drug information perspectives
Volume 26 (3), 2006

Contents

VERTEPORFIN

TRADE NAME: Visudyne

CLASSIFICATION: Photosensitizer (second generation); photodynamic therapy

ACTION
A light-activated dye derived from porphyrin. Acts by photochemistry. When activated by light, in the eye it temporarily occludes new and older choriocapillaries, with usually minimal damage to other structures including retinal vessels, photoreceptors and optic nerve. Red laser light at a wavelength of 689nm provides maximum absorption by the drug but is not strong enough to create thermal (photocoagulation) damage. When activated by laser light directed at the eye lesion, it generates singlet oxygen and possibly oxygen free radicals that damage vascular endothelium, initially breaking down vascular barriers and leading to enhanced leakage, then slowly leading to temporary vascular occlusion and nonperfusion. Theoretically selective for new vessels in the eye area where the light is directed, because verteporfin forms a complex with LDL, which binds to LDL receptors in endothelium, and growing vessels such as choroidal neovascularization (CNV) have a high concentration of LDL receptors. However, while there are minimal effects on nearby retina and choroid, it may not spare physiological choroidal capillaries, depending on the dose of light. Has caused reversible damage to the retinal pigment epithelium and outer retina in animals. Triggers platelet binding and aggregation at the site of damage, leading to thrombosis and vasoconstriction. Release of inflammatory cytokines may also be involved. Angiogenic: induces vascular endothelial growth factor (VEGF) in endothelial cells in the choriocapillaries. In tumors, it is considered to be selectively taken up by tumor neovascular endothelium, inducing thrombus occlusion and obliterating the blood supply to the tumor.

PHARMACOKINETICS
- ***Half-life***: 5-6 hours.
- ***Absorption***: Administered intravenously as a liposomal preparation that enhances distribution to provide high

concentrations in neovasculature and tumors, and better photosensitization.
- ***Distribution***: Transported by lipoproteins, primarily low-density lipoprotein (LDL), through the blood stream. Primarily taken up by cells with high levels of LDL receptors, including neovascular endothelial cells and tumor cells. Rapidly accumulates in the vessels of choroid, retinal pigment epithelium and photoreceptors in rabbits; does not accumulate in cornea, lens or vitreous body. Distributes throughout the body, especially to liver and spleen.
- ***Metabolism***: A small amount is metabolized to a less active form by liver and plasma esterases. P450 enzymes are not involved.
- ***Elimination***: Biliary elimination into feces. Renal elimination 0.004%. Skin exposure to ambient indoor light helps to inactivate the drug through photobleaching.
- ***Special populations***: Hepatic impairment: Half-life slightly prolonged (20%) and AUC tends to increase in mild impairment. Elderly over age 65: levels increase 20-40%; not considered clinically significant.

USES AND EFFICACY
Uses: Treatment of predominantly classic subfoveal choroidal neovascularization (CNV) of the eye due to ***exudative (wet) age-related macular degeneration, pathologic myopia, or presumed Histoplasmosis***.

Major clinical trials
TAP (Treatment of Age-related macular degeneration with Photodynamic therapy, 1999): Patients with subfoveal choroidal neovasvularization (CNV) secondary to exudative age-related macular degeneration were randomized to treatment with verteporfin or placebo, given every 3 months unless no leakage was detected (n=609, mean age 75). At baseline, 90% of patients had evidence of classic CNV, 76% also had occult CNV, and visual acuity was 20/40-20/200, mean 20/80-2; the lesions had greatest linear dimensions of 5400 micrometres or less. After 3 months and 12 months, patients given verteporfin were more likely to benefit (no change, mild decreases or increases in visual acuity in 61.2% vs. placebo 46.3% at 12 months, absolute difference 15%). This visual acuity benefit was greatest if the lesion area was at least 50% classic CNV (67% vs. placebo 39%), especially if there was no occult CNV (77% vs. placebo 27%). Improvement in visual acuity was mild and rare (16.4% vs. placebo 7.2%). Loss of contrast sensitivity and lesion area increases were less with verteporfin in all patients. After 2 years, results were similar; more patients given verteporfin had mild or no visual acuity loss (53% vs. placebo 38%), contact sensitivity was better, and there was less lesion progression. However, after 2 years 70% of patients given verteporfin had some vision loss compared with 77% given placebo. In patients with minimally classic CNV, verteporfin did not improve visual acuity although there was a benefit in contrast sensitivity and angiographic progression. Patients with smaller lesions and worse visual acuity at baseline did better. For contrast sensitivity, the best response was in younger patients with mainly classic CNV. Study limitations: Major benefit was derived from subgroup analysis and is therefore uncertain. The primary outcome measure of response includes patients who had mild vision loss, which may not coincide with a patient's idea of stabilization.

VIP (Verteporfin In Photodynamic Therapy): Age-related macular degeneration arm: A randomized, placebo-controlled trial studied patients with exudative age-related macular degeneration classified as occult with no classic subfoveal CNV, or early classic subfoveal CNV with good visual acuity. There was no statistically significant benefit at 12 months, but for those with only occult lesions there was a significant absolute risk reduction of 13% in visual acuity after 2 years of verteporfin treatment (45% avoided moderate-severe vision loss vs. placebo 32%). Over 2 years, some vision loss occurred in 72% of patients given verteporfin and in 80% of patients given placebo. Patients treated with verteporfin were less likely to develop classic CNV and had better contrast sensitivity. Small lesions and lower visual acuity at baseline were associated with better outcomes. Pathologic myopia arm: A similar study in patients with subfoveal CNV secondary to pathologic myopia was conducted in 120 patients (80% had predominantly classic lesions). Statistically significant benefit was seen at one- and two-year follow-up. At the end of two years, visual acuity improved in 39% of patients treated with verteporfin (vs. placebo 13%), stabilized in 15% (vs. placebo 31%), and decreased in 46% (vs. placebo 57%). Subretinal or intraretinal hemorrhage occurred in similar rates (7% with verteporfin vs. 5% with placebo).

VIM (Visudyne in Minimally Classic CNV) 2005: 117 patients with subfoveal minimally classic CNV secondary to exudative age-related macular degeneration, with lesion size maximum 6 MPS, were randomly assigned to treatment with verteporfin and light therapy at either 25 or 50 J/cm2, repeated every 3 months if needed. After 1 year, response (defined as avoidance of moderate-severe vision loss) was seen in 86% with the lower laser dose and 72% of patients given the higher laser light dose, compared with 53% of placebo-treated patients. After 2 years, response rates were 74%, 47%, and 38%, respectively. The difference from placebo was only statistically significant for the lower light regimen. Median visual acuity effects favoured the lower light treatment but were only significant at 12

months. Patients treated with verteporfin were less likely to progress to classic CNV. Investigators concluded verteporfin therapy is useful in patients with small lesions of this type. Study limitations: Small study size.

Clinical course: In subfoveal CNV, benefit is immediate after one treatment. After one week, CNV occlusion is most pronounced and most leakage is stopped. Leakage recurs in half of patients within 4 weeks and in most patients within 12 weeks of the first treatment, hence patients are reassessed every 3 months. Superiority to placebo treatment is apparent at the first 3-month reassessment in clinical trials. With time, fewer treatments are given: average 3.6 in the first year, 2.4 in the second year.

Place in therapy
Exudative age-related macular degeneration: In exudative age-related macular degeneration, this therapy reduces the risk of moderate and severe vision loss. Absolute response difference over placebo for avoiding moderate and severe visual acuity loss: if mainly classic CNV with no occult lesions, after one year 50% do better than placebo (NNT=2); if mainly classic CNV, 28% do better after 1 and 2 years (NNT=3.6). Overall, this treatment is better than previous therapies for subfoveal CNV and better than no therapy, but it rarely improves vision and most patients have a progressive decline in vision. Most patients will not retain the ability to read and drive. It is not as effective alone as newer therapies, e.g. ranibizumab (not available in Canada) or bevacizumab (off-label intravitreal injection), but it is effective and its use should be retained in the treatment of macular disease. Current evidence indicates that it may be helpful in patients with mainly classic subfoveal CNV, especially classic with no occult lesions, smaller lesions and better baseline visual acuity. Evidence is suggestive but less strong to support use in (1) minimally classic small subfoveal CNV lesions, and (2) occult subfoveal CNV with no evidence of classic CNV especially with small lesions or poor baseline visual acuity. Some experts would treat juxtafoveal lesions if close to the fovea because it may be useful in juxta/extrafoveal lesions although foveal spread can still occur. It is not used in nonexudutive (dry) disease.
For pathologic myopia, it is effective in patients with subfoveal and juxtafoveal lesions especially in younger adults or those with better initial visual acuity. In pathologic myopia, vision may improve or stabilize (absolute response difference is 10% for the rate of visual acuity improvement or no change, verteporfin 54% vs. placebo 44% at two years, NNT=10).
In presumed ocular Histoplasmosis, an open study found improved vision in 56%, no change in 28%, and decreased vision in 16% of patients after 2 years.

Advantages
- No thermal damage (laser photocoagulation causes immediate and irreversible vision loss due to local thermal damage, there is recurrence in 50% of patients, and it is not used for subfoveal CNV; more patients are candidates for verteporfin).
- May be used in patients with subfoveal CNV leakage after other therapies, e.g. external beam radiotherapy, focal laser photocoagulation.
- The procedure is painless and minimally invasive and usually well tolerated.

Disadvantages
- Approval for use in Canada is limited to predominantly classic subfoveal lesions, which means that only 40% of patients with age-related macular degeneration are eligible.
- Many off-label uses, difficult classification of lesions, and strong patient demand for treatment complicate therapy.
- There is a poorer response in patients with exudative age-related macular degeneration who are over age 75, have dark eyes, larger lesions, better baseline visual acuity, or have occult lesions.
- Sudden severe vision loss may occur.
- Age-related macular degeneration is not cured by this drug; CNV can progress.
- Most patients with age-related macular degeneration do not have any improvement in vision, new vessels form, and their vision continues to decline.
- Benefit in exudative age-related macular degeneration is small: after two years, 70-72% of patients have vision loss compared with 77%-80% of placebo-treated patients.
- Variable, unpredictable response.
- Avoidance of light after therapy may be difficult for isolated elderly patients.

Investigational/Unapproved Uses:
- **Angioid streaks**: Some cases of benefit for subfoveal or juxtafoveal CNV, but it has not been shown to prevent progression of juxtafoveal to subfoveal CNV. Longer term followup in an open study of 24 eyes with subfoveal or

juxtafoveal CNV found it ineffective, with decreased visual acuity in 90%.
- **Basal cell carcinoma**: Good response in some patients.
- **Central serous chorioretinopathy (CSC):** Promising case reports of rapid resolution of subretinal fluid, improved or stabilized vision, resolution of retinal detachment with good long-term outcomes. In one series of 26 eyes with subfoveal CNV, roughly 50% had improved vision, 40% were stable, and 10% were worse at 2 years.
- **Children**: Small numbers of pediatric patients with idiopathic CNV or CNV due to Histoplasmosis or other causes have been treated with the standard regimen with some visual improvement. RPE atrophy was noted in 4/5 children in one series; although this did not impair vision, the long-term consequences are unknown.
- **Chorioretinal anastamoses in AMD**: May stabilize vision.
- **Choroidal hemangioma**: In circumscribed choroidal hemangioma, partial or complete regression of hemangiomas, resolved edema, and commonly improved vision, stabilization or less commonly worse vision, and no recurrences have been reported. Some experts recommend it as first-line treatment, based on indications that visual acuity is improved in 73-100%, stable in 2-21%, and decreases in 5-12%. In the diffuse type or Sturge-Weber syndrome, the size of the hemangioma has decreased and vision has improved in a few cases.
- **Choroidal metastasis**: Tumor regression and improved visual acuity were reported in one case.
- **Choroidal nevus**: Varied results in a few cases with subfoveal or juxtafoveal CNV.
- **Choroidal osteoma**: Successful in 1 case with extrafoveal CNV.
- **Combination with intravitreal triamcinolone**: Intravitreal triamcinolone, either alone in randomized controlled trials or combined with verteporfin in nonrandomized controlled trials, has produced mixed results. Overall, there is a suggestion that the combination may be more likely to stabilize vision than verteporfin alone in exudative age-related macular degeneration, but large randomized trials are needed. There have been many case reports of improved visual acuity. Increased intraocular pressure and cataract progression are common, in rare cases requiring surgery. Infectious ophthalmitis has occurred rarely.
- **Idiopathic CNV, subfoveal**: Many cases of improved vision.
- **Melanoma**: In four cases of choroidal melanoma, one decreased in size and then regrew, one stabilized, and two progressed.
- **Multifocal choroiditis and panuveitis**: Subfoveal CNV may stabilize. In 7 cases with juxtafoveal CNV followed for 2 years, visual acuity improved in 43%, there was no change in 43%, and it worsened in 14%.
- **Papillary capillary hemangioma**: In 5 cases on the optic nerve, tumors regressed and macular exudate resolved, but 3/5 had vision decline, and complications occurred: retinal vessel occlusion, ischemia of optic nerve, and vaso-occlusion of retina and optic nerve. Investigators' conclusion: anatomic benefit, mixed functional benefit, and discouraging complications.
- **Polypoidal choroidal vasculopathy**: Promising for subfoveal CNV and possibly extrafoveal CNV. In 16 subfoveal cases: 56% improved, 30% were stable. In 22 cases of the macular type with macular exudates or hemorrhage, visual acuity improved in 59%, stabilized in 36%, and was worse in 5%; 91% had resolution of fluid, exudates and hemorrhages and regression of polypoidal vessels.
- **Punctate inner choroidopathy (PIC):** There have been cases of decreased leakage and improved vision.
- **Radiation retinopathy**: Some good results for macular edema.
- **Retinal capillary hemangioma**: Some success in individual cases.
- **Rubella retinopathy**: Improved vision in one case with subfoveal CNV.
- **Sorsby's fundus dystrophy**: Improved vision in one case after repeated treatments.
- **Squamous cell cancer of the conjunctiva**: In case reports, 2 had short-term complete regression, one partial regression.
- **Telangiectasis**: May stabilize vision in type 2A retinal juxtafoveal retinal telangiectasis.
- **Vitelliform lesions**: In 8 cases, 4 remained stable, and 4 had severe vision loss; not considered useful.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity**
- **Porphyria** (skin photosensitivity may increase)
- **Severe liver impairment** (no data)
- **Retinal pigment epithelium tear or large retinal pigment epithelium detachment** (to avoid vision loss or the risk of a tear).
- **History of acute severe decrease in visual acuity after verteporfin**: Do not retreat until vision has returned to pretreatment levels and the risk-benefit ratio has been reassessed. Most patients have not been retreated, one retreated patient experienced a second similar reaction, and a few patients have tolerated retreatment.
- For use only by physicians trained in photodynamic therapy.

- Compatible lasers must be used (undertreatment or overtreatment with tissue damage could occur)

Precautions

- *Light sensitivity*: Warn patients to avoid exposing uncovered skin or eyes to direct sunlight or strong indoor light for at least 48 hours after treatment (severe sun damage may occur). Strong light includes tanning salons, strong lights in medical offices, bright halogen lights, and light-emitting pulse oximeters. If patients must go outdoors within 48 hours, they must cover all areas of skin with clothing and their eyes with dark glasses. Sunscreen is not effective protection. However, patients should not remain in the dark, since exposure to ambient indoor light will speed inactivation of the drug. If extravasation occurs, protect the area from light until any swelling and colour changes have resolved (severe skin damage can occur). If surgery is needed within 48 hours, protect internal tissues from intense light.
- *Extravasation hazard:* Avoid extravasation: administer in the largest vein possible, ideally the antecubital vein, in elderly patients (smaller veins in the back of the hand may be fragile). If extravasation occurs, immediately stop the infusion and apply cold compresses, keeping the area out of direct sunlight and strong light until any reaction or skin discolouration has resolved.
- *Moderate hepatic impairment*: caution (no data)
- *General anesthesia*: caution (severe hemodynamic effects including death have occurred due to complement activation in anesthetized pigs). No problems reported in limited human data.
- *Vision loss after treatment*: decreased vision within a few weeks may be due to a transient disturbance in vision or new CNV bleeding. Evaluation and fluorescein angiography may be required.
- Report any unexpected or serious reactions to Health Canada's adverse reaction monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789).

PREGNANCY AND LACTATION

In rats, exposure to 40 times the human exposure increased the incidence of anopthalmia or microphthalmia in the offspring. Limited human data. In one case report, a woman was treated once with verteporfin when the fetus was in the third week of gestation; she delivered a normal infant. Despite this good outcome, the clinicians advise caution since the baby was not exposed during the most sensitive period for eye development, the 6th week of gestation. Consider risk versus benefit. Excreted into breast milk at up to 66% of maternal plasma levels. Wait at least 96 hours after treatment before breast-feeding.

SIDE EFFECTS

Frequency of occurrence is given in brackets.

Cardiovascular: Vasovagal reactions, chest pain (may be severe). Atrial fibrillation, hypertension (1-10% of patients). Vasovagal reaction with cardiac arrest (1 case). Dizziness.
CNS: Headache, syncope.
Dermatologic: Extravasation-related pain, swelling, discolouration (10-30%; protect area from light until healed). Photosensitivity (3%, usually mild-moderate, usually within 24 hours but may occur after 0-3 days, sunburn, itch or rash, usually occurs if exposed to sunlight or strong light within 48 hours or after extravasation; if excessive dose is given, the sensitive period is longer). Pruritus (rare).
Gastrointestinal: Nausea (1-10% of patients). Ulcerative colitis, melena (cases).
Hematologic: Anemia, leukopenia (1-10%).
Hypersensitivity: Urticarial rash to fluorescein dye. Anaphylactoid reaction (case).
Neuromuscular: Paresthesia, hypoesthesia (2%).
Ocular: Visual disturbances (42% vs. placebo 23%: blurred vision, visual field defects, decreased visual acuity, flashing lights, grey or dark halos, black spots, scotoma; usually resolve in days to weeks, mild-moderate, may occur at first treatment or any subsequent treatment, may be due to transient subretinal fluid accumulation and increased retinal thickness). Blepharitis, cataracts, conjunctivitis, itch (1-10% of patients). Acute severe vision decrease within 7-15 days of therapy (4% of patients, more common if good baseline visual acuity, some patients have partial or complete recovery; may be due to subretinal fluid, subretinal hemorrhage, retinal detachment, retinal pigment epithelium tear, retinal capillary nonperfusion, retinal depigmentation, a greenish lesion, or unknown causes; may occur on first treatment and rarely later in therapy; retinal pigment tears may cause severe permanent vision loss). Extensive retinal hemorrhage (2%, may occur within 48 hours, may cause irreversible vision loss). Retinal damage (collateral damage); retinal detachment; retinal tear, RPE atrophy, retinal or choroidal nonperfusion, choroidal infarct (rare). Extensive submacular hemorrhage (delayed, may detect at 3 month examination, may affect vision).

Excessive laser light leads to retinal ischemia and vision loss. Nonarteritic anterior ischemic optic neuropathy (case).Visual hallucinations (5%, onset 2 days to 1 month). Transient angiographic hypofluorescence after treatment (related to occlusion of choriocapillaries and swelling of retinal pigment epithelium; ischemia leads to angiogenesis and neovascularization).
Other: Back pain during infusion (8%; diphenhydramine prior to treatment may prevent this; slowing the infusion rate to administer over 12 minutes and still administering laser light at 15 minutes after start of therapy may reduce back pain; associated with a temporary drop in circulating neutrophils). Other pain in chest, leg, groin, buttocks, or arm during infusion (5%, usually not accompanied by flushing, sweating, rash or dyspnea, resolves at end of infusion, standing up may help). Reaction involving chest pain, right-sided pain, back pain, flushing, dyspnea, transient increase and decrease in blood pressure, syncope (<1%, dose-dependent, may be due to complement activation). Fever, nausea, dyspnea, flushing, flu syndrome during the infusion. Increased liver transaminases. Cardiopulmonary arrest and seizure (1 case). Pancreatitis (1 fatal case).

INTERACTIONS

DRUG	EFFECT	MECHANISM	IMPORTANCE
Anticoagulants	Decreased verteporfin effect	Antagonism	Caution (theoretical)
Antiplatelet drugs	Decreased verteporfin effect	Antagonism	Caution (theoretical)
Calcium channel blockers	Increased verteporfin effect	Increased uptake by vascular endothelium	Caution (theoretical)
Photosensitizing drugs*	Increased photosensitivity	Additive	Caution (theoretical)
Polymyxin B	Increased verteporfin effect	Increased uptake by vascular endothelium	Caution (theoretical)

*Photosensitizing drugs include: Sulfonamides, sulfonylureas, thiazide diuretics, griseofulvin, phenothiazines, tetracyclines.

PARENTERAL ADMINISTRATION
Intravenous: Reconstitute powder with 7mL Sterile Water for Injection ONLY, giving a solution of 2mg/mL. Reconstituted opaque dark green solution must be protected from light, stored at room temperature, and used within 4 hours. Withdraw the prescribed dose and dilute with D5W to a total final volume of 30mL. This diluted solution should be used immediately and no later than 4 hours after dilution. Give as an IV infusion over 10 minutes at a rate of 3mL/minute using an inline filter. Protect the solution from light during infusion.

DOSAGE

Adult:
Intravenous: 6mg/meter squared body surface area as a 10 minute IV infusion. Fifteen minutes after the start of the 10-minute infusion, 689 nm wavelength light from a nonthermal diode laser is delivered to the retina over 83 seconds. For first time patients, it is safer to treat only one eye, observe for a week, then treat the second eye if needed if the first treatment was tolerated. If both eyes are being treated concurrently, treat the most aggressive lesion first. Immediately after light delivery is finished for the first eye, begin light delivery to the second eye, not more than 20 minutes after the start of the drug infusion. Eyes are evaluated at three month intervals and treatment is repeated if there is leakage from the choroidal neovascularization. Retreatment might be considered before three months if there is vision loss and enlargement of the lesion. Therapy is stopped when there is no further evidence of CNV leakage.

Renal impairment: No dosage adjustment.

Hepatic impairment: No dosage adjustment in mild impairment. No data available in moderate or severe impairment.

NURSING IMPLICATIONS
This drug can cause sensitivity to light, resulting in severe sunburn or eye damage. While administering it, wear gloves and eye protection and avoid skin and eye exposure to the solution. If you are accidentally exposed to the drug, protect yourself from light for 48 hours to avoid sunburn. (see PATIENT INSTRUCTIONS). Wipe up any spills with a damp cloth.

Avoid extravasation during the infusion. See PRECAUTIONS. Carefully observe the patient during the infusion, since serious hypersensitivity reactions can occur: difficulty breathing, flushing, syncope, chest pain.

Carefully instruct the patient on the need to avoid strong light for 48 hours after each treatment (see PATIENT INSTRUCTIONS). If needed, provide protective clothing, dark glasses and a hat for the patient to wear while returning home after treatment. Ensure that the patient fully understands the instructions, and provide written instructions in large size lettering. The patient will require transportation after each treatment and must not drive.

Store at room temperature.

PATIENT INSTRUCTIONS
Verteporfin (ver-te-POR-fin) is most commonly used to stabilize vision in patients with age-related macular degeneration of the wet (exudative) type. It is effective in other eye conditions as well.

Immediately after each treatment, you will be sensitive to light. For the 48 hours after each treatment, avoid exposing your skin or eyes to sunlight or strong indoor light, including tanning salons, strong lights in dental offices, and halogen lights. Wear a wrist band that reminds you of this and tells others in case of accident. If you must go outside in the 48 hours after treatment, all skin should be covered with protective clothing and dark glasses should be worn. Sunscreen lotions do not provide any effective protection. However, do not remain in darkness; use ambient indoor light to help inactivate the drug.

In the week or so after a treatment, your vision may be blurry, or slightly lessened, or you may have gaps in your vision. This is not uncommon and is usually temporary. If your vision is decreased, avoid driving or operating dangerous machinery.

However, if you notice a strong decrease in your vision in the week or so after a treatment, contact your physician immediately.

If you have experienced any unexpected or serious reactions to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number. Also ensure that your physicians are informed and record all reactions for the future.

PRESENTATION:
Powder for intravenous solution: 15mg/7.5 mL vial.

References are available on request.