

ANTIBIOTIC-IMPREGNATED POLYMETHYLMETHACRYLATE BEADS IN THE TREATMENT OF BUMBLEFOOT, OSTEOMYELITIS AND OTHER LOCALISED INFECTIONS IN BIRDS.

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ABSTRACT

Bumblefoot has historically and remains to be one of the most common and potentially serious afflictions of captive raptors. This paper describes a novel method of treatment using antibiotic-impregnated polymethylmethacrylate (AIPMMA) beads inserted at the site of infection, after surgical debridement of infected tissues. The method has, in the hands of the author, brought about a considerably improved response rate to this problematic and potentially serious disease (as first described Remple and Forbes 2000). The use of similar beads has previously been reported to be effective in the treatment of osteomyelitis in an eagle, the author discusses this and various other similar uses.

Introduction

Bumblefoot (more specifically referred to as raptor pododermatitis) is a common disease of large species of raptors maintained in captivity and tends to become chronic, progressive, invasive and eventually disabling (Halliwell 1975, Cooper 1978, Halliwell & Graham 1978, Riddle 1980, Sawyer 1983, Remple & Remple 1987, Oaks 1993, Remple & Al-Ashbal 1993, Harcourt-Brown 1996) in the absence of appropriate therapy. The condition most commonly affects falcons (long-wings), snowy owls (*Nyctea scandiaca*) and eagle owls (*Bubo bubo*), whilst short-wing hawks (members of the genus *Accipiter*), broad-wing hawks (members of the genus *Buteo*) and Harris hawks (*Parabuteo unicinctus*) are rarely affected. The condition is common in raptors maintained in captivity (wild-caught and captive-bred) but is rare in wild birds. The etiological agent most commonly isolated is *Staphylococcus aureus* (Cooper & Needham 1976, Riddle 1980, Sawyer 1983, Cooper 1987, Remple & Remple 1987, Oaks 1993, Remple & Al-Ashbal 1993); however, *Streptococcus* spp., *E. coli*, *Proteus* spp., *Pasteurella* spp., *Pseudomonas aeruginosa*, *Klebsiella* spp., *Clostridium* spp., *Corynebacterium* spp., *Nocardia* spp., *Actinobacillus* spp. and *Actinomyces* spp. have all been isolated (Remple & Remple 1987). Infection appears to be seeded by two routes: direct inoculation through puncture of the dermis and devitalisation of the epithelium (a barrier to infection) permitting microbial entry into underlying tissues (Remple 1993). Pressure necrosis compromises the immune status of the skin, reduces the vascular supply to the area and the swelling associated with the infection further reduces blood supply to the affected area (Griner 1983, Harcourt-Brown 1996). Such a reduction in blood supply is a key patho-aetiological factor in resolution failures experienced in many cases.

Remple and Al-Ashbal (1993) studied the pathophysiology of staphylococcal bumblefoot in falcons. In all cases studied the presence of perivascular cellular reactions was evident with some showing a perivascular inflammatory infiltrate, oedema, degeneration of collagen and a necrotising vasculitis. Non-necrotising epithelioid and multinucleated giant cell granulomata were often abundant in affected tissues. In all cases there was vascular luminal narrowing, representing endarteritic obliterative vascular changes. Such changes inevitably reduce cellular perfusion at the site of the lesion, and hence perpetuate the disease. The formation of a fibrin barrier, catalysed by coagulase, within three to five days of initial invasion of the pathogen (Cooper 1978) insulates the pathogen from phagocytosis and antimicrobial factors (Turk and

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Stamm 1970). The above factors all lead to a reduction in pedal blood supply within the affected foot. Consequently, immune factors as well as a delivery of systemic antibiotics within or above the pathogen's minimum inhibitory concentration are shielded from the pathogen, and the disease may progress or become quiescent for a period ranging from a few weeks to years (as is common for granulomatous disease) and then recur with a vengeance.

Treatment failure for bumblefoot is common. Previous regimes have been diverse and have included hypertonic foot baths and poultices, topical dimethylsulfoxide-antibiotic-corticosteroid application (Stefanatos 1974), radiation therapy (Bird & Lague 1975), immunomodulation and vaccination (Satterfield & O'Rourke 1980), surgery with secondary healing by granulation (Gandal 1969) and surgery with first intention healing (Cooper 1980, Riddle 1980, Remple & Remple 1987, Remple 1993). All procedures have met with varying degrees of success. Of the above regimes it is the authors' agreed opinion that surgery represents the treatment of choice for the majority of bumblefoot cases. Surgery debulks the antigen load and inflammatory debris and allows for vascular perfusion of debrided tissues with delivery of systemic antibiotics. Whether or not the disease resolves is essentially a race between sustained antibiotic delivery and the above mentioned pathological processes that would impair the delivery of antibiotic to infected tissues and intraleukocytic pathogen.

The use of AIPMMA beads, following aggressive surgical debridement, offers an alternative method for the delivery of antibiotics to an infected site (Klemm 1993). This technique has been used safely and efficaciously in birds for the treatment of cellulitis and osteomyelitis (Wheler et al 1996) and reptiles with osteomyelitis and septic arthritis (Divers 1999). By this method higher local concentrations of antibiotic can be achieved than with systemic administration without relying on vascular supply and soft tissue integrity (Marks et al 1976, Wahlig & Dingeldein 1980, Kanellakopoulou et al 1993, Evans & Nelson 1993, Tobias et al 1996). Ototoxic and nephrotoxic serum levels, and other undesirable side effects such as allergies and nausea, are avoided as minimal systemic uptake occurs (Chapman & Hadley 1976, Marks et al 1976, Wahlig et al 1980, Henry et al 1993, Klemm 1993). AIPMMA beads are easily made and may be sterilised with ethylene oxide or gamma irradiation (Flick et al 1987, Tobias et al 1996) – see below. AIPMMA beads, with a range of different antibiotics and antibiotic combinations, have been used in a number of cases of bumblefoot ranging in severity from Class II to Class IV, following the classification of Oaks & Remple (1993), in a range of raptor species, resulting in a marked improvement in long term resolution and cure rates (Remple and Forbes 2000).

Materials and Methods

A variety of heat-stable antimicrobials may be used in AIPMMA bead manufacture including gentamycin, amikacin, neomycin, lincomycin and clindamycin (Marks et al 1976, Wahlig & Dingeldein 1980). Heat labile antibiotics such as tetracyclines, chloramphenicol, polymixin B, erythromycin, bacitracin, fusidic acid, ceftazidime are not suitable, in view of the heat generated as the methylmethacrylate sets. Good preparation is essential prior to bead manufacture. Although some human AIPMMA beads are manufactured, these are generally too large for birds and other small species.

Required equipment

- Sterile mixing bowl (eg Petri dish) and spatula
- Sterile gloves and work surface
- Sterile syringes (20ml)
- PMMA bone cement polymer and liquid monomer
- Sterile antibiotic powder
- Scalpel blade and sterile containers

In the above list it is stressed that items need to be sterile. Some clinicians (Divers 1999) have suggested that if beads are kept sterile, then the beads can be stored and used directly as such. This author does not favour that option, but instead advises that all beads should be sterilised by irradiation or gas (not heat), following manufacture. If post manufacture sterilisation is to be used, then less hygiene care is required during manufacture.

1-2g of antibiotic powder is mixed with 40-60g (Marks et al 1976, Murray 1984) or 20g (Bennett 1999) of PMMA powder. Antibiotic combinations can be used in beads. Although it is preferable to harvest material pre operatively and gain bacterial culture and sensitivity results, such material can be notoriously difficult to culture from, and repeated surgeries may not be an option, hence antibiotic combinations can on occasions be used to give a as broad as possible range of cover against pathogens.

Using the mixing bowl and spatula, the antibiotic powder is added to the polymer and mixed thoroughly. Chilling the constituents prior to adding the liquid will slow the rate of maturation and hence increase working time. The liquid monomer is then added and mixed well to achieve a smooth well mixed consistency. The semi solid cement is transferred to a 20ml syringe using the spatula. Cement is slowly expelled from the nozzle onto the surface (e.g. a glazed tile), as long lines of approximately 1.5mm diameter. If the dough is expelled faster than the roll is laid onto the surface, the roll will tend to be thick in diameter. Conversely, by 'stretching' the roll as it is laid out, the diameter will decrease to 1 mm or less. Once the roll was laid out, it was cut in 1 mm pieces with a scalpel blade. While still malleable each piece was isolated and gently rolled into a bead and left to harden. By stretching the roll in various segments a variety of bead sizes could be produced.

Whilst making beads it is sensible to create beads containing a number of different antibiotics. Care should be taken to keep beads with different constituents separate. Beads are then bagged up into autoclave bags, in preparation for gas or radiation sterilisation.

The smallest beads seemed preferable for bumblefoot, because of their size in a relatively small surgical site. More importantly, however, is the greater elution of antibiotic that occurs from the total surface area of a large number of small beads compared to that of a small number of large beads (Klemm 1993, Wahlig & Dingeldein 1980). Following sterilisation, the packets were labelled according to the antibiotic the beads contained and stored under refrigeration.

Case Management

Each case should be considered on its own merits, antibiotic selection, size and number of beads and duration of application will vary. It is essential that in all cases full surgical debridement and removal of all necrotic and inspissated material is achieved. Aggressive debridement is essential. Following this beads are placed in appropriate positions. In Remple and Forbes 2000, Remple describes how he would place up to 20 very small (<0.5mm) beads together sub cutaneously in the ball of the foot (where most lesions are). Remple desired that the birds should then walk on these believing that the continued movement would assist breakdown any remaining adhesions, encapsulations or barriers and then removed the beads 7 days later, this achieved a dramatic improvement in response rates to bumblefoot therapy. In the same paper Forbes described a technique were following debridement, he placed 3-4 beads in most feet, typically positioning one between each of digits 1 and 2, one between 2 and 3, and then one or more on the lateral aspect of the foot 2-3 mm above the plantar aspect. In the latter cases, beads were only ever removed if they appeared to cause a clinical problem.

When dealing with osteomyelitis cases, a larger number of beads (up to 12 beads of 2-3mm diameter) have been applied by the author, following aggressive debridement. One cautionary note – clinicians should be aware of the potential for *M avium* cysts in bones, which will not grow under normal circumstances on agar, but equally are unlikely to respond to bead therapy. Fungal infections should also be eliminated as potential cause. Beads placed in osteomyelitis situations are generally not removed. If beads are used in a septic arthritis then they should be removed (following cytological testing) generally after 1 week, so as to minimise the chances of long term joint degenerative problems. Beads can be used in any refractory infective situations (e.g eye sockets following enucleation of a septic orbit).

Discussion

Reference to bumblefoot in falconer's birds can be found in the earliest records on the subject of falconry.

A detailed description was made by Holy Roman Emperor Frederik II of Hohenstaufen (1194-1250) in his monumental treatise, *De Arte Venanci Cum Avibus*. The earliest reference to surgical treatment of the disease appears in *Falconry, or the Falcons Lure and Cure* published in 1615 (Cooper 1980). Yet despite its recognition and varied treatment attempts over the centuries, it still occurs commonly in raptors maintained in captivity, and it continues as one of the most refractory to medical treatment. Recent studies on inflammatory and immune responses and histopathological progression of the disease have shown bumblefoot (more specifically raptor staphylococcal pododermatitis) to be an immunologically complex, chronic, degenerative, granulomatous disease (Cooper & Needham 1976, Satterfield & O'Rourke 1980, Cooper 1987, Oaks 1993, Remple & Al-Ashbal 1993).

Bumblefoot bears a striking resemblance to the chronic, cutaneous disease known as bacterial granuloma (botryomycosis). Bacterial granuloma is most commonly caused by coagulase-positive staphylococci, but other bacteria, alone or associated with staphylococci, may be responsible (Walton et al 1983). It bears histological resemblance to bumblefoot by a non-specific inflammatory infiltrate of lymphocytes, plasma cells, histiocytes and giant cell granulomata, which together form a barrier against antibiotic penetration (Ackerman 1988). It is also thought that trauma or foreign body penetration initiates the disease. The granuloma develops because a delicate balance exists between the virulence of the organism and the response of the host, that is to say the host contains the organism but is unable to eradicate it. The work of Oaks (1993) supported a similar finding with staphylococcal pododermatitis in raptors: phagocytosis by heterophils or macrophages was rarely observed, and when it was observed degradation of pathogen was minimal to non-existent. The inability to contain and to degrade phagocytosed pathogen is a hallmark of bacterial granulomatous disease. The use of long-term antibiotics in combination with surgical debridement is the accepted therapy of bacterial granuloma (Ackerman 1988, Muller, Kirk, Scott 1989). Full surgical debridement, in an aim to minimise pathogen loading and breakdown the fibrin barrier surrounding pathogens is still considered to be essential for successful adjunctive therapy employing the use of AIPMMA beads. Bumblefoot similarly relies upon long-term antibiotic therapy in combination with surgical resection and debridement (Riddle 1980, Remple 1993). Also, in both diseases frequent recurrence is the rule, since granulomatous tissues are relatively impermeable to antibiotic penetration, and non-degraded intraleukocytic pathogen is free to reinitiate disease.

The antibiotic choice for chronic, bacterial granulomatous disease must target not only the pathogen but the pathogenesis of the disease. That is to say, since the antibiotic(s) must be used over a long period of time (weeks to months), it should not be overly immunosuppressive; it should be able to deliver adequate or high MIC values for the pathogen at the site of local infection without the use of systemically high doses; it should be relatively devoid of systemic side effects; it should ideally withstand the development of bacterial resistance; it should be synergistic in combination with other chosen antibiotics; and finally it should be capable of granuloma penetration with the ability to kill intraleukocytic pathogen.

Remple (Remple and Forbes) used beads consisting of piperacillin-rifampicin and pefloxacin-rifampicin combinations. Piperacillin and pefloxacin were chosen because they are the most commonly efficacious, shown by sensitivity, against the bacteria most commonly isolated from bumblefoot cases at the Dubai Falcon Hospital. Both are bactericidal, can be used long-term, and are relatively free of side effects. Rifampicin was added to each because of its anti-staphylococcal and efficient granuloma penetrating properties. It is the most active antibiotic known against staphylococci, and because of its ability to enter leukocytes, it is capable of killing intracellular bacteria. Because of its tissue penetration and intracellular activity, rifampicin has been used successfully to treat chronic granulomatous diseases such as tuberculosis and severe cutaneous staphylococcal infections such as canine bacterial granuloma (Ackerman 1988, Frank 1990). The primary drawback to rifampicin monotherapy is the relatively rapid development of resistant strains; however, this can be diminished with combination antibiotic treatment (Frank 1990). In vitro sensitivities to staphylococcal organisms often show resistance, reflecting low MIC values obtained systemically; however, the high AIPMMA bead elution of rifampicin at the site of infection probably overcomes this drawback. Additionally rifampicin adds a dark red color to the AIPMMA beads making them easy to find in subcutaneous tissues when surgical removal is warranted. An improved treatment response with the use of rifampicin could only be expected when *Staphylococcus* spp. was isolated, since *E. coli*, *Pseudomonas* spp., *Proteus* spp. and other Gram negative bacteria often associated with bumblefoot display a resistance.

Forbes in (Remple and Forbes) used a greater variety of antibiotics in the AIPMMA beads. Because very broad spectrum aminoglycoside antibiotics such as gentamicin could be safely used in beads without risk of nephrotoxicity (see below), Forbes focused on targeting the causative pathogen(s) with monotherapy rather than with combination antibiotic therapy, as was used by Remple.

The problems associated with the treatment of a chronic, granulomatous, pedal, plantar disease focus on (1) weight-bearing pressure, and the associated ischemia, trauma and spread of infection that occurs (Remple 1993), and (2) the nature of the chronic granulomatous infection itself. The associated weight-bearing concerns seem to have been adequately addressed by various foot-casting regimes (Remple & Remple 1987, Remple 1993, Riddle 1993). AIPMMA beads seem an attractive way to address the therapy of localised granulomatous disease. The high levels of antibiotic(s) eluted from the beads may exceed the MIC values for most pathogens and thereby avoid the development of resistance. The minimal systemic uptake of antibiotic from the beads allows the use of potentially ototoxic and nephrotoxic antibiotics without risking adverse effects. Forbes (Remple and Forbes) was happy to use gentamicin beads, despite the potential for systemic side effects, as previous workers (Wheler et al 1996, Klemm 1993, Marks et al 1976, Wahlig and Dingeldein 1980, Henry et al 1993, and Chapman and Hadley 1976) have shown that systemic effects are minimal. No untoward sign were seen in any cases in this study. AIPMMA beads may elute effective levels of antibiotic for several weeks (Calhoun & Mader 1989, Klemm 1993, Kanellakopoulou et al 1993, Bowyer & Cumberland 1994), allowing long-term antibiotic therapy to be delivered directly to a localised granulomatous infection, a feature systemic therapy cannot achieve. The long-term implantation of beads in selected sites, where they will not interfere with pedal function or the use of traditional falconry jesses, may reduce the likelihood of recurrence of bumblefoot following surgery. Beads appear to be histologically non-reactive with tissues and can be left in place indefinitely (Henry et al 1993), however the author does report that in a small number of cases, a localised reaction does seem to occur (weeks or months after implantation), which regresses after bead removal.. AIPMMA beads implanted in the plantar aspect of a raptor's foot may enhance antibiotic penetration by mechanical stimulation and tissue massage.

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