INSECT BITE HYPERSENSITIVITY: PREVENTION AND MANAGEMENT

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David Rendle emphasises the importance of tackling sweet itch before clinical signs develop and advises on the need for owner compliance in management

Summary

By the time we are faced with treating sweet itch we are already fighting an uphill battle. Despite a large amount of research in recent years into the aetiopathogenesis of sweet itch (more appropriately termed insect bite hypersensitivity or IBH) there has been little progress in treatment. The absence of universally effective treatments has left the door open for a plethora of products. Prevention and management of the condition is more valuable than any treatments employed after clinical signs have developed.

Key words

equine, sweet itch, insect bite hypersensitivity, Culicoides, midges, allergy

INSECT bite hypersensitivity (IBH) is a type I and type IV hypersensitivity to salivary allergens from numerous species of *Culicoides* midges and, possibly, other biting insects.

The evidence for other biting flies contributing to the disease is weak and the reactions that have been identified to these species may be a result of crossreactivity with salivary proteins from *Culicoides*. While other biting insects may exacerbate clinical disease it is without question that

Culicoides salivary proteins are the predominant allergens in horses with IBH.

However, the clinical features of IBH may be indistinguishable from atopy and humans with atopic skin disease may become sensitised to a range of allergens as a result of compromised epithelial barrier function. Intradermal skin testing may, therefore, be valuable to investigate the potential role of other allergens.

Where *Culicoides* is implicated, prevention and management of clinical disease depends on reducing exposure to, and biting by, *Culicoides* midges. For further information on the aetiopathogenesis of IBH the readers are referred to Schaffartzik et al, 2012.

Preventing exposure to midges

Knowing the enemy is critical to preventing exposure. *Culicoides* midges are most active around dawn and dusk and in hot and humid conditions. They are poor fliers and are therefore less prevalent in exposed and windy areas with well-draining soil. Greater numbers of midges will be found where grazing is bordered by high hedging or wooded areas. *Culicoides* breed in standing water, including chronically waterlogged soil, and are only able to fly approximately half a mile from breeding sites.

Horses with IBH should be kept in open, windy locations away from wooded areas and standing water. Affected horses should be stabled around dawn and dusk, especially in hot, humid weather and, in severe cases, stabling may be beneficial for most, if not all, of the day.

Within the stable environment, measures should be taken to minimise the entry of *Culicoides*. Stabling should be sealed where possible and netting may be placed over the stable door, windows and other necessary openings.

Mosquito netting (typical pore size of around 1.6mm^2) is inadequate and ultra-fine netting with pore sizes of less than 0.9mm^2 is required. Even at this pore size, a few (estimated at five per cent in one study) midges will be able to pass through; however, any further reduction in pore size is likely to unacceptably compromise light and ventilation within the stable.

Rolls of No-See-Um netting designed to prevent *Culicoides* midges can be purchased online. Spraying netting with chemical insecticides/repellents, such as pyrethroid fabric sprays, provides further protection and although some products claim a very long duration of efficacy, pyrethroids are degraded in sunlight and may also be washed off, so re-application every few days is likely to be required.

A chemical insecticide should be used either on the animal or within the stable in conjunction with nets to eliminate any midges that do enter the stable and prevent nets from merely trapping midges in the stable.

Plug-in pyrethroid vapourisers (marketed for travelling) can be used safely within the stable to kill and deter midges and can be used with an automatic timer device set to switch on and off around high-risk periods in the day. Care should obviously be taken to site power supplies and devices out of reach of horses and to use products known to be safe for people when used indoors.

A non-chemical alternative to provide some protection within the stable environment is installing high-speed fans to deter midges in flight.

Reducing insect attack at turn-out

When horses are turned out, fly hoods and body sheets should be used to cover as much of the animal as possible. A number of rug and hood combinations are marketed for use in horses with sweet itch and some have addons such as udder/prepuce/ forelimb attachments that can be used to increase coverage.

In my view, some designs are considerably better than others. Options include the “Boett” or “Snuggy Hood” that retail at around £200, although there are cheaper products (under £100). As with stable netting, no physical barrier is likely to be 100 per cent effective and rugs/hoods should be treated with pyrethroid fabric sprays. Frequency of application will depend upon the product and weather conditions but, as with stable netting, application daily or every other day is likely to be required.

The list of available chemical insecticides/repellents can be bewildering.

The pyrethrins are a group of compounds extracted from chrysanthemum flowerheads that have repellent activity at low levels and are neurotoxic to insects at high levels. While they remain effective, pyrethrins have been largely superseded by synthetic, but chemically very similar, pyrethroids. Second- generation pyrethroids, such as permethrin, cypermethrin and deltamethrin, are more resistant to degradation by light and air and are more suitable for use in IBH.

Different products are available within this group, both for human and animal use, and all are likely to be effective as repellents or insecticides when used at appropriate concentrations.

Some products contain considerably more active ingredient than others and those with at least two per cent permethrin or equivalent are preferred. Livestock products may contain greater concentrations of pyrethroids, but their use needs to be justified on the cascade and patch testing should always be performed prior to generalised application, as adverse reactions are reported to be common in horses.

Cattle ear tags containing pyrethroids can be tied to the mane, tail, tack or rugs, but are probably less effective than treating the horse or its rugs with a topical or fabric treatment respectively. Piperonyl butoxide is used widely in combination with pyrethrins and pyrethroids as it blocks

metabolism of the insecticide within the insect.

N,N-diethyl-meta-toluamide (DEET) is an effective midge repellent that is used widely for people, but is not licensed for use in animals. When used topically in horses at higher concentrations (greater than 50 per cent) adverse local reactions have been reported. Other “more natural” repellent/ insecticidal alternatives are available but in the author’s opinion are rarely effective. Citronella, benzyl benzoate and Skin So Soft (Avon) seem to be effective in some horses but, in general, where the client is keen on pursuing a “natural” product the author prefers chrysanthemum-derived products.

Alleviating pruritus

Topical treatments are appealing as they avoid the potential risks associated with systemic treatment. However, their effects tend to be short-lived and application daily or twice daily is generally required.

Corticosteroid creams are effective and, although none are licensed for horses, Cortavance (Virbac) and Fuciderm (Dechra) are licensed for dogs and numerous human preparations are also available.

Fluorinated corticosteroids (for example, betamethasone) are thought to penetrate the skin better and have greater potency than non-fluorinated corticosteroids (such as hydrocortisone), but are also associated with a greater risk of adverse effects.

Concentrations of active constituents vary between different products, which may negate some of the benefits of using a more potent class of corticosteroid.

Local anaesthetic creams do nothing to address the cause of pruritus, but may reduce the clinical signs. Pramoxine is reported to be beneficial in horses with pruritus and, although it is not licensed for veterinary use in the UK, sprays and rinses may be used in accordance with the cascade. Ice or cold water may also be very effective in providing short-term relief.

Colloidal oatmeal shampoos (for example, Epi-soothe; Virbac and Coatex; VetPlus) have anti-pruritic and moisturising properties, in addition to cleansing the hair and skin. The author advises their use once per week as an adjunct to other treatments. Epi-soothe contains microvesicles that reportedly bind to the hair, coat and skin and release active ingredient as they decay, resulting in prolonged activity. For the microvesicles to be effective, the correct contact times need to be observed, so client compliance is important.

Where a combination of prevention and topical therapy prove inadequate, systemic medication may be required. Antihistamines are unlicensed and rarely effective, but of the choices available hydroxyzine (1.0mg/kg to 2mg/kg q 8-12 h PO) and doxepin (0.5mg/kg to 1.0mg/kg BID PO) are, in

the author's opinion, the most likely to be efficacious. Even if they are ineffective alone they may be synergistic with glucocorticoids and allow a reduction in dose of the latter. Systemic glucocorticoids (prednisolone 1.0mg/kg to 2mg/kg PO SID or dexamethasone 0.01mg/kg to 0.1mg/kg PO SID to EOD) are effective in virtually all cases, although it may take several days to see a response. While chronic therapy is undesirable due to the risk of associated side effects, glucocorticoids can be invaluable in alleviating exacerbations of disease and preventing an escalating spiral of pruritus and self-trauma.

There are numerous anecdotal reports of omega-3 and omega-6 fatty acids being beneficial in horses with atopic skin disease and IBH. In one investigation supplementation with a flaxseed supplement reduced reactivity to intradermal *Culicoides* antigen (O'Neill et al, 2002). However, in the two placebo-controlled studies that have been performed in horses with atopy and IBH no benefit was identified (Craig et al 1997; Friberg and Logas, 1999).

Omega-3 and omega-6 fatty acids (particularly gamma-linolenic and eicosapentaenoic acid) are thought to exert an antiinflammatory effect by competing with arachidonic acid as a substrate for cyclooxygenase and lipoxygenase, resulting in generation of less inflammatory products. These fatty acids are found in high concentrations in evening primrose oil, marine fish oils and flaxseed oil.

Flaxseed and linseed oils are both produced from flaxseed but the latter is produced under "hot press" conditions using a chemical solvent and may cause anorexia, depression and colic when fed to horses. Flaxseed is produced under "cold-press" conditions without chemical solvents and is not associated with adverse effects. The studies mentioned used a wide range of doses (around 0.01g/kg, 0.2g/kg and 1.0g/ kg) and it was the highest dose that was effective in reducing the response to intradermal *Culicoides* allergen. At this dose rate issues of palatability, cost and obesity are found. Palatability issues may be overcome by feeding capsules or gradually increasing the quantity of oil in the diet, but even when buying flaxseed oil in bulk the costs run into many pounds per day. Many horses and pony breeds with a predisposition towards IBH also have a predisposition to obesity and laminitis, so feeding large amounts of oil may be contraindicated especially if glucocorticoids are being considered.

Nicotinamide, or vitamin B3, is marketed as a nutraceutical and topical gel in horses (Cavalesse; Elanco). Nicotinamide has multiple potential antiinflammatory effects, improves epithelial barrier function and is an effective moisturiser in atopic human skin. Unfortunately, evidence to support the use of nicotinamide in humans and horses with allergic skin disease is limited. In two placebocontrolled studies performed by the manufacturer, the results in horses with summer allergies were very promising, however, this work has not been subjected to peer review.

Modulating the immune response to insect bites

Treatments that modify or suppress the immune response to insect bites are the holy grail in

managing IBH. Two options are available – allergen-specific immunotherapy with *Culicoides* extracts and administration of Actinomycete bacterial extracts. To be effective, both treatments need to be administered prior to the onset of clinical signs in the summer and it may take up to a year, or longer, for a benefit to be observed.

Allergen-specific immunotherapy is effective in horses with atopy, but its benefits in horses with IBH are less clear. Immunotherapy influences the response of antigen presenting cells, modulates lymphocyte responses, reduces mast cell degranulation and increases immunoglobulin G (IgG) activity “blocking” immunoglobulin E (IgE) production and mast cell degranulation. Concern is frequently expressed at the lack of a pure extract that contains the *Culicoides* salivary proteins to which horses are allergic and rather the use of extracts of the midges themselves. Investigations of the efficacy of immunotherapy in horses with IBH are all limited by low case numbers and short follow-up periods and have had mixed, but generally disappointing, results. There is, however, optimism that with the development of pure allergens of salivary proteins from different *Culicoides* species immunotherapy will be more effective.

An Actinomycete extract known as BE-T101 or more commonly the “sweet itch vaccine” is proposed to modulate the immune system and reduce clinical signs in horses with IBH. Cell-wall adjuvants of selected aerobic Actinomycetes are potent immunomodulators resulting in a bias toward T helper 1 (Th1) rather than Th2 responses, which is potentially beneficial in IBH and numerous other allergic and inflammatory diseases.

The BE-T101 product was developed by BioEos (a company set-up from University College, London where the immunomodulatory properties of Actinomycetes were investigated extensively) and is marketed in association with The National Sweet Itch Centre.

Extensive research has been performed on the immu- nomodulatory properties of Actinomycete preparations in other conditions in other species. Phased trials of different treatment regimens have been performed in hundreds of horses over 10 years with the manufacturers reporting good responses in 70 per cent of cases and some improvement in a further 20 per cent. However, the results have not been subjected to peer review and the treatment has not been widely accepted by equine dermatologists. The latest recommendation is to give an oral capsule containing a 2mg (approximately 2 x 109 bacilli) dose of *Tsukamurella inchonensis* in a starch capsule orally on a weekly basis.

Conclusions

Preventing contact between affected horses and *Culicoides* midges is fundamental to management of horses with IBH and none of the treatment options available are likely to be effective in the face of significant *Culicoides* exposure.

A combination of physical barriers and chemical repellents will be the most effective approach;

however, the limiting factor is usually the commitment and compliance of the client in keeping up labourintensive preventive measures.

Immunomodulators may help to reduce the severity of clinical signs, but evidence to support their use is weak and clients need to be patient and be prepared for the expense of more than a year of therapy before any benefit is likely to be observed. Weekly shampooing with oatmeal shampoos from spring to autumn may help to reduce pruritus, and topical therapies may also be applied to localised areas. Where these measures are insufficient, systemic therapies may also be employed – however, with the exception of glucocorticoids, their benefits are unproven. The potential for adverse effects with glucocorticoids is well known but they are very effective in reducing pruritus in horses with IBH and may be very useful in preventing a self-perpetuating cycle of spiral of itching and self-trauma.

Finally, IBH is an inherited disorder and, given the welfare implications for horses severely affected by the condition, we have a responsibility to encourage owners not to breed from affected animals.

References and further reading

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