
**SESSION 3: New Developments in
Veterinary and Human Pharmacology**

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Ectoparasiticides

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Introduction

The control of ectoparasitic arthropods of medical and veterinary importance has been slowly evolving over the past 50 years. There are many classes of parasiticides used to control the various parasitic and nuisance arthropods found around livestock and pets (Fraser, 1991). Formulations and product forms are numerous, representing the many advances in packaging technology and pesticide chemistry (Bay & Harris, 1988).

Insecticide/acaricide resistance and "environmental awareness" have dictated the necessity to pursue replacement chemistry to confront these problems in an era of changing economic and regulatory climates. The increasing use of the concept of integrated pest management (IPM) and the nearly identical concept of integrated resistance management (IRM) bode well in these times of corporate product stewardship.

The two groups of ectoparasiticides I will emphasize are the insect growth regulators (IGRs) and the abamectins and ivermectins. The topics to be discussed will include: discovery, mode of action, some product forms, and use within an IPM strategy.

Insect Growth Regulators

The field of insect endocrinology was pioneered by the British entomologist Sir Vincent Wigglesworth. His work with the blood-sucking bug, *Rhodnius prolixus* during the 1930s led to the discovery of the mechanisms for molting and metamorphosis in insects (Wigglesworth, 1970). Wigglesworth postulated that these processes were under the hormonal control of glands found near the insect's brain. It was not until the late 1960s that the

identity of the two hormones were discovered. In 1968, Zoecon Corporation was founded, and the first commercially successful IGR, methoprene, was registered in 1975 (Staal, 1985). In the years that followed, numerous IGRs were discovered, evaluated, and registered for use in a variety of markets.

Insect Hormones

The current or soon to be available IGRs can be divided into two primary groups: the juvenile hormone analogs (JHA) or mimics; and the chitin synthesis inhibitors (CSIs).

These compounds mimic the action of two naturally occurring insect hormones, juvenile hormone (JH) and ecdysone, which are responsible for metamorphosis and molting. JH is produced by paired glands called the corpora allata located at the base of the insect's brain. JH is responsible for the larval "status quo" and maintains the insect in the immature stages through successive larval molts. As JH titer decreases, genes are activated to produce pupal cuticle at the next molt. Finally, as the JH titer reaches zero, genes are activated to produce adult cuticle and other characteristics such as reproductive organs.

Ecdysone is the molting hormone and is responsible for the initiation of the molting process in insects. The deposition of new insect cuticle is an elaborate process involving the laying down of new chitin which is reabsorbed from the old cuticle. Other layers of the cuticle are also added to provide strength, waterproofing and protection from abrasion. Juvenile hormone and ecdysone work together to ensure the successful metamorphosis and ultimate survival of the insect (Wigglesworth, 1984; Chapman, 1982).

Juvenile Hormone Analogs (JHAs) and Mimics

Methoprene was the first JHA to be used for the control of ectoparasites of animals. It was incorporated into mineral supplements for control of the horn fly, *Haematobia irritans* and later for the control of the cat flea, *Ctenocephalides felis*. Control of horn flies is achieved indirectly as cattle consume the methoprene in feed supplements. Most of the compound passes through the animal unmetabolized and is incorporated into the feces. Female horn flies lay their eggs in the freshly deposited feces, and it is there that the immature flies develop. Methoprene prevents the fly larvae from pupating, thus eliminating the next generation of horn flies. Treatment of the entire herd is required to effectively control the pest population.

The use of methoprene to control cat fleas exploits methoprene's ovicidal activity together with the flea's biology. Methoprene applied to the hair coat of dogs and cats acts as an ovicide to the newly laid eggs of the cat flea. Since the adult cat flea feeds, mates, and lays its eggs on the host (Dryden, 1989), an ovicidal control strategy is effective for this ectoparasite (Donahue & Young, 1992). Fenoxycarb is another JH mimic that is a potent flea ovicide (Marchiondo *et al.*, 1990). Both methoprene and fenoxycarb are registered for use as flea ovicides for on-animal application.

Pyriproxyfen is a new JH mimic in the final stages of development and should be registered soon for use in the United States. This compound also acts as a potent flea ovicide (Palma *et al.*, 1993; Meola *et al.*, 1993), but is a unique IGR in that it is also active against ticks. The observed effects on the lone star tick, *Amblyomma americanum* include: molting inhibition of the larvae, hastened mortality of the larvae and nymphs, and ovicidal activity (Donahue *et al.*, In press; Teel *et al.*, In press). The unexpected activity of pyriproxyfen against a non-insect species indicates that some of the newer JH mimics may have a greater spectrum of activity than earlier compounds, a fact which may encourage further development of these potential ectoparasiticides.

Chitin Synthesis Inhibitors (CSIs)

Diflubenzuron was the first CSI developed for ectoparasite control, targeting the horn fly. Like methoprene, this compound also passes unmetabolized through the digestive tract of the bovine, affecting the larvae developing in the manure pat. However, unlike the JHAs and mimics, the CSIs disrupt the larval to larval molt of the insect rather than the larval to pupal molt. The primary mode of action of the CSIs is the disruption of chitin deposition during the molting process.

The CSI triflumeron is registered in Australia for the control of developing flea larvae in the environment. It acts indirectly as an ectoparasiticide by preventing reinfestation of future generations of fleas while having no effect on the adult fleas. Many of the IGR products target the pest species in the environment before they become a problem to animals. It is because of this method of use that IPM has been such a compatible concept with the use of IGRs.

The IGRs have been used to control ectoparasites as topical treatments and as feed-throughs. Cyromazine is an IGR fed to chickens to control house flies in poultry barns. House flies are not ectoparasites per se, but this use represents a management technique using IGRs for the control of pests associated with animals.

A new CSI recently introduced by Ciba into the veterinary market outside the U.S. is lufenuron. This compound is given orally to dogs and cats for the control of cat flea infestations. Lufenuron acts systemically as the adult female flea takes a blood meal from the treated host. The flea receives an ovicidal dosage and, as is true with other IGRs, lufenuron prevents future generations of fleas. At the prescribed dosage, lufenuron is not 100% active as an ovicide; however, it demonstrates a latent activity, killing any early instar flea larvae that may hatch (Hink *et al.*, 1991). Systemic IGRs administered at monthly intervals may fit in well with the current anthelmintic treatments used by many pet owners.

Abamectins and Ivermectins

Mode of Action

The avermectins are products or chemical derivatives of *Streptomyces avermitilis* and have a potent, broad, antiparasitic spectrum at low dose levels. The mode of action of the avermectins is receptor mediated. The consequence of the avermectin-receptor interaction is an increased membrane permeability to chloride ions. In roundworms and arthropods, avermectins potentiate the ability of the neurotransmitters such as glutamate and γ -aminobutyric acid (GABA) to stimulate an influx of chloride into nerve cells resulting in loss of cell function. This effect disrupts nerve impulses resulting in paralysis and death of the parasite. Avermectins do not readily interact with mammalian neurotransmitter receptors. However, there also is evidence that ivermectin affects chloride channels independently of GABA. The precise mode of action is unclear, but the result is paralysis, and eventually, death of the parasite (Fraser, 1991). Further evidence of this mode of action is that the reduction of both excitatory potentials and input resistance was reversed by picrotoxin which is a GABA antagonist active at the chloride channel (Campbell, 1989).

Ectoparasitic Activity

The abamectins and ivermectins have demonstrated activity against many economically important ectoparasites of livestock at rates efficacious against nematode parasites. Ivermectin has been shown to be effective in treating some of the ectoparasites of cattle, sheep, goats, swine, and horses. Included in the list of the parasites in which activity has been demonstrated are cattle grubs, lice, mites, ticks, screwworms, and nasal bots.

Many product forms exist or are being developed including injectable, oral, and topical formulations, and a sustained release bolus (Campbell, 1991).

The use of ivermectin against ectoparasites of dogs and cats also has been investigated. Studies have shown

that *Sarcoptes scabiei* infestations on dogs can be effectively controlled with dosage rates between 50-400 $\mu\text{g}/\text{kg}$ s.c. at various time intervals between 1 and 3 weeks. *Otodectes cynotis* also was effectively controlled. Despite anecdotal reports of efficacy, neither ivermectin or abamectin has been shown to be significantly active against the cat flea, *Ctenocephalides felis* or the mange mite, *Demodex canis* on dogs (Campbell, 1991).

Two mite species, *Notoedres cati* and *Otodectes cynotis* were effectively controlled on cats using ivermectin. Findings similar to those reported with dogs suggest that ivermectin is not efficacious against the cat flea, *Ctenocephalides felis*; however, anecdotal reports of efficacy in cats do exist.

Ivermectin also has demonstrated efficacy against a wide range of ectoparasites in laboratory and exotic mammals and in birds, fish, and reptiles (Campbell, 1991).

Conclusions

The control of ectoparasites on both livestock and companion animals continues to be an area of devoted research. Many of today's ectoparasiticides such as the IGRs are species specific or only active on certain life stages of the pest. Compounds such as the abamectins and ivermectins have a broader spectrum of activity which enhance the commercial success of the compounds. Many of the compounds under development today are scrutinized for their human, animal, and environmental safety before, during, and after registration. Product stewardship will become increasingly important in the future to maintain safe and effective chemicals for use as ectoparasiticides.

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