is recommended the patient to use capsaicine patch after the blisters have dried. In addition, the patients can apply topical aspirin, which have been cut off in acetone (Kanazi GE., et al 2000).

11. Vaccination

Herpes zoster is caused by varicella zoster virus, which remains dormant for decades in dorsal root ganglia and can be reactivated when finding opportunity. The most important complication is the postherpetic neuralgia, which affects the elderly, especially people older than 60 years. The greater age one has, the greater chances have to develop herpes and postherpetic neuralgia. For this reason patient should do the vaccine, which protect him/her from herpes and PHN (Oxman MN., et al 2005).

- Who should receive the vaccine?

The vaccine for shingles is the known ‘‘Zostavax’’ and the patients older than 60 years old is recommended to receive it in order to prevent postherpetic neuralgia (McKendrick MV., et al 1989 and Alper BS., et al 2000). The greater age one has, the greater chances have to develop PHN and herpes zoster. This vaccine is used against herpes zoster, not against herpes virus and is used for protection and not for treatment. Zostavax can reduce the postherpetic neuralgia for about 50% in patients older than 60

years old and the duration of action of the vaccine is for about 4 years and more (Oxman MN., et al 2005).

Zostavax is important for patients older than 60 years even though did not have developed chickenpox in the past. FDA authorizes this vaccine and it is necessary to receive it when the patient does not have any shingle. Zostavax is administered in a single dose by injection usually in the arm subcutaneously (Mitka M., 2006 and Merck & Co, 2011).

The Zostavax should not be administered in patients with allergy to gelatin and to neomycin because are contained in the vaccine. For this is important the patient to inform the doctor about any allergy may have. In addition, the immunosuppressant patients with HIV, AIDS and those who do chemotherapy in order to treat cancer should avoid receiving it. Although should not be administered in patients which are using drugs that reduce the immune system, as for example the steroids. Last patients with leukemia, pregnant women or expectant pregnant women must avoid receiving it.

- Does the vaccine cause serious complications?

Zostavax does not cause any serious complication. The most usual complications are the itching and the redness at the site of injection, swelling and headache. The people who received the vaccine Zostavax can come in contact with pregnant women, babies and patients with reduced immune system and this is possible because until now there are no documents to show the transport of chickenpox from people who receive the vaccine.

12. Homeopathic treatment for Herpes zoster

First of all the word homeopathy takes its name from the Greek language from the word ‘‘homoios’’ that in english means like and from the word ‘‘pathos’’ that means suffer. Homeopathy is a system of remedy, which is non-toxic. Is a philosophy which supports that the patients can be treated by himself, that the body can be treated itself by

its nature. Homeopathy supports that the symptoms will occur in the patients who take large amount of a substance in order to treat these symptoms can take small amount of the same substance.

In this remedy the homeopath use only plants and natural products in order to treat the disease. Homeopathy is used for several diseases like osteoarthritis, cancer, constipation, headache, insomnia, diabetes and in many other diseases. The amounts that are used are diluted and can be used by anyone even the elderly, the pregnant and the babies (<http://www.webmd.com/balance/guide/homeopathy-topic-overview>, accessed at 26.06.2013).

Herpes zoster causes blisters along the nerves and is a painful situation. First fever and discomfort shown and then blisters appear at the one side of the body, like the back, the abdomen and the face. Except the conventional therapy which analyzed above, very helpful is and the homeopathic treatment. Homeopathic therapy helps to relief the pain and to recovers the skin. Some examples are:

- *Arsenicum album*

Herpes usually affect the face, the lips and the eruptions getting worse in the exposure to the cold and after midnight. Patient with the feeling of warmth gets better but the mood changes constantly. The patient usually feels anxiety, depressed and irritable. So arsenicum album is recommended (<http://www.truestarhealth.com/Notes/2257003.html>, accessed at 26.06.2013).

- *Clematix*

Blisters, redness, itching, burning and the bad feeling when the patient washes her face with cold water are some symptoms exhorting the usage of clematix. This one can be used also by those that have genitor-urinary problems (<http://www.truestarhealth.com/Notes/2257003.html>, accessed at 26.06.2013).

- *Graphites*

Mainly obese women that have herpes use this drug. Also it is used by patients, which appear blisters in the one side of the body, in the spine and by those that have intense

itching and cannot come in contact with clothes or any foreign matter (<http://health.hpathy.com/herpes-zoster-symptoms-treatment-cure.asp>, accessed at 26.06.2013).

- *Ranunculus bulbosus*

This is used mainly when shingles appear at the back or on the chest (ribcage), over the fingers and then to the whole body. This is very painful situation because it is not so pleasant to wear clothes or the contact with something else (<http://www.truestarhealth.com/Notes/2257003.html>, accessed at 26.06.2013).

- *Rhus toxicodendron*

This is recommended when rash appears with the form of many red and small blisters that are itchy and are comforted with the usage of rhus toxicodendron and the usage of hot compresses (<http://www.truestarhealth.com/Notes/2257003.html>, accessed at 26.06.2013).

13. Herpes diet information

Persons who have been infected with varicella zoster virus, this virus will remain dormant in the dorsal root ganglia forever. These persons will develop herpes zoster sometime in their life with the characteristic blisters on the one side of the body. The risk to develop someone herpes increases with the older age and if someone is immunosuppressant. For this reason in order to prevent herpes zoster there are some foods, which the patient should consume.

- What foods the patient should enjoy?

The patient should add to his/her nutritional program foods rich in vitamins like vegetables and fruits. Fruits rich in vitamin A, which promote and help in the healing of the skin are the eggs, the fish, the mangoes and papaya. In addition, the onions, the oranges, the paprika and the apricots are good choice because are rich in vitamin C that also helps to the healing of the skin and increase the immune system.

Very good choice to consume the patient is the lysine and this because attacks the arginine, which promote the herpes virus replication. So the patient should consume chicken, beef, parmesan cheese and seafood. It is recommended the consumption of 500/1000mg lysine about three times daily. Moreover, the patient should add in the nutritional program foods that contain Vitamin B12 and zinc because are fighting herpes zoster. Vitamin B12 found in the milk and blue cheese.

- What foods the patient should avoid?

The patient in order to antagonize herpes zoster should avoid foods high in fats and this because such foods cause changes in emotional mood, which is risk for herpes zoster. Foods rich in oils, fats, carbohydrates and sugar contain low amounts of vitamins and so the patient should avoid consuming. It is important to replace these foods with fruits or with foods, which mentioned above. Also prohibited the consumption of alcohol because is depressant as well as prohibited the consumption of cigarettes. White flour, white rice, pasta and other foods that contain carbohydrates is preferred to limit them (<http://www.livestrong.com/article/284378-diet-for-herpes-zoster/>, accessed at 18.06.2013).

- Can the patient use/consume complementary herbs?

Of course, the patient can apply local supplement in the affected skin with blisters. He/she can apply gel of aloe vera and the oil of vitamin E. Although the patient should consume herbs of Echinacea that have antiviral properties and which are found on the market and in tea form. In addition, a plant, which can calm the affected nerves and is sedative, is the passion flower (<http://www.livestrong.com/article/284378-diet-for-herpes-zoster/>, accessed at 18.06.2013).

14. Home remedies for herpes zoster

General, almost no one can avoid shingles, even though avoid to contact with someone which have active herpes or chickenpox, sometime will have because of his own varicella zoster virus. Someone with shingles if come in contact with others can transmit

the virus to them. For this reason is an important patient with herpes to stay isolated at home for 7-9 days till the blisters gain crust.

Also must avoid come in contact with pregnant women, people older than 50 years old because have weak immune system and with immunosuppressed patients such as those with HIV, AIDs and with organ transplantations. It is good patients with herpes to put on the blisters cool and wet compresses for at least 1 hour, 5 times daily. This will help the patients to reduce the feeling of pain and the itching.

In addition, they can use anti-itch creams and lotions, like calamine or aveeno, in order to reduce the itching, as the meaning of the word 'anti-itch'. More over patients with herpes can take a bath with a normal hot water or can take an oatmeal bath in order to reduce the pain of the shingles. Except the oatmeal bath, someone can just put over the shingles oatmeal, which will not be cooked, with a little quantity of water. Therefore, this will create something like paste. Moreover, it is better to wear baggy clothes so to avoid the pain that caused from the friction of the blisters with the clothes. Finally, patients must keep the blisters clean, dry and cover then with a non-sticky bandage (http://www.specialityclinic.com/Herpes_Z.aspx, accessed at 05.07.2013).

Conclusion

Herpes virus also known as Herpes virus 1 belongs to a class of virus that can cause the Varicella zoster virus and Herpes zoster. Herpes can appear only in those patients who have been infected by varicella zoster virus. After the primary infection, the virus remains dormant for decades in the dorsal ganglia root and can be reactivated when finding opportunity.

Herpes zoster is a dermatomal disease and most often occurs at the lumbar or at the thoracic nerve part. The herpes virus can cause several infections in the human like herpes zoster or herpes genital. In the herpes are created shingles, which are itchy and are very dangerous when appearing in parts of the face.

Herpes is a painful situation and the most common symptoms are the feeling of burning, itching, headache, fever and paresthesia. Also in this thesis are analyzed the risk factors that increase the appearance of herpes and are the primary infection with VZV, the age because the greater age one has the greater chances have to develop herpes, the immunosuppressant patients, certain drugs that decrease the immune system, the female has greater chances to develop and the white race.

In order to avoid all the complications that cause the herpes this thesis analyzes and informs the patients about all the signs, the symptoms and the prognosis of herpes. Some of the complications are the postherpetic neuralgia, Ramsay Hunt syndrome, glaucoma, retinitis, hematuria and many others.

This diploma thesis wants to emphasize that just from the first symptoms the patient should contact with the doctor in order to give him the proper therapy. For the treatment of herpes zoster can be used many drugs like antiviral drugs, analgesics, opioids, corticosteroids and tricyclic antidepressants. However, the drugs that are preferred more are the antiviral drugs, the acyclovir and the valacyclovir. In addition, this thesis analyzes and discloses the causes of herpes zoster and what this can causes.

Prophylactic ways are marked for herpes especially for elderly, which are at high risk to develop zoster. Consequently, it is important for them to follow the right treatment when become infected and protect themselves from other people that are affecting of herpes so as not to spread the virus. Also are marked except the drugs, which can be used

and home remedies for patients with herpes. The diagnosis of herpes zoster usually is done clinically with Tzanck test, direct immunofluorescent test or immunoglobulin test.

In this thesis is highlighted the severity of herpes and the complications that causes in elderly people who exceed the population of younger people. For this reason, this thesis wants to point that the elderly people should receive the vaccine Zostavax that is against herpes zoster.

Many researches have been conducted and continue until nowadays about Herpes zoster. Vaccination strategies for both varicella and herpes zoster will need to evaluate and adjusted periodically as changes in the epidemiology of these varicella zoster virus diseases become more evident.

Science is constantly evolving; many researchers are in laboratories and give daily struggle to find new drugs and vaccines. In such way, we will be able to avoid the most painless way inconveniences caused by the virus, faster and more efficiently. Everyone nowadays with the fast pace of life and the constant stress we want to continually improve the quality of life. For this reason it is important the awareness and the action by all of us with the dominant role of world health organization.

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