OCULAR ISSUES: THE INVISIBLE AND THE INVASIVE INSULT

Ocular disease or injury can be among the most difficult conditions to treat because of the risk of vision loss, the disfigurement that often accompanies the initiating insult, and the corrective surgery that may be required to resolve the presenting ocular disease. In this article, Dr Aine Seavers MVB MRCVS, highlights two evolving topical therapies that can replace the need for mutilative ocular surgeries, while still addressing the primary insult and protecting both vision and appearance. The article also emphasises the importance of ocular safety both for the vet patient and vet team to prevent complacency when utilising new technologies, such as laser surgery or laser/photobiomodulation (PBM) medical therapy in our workplace

A. Utilisiing laser/photobiomodulation technology: be alert, not alarmed

Medical photobiomodulation (PBM) laser therapy machines, when used correctly, are some of the safest devices one can apply to a veterinary patient. Unfortunately, that high level of safety can induce complacency around the use of these machines, especially because many of the therapeutic wavelengths in operation are not visible to the human eye. Lasers below the visible spectrum are especially dangerous because the eye does not have a natural aversion at these wavelengths. We do not blink fast enough to stop the damage from the beam.

Light entering the eye from a collimated beam in the retinal hazard zone area is concentrated by a factor of 100,000 times when it strikes the retina, so even a low-power beam is a concern.

A medical laser beam hit can be 120 times hotter than 12W direct sun viewing.

Hazards

On the electromagnetic spectrum, the greatest ocular hazards are:

- the 400-1,400nm wavelengths, which can damage the retina;
- near-UV region and near-IR, at certain wavelengths, the lens may be damaged;
- at far-UV and far-IR regions of the spectrum, the cornea will absorb the laser energy and be damaged.

Therefore, where the adherence to laser/PBM safety guidelines is substandard, there remains a constant concern of the risk of catastrophic ocular damage to any patient or staff inside the nominal ocular hazard zone (NOHZ). The good news is that it is relatively simple and cheap to maintain an appropriate level of safety in any and all veterinary laser/PBM workplace scenarios.

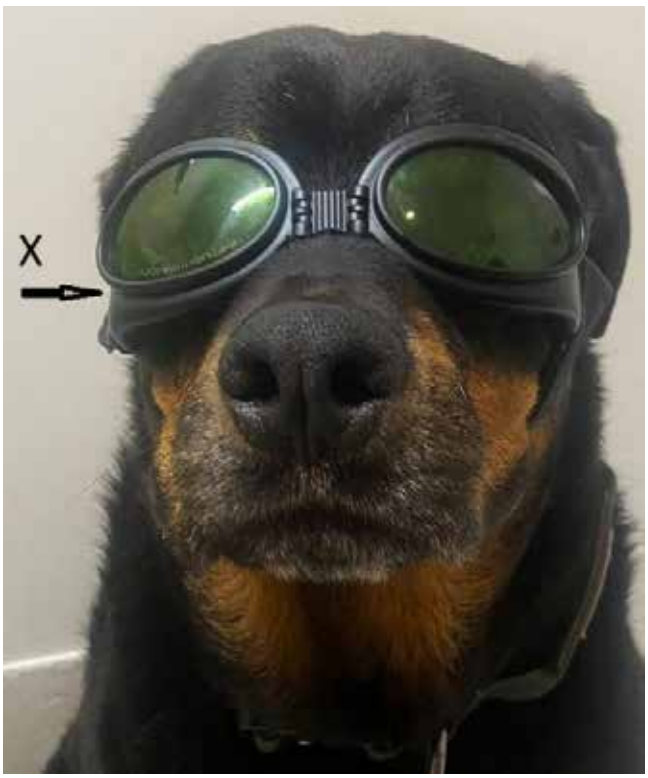

Figure 1: Incorrect placement of safety goggles.

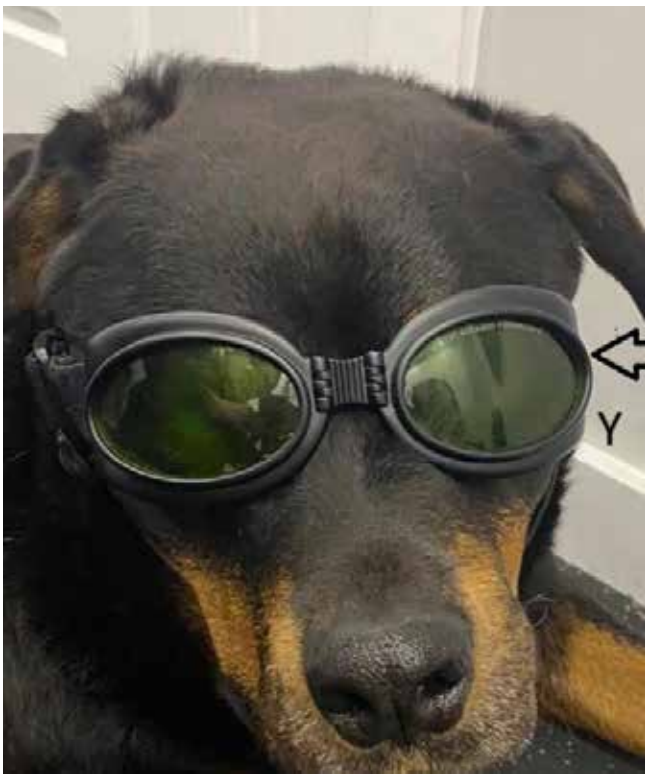

Figure 2: Correct placement of safety goggles.

Figure 3. Squamous cell carcinoma. Photograph courtesy of Dr Stephen Metcalf.

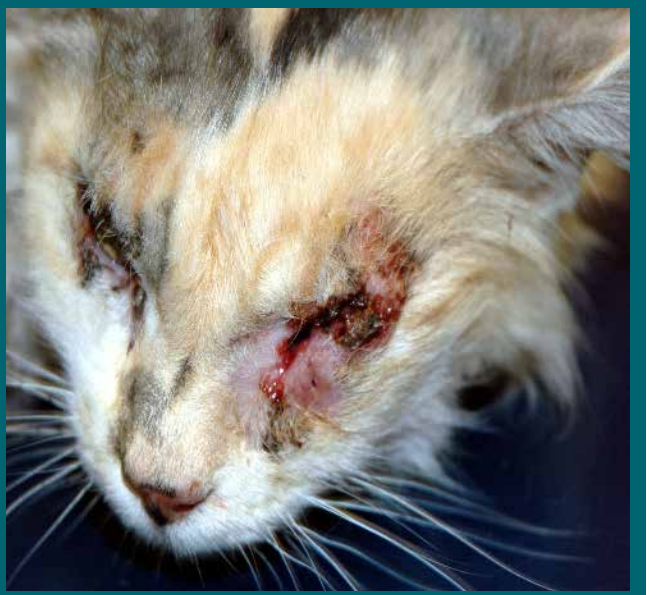

Figure 4. Squamous cell carcinoma. Photograph courtesy of Professor W.H. Miller.

A. Blood is deep to the epidermis so colouration is less intense than with a haemangiosarcoma.
B. Early/superficial squamous cell carcinoma shows some thickening of the epidermis and epidermal crusting, later lesions thicker and can be ulcerated or eroded.
C. Squamous cell carcinoma tends to be pruritic.

Shielding

The first and foremost priority is the use of ocular shielding devices for the therapist and the pet. Too many images abound on social media wherein the veterinary laser/PBM patient is without protective safety googles and hence left at an increased risk of ocular injury. The 'I'm not bothered' attitude about the pet wearing proper eye protection in a laser session is simply not acceptable. This is a safety issue: no one gets to ignore the rules. Where a laser machine is in use, there are no situations where it is acceptable for the animal not to be wearing some form of protective eye shielding.

The pet should be fitted with certified animal laser safety glasses and all personnel in the room should also be wearing a set of laser safety glasses certified for humans.

Important points to note:

- All laser therapy safety glasses supplied are specific to the wavelength of the machine supplied. Your safety glasses must be marked with the exact wavelengths at which your therapy machine works, otherwise the glasses do not protect you.
- As stated above, all laser therapy safety glasses supplied are specific to the wavelength of the machine supplied. Therefore, all replacement laser therapy safety glasses must comply with these wavelengths, which are marked on the glasses.
- The abbreviation 'OD' stands for 'optical density' the capability to block most of the laser light. An OD >/= 6 is extreme blocking which is the rating of the human safety glasses with which most veterinary machines are supplied. While the OD range is 1-10, most medical therapy safety glasses stop at OD6; therapists cannot see properly in the darkness of OD7 and beyond. Beware of human safety glasses marked as the correct wavelengths but with an OD < 6.
- The OD for dog safety glasses usually ranges from OD4+ to OD5+. Any darker and the dogs start to reject the glasses.
- The glasses are there to protect from inadvertent accidental transient exposure to the laser. The glasses do not protect against a laser beam being shone directly and persistently at the eye.

Tip

All laser glasses will have the safety numbers printed on the top edge of the glass lens. This is a handy way to know how to put the safety glasses on the correct way up on the pet (see Figures 1 and 2).

B. Chemotherapeutic options for the neoplastic invader: safer selection of topical agents

Globe and eyelid tumours, and the surgeries to address those lesions, are most often vision-impairing and disfiguring.

The patient cohort most at risk is the elderly patient, which brings an additional set of concerns in relation to the impact that surgery may have on the recovery of such patients. Many owners decline enucleation or partial resections and simply allow the tumour to take its course.

Often owners of elderly animals will decline even the most basic harvesting of diagnostic samples. This forces the veterinarian to rely on pattern recognition[1] to elucidate an identification of tumour type. The two instances shown in Figures 3 to 6 are examples of a squamous cell carcinoma and a haemangiosarcoma that veterinary practitioners may find a useful visual guide to some of the pattern differences in the clinical presentation of these lesions.

However, we no longer need to resort to neglect or surgery to offer effective and life-extending treatments to these ocular presentations. There is now sufficient peer-reviewed

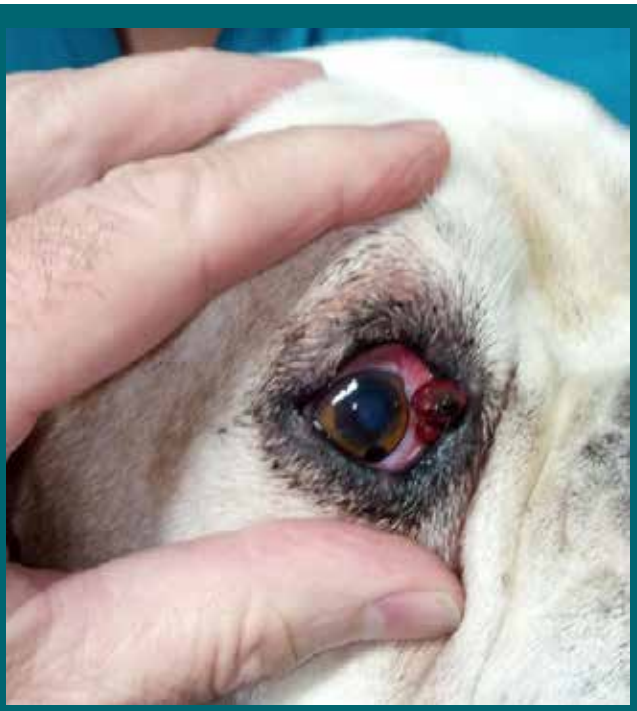

Figure 5: Haemangiosarcoma.

Figure 6: Haemangiosarcoma.

A. Pattern recognition: intense deep red, focal lesion, located in the poorly-pigmented leading edge of the nictitating membrane.
B. Usually elderly dog, high ultraviolet-light exposed, outdoor-living, lightly-pigmented, often in a giant breed dog.
C. Not pruritic but pet may rub the eye due to annoyance at a foreign object in its vision.

evidence[2] to indicate that some topical chemotherapeutic agents such as Mitomycin C can be used pre-surgery, wherein the tumour may:

i. completely remit, rendering the need for surgery obsolete; or,
ii. be so cytoreduced pre-surgery as to make any subsequent surgery less invasive.

Mitomycin C

The use of a safer topical agent like Mitomycin C post-surgery for squamous cell carcinoma or haemangiosarcoma also has a dramatic positive effect on remission rates without having severe adverse systemic effects on the patients. Topical Mitomycin C is used routinely in human corneal surgery or post trabulectomy,[3-5] and as an adjunct therapy to treat squamous cell carcinoma in cats,[6] dogs[7,8] and vascular tumour in horses.[9]

The Mitomycins, produced from the fermentation process of the microorganism Streptomyces, are a family of natural products that includes Mitomycin A, B and C. Mitomycin C was the first recognised bio-reductive alkylating agent and has been widely used clinically for antitumour therapy.[10] Topical application of Mitomycin C drops in the somewhat self-contained ocular globe allows the drug to flow to the wider ocular tissues and fornices of the globe, addressing the need to treat an 'entire conjunctiva at risk' and any local metastatic concerns, with less dependence on defining tumour margins.[11]

Mitomycin C is activated by reduction which is important in its selectivity of its anti-tumour activity.[10,12,13] As activation is inhibited by an oxidising environment, Mitomycin C has selective toxicity for hypoxic tumours and potentially suppresses their growth.[10,12,13] Tumour hypoxia and an increased expression of bio-reductive enzymes in malignant cells create a selective environment for drug activation. This makes Mitomycin C an attractive agent for antitumour[13] therapy, including potentially haemangiosarcoma specifically, because haemangiosarcoma express factors induced by hypoxia such as VEGF and HIF-1.[14]

Mitomycin C therapy provides a simple, affordable, well-tolerated therapy that can:

- resolve the primary complaint;
- preserve vision and function;
- preserve cosmetic appearance;
- avoid major collateral patient ill-effects; and,
- extend both the quality and quantity of life for advanced-age patients.

In human medicine, because of reports of suspected dose and frequency-related ocular side-effects of erythema, chemosis, and itch, Mitomycin C is currently recommended at as minimal a dose and frequency as possible.

A seven-day-breach vial applied four times daily for seven days in an alternate week protocol has been used[2] to: minimise the risk of adverse reactions in the patient; improve compliance; decrease client financial outlay; and reduce exposure of both patient and client to a cytotoxic agent.

Low doses are extremely effective, and hence, despite the potential for systemic toxicity of Mitomycin C in the dog, per os doses up to 4mg/kg have been shown to have little effect, as the alkylating Mitomycin C is neutralised by acid[15] thus inactivating any inadvertent ingestion of Mitomycin C.

Fluorouracil

The same safety profile in dogs and cats cannot be said to apply to the topical chemotherapy agent Fluorouracil, also called '5-FU' or '5-Fluorouracil.'

5-FU works. It has been used for many years with great success in human oncology patients. The problem now is, because of that popularity, 5-FU has become scarily accessible (illegally) online, often in bulk containers, to laypersons who do not have any true understanding of what they are dealing with. That popularity places many pets, not just those with neoplasia, at risk of accidental exposure and poisoning by naïve owners. The issue is so concerning in the USA that the FDA has issued a broad alert to vets and pet owners to be aware of the catastrophic effects that can occur in cats and dogs within 30 minutes of either transcutaneous or oral exposure to this product.

Signs of 5-FU poisoning in pets can start within 30 minutes, and include: vomiting, shaking, seizures, difficulty breathing, and diarrhoea. Death can happen in as little as six to 12 hours after a pet is exposed to 5-FU. 5-FU is also used in horses for certain tumours but the systemic toxicity dose is mitigated by the body size and ensuring the horse doesn't lick the product.

Sadly, many owners, unaware of this risk, are themselves being treated with or self-treating with 5-FU and, inadvertently, passively transferring the ointment onto their pets or allowing their pets to lick the treated area. Equally, some owners are asking vets to use this product on their pet due to the good response in humans, with neither the vet nor the owner realising the tiny margin of safety in which this product could be used. **Veterinarians thus need to make themselves aware of the signs of 5-FU poisoning in companion animals and be alert to asking owners about personal or shared use of their medication with their pet.**

Conclusion

It goes without saying that no chemotherapeutic agent is completely 'clean' or risk-free. However, when it comes to our veterinary patients, my personal preference is encouraging consideration of selecting Mitomycin C rather than 5-FU. I would encourage veterinary practitioners to download papers, referenced at 1, 6, 7, 8, and 9 below, on the use of Mitomycin C in the veterinary patient; note and record the different protocols and doses used in each case in order to provide yourself with a reference guide for a variety of patients and lesions that may present to you for treatment.

References available on request

READER QUESTIONS AND ANSWERS

1. WHICH OF THE FOLLOWING STATEMENTS IS TRUE?

A. Lasers below the visible spectrum are very safe because the eye does not have a natural aversion at these wavelengths
B. Mammals blink fast enough to stop the damage from the laser beam
C. Light, entering the eye from a collimated beam in the retinal hazard zone area, is concentrated by a factor of 100,000 times when it strikes the retina, *so even a low-power beam is a concern*
D. A medical laser beam hit can be cooler than a 12 W direct sun viewing

2. LASER THERAPY SAFETY GLASSES SUPPLIED SHOULD:

A. Be specific to the wavelength of the machine supplied
B. Have the wavelengths marked on the glasses themselves at the top of the lens
C. Provide protection from inadvertent accidental transient exposure to the laser
D. When replaced, be replaced with safety glasses that comply with the wavelengths of the machine supplied
E. All of the above

3. WHICH STATEMENT IS TRUE IN RELATION TO FLUOROURACIL?

A. High safety margin in dogs and cats
B. Death may occur within six to 12 hours of exposure
C. Exposure via skin contact or oral ingestion is not toxic to the veterinary patient
D. Poisoning signs appear several days post exposure

4. WHICH STATEMENT IS TRUE IN RELATION TO MITOMYCIN C?

A. Mitomycin C was the first recognized bio-reductive alkylating agent and has been widely used clinically for antitumour therapy
B. Topical application of Mitomycin C drops in the somewhat self-contained ocular globe allow the drug to flow to the wider ocular tissues and fornices of the globe addressing the need to treat an 'entire conjunctiva at risk' and any local metastatic concerns, with less dependence on defining tumour margins
C. Topical Mitomycin C is used routinely in human corneal surgery and as an adjunct therapy to treat squamous cell carcinoma in cats and dogs, and vascular tumour in horses
D. Topical Mitomycin C now has indications for use in ocular haemangiosarcoma topically as the sole and primary use to treat these lesions or as a topical adjunct post-surgery
E. All of the above

5. PATTERN RECOGNITION FOR A HAEMANGIOSARCOMA WOULD BE:

A. Blood is not deep to the epidermis, so colouration is more intense than in squamous cell carcinoma
B. Favours the poorly-pigmented leading edge of the nictitating membrane
C. The patient is usually elderly, outdoor-living, lightly-pigmented
D. Not pruritic, but pet may rub the eye due to the annoyance of a foreign object in their vision
E. All of the above

6. ON THE ELECTROMAGNETIC SPECTRUM, THE GREATEST OCULAR HAZARDS FOR THE RETINA ARE:

A. The 400-1,400nm wavelengths
B. Near-UV region
C. Far-UV and far-IR regions of the spectrum
D. None of the above

ANSWERS: 1C; 2E; 3B; 4E; 5E; 6A.