Vincristine Sulfate

- **(vin-kris-teen)**
- **Oncovin®**
- **Antineoplastic**

**Prescriber Highlights**

- A Vinca alkaloid antineoplastic used for a variety of tumors in dogs & cats (primarily lymphoid & hematopoietic neoplasms); also used for the treatment of immune-mediated thrombocytopenia.
- Caution: Hepatic disease, leukopenia, infection, or preexisting neuromuscular disease; reduce dose if hepatic disease. Use with caution in herding breeds (e.g., Collies) that may have the gene mutation (MDR1; ABCB1).
- Adverse Effects: Much less myelosuppressive than vinblastine, but may cause more peripheral neurotoxic effects; neuropathic clinical signs can include proprioceptive deficits, spinal hyporeflexia, or paralytic ileus with resulting constipation; Cats can develop neurotoxicity causing constipation or paralytic ileus & aggravating anorexia; can also develop reversible axon swelling & paranodal demyelination.
- Potentially teratogenic.
- Avoid extravasation; wear gloves & protective clothing when preparing or administering.
- Drug Interactions.

**Uses/Indications**

Vincristine is used as an antineoplastic primarily in combination drug protocols in dogs and cats in the treatment of lymphoid and hematopoietic neoplasms. In dogs, it may be used alone in the therapy of transmissible venereal neoplasms.

A prospective clinical trial in cats (n=40) to compare vincristine and vinblastine response rates, outcomes, and toxicities in a COP-based protocol for lymphoma, found that both arms had similar response rates, progression-free survival (PFS) times, lymphoma-specific survival (LSS) times, but vincristine treated cats had a higher incidence of gastrointestinal adverse effects (Krick *et al.* 2013).

Because vincristine can induce thrombocytosis (at low doses) and has some immunosuppressant activity, it may also be employed in the treatment of immune-mediated thrombocytopenia (ITP). A prospective, randomized study in dogs (n=20) to compare the effect of hIVIG versus vincristine on platelet recovery in dogs with ITP found no significant differences in groups in platelet recovery time, hospitalization time, or survival at discharge, 6 months, and 1 year after entry into the study.
The authors concluded that because of lower cost and ease of administration, vincristine should be the first-line adjunctive treatment for the acute management of canine ITP (Balog et al. 2013).

Pharmacology/Actions
Vincristine apparently binds to microtubular proteins (tubulin) in the mitotic spindle, thereby preventing cell division during metaphase. It also interferes with amino acid metabolism by inhibiting glutamic acid utilization and preventing purine synthesis, citric acid cycle and urea formation. Tumor resistance to one Vinca alkaloid does not imply resistance to another.

Vincristine can induce thrombocytosis (mechanism unknown) and has some immunosuppressant activity.

Pharmacokinetics
Vincristine is administered IV as it is unpredictably absorbed from the GI tract. After injection it is rapidly distributed to tissues. In humans, ≈ 75% is bound to tissue proteins and the drug does not appreciably enter the CNS.

In cats, vincristine and cyclophosphamide given intraperitoneally (IP) was considered safe and effective (Teske et al. 2014).

Vincristine is extensively metabolized, presumably by the liver and primarily excreted in the bile/feces; lesser amounts are eliminated in the urine. The elimination half-life in dogs is reportedly biphasic with an alpha half-life of 13 minutes and a beta half-life of 75 minutes.

Contraindications/Precautions/Warnings
Vincristine should be used with caution in patients with hepatic disease, leukopenia, infection, or preexisting neuromuscular disease.

Doses of vincristine should be reduced in patients with hepatic disease. A 50% reduction in dose should be considered if serum bilirubin levels are >2 mg/dL.

Because vincristine is potentially a neurotoxic substrate of P-glycoprotein, it should be used with caution in those herding breeds (e.g., Collies) that may have the gene mutation (MDR1; ABCB1) that causes a nonfunctional protein. Bone marrow suppression (decreased blood cell counts, particularly neutrophils) and GI toxicity (anorexia, vomiting, diarrhea) are more likely to occur at normal doses in dogs with the ABCB1 mutation. To reduce the likelihood of severe toxicity in these dogs (mutant/normal or mutant/mutant), the Veterinary Clinical Pharmacology Laboratory at Washington State University recommends reducing the dose by 25-30% and carefully monitoring these patients (Anon 2009).

Border Collies, unrelated to their ABCB1 status, appear to be more susceptible than typical for developing vincristine-associated myelosuppression (Lind et al. 2013).
As vincristine may be a skin irritant, gloves and protective clothing should be worn when preparing or administering the medication. If skin/mucous membrane exposure occurs, thoroughly wash area with soap and water.

Do not confuse vinBLAStine with vinCRIStine; consider using “tall man lettering” when writing orders.

**Adverse Effects**

Although structurally related to and having a similar mechanism of action as vinblastine, vincristine has a different adverse reaction profile. Vincristine is much less myelosuppressive (mild leukopenia) at usual doses than is vinblastine, but may cause more peripheral neurotoxic effects. Neuropathic clinical signs may include proprioceptive deficits, spinal hyporeflexia, or paralytic ileus with resulting constipation. In humans, vincristine commonly causes mild sensory impairment and peripheral paresthesias. These may also occur in animals, but are not usually noted due to difficulty in detection. Cats, however, can develop neurotoxicity that can be associated with constipation or paralytic ileus thereby aggravating anorexia. They can develop reversible axon swelling and paranodal demyelination.

Additionally, in small animals, vincristine may cause vomiting, diarrhea, anorexia, impaired platelet aggregation, increased liver enzymes, inappropriate ADH secretion, jaw pain, alopecia, stomatitis, or seizures.

A case report of cat developing pulmonary edema attributed to vincristine administration has been published (Polton *et al.* 2008).

While deemed not clinically significant, vincristine can cause erythrocyte dysplasia in dogs (Collicutt *et al.* 2013).

Extravasation injuries associated with perivascular injection of vincristine can range from irritation to necrosis and tissue sloughing. Because of the vesicant action of this drug, it is recommended to use a different needle for injecting the drug than the one used to withdraw it from the vial. Recommendations of therapy for extravasation include discontinuing the infusion immediately at that site and applying moderate heat to the area to help disperse the drug. Injections of hyaluronidase have been suggested to help diffuse the drug. Others have suggested applying ice to the area to limit the drug’s diffusion and minimize the area affected. Topical dimethyl sulfoxide (DMSO) has also been recommended by some to treat the area involved.

**Reproductive/Nursing Safety**

Little is known about the effects of vincristine on developing fetuses, but it is believed that the drug possesses some teratogenic and embryotoxic properties. It may also cause aspermia in males. In humans, the FDA categorizes this drug as category D for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be*
acceptable despite its potential risks.) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: C (These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.)

It is not known whether this drug is excreted in milk. Because of the potential for serious adverse reactions in nursing offspring, consider using milk replacer if dams are being given this drug.

**Overdosage/Acute Toxicity**

In dogs, it is reported that the maximally tolerated dose of vincristine is 0.06 mg/kg every 7 days for 6 weeks. Animals receiving this dose showed signs of slight anemia, leukopenia, increased liver enzymes, and neuronal shrinkage in the peripheral and central nervous systems.

In cats, the lethal dose of vincristine is reportedly 0.1 mg/kg. Cats receiving toxic doses showed clinical signs of weight loss, seizures, leukopenia, and general debilitation. A case report of cat receiving a 5 mg/m\(^2\) (10X) overdose has been published (Hughes et al. 2009). Despite intensive treatment including using calcium folinate, the cat died 72 hours after the overdose.

In humans, cardiovascular and hematologic monitoring are performed after an overdose. Treatment can include anticonvulsants, and prevention of ileus. Additionally, an attempt is made to prevent the effects associated with the syndrome of inappropriate antidiuretic hormone (SIADH) with fluid restriction and loop diuretics to maintain serum osmolality. There have been some reports of leucovorin calcium being used to treat vincristine overdoses in humans, but efficacy of this treatment has not yet been confirmed.

**Drug Interactions**

The following drug interactions have either been reported or are theoretical in humans or animals receiving vincristine and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Asparaginase**: Additive neurotoxicity may occur; is apparently less common when asparaginase is administered after vincristine.
- **Mitomycin**: In humans who have previously or simultaneously received mitomycin-C with Vinca alkaloids, severe bronchospasm has occurred.

Caution is advised if using other drugs that can inhibit \textit{p-glycoprotein} particularly in those dogs at risk for MDR1-allele mutation (e.g., Collies, Australian Shepherds, Shelties, Long-haired Whippet, etc. “white feet”), unless tested “normal”. Drugs and drug classes involved include:
• Amiodarone
• Azole Antifungals (e.g., ketoconazole, itraconazole)
• Carvedilol
• Cyclosporine
• Diltiazem
• Erythromycin; Clarithromycin
• Quinidine
• Spironolactone
• Tamoxifen
• Verapamil

LABORATORY CONSIDERATIONS

• Vincristine may significantly increase both blood and urine concentrations of uric acid.

DOSES

Note: Because of the potential toxicity of this drug to patients, veterinary personnel and clients, and since chemotherapy indications, treatment protocols, monitoring and safety guidelines often change, the following dosages should be used only as a general guide. Consultation with a veterinary oncologist and referral to current veterinary oncology references [e.g., (Withrow et al. 2012); (Dobson et al. 2011); (Henry et al. 2009); (North et al. 2009); (Argyle et al. 2008)] are strongly recommended.

Dogs:

• For neoplastic diseases (extra-label): Usually used in combination protocols with other drugs; consultation with a veterinary oncologist is encouraged before use; see above. Vincristine is usually dosed in dogs at 0.5 – 0.75 mg/m\(^2\) (NOT mg/kg) IV and administered every 1-2 weeks. When used for transmissible venereal tumor, vincristine is used as sole therapy usually at 0.5 mg/m\(^2\) (maximum dose 1 mg) IV once weekly for 4-6 weeks of therapy.

• For adjunctive treatment of immune-mediated thrombocytopenia (extra-label): In the study, dogs received vincristine at 0.02 mg/kg IV bolus once. Dogs also received glucocorticoids (usually prednisone at 1.5 – 2 mg/kg PO q12h) and doxycycline until results of serologic testing was confirmed negative. In dogs that did not have an increase in platelet count 7 days after treatment azathioprine (2 mg/kg PO q24h) was added. Note: At this dosage of vincristine, clinically significant myelosuppression has not been described. (Balog et al. 2013)

Cats:
For neoplastic diseases (extra-label); (consultation with a veterinary oncologist is encouraged before use; see above): Vincristine is usually dosed in cats at 0.5 – 0.75 mg/m² (NOT mg/kg) IV and administered every 1-3 weeks.

Horses:

For neoplastic diseases (extra-label); consultation with a veterinary oncologist is encouraged before use: Usual doses used in horses are: 0.5 mg/m² (usually 2.5 – 3 mg total dose per horse) IV weekly. For generalized lymphoma the CAP protocol was used at the time of publication by one of the authors: cytarabine (cytosine arabinoside) at an average dose of 1 – 1.2 grams (total dose), SC or IM once every 1-2 weeks; cyclophosphamide at a dose of 1 gram (total dose) IV every 2 weeks (alternating with cytarabine); and prednisolone at a dose of 1 mg/kg PO every other day. Vincristine at 2.5 mg (total dose) IV is added on the weeks when the cytarabine is administered if there is no response. These are starting doses; the total doses can be increased by 20-30% without expecting complications. With remission, the starting doses are maintained for 2-3 months and then the horse is switched onto a maintenance protocol. The first cycle of maintenance therapy increases the treatment interval for each drug by one week (except prednisolone which is kept at the same frequency but with a reducing dose). If horse is still in remission after 2-3 months of the first cycle, the second cycle is begun by adding a further week to the treatment intervals of each drug. (Mair et al. 2006)

Monitoring

- Efficacy (tumor burden reduction or platelet count).
- Toxicity (peripheral neuropathic clinical signs; complete blood counts with platelets; liver function tests prior to therapy and repeated as necessary; serum uric acid).

Client Information

- Vincristine is a chemotherapy (cancer) drug. The drug and its byproducts can be hazardous to other animals and people that come in contact with it. On the day your animal gets the drug and then for a few days afterward, all bodily waste (urine, feces, litter), blood, or vomit should only be handled while wearing disposable gloves. Seal the waste in a plastic bag and then place both the bag and gloves in with the regular trash.
- Vincristine can be very toxic to Collie-like breeds that are positive for the MDR1 genetic mutation.
- Vincristine can cause a serious neurological toxicity that can result in weakness, severe constipation and loss of appetite.
- If leaked outside the vein, vincristine is very irritating and can cause severe damage to the affected limb.
**Chemistry/Synonyms**

Commonly referred to as a Vinca alkaloid, vincristine sulfate is isolated from the plant *Cantharanthus roseus* (*Vinca rosea* Linn) and occurs as a white or slightly yellow, hygroscopic, amorphous or crystalline powder that is freely soluble in water and slightly soluble in alcohol. The commercially available injection has a pH of 3-5.5. Vincristine sulfate has pKₐ values of 5 and 7.4.

Vincristine Sulfate may also be known as: leurocristine sulfate, VCR, LCR compound 37231, leurocristine sulphate, NSC-67574, 22-oxovincaleukoblastine sulphate, sulfato de vincristina, vincristini sulfas and Oncovin®; many other trade names are available.

**Storage/Stability**

Vincristine sulfate injection should be protected from light and stored in the refrigerator (2-8°C).

**Compatibility/Compounding Considerations**

Vincristine sulfate is reportedly physically compatible with the following intravenous solutions and drugs: D5W, bleomycin sulfate, cytarabine, fluorouracil, and methotrexate sodium. In syringes or at Y-sites with: bleomycin sulfate, cisplatin, cyclophosphamide, doxorubicin HCl, droperidol, fluorouracil, heparin sodium, leucovorin calcium, methotrexate sodium, metoclopramide HCl, mitomycin, and vinblastine sulfate.

Vincristine sulfate is reportedly physically incompatible with furosemide. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

**Dosage Forms/Regulatory Status**

***Veterinary-Labeled Products: None.***

***Human-Labeled Products:***

Vincristine Sulfate Injection: 1 mg/mL in 1 mL, 2 mL & 5 mL vials and flip-top vials; Vincasar® PFS, generic; (Rx)

**Revisions/References**

*Monograph revised/updated August 2014.*


