

Criston

Vincristine Sulfate Injection

COMPOSITION

Criston 1 Injection : Each vial contains 1 ml solution containing Vincristine Sulfate USP 1 mg.
Criston 2 Injection : Each vial contains 2 ml solution containing Vincristine Sulfate USP 2 mg.

DESCRIPTION

Vincristine Sulfate is the salt of an alkaloid obtained from the periwinkle plant (*Vinca rosea* Linn). Vincristine sulfate is a white or slightly yellow, hygroscopic, amorphous or crystalline powder and is freely soluble in water and slightly soluble in alcohol.

CLINICAL PHARMACOLOGY

The precise mechanism of action of vincristine sulfate remains under investigation. It appears to bind to or crystallise critical microtubular proteins of the mitotic spindle, thus preventing their proper polymerisation and causing metaphase arrest. The antineoplastic effects of the vinca alkaloids are related to their ability to bind specifically with the intracellular protein tubulin, a key component of cellular microtubules.

Pharmacodynamics/Kinetics:

Distribution of vincristine and its metabolites into human body tissue and fluids has not been fully characterised, but the drug is rapidly and apparently widely distributed following intravenous administration.

Vincristine sulfate is extensively protein bound (75%) and is reported to be concentrated in blood platelets. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly, bound.

Vincristine sulfate and its metabolites are rapidly and extensively distributed into bile, with peak biliary concentrations occurring within 2 to 4 hours after rapid intravenous injection.

Central nervous system leukaemia has been reported in patients undergoing otherwise successful therapy with vincristine sulfate. This suggests that vincristine sulfate does not penetrate well into cerebro-spinal fluid. Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours and 85 hours respectively; however the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the faeces and 10% to 20% can be found in the urine.

INDICATIONS

Vincristine sulfate is indicated in acute leukemia. Vincristine sulfate has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular, and diffuse types), rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.

Use in Pregnancy

Category D. Vincristine Injection can cause foetal harm when administered to pregnant women.

Use in Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to vincristine in breast-fed infants, a decision should be made either to discontinue breast-feeding or the drug, taking into account the importance of the drug to the mother.

DOSAGE AND ADMINISTRATION

Extreme care must be used in calculating and administering the dose of vincristine, since overdosage may have a very serious or fatal outcome. The drug is given i.v. at weekly intervals. Fatal if given intrathecally.

Adults: The usual dose of vincristine is 1.4 mg/m²

Children: The usual dose of vincristine is 2 mg/m². For children weighing 10 kg or less, the initial dose of vincristine should be 0.05 mg/kg once a week, with careful increasing of dosing thereafter based on effects.

Vincristine should not be administered to patients receiving radiation therapy through ports that include the liver.

When vincristine is used in combination with L-asparaginase, it should be given 12 to 24 hours prior to administration of the enzyme in order to minimize toxicity because L-asparaginase may reduce hepatic clearance of vincristine.

Administration: Vincristine solution may be injected either directly into a vein or into the tubing of an i.v. infusion. Injection of the solution may be completed in about 1 minute. Further dilution: The solution may be further diluted with 0.9% sodium chloride injection or 0.5% dextrose injection if desired.

CONTRAINDICATIONS

Patients with the demyelinating form of Charcot-Marie-Tooth Syndrome should not be given vincristine sulfate.

Vincristine should not be administered to patients while they are receiving radiation therapy through ports that include the liver.

Patients with known hypersensitivity to vinca alkaloids or mannitol should not be given vincristine sulfate.

PRECAUTIONS

It is extremely important to be certain that the needle is properly positioned in the vein before any vincristine is injected. If leakage into the surrounding tissue should occur during i.v. administration of vincristine, it may cause considerable irritation. The injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

Vincristine should be used only by physicians experienced in cytotoxic chemotherapy. The drug is very irritating and should not be given intramuscularly, subcutaneously or intrathecally. Intrathecal administration of vincristine is usually fatal. Treatment of patients following accidental intrathecal administration of vincristine has included immediate removal of spinal fluid and flushing with Lactated Ringer's solution, as well as other solutions and has not prevented ascending paralysis and death. In one case, progressive paralysis in an adult was arrested by the following treatment initiated immediately after the intrathecal injection:

1. As much spinal fluid was removed as could be safely done through lumbar access.
2. The subarachnoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150 mL/hour. The fluid was removed through a lumbar access.
3. As soon as fresh frozen plasma became available, the fresh frozen plasma, 25 mL, diluted in 1 L of Lactated Ringer's solution was infused through the cerebral ventricular catheter at the rate of 75 mL/hour with removal through the lumbar access. The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150 milligrams/dL.
4. Glutamic acid, 10 grams was given intravenously over 24 hours followed by 500 milligrams 3 times daily by mouth for 1 month or until neurological dysfunction stabilised. The role of glutamic acid in this treatment is not certain and may not be essential.

Vincristine is a vesicant and may cause a severe local reaction on extravasation. If leakage into the surrounding tissue should occur during intravenous administration of vincristine, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase with the application of heat has been used to disperse the drug in order to minimise discomfort and the possibility of tissue damage.

Leucopenia is less likely following therapy with vincristine than is the case with other oncolytic agents. However, because of its possibility both physician and patient should remain alert for signs of any complicating infection. If leucopenia or a complicating infection is present, then administration of the next dose of vincristine warrants careful consideration.

The risk/benefit should be considered in patients with a history of gout or urate renal stones, as acute uric acid nephropathy, which may occur after the administration of oncolytic agents, has also been reported with vincristine.

As vincristine penetrates the blood-brain barrier poorly, additional agents and routes of administration may be required for central nervous system leukaemia. The neurotoxic effect of vincristine may be additive with other neurotoxic agents or increased by spinal cord irradiation and neurological disease.

Particular attention should be given to dosage and neurologic side effects if vincristine is administered to patients who have had previous cytotoxic drug therapy or irradiation and in those with pre-existing neuromuscular disease (including sensory peripheral neuropathy and steroid-induced myopathy), and also when other drugs with neurotoxic potential are being used. Care should also be taken in elderly patients, who may be more susceptible to neurotoxicity.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin and may require aggressive treatment, particularly when there is pre-existing pulmonary dysfunction. The onset of these reactions may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea requiring chronic therapy may occur. Vincristine should not be readministered.

Because of the hepatic metabolism and biliary excretion of vincristine, a dosage modification may be required in patients with liver disease or jaundice.

Care should be taken to avoid accidental contamination of the eyes, because vincristine is highly irritant and can cause corneal ulceration. The eyes should be washed with water immediately and thoroughly.

Monitoring and laboratory tests

Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (eg. history, physical examination) is necessary to detect the need for dosage modification. Following administration of vincristine sulfate, some individuals may have a fall in the white-blood-cell count or platelet count, particularly when previous therapy or the disease itself has reduced bone-marrow function. Therefore a complete blood count should be done before administration of each dose. Acute elevation of serum uric acid may also occur during induction of remission in acute leukaemia; thus, such levels should be determined frequently during the first 3 to 4 weeks of treatment or appropriate measures taken to prevent uric acid nephropathy (see above). The laboratory performing these tests should be consulted for its range of normal values.

OVERDOSE

Overdosage with vincristine produces adverse reactions that are mainly extensions of the common adverse effects as these are dose related. As no antidote for vincristine has been found to date, treatment is purely supportive and symptomatic.

In children under 13 years of age, death has occurred following doses of vincristine that were ten times those recommended for therapy. Severe symptoms may occur in this patient group following dosages of 3 to 4 milligrams/m². Adults can be expected to experience severe symptoms after single doses of 3 milligrams/m² or more.

Anticonvulsants such as phenobarbitone may be beneficial in controlling seizures. If profound neutropenia develops, surveillance for the presence of infection by culture, protective isolation and early treatment with antibiotics when infection is suspected, may be necessary. Fluid restriction and possibly the use of an appropriate diuretic may have to be instituted to prevent side effects resulting from hypersecretion of antidiuretic hormone. Enemas may be used to prevent ileus (in some cases decompression of the GI tract may be necessary). Routine monitoring of the cardiovascular system is also recommended together with daily blood counts as an indicator for transfusion requirements.

Folinic acid has been observed to have a protective effect in normal mice which were administered lethal doses of vincristine sulfate. Isolated reports suggest that folinic acid may be helpful in treating humans who have received an overdose of vincristine. A suggested schedule is to administer 15 milligrams of folinic acid intravenously every 3 hours for 24 hours and then every 6 hours for at least 48 hours. Theoretically, based on pharmacokinetic data, tissue levels of vincristine can be expected to remain significantly elevated for at least 72 hours. Treatment with folinic acid does not eliminate the need for the above-mentioned supportive measures.

Most of the intravenous dose of vincristine sulfate is excreted into the bile after rapid tissue binding because only very small amounts of the drug appear in dialysate, haemodialysis is not likely to be helpful in cases of overdosage. An increase in the severity of side effects may be experienced in patients with liver disease with diminished biliary excretion.

Enhanced faecal excretion of parenterally administered vincristine has been demonstrated in dogs pretreated with cholestyramine. There are no published clinical data on the use of cholestyramine as an antidote in humans. Nor is there published clinical data on the consequences of oral ingestion of vincristine. Should oral ingestion occur the stomach should be evacuated, and activated charcoal administered orally.

ADVERSE EFFECTS

Prior to the use of this drug, patients and or parents/guardians should be advised of the possibility of untoward symptoms.

In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss, the most troublesome adverse reactions are neuromuscular in origin. When single, weekly doses of the drug are employed, the adverse reactions of leucopenia, neuritic pain, and constipation occur but are of short duration (ie. less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions such as hair loss, sensory loss, paraesthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued. Generalised sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The following adverse reactions have been reported:

Hypersensitivity

Rare cases of allergic-type reactions, such as anaphylaxis, rash, and oedema, that are temporarily related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

Gastrointestinal

Autonomic toxicity such as constipation and paralytic ileus are not uncommon and are frequently associated with abdominal cramps. Stool softeners, mild laxatives and enemas may be helpful. A routine prophylactic regimen of laxative and enemas is usually recommended for patients receiving vincristine.

Constipation may take the form of upper colon impaction, and on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the physician. A flat film of the abdomen is useful in demonstrating this condition.

Paralytic ileus (which mimics the 'surgical abdomen') may occur, particularly in young children. The ileus will reverse itself with temporary discontinuance of vincristine and with symptomatic care. Nausea, vomiting, diarrhoea, stomatitis and oral ulceration occur occasionally.

Genitourinary: Hyperuricaemia may occur in some patients receiving vincristine, especially those with non-Hodgkin's lymphomas or leukaemia. In some patients uric acid nephropathy may result. These effects may be minimised by adequate hydration, alkalisation of the urine and/or administration of allopurinol.

Polyuria, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to have caused urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate.

Cardiovascular

Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Neurologic

Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paraesthesiae may be encountered. With continued treatment, neuritic pain and later, motor difficulties may occur. There have been no reports made of any agent that can reverse the neuromuscular manifestations that may accompany therapy with vincristine.

Loss of deep-tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, including isolated paresis and/or paralysis of muscles controlled by cranial motor nerves, may occur in the absence of motor impairment elsewhere; extra-ocular and laryngeal muscles are those most commonly involved. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in children. Transient cortical blindness and optic atrophy have been reported. Depression, agitation, insomnia and hallucinations have been reported.

Endocrine

Hypersecretion of antidiuretic hormone (SIADH) has occurred rarely in patients receiving vincristine therapy. In these patients, hyponatraemia associated with increased urinary sodium excretion occurs without evidence of renal or adrenal disease, hypotension, dehydration, azotaemia or clinical oedema. With fluid deprivation, improvement occurs in the hyponatraemia and in the renal loss of sodium.

Haematologic

Vincristine sulfate does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone-marrow depression is usually not a major dose-limiting event. However, anaemia, leucopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine is begun, may actually improve before the appearance of bone marrow remission.

Skin/hair

Alopecia is reported to occur in about 20 to 70% of patients who receive vincristine. It is reversible when the drug is discontinued. Rash has also been reported, as have photosensitivity reactions.

Other

Fever and headache have occurred. Also other side effects include defective sweating, myoclonic jerks, abnormal Valsalva response, impotence and diminished libido. Weight loss has been reported at high doses.

DRUG INTERACTIONS

Allopurinol may increase the incidence of cytotoxic induced bone-marrow depression. The mechanism for this potentiation has not been fully classified. The neurotoxicity of vincristine may be additive with that of asparaginase isoniazid and other drugs acting on the peripheral nervous system. The concurrent use of doxorubicin with vincristine and prednisone may produce increased myelosuppression; it is recommended that the combination be avoided.

Vincristine appears to increase the cellular uptake of methotrexate by malignant cells and this principle has been applied in high-dose methotrexate therapy. The clinical importance of this interaction is not known however. It has also been reported that a 2.5 fold increase of methotrexate levels in CSF occurred when vincristine was given 23 hours after high dose methotrexate therapy was initiated. The effect lasted approximately 3 hours.

Because normal defence mechanisms may be suppressed by vincristine sulfate therapy, concurrent use with a live virus vaccine may potentate the replication of the vaccine virus, and may increase adverse effects of the vaccine virus, and /or may decrease the patient's antibody response to the vaccine. The patient's antibody response to killed virus may also be decreased. Immunisation of a patient who is receiving or who has received vincristine, should be undertaken only with extreme caution after careful review of the patient's haematologic status and only with the knowledge and consent of the physician managing the vincristine therapy. The interval between discontinuation of medications that cause immune suppression and restoration of the patient's ability to respond to the vaccine depends on many factors; estimates vary from 3 months to 1 year.

Due to decreased absorption of the antimicrobial agent, the antimicrobial effect of oral quinolones (ciprofloxacin, norfloxacin and ofloxacin) may be decreased by administration of vincristine.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination. Nifedipine decreases the clearance of vincristine.

PHARMACEUTICAL INFORMATION

Storage condition

Store in a refrigerator at 2° C - 8° C. Do not freeze. Protect from light. Keep out of the reach of children.

Packaging

Criston 1 Injection : Each commercial box contains 1 vial containing Vincristine Sulfate 1 mg/1 ml.
Criston 2 Injection : Each commercial box contains 1 vial containing Vincristine Sulfate 2 mg/2 ml.