An Integrative Review on Incurable Diseases: Pathophysiology, Risk and Possible Treatments

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Abstract:

Genetic, metabolic, neoplastic, infectious, non-infectious, hereditary, and autoimmune disorders are among the ailments with no known cure. Rare diseases are included on the list of incurable diseases since they are inherited approximately 80% of the time. Modified Words Structural changes Longest. Everyone in the community is susceptible to fatal diseases. While some of these diseases are inherited in nature, others may be the result of poor lifestyle choices, poor eating habits, or other detrimental behaviors. The early start of the disease is usually impacted by the environment. The following medical concerns are commonly prevalent in persons who require care as they approach death: Alzheimer's disease, Parkinson's disease, advanced cancer, multiple sclerosis, advanced lung, heart, kidney, and liver disorders, frailty, and multimorbidity exists.

Keywords: Incurable diseases, Cancer, Varicella-zooster, Huntigton's diseases, Pathophysiology.

Introduction

Genetic, metabolic, neoplastic, infectious, non-infectious, hereditary, and autoimmune disorders are among the illnesses for which there is no known treatment. The list of incurable diseases includes rare diseases, which are inherited around 80% of the time. Modified Words structural alterations Longest. Everyone in the community is vulnerable to fatal illnesses. While some of these diseases have a genetic basis, others may be caused by bad lifestyle choices, poor eating choices, or other harmful habits. The early onset of the disease is typically influenced by the surroundings. The following medical issues are typically present in those who require care as they approach death: Alzheimer's disease, Parkinson's disease, advanced cancer, multiple sclerosis, advanced lung, heart, kidney, and liver diseases, frailty, and the multimorbidity is the existence of multiple diseases or conditions. Many persons could offer care to the terminally ill, including allied health professionals such as social workers, physiotherapists, occupational therapists, psychologists, pharmacists, dietitians, speech pathologists, and recreation therapists; family members and informal carers; nurses, including general and specialized nurses in the community, hospitals, palliative care units, residential aged care facilities, and hospices; doctors, including general practitioners, palliative care specialists, and other specialist doctors.

The production of abnormal leukocytes, whether as a main or subsequent process, characterizes leukemia. According to how quickly they spread obsessive-compulsive disorder is among the distressing psychological symptoms that HD patients frequently encounter.

Genetics and Pathophysiology of Leukemia: An IntroductionIntroduction

Either a primary or secondary process, leukemia is defined by the generation of aberrant leukocytes. They can be categorized as acute or chronic depending on how quickly they proliferate and myeloid or lymphoid depending on the cell that gave rise to them [1]. Acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML) are the three most common subtypes, all of which affect the myeloid lineage. White blood cells that have reached adulthood give birth to a variety of uncommon types, including mature B-cell and T-cell leukemias, and NK cell-related leukemias, to mention a few. However, the World Health Organization (WHO) classification was modified in 2016, introducing numerous changes to the conventional classification for acute diseases as a result of the development of next-generation sequencing (NGS) and the finding of new biomarkers. Normal marrow cell composition ranges from 1% to 5% defective cells. Greater than 20% blasts in the bone marrow or peripheral blood smear are a hallmark of acute leukemias, which cause symptoms to appear more quickly. Contrarily, chronic leukemia has a relatively slow onset of symptoms and less than 20% blasts. In the accelerated/blast phase, chronic myeloid leukemia is converted into an acute phase with a markedly greater level of blasts [1,3,4]. The four primary leukemia subtypes are as follows: Leukemia acute lymphoblastic (ALL): Patients with B and T cell blastic transformation are diagnosed with ALL. It is the most prevalent leukemia in children, where incidence can reach 80%, compared to 20% in adult instances [7]. Adolescent and young adult treatment plans are primarily influenced by pediatric regimens that have higher odds of survival. Acute myelogenous leukemia (AML): The most prevalent form of acute leukemia in adults, AML is defined by more than 20% myeloid blasts. Depending on the molecular subtypes, the prognosis for this most aggressive malignancy can vary. Monoclonal lymphoid cell proliferation is the cause of chronic lymphocytic leukemia (CLL). The majority of instances affect persons in their 60s and 70s. Since most cases of CLL are considered indolent, not every patient who receives a diagnosis will require therapy until they exhibit symptoms. The most common cause of chronic myelogenous leukemia (CML) is reciprocal translocation and fusion of BCR resulting in dysregulated tyrosine kinase on chromosome 22, also known as the Philadelphia (Ph) chromosome, on chromosome 22 and ABL1 on chromosome 9. A monoclonal population of defective granulocytes, primarily neutrophils, basophils, and eosinophils, are the result of this [9,6].

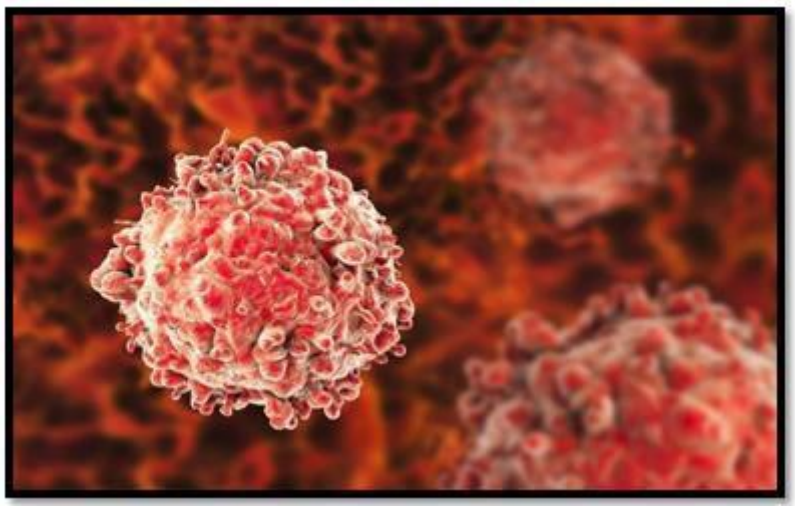

Fig:1 Lukemia Cell

The malignant transformation of pluripotent hematopoietic stem cells—i.e., stem cells that can develop into both myeloid and lymphoid precursors—causes leukemia. In rare cases, a more dedicated stem cell with a restricted potential for self-renewal may also be involved. These malignant cells are typically immature, poorly differentiated, aberrant leukocytes (blasts), which can be either lymphoblasts or myeloblasts, in acute leukemias. These blasts can proliferate and expand clonally, which can replace regular blood cells and interfere with their growth and function, resulting in clinical symptoms [10,13,15].

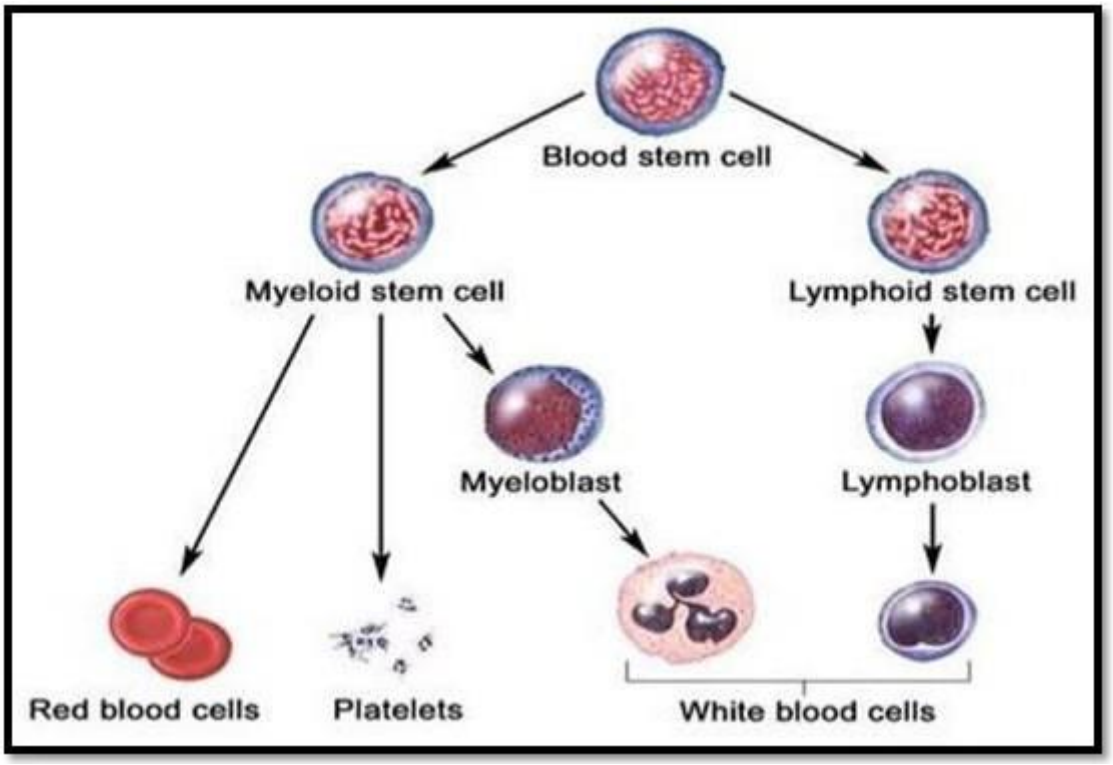

Fig:2 Pathophysiology of Leukemia

Acute Lymphoma

Typical chromosomal numbers or chromosomal translocations in ALL can result in mutations in precursor lymphoid cells that eventually give rise to lymphoblasts. There are two common mutations: t(12;21) and t(9;22). Chromosome rearrangements, gain or loss of chromosomes, and translocations can result in mutations and aberrant myeloblast formation in AML. A significant translocation is t(15;17), which results in the combination of a promyelocytic leukemia transcription factor (PML) and retinoic acid receptor alpha (RARA) [3,8]. Acute promyelocytic leukemia results from this, which might exhibit symptoms similar to disseminated intravascular coagulation and require immediate all-trans retinoic acid treatment.

Prolonged Leukemia

The most frequent cause of persistent leukemia is chromosomal abnormalities in hematopoietic stem cells, which are progenitors to leucocytes. Extra chromosomes, translocations, and deletions are a few examples of anomalies. Mutations primarily impact lymphocytes (particularly B cells) in CLL and granulocytes (most commonly the t(9;22) translocation) in CML. Cells in chronic leukemias are partially mature, in contrast to acute leukemias. These partially developed cells divide too quickly and perform poorly. They can cause leukopenia, thrombocytopenia, and anemia when they build up in the lymphoid organs and peripheral blood [8,13,16].

GENETICS AND PATHOLOGY OF HUNTINGTON'S DISEASE: AN INTRODUCTION

Introduction

The autosomal dominant condition known as Huntington's disease (HD) is typified by cognitive decline and mobility abnormalities. Loss of coordination and chorea are common motor abnormalities. In addition to being common in HD, psychiatric symptoms such as depression, psychosis, and obsessive-compulsive disorder are often very upsetting for patients (Rosenblatt). In populations of Western European descent, the mutation is prevalent in four to ten cases per 100,000 [19]. In particular, efferent medium spiny neurons (MSNs) are lost in HD, along with a generalized shrinking of the brain and degeneration of the striatum (caudate nucleus and putamen). Though the brain's striatum seems to be the most afflicted area, a locally distinct weakening of the Patients with HD was observed to have cortical ribbon. As the disease progresses, this loss of cortical mass moves from posterior to anterior cortical regions, marking an early event in the pathophysiology of HD. The varied clinical manifestations of HD could be explained by this locally specific cortical degeneration. Patients with HD frequently exhibit additional characteristics such as heart failure, skeletal muscle atrophy, and weight loss (Arenas et al. These other indications, while typically receiving less attention than neurological ones, may be caused by the widespread production of mutant huntingtin, the toxic protein responsible for HD [21,22].

Mutations in the HTT gene, which codes for the 350 kDa protein huntingtin, are the cause of Huntington's disease (HD). In the first exon of HTT, Huntington's disease is associated with a polyglutamine tract encoded by continuous CAG trinucleotide repeats. HD patients had expansions of 36 or more CAG repeats, whereas wild- type alleles had up to 35 repeats. Only a fraction of people with a CAG repeat length of 36–41 exhibit indications or symptoms of HD within a normal life span, even though complete penetrance of HD is documented for CAG values of ≥42. Pearce and Kopito provide an overview of polyglutamine-containing proteins and their function in neurodegenerative diseases.

Huntington's disease (HD) is caused by mutations in the HTT gene, which codes for the 350 kDa protein huntingtin. Huntington's disease is linked to a polyglutamine tract in the first exon of HTT that is encoded by repeating CAG trinucleotides. While wild-type alleles include up to 35 repeats, HD patients reported expansions of 36 or more CAG repeats. While complete penetrance of HD is recorded for CAG values of ≥42, only a small percentage of individuals with a CAG repeat length of 36–41 show signs or symptoms of HD over a normal life span. Pearce and Kopito give a summary of proteins that include polyglutamine and their part in neurological illnesses, see to Pearce and Kopito. Many mouse models have been created to investigate the pathophysiology of HD. See reviews by Lee et al. 2 and Menalled and Chesselet for a thorough explanation of those models.

In 1842, Waters published the first account of a patient who had what is now known as Huntington's chorea. However, Huntington's chorea was not the name given to the illness until 1872, following George Huntington's speech and description of it. It is a neurological disease that starts in middle life and runs in families. Symptoms include dementia, unwanted choreatic movements, and behavioral and mental abnormalities. Its name stayed the same for many years until the 1980s, when, finally finding several non-motor symptoms and signs led to the diagnosis being changed to Huntington's disease (HD). Following the identification of a link on chromosome 4 in 1983, the HD gene was discovered in 1993 [23]. It was around that time that interest in HD and neurogenetic illnesses began to grow significantly. HD was used as a model for several medical studies when novel illnesses involving trinucleotide repeats of CAG were identified, which made it possible to create the first-ever premanifest diagnoses. Trinucleotides, often known as CAG

(cytosine (C), adenine (A), and guanine (G), are the building blocks of DNA. The codon for the amino acid glutamic is CAG. Finding the gene offered new insights, updated models, and the first tangible explanation for treat this terrible illness [24,25]. Although there are a lot of symptomatic therapies available today, more effective medications that modulate symptoms are still needed [26].

In addition to cognitive and behavioral abnormalities, Huntington disease (HD) is an autosomal dominant neurodegenerative condition marked by involuntary choreatic movements. The Huntingtin (HTT) gene's short arm of chromosome 4p16.3 contains repeats of the cytosine, adenine, and guanine (CAG) trinucleotide, which is the cause of it [27,28,29]. Neurodegeneration results from this mutation's excessively prolonged polyglutamine growth in the HTT protein [32,34]. Additionally, the enlargement makes the HTT protein more prone to accumulation and aggregation, which reduces the ability of the protein to fold. Patients with HD often range in age from 30 to 50. But the earlier the beginning of, the longer the CAG repeats sickness that manifests before the age of twenty and is marked by behavioral issues at school in addition to learning challenges [29,30].

When a patient has cognitive, behavioral, or motor impairments and their parent has been diagnosed with HD, the diagnosis can be made clinically and verified by DNA testing. Pre-manifest diagnosis can identify gene carriers in patients who are at-risk for the disease. The illness has no known treatment, and as it worsens, afflicted individuals typically become totally reliant on their caregiver. Consequently, the goal of treatment is to lessen problems while also enhancing quality of life. Suicide is the second most common cause of mortality after pneumonia. [28,36,37].

Physiopathology

The main characteristic is the degradation of neurons in the cerebral cortex, caudate, and putamen. Chorea is caused by the selective degeneration of medium spiny neurons in the basal ganglia that contain enkephalin through the indirect pathway. Dystonia and akinesia arise as a result of further loss of substance-P-containing medium spiny neurons in the direct pathway. The phenotypic diversity in the affected patients may be explained by a region-specific pattern of neuronal death in the brain and basal ganglia [27]. The pathophysiology of HD is the subject of several theories, and multiple processes may be active at the same time. Groups of neurons: The HD proteolytic pathway includes both intracytoplasmic and intranuclear inclusions carrying the mutant HTT. The ubiquitin-proteosome process may be hampered if these mutant protein clumps build up [39]

Introduction of Herpes Zoster

Herpes zoster is a self-limited condition that often goes away without any problems. During the acute stage of the disease, herpes zoster might cause complications in certain patients. Herpes zoster is a highly uncomfortable skin condition. It doesn't spread from one individual to another. Varicella zoster virus reactivation causes herpes zoster. Because the varicella-zoster virus is infectious, it can spread from person to person. Chickenpox is another disease caused by this virus. In the kingdom Heunggongvirae, class Herviviricetes, and family Herpes viridian, the varicella-zoster virus is classified. The respiratory system of the human body is a route of transmission for the varicella-zoster virus. Another method of transmission is through airborne droplets or particles. The envelope that the varicella-zoster virus is in is shaped like a sphere. This is relatively small— about 150—in size.

Pathophysiology of Herpes Zoster

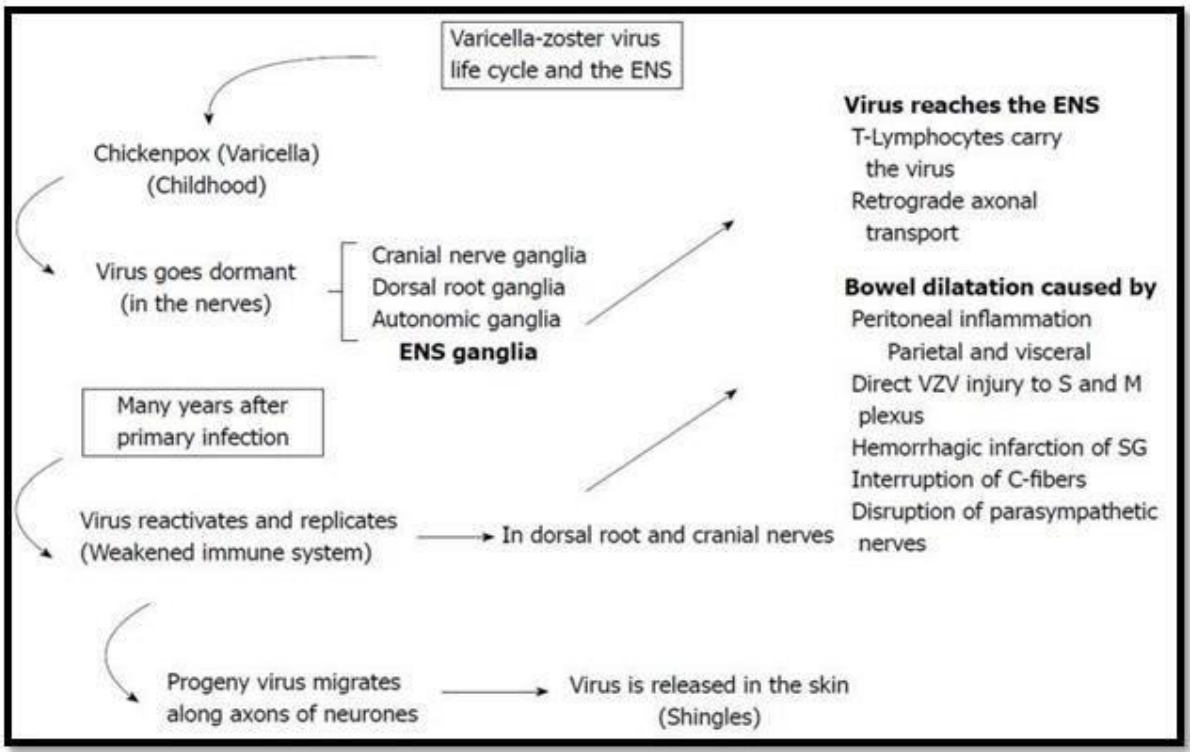

Fig:3 Pathophysiology of Herpes Zoster

Acute stage

There will likely be pain as a rash starts to appear. In the vicinity of the injured nerve, there may be itching or tingling. A few days later, a painful, fluid-filled rash typically appears on one side of the face or torso. Blisters with fluid inside that break open, crust over, and disappear in 2 to 4 weeks.

Diagnosis of singles

A skin sample that has the varicella-zoster virus infected it. White blood cell count rises during a blood test. Within 24 hours of the onset of the first symptom, antiviral treatment for acute herpes zoster should be initiated to lessen pain and complications. Acyclovir (Zovirax), Valacyclovir (Valtrex), and Famciclovir (Famvir) were all ingredients in this drug.

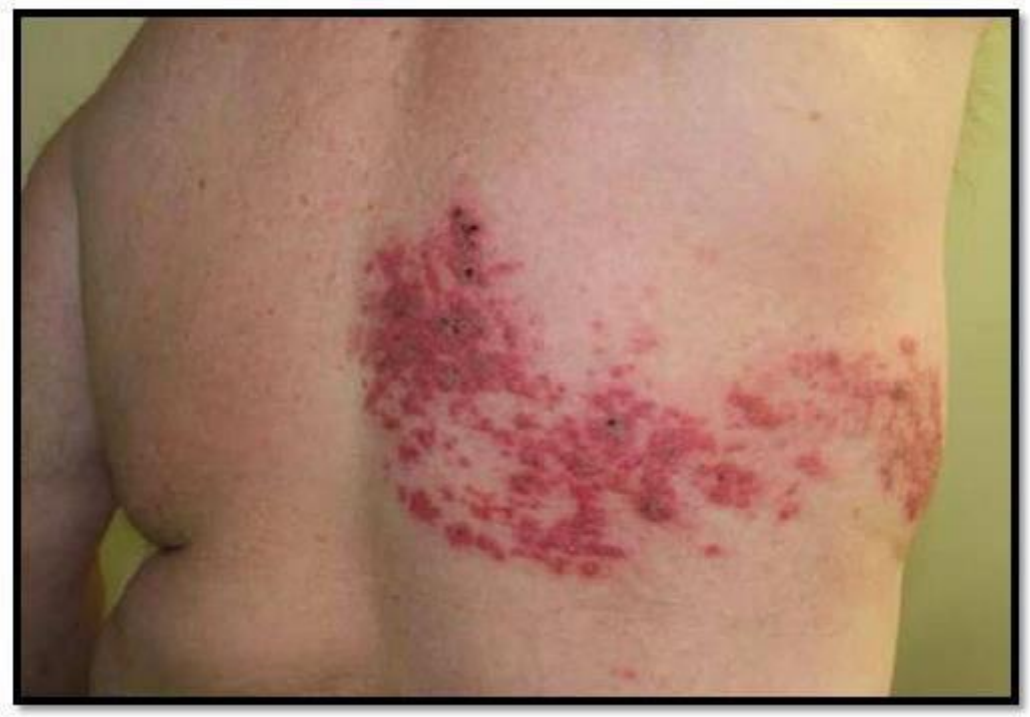

Fig:4 Infection of Herpes-Zoster

Infection of Herpes-Zoster and its Risk Factors:

1. Age - A common factor among persons over 50.
2. Illnesses that compromise the immune system, such as cancer and HIV/AIDS.
3. Cancer treatment: Radiation and chemotherapy can weaken the immune system and lead to shingles.
4. Immunosuppressive medications - protracted usage of steroids like Prednisone.

Clinical symptoms Prodromal stage one

The following are possible symptoms of shingles:

1. Headache
2. experiencing widespread malaise
3. myalgia
4. Fever

Genome

The 125 KBP-sized genomes of the varicella-zoster virus are made up of a linear double-standard DNAmolecule and have more than 70 identified open reading frames.

Herpes Zoster vaccine

For those 60 years of age or older, the Centers for Disease Control and Prevention advised a single dose of Zostavax R. (zoster vaccine live). It is administered to those who have had chicken pox and are 60 years of age or older. The shingles shot is a live vaccine that is often administered in the upper arm.

Redness, discomfort, tenderness, swelling, and headache at the injection site are the most frequent adversereactions to a shingle vaccine [41].

Transmission

The human respiratory system is the route by which the varicella-zoster virus is transmitted. Person-to-person contact with contaminated respiratory tract discharge is the most frequent method of transmission [42].

Morphology

This herpes virus is encased, has an icosahedral capsid (a sphere-like form), and is a member of the herpes viridae family. Varicella and zoster are caused by viral infections. Most transmission happens by airborne droplets or particles [43].

Non-pharmacological treatment

Use cool water compresses on your skin or take a chilly bath to relax. To the birthtub, add oatmeal that has been coarsely ground. Calamine lotion should be used on the afflicted regions. To prevent infection, trim your fingernails. Put on comfortable clothing [44].

Acyclovir

Acyclovir is classified as biopharmaceutical class 3 (400 MG tablet), which has a high solubility and low permeability. Several nations only offer drugs (800 mg tablets) that come under biopharmaceutical classification 4 (poor solubility and low permeability) [45]. Amphoteric means that acyclovir can react as both a basic and an acid. A PH of about 11. On March 29, 1982, the FDA approved acyclovir. Bioavailability is 10 to 20%, although it falls off when the dose is increased. The absorption rate of acyclovir cream is 0.02 2 9.4% [46]. Both the optical ointment and buccal pill of acyclovir are barely absorbed. Acyclovir's bioavailability is unaffected by meals. The average T max for acyclovir is 1.1; 0.4 hours, the average C max is 593.7 - 2656.5 ng/ml, and the average AUC is 295 6.6 - 31 02.5 ng/ml. Acyclovir's distribution volume is 0.6 [46].

Route of administration

The bulk of Acyclovir is eliminated as an unaltered medication in the urine. Through tubular secretion and glomerular filtration, 90 to 92% of the medication can be eliminated intact [47]. Depending on the patient's creatinine clearance, the half-life is 2.5 hours [48].

Character

A crystalline powder that is white or nearly white, readily soluble in dimethyl sulfoxide, and only very slightlysoluble in ethanol (96%). It dissolves in a diluted mixture of alkali hydroxide and mineral acids [49].

Identification

Check using infrared absorption spectrophotometry and compare the results to the spectrum produced by the acyclovir CRS. A paste made of Kola nitida (red cola nut), Paullinia pinnata (root bark), and Clausena anisata (root bark) is applied locally to treat herpes zoster [50]. Paullinia pinnata's cola nuts, roots, and bark are also chewed, and the juice is then ingested. Within seven days, the condition is cured with this treatment [51]. There are further therapies that Dr. Oku Ampofo has utilized that can heal the illness in seven. Apply a paste made from the root bark of Balannites aegyptiaca, the blooms of Hoslundia opposita and Kola nitida, or the leaves of Psidium guajava, Kaolin, and Piper guineense locally during fourteen days [52].

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