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كليـــة الصيدلـــة

Toxoplasmosis

Toxoplasmosis is infection with Toxoplasma gondii, one of the world's most common parasites. Symptoms range from none to benign lymphadenopathy (a mononucleosis-like illness) to life-threatening CNS disease or involvement of other organs in immunocompromised people. Retinochoroiditis, seizures, and intellectual disability occur in congenital infection. Human exposure to toxoplasmosis is common wherever cats are found; 20 to 40% of healthy adults in the US are seropositive. The risk of developing disease is very low except for a fetus infected in utero and people who are or become immunocompromised.

Pathophysiology

T. gondii is ubiquitous in birds and mammals. This obligate intracellular parasite invades and multiplies asexually as tachyzoites within the cytoplasm of any nucleated cell. When host immunity develops, multiplication of tachyzoites ceases and tissue cysts form; cysts persist in a dormant state for years, especially in brain and muscle. The dormant Toxoplasma forms within the cysts are called bradyzoites. Sexual reproduction of T. gondii occurs only in the intestinal tract of cats; the resultant oocysts passed in the feces remain infectious in moist soil for months.

Infection can occur by:

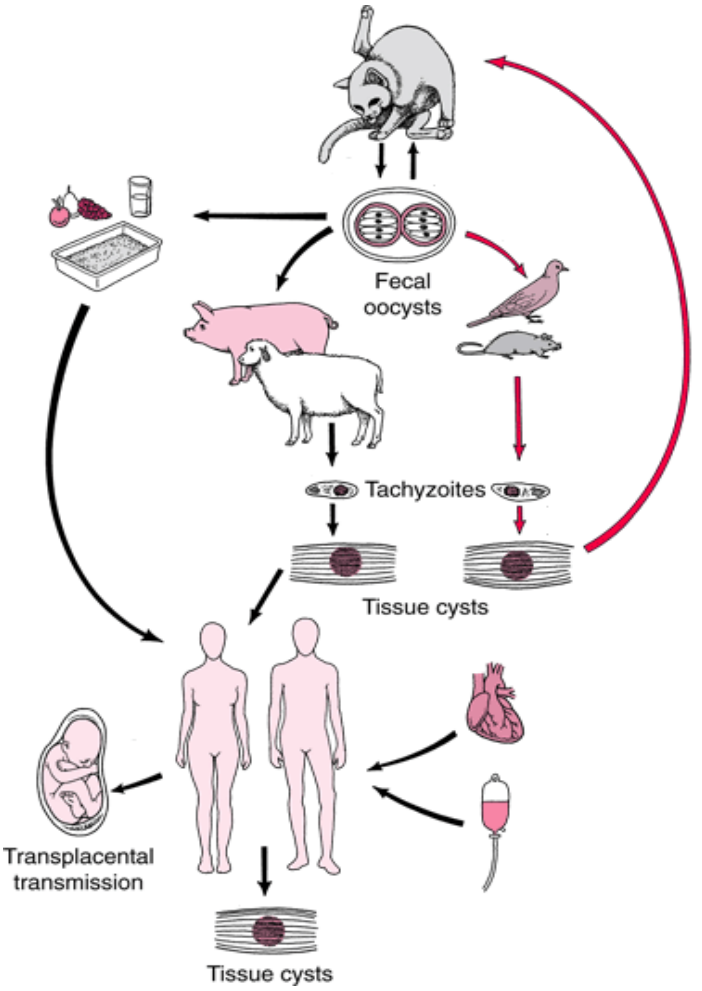
- Ingestion of oocysts in food or water contaminated with cat feces is the most common mode of oral infection. Infection can also occur by eating raw or undercooked meat containing tissue cysts, most commonly lamb, pork, or rarely beef or drinking raw milk from an infected goat as goats can be an intermediate host for the parasite. Kitchen utensils that come in contact with raw meat can harbor the parasites unless the utensils are washed thoroughly in plenty of hot, soapy water.. After ingestion of oocysts or tissue cysts, tachyzoites are released and spread throughout the body. This acute infection is followed by the development of protective immune responses and the formation of tissue cysts in many organs. The cysts can reactivate, primarily in immunocompromised patients. Toxoplasmosis reactivates in 30 to 40% of AIDS patients who are not taking antibiotic prophylaxis, but the widespread use of trimethoprim/sulfamethoxazole for Pneumocystis prophylaxis has dramatically reduced the incidence.

In This Issue

- Toxoplasmosis can be transmitted transplacentally if the mother becomes infected during pregnancy or if immunosuppression reactivates a prior infection. Transmission of Toxoplasma to a fetus is extraordinarily rare in immunocompetent mothers who have had toxoplasmosis earlier in life.
- Transmission may occur via transfusion of whole blood or WBCs or via transplantation of an organ from a seropositive donor. In otherwise healthy people, congenital or acquired infection can reactivate in the retina. Past infection confers resistance to reinfection.

Symptoms and Signs

Infections may manifest in several ways:



- ***Acute toxoplasmosis:*** Acute infection is usually asymptomatic, but 10 to 20% of patients develop bilateral, nontender cervical or axillary lymphadenopathy. A few of these also have a mild flu-like syndrome of fever, malaise, myalgia, hepatosplenomegaly, and less commonly, pharyngitis, which may mimic infectious mononucleosis. Atypical lymphocytosis, mild anemia, leukopenia, and slightly elevated liver enzymes are common. The syndrome may persist for weeks but is almost always self-limited.

- ***CNS toxoplasmosis:*** Most patients with AIDS or other immunocompromised patients who develop toxoplasmosis due to reactivation present with ring-enhancing intracranial mass lesions or encephalitis. These patients typically have headache, altered mental status, seizures, coma, fever, and sometimes focal neurologic deficits, such as motor or sensory loss, cranial nerve palsies, visual abnormalities, and focal seizures.

- ***Congenital toxoplasmosis:*** This type results from a primary, often asymptomatic infection acquired by the mother during pregnancy. Women infected before conception ordinarily do not transmit toxoplasmosis to the fetus unless the infection is reactivated during pregnancy by immunosuppression. Spontaneous abortion and stillbirth may occur. The percentage of surviving fetuses born with toxoplasmosis depends on when maternal infection is acquired; it increases from 15% during the 1st trimester to 30% during the 2nd to 60% during the 3rd. Disease in neonates may be severe, particularly if acquired early in pregnancy; symptoms include jaundice, rash, hepatosplenomegaly, and the characteristic tetrad of abnormalities: bilateral retinochoroiditis, cerebral calcifications, hydrocephalus or microcephaly, and psychomotor retardation. Prognosis is poor. Many children with less severe infections and most infants born to mothers infected during the 3rd trimester appear healthy at birth but are at high risk of seizures, intellectual disability, retinochoroiditis, or other symptoms developing months or even years later.

- ***Ocular toxoplasmosis:*** This type usually results from congenital infection that is reactivated, often during the teens and 20s, but rarely, it occurs with acquired infections. Focal necrotizing retinitis and a secondary granulomatous inflammation of the choroid occur and may cause ocular pain, blurred vision, and sometimes blindness. Relapses are common.

- ***Disseminated infection and non-CNS involvement:*** Disease outside the eye and CNS is much less common and occurs primarily in severely immunocompromised patients. They may present with pneumonitis, myocarditis, polymyositis, diffuse maculopapular rash, high fevers, chills, and prostration. In toxoplasmic pneumonitis, diffuse interstitial infiltrates may progress rapidly to consolidation and cause respiratory failure, whereas endarteritis may lead to infarction of small lung segments. Myocarditis, in which conduction defects are common but often asymptomatic, may rapidly lead to heart failure. Untreated disseminated infections are usually fatal.

Diagnosis

- Serologic testing: The diagnosis is usually made serologically using an indirect fluorescent antibody (IFA) test or enzyme immunoassay (EIA) for IgG and IgM antibodies. The diagnosis of acute toxoplasmosis during pregnancy and in the fetus or neonate can be difficult, and consultation with an expert is recommended.

Toxoplasma are occassionally demonstrated histologically. Tachyzoites, which are present during acute infection, take up Giemsa or Wright's stain but may be difficult to find in routine tissue sections. Tissue cysts do not distinguish acute from chronic infection. Toxoplasma must be distinguished from other intracellular organisms, such as Histoplasma, Trypanosoma cruzi, and Leishmania. PCR tests for parasite DNA in blood, CSF, or amniotic fluid are available at several reference laboratories. PCR-based analysis of amniotic fluid is the preferred method to diagnose toxoplasmosis during pregnancy.

- For CNS involvement, CT or MRI and lumbar puncture: If CNS toxoplasmosis is suspected, patients should have head CT with contrast agent, MRI, or both plus a lumbar puncture if there are no signs of increased intracranial pressure. MRI is more sensitive than CT. CSF may show lymphocytic pleocytosis and elevated protein levels. CT typically shows single or multiple dense, rounded, ring-enhancing lesions. Although these lesions are not pathognomonic, their presence in patients with AIDS and CNS symptoms warrants a trial of chemotherapy for T. gondii. If the suspected diagnosis of toxoplasmosis is correct, clinical or radiographic improvement should become evident within 7 to 14 days. If symptoms persist, a brain biopsy should be considered.

Treatment

Most immunocompetent patients do not require therapy unless visceral disease is present or severe symptoms persist. However, specific treatment is indicated for acute toxoplasmosis of neonates, pregnant women, and immunocompromised patients.

The most effective regimen in immunocompetent patients is pyrimethamine (a folic acid antagonist) plus sulfadiazine (antibiotic).

- Dosage for pyrimethamine is 50 to 100 mg po q 12 h for 1 day, then 25 to 100 mg once/day for 3 to 4 wk in adults (1 mg/kg q 12 h for 3 days, then 1 mg/kg once/day for 4 wk in children; maximum 25 mg/day).
- Dosage for sulfadiazine is 1 to 1.5 g po qid for 3 to 4 wk in adults (25 to 50 mg/kg qid for 4 wk in children).

- Higher doses of pyrimethamine are used in HIV-infected patients with CNS toxoplasmosis. Some clinicians use a loading dose of pyrimethamine 200 mg the first day, then 50 to 100 mg/day plus sulfadiazine for 4 to 6 wk. In patients who have or develop sulfonamide hypersensitivity,clindamycin 600 to 800 mg po tid is given instead of sulfonamides. Another option is atovaquone 1500 mg q 12 h plus pyrimethamine, starting with a 200-mg loading dose followed by 75 mg/day for 6 wk. Relapses of toxoplasmosis are common in patients with AIDS, and suppressive treatment should continue indefinitely unless the CD4 count (the amount of T-helper cells in blood) increases and remains above 200/μL. Pyrimethamine bone marrow suppression can be minimized with leucovorin (also called folinic acid; not folate, which blocks the therapeutic effect). The dosage is 10 to 25 mg po once/day. Patients with ocular toxoplasmosis should also be given corticosteroids.
- Treatment of pregnant women with primary infection can decrease the incidence of fetal infection.Spiramycin 1 g po tid or qid has been used safely to reduce transmission in pregnant women during the 1st trimester, but spiramycin is less active than pyrimethamine plus sulfonamide and does not cross the placenta. Spiramycin is continued until fetal infection is documented or excluded at the end of the 1st trimester. If no transmission has occurred, spiramycin can be continued to term. If the fetus is infected, pyrimethamine plus sulfadiazine is used. Pyrimethamine is a potent teratogen and should not be used during the 1st trimester. Consultation with an infectious diseases expert is recommended.
- Congenitally infected infants should be treated with pyrimethamine every 2 to 3 days and with sulfadiazine once/day for about a year. Infants should also receive leucovorin while receiving pyrimethamine and for 1 wk after pyrimethamine is stopped to prevent bone marrow suppression.

Prevention

Washing hands thoroughly after handling raw meat, soil, or cat litter is essential. Food possibly contaminated with cat feces should be avoided. Meat should be cooked thoroughly. Chemoprophylaxis is recommended for patients with HIV and a positive IgG T. gondiiserologic test once CD4+ cell counts are < 100/μL. One double-strength tablet of trimethoprim/sulfamethoxazole once/day, which also is prophylactic against Pneumocystis jirovecii, is one regimen. Alternatively, pyrimethamine plus dapsone or atovaquone with or without pyrimethamine can be used.

References:

1) ***merckmanuals.com***
2) ***mayoclinic.com***
3) ***medicinenet.com***

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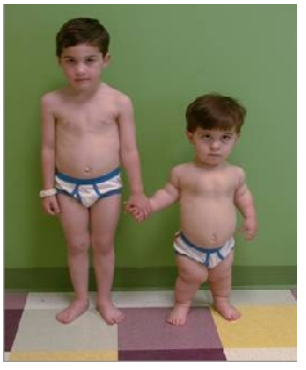
Terminology

Achondroplasia



The commonest form of inherited retarded growth. It is a dominant hereditary disorder of endochondral ossification, caused by mutations of fibroblast growth factor receptor 3 genes.The long bones of the arms and legs fail to grow properly, while the trunk and head develop normally. Achondroplasia affects both sexes and, while many infants are stillborn or die soon after birth, those who survive have normal intelligence, a normal expectation of life and good health.

Reference: Harvey Marcovitch: Black's Medical Dictionary, 41th ed, page 8. London, A & C Black Publishers Limited, 2005.

Drug- Drug Interaction

Benzodiazepines + Calcium-channel blockers

Midazolam or Triazolam

The serum levels and effects of midazolam are markedly increased by diltiazem or verapamil. This also occurs with triazolam and diltiazem, and is predicted to occur with triazolam and verapamil.

Monitor the outcome of concurrent use. Consider using a lower initial dose of midazolam or triazolam.

Other benzodiazepines

There appear to be no significant interactions between diazepam and diltiazem, felodipine or nimodipine; between midazolam and nitrendipine; between temazepam and diltiazem; or between triazolam and isradipine. Lercanidipine absorption is increased by 40% by midazolam, but the clinical significance of this is unclear.

Source: Karen Baxter: Stockley's Drug Interactions Pocket companion, 1st ed., Page 129. UK, London, Pharmaceutical Press, 2009.

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FDA News

July 17, 2012 (Mountain View, California) — The **FDA** has approved the weight-loss drug **Qsymia** (formerly named Qnexa; Vivus, Mountain View, CA), which now joins **lorcaserin** (Belviq, Arena Pharmaceuticals, San Diego, CA) as the first anti-obesity medications to enter the US market since 1999. News of the agency's decision was announced late Tuesday.

Qsymia, a controlled-release preparation of **phentermine** and **topiramate** in one capsule, is now indicated for use in adults with a body mass index (BMI) $\geq$30 kg/m^2 or adults with a BMI of $\geq$27 kg/m^2 and at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia.

The approval is accompanied by a Risk Evaluation and Mitigation Strategy (REMS), including a medication guide advising patients about important safety information and specific requirements for prescriber training and pharmacy certification. The drug "will only be dispensed through specially certified pharmacies," according to the FDA statement. Of special note, the drug must not be used during pregnancy; details about the risk of the drug combo in pregnant women are included.

The agency's statement also notes that the drug can increase heart rate, which warrants regular monitoring, and should be used with caution in people with recent unstable heart disease or stroke. The sponsor will be required to conduct a long-term, postmarketing cardiovascular outcomes trial to assess the effect of Qsymia on the risk of major adverse cardiac events.

In February, an FDA advisory panel voted overwhelmingly in favor of the drug's approval for obesity, despite some concerns about possible adverse effects, as reported by heart*wire*. The agency then took the step--not unusual in such cases--of giving the company a three-month extension on the period during which it could review its application, which ended today. That allowed the FDA to consider the REMS for Qsymia that Vivus had submitted on April 4. Many on the advisory panel had stated that their vote favoring Qsymia--it was ultimately 20 to 2--assumed that the company would in fact submit and implement a REMS, parts of which Vivus described at the hearing. That regulators granted an extension to

facilitate that process was as good a sign as any that it was leaning toward a positive decision.

Both the FDA and its advisory committee had decided against approval of Qsymia during its first round of consideration in October, 2010, pending a more comprehensive safety assessment. Lorcaserin had followed a similar path in the premarket process, having been denied approval the same week for similar reasons; the agency approved lorcaserin just a few weeks before **Qsymia**.

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Test Your Knowledge

1) **Concern the following:**

A - tachypnoea
B - hypoxia
C - afterload
D - myopathy
E - dysphasia

Select, from A to E, which one of the above is manifested by:
Q1 muscle weakness and muscle wasting
Q2 rapid rate of breathing
Q3 an impairment of the language aspect of speech

2) **Possible causes of resistance to cytotoxic chemotherapy include:**
A - increased cellular uptake
B - increased repair of DNA damage
C- poor penetration into tumour
D- both B and C are correct

3) **Creatinine clearance:**
A- is an index used to measure glomerular filtration rate
B - measurement involves a 24-hour urine collection
C- measurement requires 24-hour monitoring of plasma creatinine
D- both A and B are correct

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional health team as well as from others. Here's one of the enquiries received at the center!

Enquiry received from Ph/ Sabah Souky Pharmacist at Assiut University Hospital

Enquiry: Is insulin adsorbed to surfaces of IV infusion solution containers?

Summary of Answer:

The adsorption of insulin to the surfaces of IV infusion soln., containers (both glass & plastic), tubing, and filters has been demonstrated. Estimates of the potency loss range up to about 80%, although varying results have been obtained. The percent adsorbed is inversely proportional to conc. However, the clinical significance of this adsorption is uncertain. However, adsorption can be decreased by using small-volume containers, e.g. syringe pumps rather than large infusion bags.

References: 1) Trissel: Pocket Guide to Injectable Drugs , 13th edition
2) Alistair Gray, Jane Wright, Vincent Goodey, Lynn Bruce: Injectable Drugs Guide, 1st ed, page 454, London, Pharmaceutical Press, 2011.

Complementary Medicine
Hawthorn الزعرور

Latin Names

Crataegus laevigata (also known as *Crataegus oxyacantha), Crataegus monogyna*

Uses

- Hawthorn fruit has been used for heart disease since the first century. It has also been used for digestive and kidney problems.
- More recently, hawthorn leaf and flower have been used for heart failure, a weakness of the heart muscle that prevents the heart from pumping enough blood to the rest of the body, which can lead to fatigue and limit physical activities.
- Hawthorn is also used for other heart conditions, including symptoms of coronary artery disease (such as angina).

How It Is Used

The hawthorn leaf and flower are used to make liquid extracts, usually with water and alcohol. Dry extracts can be put into capsules and tablets.

What Science Says

- The American Eclectic herbalist Ellingwood said of hawthorn,
... it is superior to any of the well known and tried remedies at present in use for the treatment of heart disease, because it seems to cure while other remedies are only palliative at best.
- German physician Rudolf Weiss suggests the following indications:
• Patients with "degeneration of the cardiac muscle or coronary artery disease"
• Anginal symptoms of coronary artery disease (long term treatment)
• Hypertension, primarily to improve cardiac function
• Weakness of the myocardium after infectious disease
• Muscular insufficiency in patients taking digitalis (hawthorn may optimize the effects of digitalis)
• Cardiac arrhythmias, mainly extra systoles and tachycardia

Side Effects and Cautions

- Hawthorn is considered safe for most adults when used for short periods of time. Side effects are usually mild and can include upset stomach, headache, and dizziness.
- Drug interactions with hawthorn have not been thoroughly studied. It was once thought that hawthorn interacted with the heart medicine digoxin. However, a very small study in people without heart conditions found no interaction, but evidence is limited.

Reference: 1) E-book: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Center for Complementary and Alternative Medicine Herbs at a Glance
2) David Hoffmann: Medical Herbalism; The Science and Practice of Herbal Medicine, page 294. Rochester, Vermont, Healing Arts Press, 2003

Answers:

1- Q1: D, Myopathy is a condition affecting the skeletal muscle, and which is manifested by muscle weakness and wasting. Histological changes occur in the muscle tissues, similar to those that occur in muscular dystrophies.

Q2: A, Tachypnoea is an abnormally fast breathing rate. It is characteristic of respiratory diseases and occurs in hyperpyrexia. It occurs as a result of overactivity at the level of the sympathetic nervous system.

Q3: E, Dysphasia (aphasia) is a condition resulting in impairment of the language aspect of speech. It usually occurs as a result of cerebral cortex injury, such as after surgery for a brain tumour or after a cerebral stroke. The presence of dysphasia is frequently accompanied by writing disorders.

2- (D) The administration of cytotoxic chemotherapy regimen may fail to achieve remission in an individual patient compared with a cohort of patients owing to drug resistance. Tumour cells may be inherently resistant or acquire resistance after a number of treatment sessions. Tumour cell resistance may be explained by a reduction of intracellular drug concentration, enzymatic deactivation of the drug, and by increased repair of damaged DNA. If the drugs fail to penetrate the solid tumour, then they are not in a position to achieve cell death.

3- (D) Creatinine clearance is the rate of removal of creatinine from the body by the kidney during glomerular filtration. It gives a measure of the glomerular filtration rate (GFR). The measured creatinine clearance is more accurate in the assessment of renal function compared with the calculated creatinine clearance, which is based on a formula where the serum creatinine concentration is used. To measure the creatinine clearance, a 24-h urine collection and a serum sample are required.

Cold Chaser Tea

Uses: Colds

Constituents:

1 tsp. Echinacea root جذور الاخناسيا
1 tsp. Hyssop الزوفا (أو لسنان داوود)
1/2 tsp. Licorice root جذور العرقسوس
1/2 tsp. Cinnamon القرفة
1/2 tsp. dried Ginger or 1-2 slices of fresh Ginger root جذور الزنجبيل
1 quart water

Boil the water, and then pour the water over the mixed herbs in a tea pot or a wide mouthed glass jar. Be sure to keep the lid on the pot or jar. Let steep for 20 minutes. Strain, and drink throughout the day. Sip on hot water throughout the day as well to assist the body flush out toxins.

Source: The Herbal Pharmacy CD, By Hale Software, Inc ©1997.

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