RÉCAPITULATION DES TECHNIQUES DE LUTTE CHIMIOTHÉRAPIQUES CONTRE LES MONOGÈNES

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RÉSUMÉ

Le nombre de maladies provoquées par les Monogènes a considérablement augmenté, tant en aquaculture que dans les aquariums privés. Les raisons en sont le confinement des poissons ihérent aux conditions d'élevage, ainsi que l'introduction de nouvelles espèces de parasites par l'importation de poissons infestés issus d'autres contrées.

Quel que soit le mode d'infestation, ces parasitoses importées sont souvent très virulentes et peuvent décimer un élevage ou la population d'un aquarium. Les mesures prophyllactiques sont donc une nécessité. Dans le cas de monogenoses récurrentes, malgré les mesures de mise en quarantaine, des traitements chimiothérapiques doivent être rigoureusement appliqués. Le traitement contre les Monogènes et autres ectoparasites se fait toujours par balnéation des poissons dans l'eau où les produits antiparasitaires ont été dilués. Cet article récapitule les techniques de chimiothérapie actuellement utilisées, ainsi que les nouveaux composés dont la mise au point est en cours.

UP TO DATE CHEMOTHERAPY AGAINST MONEGENEA: A REVIEW

ABSTRACT

Occurrences of broad-scale fish diseases caused by monogeneans have increased as the number and the size of mass culture facilities, public and private display aquaria has grown. This increase is due to concentration of the fishes and their parasites in confinement which results in enhanced opportunity for infestation. Also, the increased number of transfers and the introduction of new fish species from allochthonous locations enhance the risks of imported parasitoses. Whatever the way of infestation by monogeneans may be, heavily infested fish are most severely or even lethally impaired. Therefore, precaution is a must against monogenean - caused disease. In the case of an obvious monogeneosis which often occurs despite quarantine, an effective chemotherapeutic measurement must be rigorously applied. The treatment against monogeneans as well as other ectoparasites is still achieved by bathing the infested fish in water containing dissolved chemicals or drugs. The up to date practice in chemotherapy against monogeneans and novel compounds under development are presented in the following contribution.

INTRODUCTION

The culture of fish in confinement has increased significantly worldwide during the last two decades. In 1970, two million tons of edible fish were produced, whereas in the late eighties about 7,5 million tons were harvested from intensive culture facilities (Nash 1988). This trend is expected to continue. Further, the number of public aquaria, private aquarists, wholesalers and retailers serving them also are growing. Regarding the fact that in every case mentioned above the fish inhabit a relatively small volume of water compared to their natural environment, a concentration of hosts and disease factors are given. It is a matter of fact that losses occuring in aquaculture and in pet aquaria are often caused by viral, bacterial, fungal or protozoan diseases. However, among the metazoans, especially the monogeneans often cause severe losses. This is - in part - due to their single - host development cycle which is completed easily in a closed system (Bauer et al. 1981).

With the development of aquaculture in the last twenty years, there has been an increased awareness of the monogeneans as hazards to fish (Mo 1987; Molnár 1984; Sindermann 1984). Therefore, the number of investigations dealing with the methods to control monogeneans is constantly growing.

A wide spectrum of chemicals has been used to act against monogeneans in fish. Some of these chemicals, especially the fixatives and staining dyes, not only affect the parasite, but are harmful to the host. Such substances cause side effects, especially in young fry or in sensitive fish species, and, moreover, most of them lack total efficacy.

Treatment with insecticidal substances at high dilutions, especially trichlorfon, in ponds as well as in hobbyists aquaria is common practice.

In the following, insecticidals and chemotherapeutics will be discussed which have been shown to have a high efficacy or may be promising in forthcoming trials. Table I summarizes substances and treatment regimes against important monogeneans species.

Tableau I : Traitements au Trichlorfon (insecticide) et autres chimiothérapies contre d'importantes espèces de Monogènes.

(1) Noms génériques : Dipterex, Dylox, Chlorophos, Foschlor, Masoten, Neguvon.
(2) Réduction significative mais pas d'éradication.
(3) Efficacité démontrée par Schmahl et Mehlhorn (1988) ; à l'inverse Buchmann et al (1990) ne trouvent aucun effet sur *P. bini*.
(4) Complexe en cours de développement non disponible sur le marché.

Table I : Treatment regimes of the insecticidal trichlorfon and various chemotherapeutics against some important monogenean species

(1) Trading names: Dipterex, Dylox, Chlorophos, Foschlor, Masoten, Neguvon
(2) Significant reduction, but no total eradication
(3) Efficacy was demonstrated by Schmahl and Mehlhorn (1988); on contrast, Buchmann et al. (1990) found no effects on P. bini.
(4) Compound under development, not available on the market

Chemical	Treatment	Monogenean species
Trichlorfon (1)	5 mg/l for 30 min 0.4 mg/l for 6 h 0.2 mg/l for 24 h	*Dactylogyrus vastator,* *D. extensus*
	0.5 mg/l for 6 h	*Neobenedenia melleni*
	0.7 mg/l for 6 h	*Benedeniella posterocolpa*
	0.25 mg/l continuous	*Gyrodactylus* sp.
Mebendazole	0.01 mg/l for 24 h	*Gyrodactylus elegans*
	1 mg/l for 24 h	*Pseudodactylogyrus anguillae, P. bini*
	1 mg/l for 48 h	*G. bullatarudis*
	10 mg/l for 26 h	*Ancylodiscoides vistulensis* (2)
Praziquantel	10 mg/l for 3 h	*D. vastator, D. extensus*
	1 mg/l for 8 h	*P. bini*
	1 mg/l for 25 h	*P. anguillae*
	10 mg/l for 5 h	*A. vistulensis (2)*
	20 mg/l for 1.5 h	*Benediella posterocolpa*
	1 mg/l for 24 h	*Ancylodiscoides* sp. *G. groschafti*
Toltrazuril	10 mg/l for 4 h	*D. vastator, D. extensus,* *P. bini (3) G. arcuatus*
HOE 092 V (4)	10 mg/l for 3 h	*D. vastator, D. extensus,* *G. groschaffi*

INSECTICIDALS AND CHEMOTHERAPEUTICA

Insecticidal substances

Among the insecticidals one substance, trichlorfon, is in use as a treatment against monogeneans for 27 years since its effectivity in large-scale trials has been shown by Prost and Studnicka (1966). It is a relatively inexpensive chemical which is usually added to ponds or aquarium systems. In separate tanks, it can be re-used up to five times. Trichlorfon in containers can be neutralized by the addition of an equal volume of equimolar NaOH. In aequous solution, trichlorfon breaks down quickly to dichlorvos, which is the actual principle acting against monogeneans.

However, trichlorfon should be used very carefully. It works as an inhibitor of the enzyme acethylcholinesterase in generating a continous flow of stimuli from the nerve cells, which leads to a total exhaustation of the terminal organs. This effect is dose-dependent; in general, invertebrtates are more sensitive than vertebrates. Within the fish trichlorfon is rapidly metabolized to dichlorvos, and excreted into the water (Ghittino and Maletto 1971).

One must consider that improper handling with trichlorfon may cause harmful irritation if swallowed, inhaled, or percutaneously absorbed. Furthermore, it may cause seizures and tremors in mammals.

However, several disadvantages limit the use of trichlorfon:

1) Resistance: Only 81% of *Benedeniella posterocolpa* infesting cownose rays (*Rhinoptera bonasus*) were eliminated after two 6 h treatments at 0,7 mg/l (Thoney 1989). The author suggested that greater survival of these worms during the second treatment with trichlorfon might be due to more resistant individual worms. These worms might have produced resistant offspring, which might have resulted in development of highly resistant populations after repeated treatments. In the past, only a treatment for two times at 0,5 mg/l was necessary to control *Neobenedenia melleni* (Thoney 1991, according to Chueng, personal communication).

Actually, about eight treatments ranging up to 1 mg/l were necessary to eliminate the worms, suggesting an aquired resistance. Resistance was also reported for *Gyrodactylus elegans* by Goven et al. (1980).

2) Ovicidal activity: Trichlorfon is not very effective against the subadult stages and eggs of monogeneans. Eggs of *Benedeniella posterocolpa* were killed at 52 % when incubated with 0.7 mg trichlorfon for 24 h (Thoney 1990).

3) Toxicity: In some cases, trichlorfon exerts some toxicity to the host. For example, cownose rays treated with trichlorfon produced excess mucus on their skin, had poor colour, and did not feed as well as untreated controls (Thoney 1990). In treatment of various shark species some deaths occured (Thoney unpublished). Trichlorfon may be toxic to larval fishes, as it is the case in *Cichlasoma urophthalmus* (Flores-Nava and Vizcarra-Quiroz 1988).

4) Ineffectivity: In treatment of African clarid catfish (*Clarias gariepinus*) infested with *Gyrodactylus groschafti* even 70˘mg trichlorfon/l for 5h incubation failed to eradicate the parasite, but 80 % of the tested fry succumbed to the treatment (Obiekezie and Taege, 1991). In experimental trials trichlorfon also failed against *Ancylodiscoides* sp. in African catfish hybrids (*Clarias gariepinus* x *Heterobranchus bidorsalis*) (Schmahl and Obiekezie unpublished). Also in the European catfish (*Silurus glanis*) organophosphate treatment of ancylodiscoidosis has fallen short of expectation (Székely and Molnár 1990).

Thoney and Hargis (1991) recommended an employment of three exposures two or three days apart a concentration of o.5 mg trichlorfon /l for treatment on infestations in large systems. In the case of resistance, then higher doses may be used. But one should handle higher trichlorfon doses with care, because the substance may be toxic to fish.

Benzimidazole derivates

Among other benzimidazole derivates, mebendazole is a broad spectrum anthelmintic compoud acting against nematode and cestode infections in mammals

(Borgers et al. 1975). In general, mebendazole acts as a potent inhibitor of glucose uptake, and furthermore may exert its primary effects on the cytoplasmic microtubule synthesis of intestinal cells of susceptible nematodes and cestodes (Anderson and Waller 1985; Reynolds 1989; Schmahl 1991). Subsequently, cellular activities such as secretion, absorption, digestion, or formation of mitochondrial membranes are disturbed.

Recently, mebendazole has proven to be very efficacious against *Pseudodactylogyrus bini* and *P. anguillae* in European eels (*Anguilla anguilla*) at **1** mg/l and 24 h exposure (Székely and Molnár 1987; Buchmann and Bjerregaard 1990). Apparently, in recommended treatment concentration levels, this compound is relatively safe in eel culture. Pigmented eels can tolerate concentrations up to 100 mg/l for 72h, but glass eel stages exerted 20 % mortalities at only 1 mg/l. *Gyrodactylus elegans* can be removed by 0.01 mg/l (Goven and Amend 1982). However, other gyrodactylid species (i.e. *G. cyclopteri* on *Cyclopterus lumpus*) are not affected by the treatment at 0.2 mg/l (Thoney and Hargis 1991). In own test trials an eradication of *Gyrodactylus bullatarudis* infesting the guppy (*Poecilia reticulata*) was obtained at 2.5 mg/l for 48 h (Schmahl unpublished).

Dactylogyrids seemed to be more resistant against mebendazole. *D. vastator* showed no reaction even at 2 mg/l and 24 h exposure (Goven and Amend 1982). In our laboratory, a *Dactylogyrus* sp. parasitizing the swordtail (*Xiphophorus helleri*) could not be removed even at 10 mg mebendazole/l and 24 h incubation (Schmahl, unpublished). Székely and Molnár (1990) reported that 10 mg/l and 26 h exposure to mebendazole significantly reduced the intensity of *Ancylodiscoides vistulensis* in the European catfish (*Silurus glanis*), but the treatment failed in total eradication of the parasites.

Actuallly, there is only little information about the mode of action of mebendazole in monogeneans. As seen by means of transmission electron microscopy, in *Gyrodactylus bullatarudis* a vacuolization of the tegument and damages within the circular and longitudinal musculature were observed after incubation with 1 mg/l and 48 h exposure (Schmahl, unpublished). In addition, the neurons were enlarged at 2.5 mg/l and 48 h exposure. A total destruction of the neurons was observed at 10 mg/l for the same incubation period. Apparently, the prohaptor glands, the protonephridia and the reproductive system were not affected by the treatment.

All benzimidazoles exert ovicidal activites, and thus may affect monogenean eggs. Buchmann and Bjerregaard (1990) reported that egg development in *P. bini* and *P. anguillae* was inhibited at 1 mg mebendazole/l and 72 h exposure.

An advantage of mebendazole is, that the drug has no negative effects on the microfauna and microflora in biofilters.

However, fish culturists are in need for more informations on other monogenean species and host fish before a general treatment regime for mebendazole can be recommended.

Praziquantel

Praziquantel, a pyrazinoisoquinoline, is currently the drug of choice against a wide range of both veterinary and human trematode and cestode infections. It has also been demonstrated to be very efficacious against fish parasitic metacercaria and adult cestodes of both freshwater and marine fishes (Bylund and Sumari 1981; Andrews and Riley 1982; Heckmann 1984; Pool et al. 1984; Moser et al. 1986; Lewbart and Gratzek 1990). Praziquantel is also very efficacious against numerous monogenean species including *D. vastator*, *D. extensus*, *P. bini*, *P. anguillae*, and *Dermophthirius nigrelli* from the lemon shark (*Negaprion brevirostris*) (Schmahl and Mehlhorn 1985; Thoney 1989).

Treatment with 20 mg/l and 1.5 h exposure also kills oncomiracidia and 28 - 43% of the eggs (Thoney and Hargis 1991).

During treatment with praziquantel some monogeneans species did not detach from their hosts, especially when their opisthaptors were securely attached to the host skin. For example, this is the case in *D. nigrelli* and *D. pristidis*, which are fixed to their hosts by a lipoprotein that cements the opisthaptor to a placoid scale (Thoney and Hargis 1991).

Worms which are fixed by deeply penetrating hooks at their hosts (i.e. *D. extensus*) also adhere to the fish for a short while after treatment until death occurs (Schmahl and Mehlhorn 1985). In addition, *P. bini*, *P. anguillae* and *Ancylodiscoides vistulensis* are reported to react sensitive to incubation with praziquantel (Buchmann 1987; Buchmann et al. 1990; Székely and Molnár 1990). Praziquantel has also been very efficacious against skin- and gill parasitizing *Gyrodactylus groschafti* and *Ancylodiscoides* sp. in fingerlings of African catfish hybrids (*Clarias gariepinus* x *Heterobranchus bidorsalis*). A total eradication of the worm burden was achieved at 1 mg praziquantel and 24 h exposure (Schmahl and Obiekezie unpublished results).

The administration of praziquantel causes paralytic muscle contraction and tegumental disruption in susceptible worms - cestodes, digeneans and monogeneans (Campbell 1986; Schmahl and Mehlhorn 1985; Schmahl and Taraschewski 1987). These most obvious effects of praziquantel occur within seconds. In schistosomes also alterations in their metabolism, including decrease in glucose uptake, lactate release, glycogen content and ATP content were reported (Day et at. 1992). At the moment, all of the effects caused by praziqzantel seemed to be attributed to an alteration of intracellular Ca^{2+} homeostasis within the worm. Especially the membrane blebbing of the tegument and the cytoskeletal disruptions, which both are also seen in monogeneans, are due to an increased intracellular Ca^{2+}-level. The paralytic muscle contraction can obiously be attributed to an increase of intracellular Ca^{2+}-levels within the muscles. From further results obtained in our laboratory a prolongend period of exposure at lower doses seems to be more favourable than treatment with high doses and short time incubation. In general, treatment is recommended at 10 mg praziquantel/l for at least 3 h of exposure.

Symmetric and asymmetric triazine derivates

In laboratory trials the efficacy of a symmetric triazine, toltrazuril, on the gill- and skin parasitizing monogeneans *D. vastator*, *D. extensus*, *P. bini* and *G. arcuatus* has been demonstrated (Schmahl and Mehlhorn 1988; Schmahl et al. 1988). In contrast, Buchmann et al. (1990) reported that toltrazuril was not effective against *P. bini* in European eels. This negative results might be due to an improper pH-value of the water in which the eels were maintained. Investigations in our laboratory clearly revealed that the effects of toltrazuril against monogeneans are dependent of the pH-value. The drug works best in basic pH-ranges. At lower pH-values, the substance precipitates out and therefore, a parasiticidal action is completely rendered.

The asymmetric triazine derivative HOE 092 V has good efficiacy against *D. vastator*, *D. extensus* parasitic in carp (*Cyprinus carpio*) and *G. arcuatus*, a skin parasite in the three-spined stickleback (*Gasterosteus aculeatus*). Incubation was done with 5 or 10 mg HOE 092 V for 4 or 3 h, respectively. Carp measuring about 70 mm tolerated 10 mg HOE 092 for up to 16 h, but excreted more slime on their skin. However, normalisation of slime production took place when fish were replaced to normal water (Schmahl in preparation). In addition, in small scale trials HOE 092 V exerted high efficacy against *Ancylodiscoides* sp. in fingerlings of catfish hybrids (*Clarias gariepinus* x *Heterobranchus bidorsalis*) at 1.0 mg/l and 24 h exposure (Schmahl and Obiekezie in preparation). As seen by means of scanning and transmission electron microscopy, the damages in the dactylogyrid species consisted in an extended internal vacuolization of the tegument and disruption of its limiting membrane (Schmahl et al. 1992, Schmahl 1993).

Summary and conclusions

Parallel to the development of aquaculture, the growing number of public display aquaria and the private recreational aquaria numerous species of monogeneans had played a significant adversive role in fish maintenance, among biogenic diseases caused by other agents, such as viruses, funghi, protozoans and metazoans other than gill flukes. The negative effects of a monogenean infestation may be further enhanced by stress factors normally encountered in confinement. To reduce stress, some negative factors should be avoided or - as far as possible - minimalized, for example improper nutrition, unfavourable lightning, oxygen deficiency, overcrowding, aggression from predatory fishes, rigid handling, and contamination with waste products.

Fish considered for aquaculture, public or private display aquaria should be strictly quarantined and treated prophylactically. The procedures of the International Council for the Exploration of the Sea, which focus on minimizing the adversive effects arising from the introduction of non-indigenous species, especially marine, but also freshwater fishes, should be strictly adopted and followed.

Even when all preventive procedures have been observed, an infestation by monogeneans may occur which necessitates a remedial treatment. In general, treatment of fish in large-scale culture and public aquaria inflicts more difficulties than it is the case when infested fish are confined in easy to handle containers and smaller aquaria. Another point is to determine the efficacy and tolerance to the fish of the various chemotherapeutics actually involved in treatment or under development. The special physico-chemical properties of the various substances must be strictly taken in consideration under inital test situations, especially the search for the optimal solvent. For example, praziquantel is more efficacious when dissolved in dimethylsulphoxide than in ethanol. On the other hand, the water "parameters", such as the pH-value, relative hardness, electric conductance may have a serious influence on drug action. These points are often somewhat neglected in the trials on new therapeutic compounds against a certain parasitic infection. Seen from another point of view, it makes no sense to design a generalized standard procedure concerning the water parameters for testing a new compound, because the first priniciple in the system is the fish (species) and its species-specific requirements.

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