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Fumagillin is an efficacious drug against myxosporean infections of fish

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Introduction

At present no efficacious drugs are available against myxosporeans, parasites that frequently cause severe diseases in fish. Although Scolari (1954) and Bauer (1959) had reported partial efficacy of the arsenic-containing Acetarsol (Stovarsol) against Myxosoma cerebralis, their results were not substantiated by subsequent studies. The observation of Taylor, Coh and Junek (1974), that furazolidone given at a dose of 152 to 194 mg/kg of feed was efficacious against M. cerebralis, has also not been confirmed. Recently Alderman (1986) tested the efficacy of Acetarsol and some other antiprotozoan agents, but failed to get reliable results. Fumagillin was first used by Katznelson and Jamieson (1952) for controlling nosematosis of honey bees. Kano and Fukui (1982) were the first to report the successful use of fumagillin against the so-called "beko" disease of the Japanese eel (Anguilla japonica) caused by a microsporidium (Pleistophora anguillarum).

In Hungary, under intensive conditions where treatment is available, the common carp parasite Sphaerospora renicola and the eel parasite Myxidium giardi are considered the most pathogenic fish myxosporeans. The present paper reports experiments with fumagillin aimed at the prevention and treatment of diseases caused by these parasites.

Materials and methods

1. Medication trials with common carp were conducted under laboratory conditions, in aquaria. In the labora-

tory experiments pathogen-free common carp fry, of 3 to 5 body weight, were used. These fish were inoculated with a homogenate prepared from the swimbladder of common carp fry known to be infected with K-protozoans. The infected swimbladder was squeezed through a sieve of 125 µm pore size and diluted to 2 ml with fish physiological saline (0.65%). An aliquot (0.1-0.2 ml) of this solution was then injected intraperitoneally with a syringe.

In 1985 and 1986 this experiment was performed on five occasions in the laboratory. The experimentally infected fish were divided into two groups on each occasion. One of the groups (controls) received non-medicated feed, whereas the other received a diet containing 0.1% fumagillin from day 1 post-inoculation (PI) up to the end of the experiment. Apart from fumagillin, the diets fed to the two groups were identical (Table 1).

In other experiments the duration of treatment and the concentration of the fumagillin were different (Table 2).

2. Laboratory experiments with eels were performed in aquaria, using glass eels being at the start of pigmentation, in 1987 (Table 3). The glass eels had been caught in river mouths at the Atlantic Coast of France. The eels used in the experiments came from two transports. At the time of importation the fish of the first transport showed no infection, but later on it turned out that they were latently infected by the young stages of Myxidium giardi. The eels used in the second experiment (which had come from the second transport of the farm) had been found infected, although at low prevalence and intensity, already at the start of the experiment. Further experiments were conducted with eels which had also arrived with transports 1 and 2

but had spent one or two months at the farm before the experiment was started. At the beginning of the experiment these groups showed Myxidium infection of low intensity and high prevalence. In each experiment the eels were divided into groups and fed a diet continuously until they were sacrificed and dissected. The treatment period varied between 19 and 61 days.

Results

1. Experiments with Sphaerospora renicola.

During experiments conducted in 1985 and 1986, the transmission of K-parasites was successful and sphaerosporosis was produced in most of the inoculated fish under laboratory conditions (Table 1). In the control group, 43 out of 47 fish became infected. Only one of the 58 fish receiving 0.1% fumagillin in the feed developed sphaerosporosis, and the resulting infection was very mild. Although in the infected fish the pansporeblasts and young spores of sphaerospores were present as early as day 5 PI, the kidneys were usually examined only at 10-14 or more days PI to ensure reliable diagnoses.

In 1987 we partly repeated, partly improved the experiments conducted in 1985 and 1986 (Table 2). These experiments gave the same good results except when we used only a 0.01% medicated feed or if we stopped feeding the drug after the third day PI.

2. Experiments with imported glass eels (Table 3) showed that no plasmodia developed in eels fed 1.0% fumagillin in the food. In the controls, however, the latent infection gradually changed into an infection with small Myxidium giardi plasmodia in the kidney. In fish from the second import batch, when the glass eels showed an infection with small plasmodia already at the start of the experiment, the stage of plasmodial deve-

lopment and the intensity of infection remained on the same level. In the control of this group heavy infection with M. giardi plasmodia developed, and the plasmodia contained numerous spores at the end of the experiment. In fish groups brought back from the fish farm the prevalence of infection was high both in the medicated and in the control groups, but the intensity of infection was lower among medicated eels. The intensity of infection was higher in groups fed 0.1% fumagillin than in those fed 1.0% fumagillin, but the level of infection was lower than in the controls.

Discussion

Our results indicate that fumagillin is a highly effective drug against Sphaerospora renicola. In the aquarium experiments, when it was given in the feed continuously at a dose of 0.1%, fumagillin prevented the development of the parasite in the renal tubules.

Reducing the active compound concentration from 0.1% to 0.05%, efficacy still remained good. However, a tenfold reduction in the active compound concentration of the medicated feed (from 0.1% to 0.01%) resulted in lower efficacy.

If treatment is terminated too early, this may lead to exacerbation of the infection.

From the experiments we can conclude that Fumagillin DCH prevents the development of K-protozoans living in the swimbladder and of young plasmodia present in the renal tubules.

The eel experiments were conducted under entirely different conditions, since SPF eels are not available because artificial culturing of this species has not become possible yet. Until the present experiments the glass eels caught at the Atlantic Coast were thought to have been free from Myxidium giardi and to contract in-

fection only at the eel farm, after starting to feed.

Our experiments, however, have revealed that the glass eels are latently infected by certain, yet unknown, stages of M. giardi which develop further under laboratory conditions.

Our aquarium experiments have shown that at a dose of 0.1% or 1.0% in the feed, Fumagillin DCH effectively prevents the plasmodium and spore formation of Myxidium giardi (Table 3). As a result of fumagillin treatment, latently infected eels remained free from apparent infections. If the eels had shown signs of infection already at the beginning of treatment, fumagillin feeding failed to result in the disappearence of the existing plasmodia and spores from the kidneys; however it prevented the formation of new spores.

Besides Sphaerospora renicola and Myxidium giardi, fumagillin proved to be a drug of excellent efficacy also against PKX parasites (Hedrick et al., 1988) and Ceratomyxa shasta (Ching, personal communication).

Fumagillin seems to have a static effect on the plasmodia of myxosporeans, and by its preventive application the appearence of parasitosis can be avoided. Fumagillin has no effect on advanced plasmodia and spores but prevents the appearence of new stages and the manifestation of the old ones.

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Summary

Fumagillin was found to be the first efficacious drug against myxosporean infections of fish. When applied continuously at a dose of 0.1% in the feed, Fumagillin DCH prevented Sphaerospora renicola infection of the common carp (Cyprinus carpio). When fed 1.0% fumagillin in the food, latently infected glass eels (Anguilla anguilla) did not develop plasmodia of Myxidium giardi. If plasmodial development had already progressed, some plasmodia developed but the intensity of infection was significantly lower than in the controls. The intensity of infection was higher in groups fed 0.1% fumagillin than in those fed 1.0% fumagillin.

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Table 1

Results of Fumagillin DCH treatment of common carp fry inoculated with K-protozoans to induce renal sphaerosporosis (experiments conducted in 1985 and 1986)

Date of intraperitoneal inoculation	Date of examination	Number of days elapsing between inoculation and examination	Fry fed 0.1% Fumagillin DCH	Control fry
13 Aug.'85	27 Aug'85	14	0/5	3/5
16 Aug.'85	9 Sept.'85	24	0/3	3/3
23 July'86	4 Aug.'86	11	0/12[x]	10/10
23 July'86	12 Aug.'86	19	0/2	2/2
13 Aug.'86	18 Aug.'86	5	0/2	1/1
13 Aug.'86	25 Aug.'86	12	0/13	5/5
14 Aug.'86	19 Aug.'86	5	1/2	2/2
14 Aug.'86	25 Aug.'86	11	0/19	17/19

numerator: number of infected fish
denominator: number of fish tested
x : The fish had received the medicated feed for 8 days before inoculation.

Table 2

Results of Fumagillin DCH treatment of common carp fry inoculated with K-protozoans to induce renal sphaerosporosis (experiments conducted in 1987)

Experiment	I	II
Date of inoculation	21 July	25 Aug.
Date of examination	31 July	4 Sept.
Number of days elapsing between inoculation and examination	10	10
After inoculation, control feed for 3 days, followed by the 0.1% medicated feed for 7 days	-	0/5
After inoculation, 0.1% medicated feed for 3 days, followed by the control feed for 7 days	-	$2^{+}/2$
Before inoculation, 0.1% medicated feed for 2 days, followed by the control feed for 10 days	0/5	-
After inoculation, 0.1% medicated feed for 3 days, control feed for 7 days, again 0.1% medicated feed for 3 days, finally control feed for 3 days	-	$0^{x}/3$
After inoculation, 0.1% medicated feed continuously for 10 days	-	0/5
After inoculation, 0.05% medicated feed continuously for 10 days	-	0/5
After inoculation, 0.01% medicated feed continuously for 10 days	$3^{+}/7$	$1^{+}/5$
Control	$5^{+++}/5$	$5^{+++}/5$

x : examination on 10 Sept. (after 16 days), + : intensity of infection, numerator: number of infected fish, denominator: number of fish tested

Table 3

Efficacy of Fumagillin DCH against the eel parasite Myxidium giardi (experiments performed in 1987)

Origin of the eels	Duration of the experiment (days)	Fish treated with Fumagillin DCH		Control
		0.1%	1.0%	
Directly from the 1st transport	22	$1^{+}/17$	0/18	$4^{+}/12$
Directly from the 1st transport	19	-	0/8	$8^{+}/10$
Directly from the 1st transport	40	-	0/10	$10^{+}/10$
Directly from the 2nd transport	29	-	$7^{+}/20$	$17^{+}/20$
1st transport (back from farm)^{X}	36	-	$8^{+}/10$	$8^{+++}/10$
1st transport (back from farm)^{X}	48	-	$8^{+}/28$	$10^{+++}/11$
2nd transport (back from farm)^{XX}	47	$10^{++}/10$	$10^{+}/10$	$10^{+++}/10$
2nd transport (back from farm)^{XX}	61	$10^{++}/10$	$10^{+}/10$	$10^{+++}/10$

+ = low intensity, ++ = medium intensity, +++ = high intensity, numerator: number of infected fish, denominator: number of fish tested, X = the eels were reared at the farm from 20 Febr. to 15 April, XX = the eels were reared at the farm from 21 March to 23 June