Chapter 1
General Information About *Fascioloides magna*

Abstract Giant liver fluke *Fascioloides magna* is a veterinary important liver parasite of free-living and domestic ruminants. This chapter provides general characterization and basic data on the parasite, with focus on its taxonomy, morphology, life cycle, clinical signs, pathology and treatment. Different taxonomic classification and scientific names of the species, and currently accepted taxonomy of *F. magna* are provided in Sect. 1.1. The second part is dealing with morphological description of the parasite, which belongs to the largest flukes worldwide. *Fascioloides magna* utilizes aquatic snails as the intermediate hosts and a wide range of free-living and domestic ruminants as the final hosts. The life cycle of the parasite, divided into four developmental stages, is described in the third subchapter. The fourth part is focused on characterization of clinical signs of fascioloidosis, which are specific for particular type of the final host. Typical pathological changes of *F. magna* infection, described in the fifth subchapter, are fibrous pseudocysts of sedentary adult flukes leading to enlargement of the liver. The last subchapter summarizes the broad spectrum of anthelmintic drugs (e.g. benzimidazoles, salicylanilides, sulphonamides etc.) used for fascioloidosis treatment in different ruminants. Out of them, triclabendazole and rafoxanide proved high efficacy against adult and immature flukes; however, no specific therapeutics are available till now.

Keywords Giant liver fluke · Taxonomy · Morphology · Life cycle · Clinical signs · Pathology · Treatment

1.1 Taxonomic Classification

In spite of the generally accepted North American origin of *Fascioloides magna*, the first case report and description of giant liver fluke originates from Europe from the second half of the 19th century (Swales 1935). In 1875, Italian veterinarian Roberto Bassi described new parasite from the liver of a wapiti stag from the Royal

I. Králová-Hromadová et al., *The Giant Liver Fluke, Fascioloides magna: Past, Present and Future Research*, SpringerBriefs in Animal Sciences,
DOI 10.1007/978-3-319-29508-4_1

Table 1.1 Taxonomic classification of *F. magna* modified according to Jones (2005)

Phylum	Platyhelminthes
Class[a]	Trematoda Rudolphi, 1808
Subclass	Digenea Carus, 1863
Order	Echinostomida La Rue, 1957
Superfamily	Echinostomatoidea Looss, 1899
Family	Fasciolidae Railliet, 1895
Subfamily	Fasciolinae Railliet, 1895
Genus	*Fascioloides* Ward, 1917
Species	*Fascioloides magna* (Bassi, 1875) Ward, 1917
English names	Giant liver fluke, large American liver fluke, deer fluke

[a]class Trematoda belongs to the lineage Neodermata

Park La Mandria in northwestern Italy (Bassi 1875 c.i. Pybus 2001). The species was named as *Distomum magnum* Bassi (1875).

Later on, Charles W. Stiles studied liver flukes from North American cervids and found parasites, which were identical with those described as *Distomum magnum* by Bassi (Stiles and Hassall 1894 c.i. Pybus 2001). Based on these comparisons, Stiles drafted first comprehensive morphological description of the fluke and renamed it as *Fasciola magna* (Swales 1935). In 1895, Stiles noticed similarities between life cycles of *Fasciola magna* and *Fasciola hepatica* (i.e. utilization of aquatic snails as intermediate hosts), and provided description of eggs and miracidium larval stages of the parasite (Stiles and Hassall 1895 c.i. Pybus 2001).

Finally, due to the morphological differences between *Fasciola magna* and other species of the genus *Fasciola* (e.g. the lack of distinct anterior cone and localization of vitellaria in the region ventral to the intestinal branches), Henry B. Ward proposed the new genus *Fascioloides* with the only type species *Fascioloides magna* (Ward 1917) (Table 1.1).

1.2 Morphology

One of the most significant morphological characteristics of *F. magna* is its large body and thick size, due to which it belongs to one of the largest trematodes worldwide. The overall size of adult flukes varies between 40–100 mm of length and 20–35 mm of width (Fig. 1.1); body thickness ranges from 2 to 4.5 mm (Erhardová 1961).

The body is oval or leaf-shaped, dorsoventrally flattened, non-segmented and bilaterally symmetrical (Erhardová-Kotrlá 1971). The body surface is covered by *tegument* with fine spines except for the anterior part of the flukes. The reddish-brown colour of the body is caused by translucent contents of the intestine (Špakulová et al. 2003). Moreover, some internal organs can be visible through the

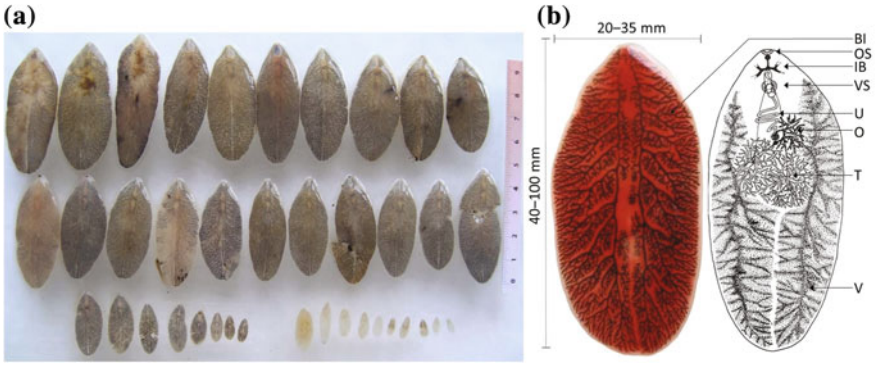

Fig. 1.1 **a** infrapopulation of *F. magna* from red deer from Danube floodplain forests, Slovakia (*Photo* M. Špakulová); **b** morphology of adult *F. magna* (*Photo* E. Bazsalovicsová, *drawing* M. Špakulová); *BI* branched intestine, *OS* oral sucker, *IB* intestine bifurcation, *VS* ventral sucker, *U* uterus, *O* ovarium, *T* testes, *V* vitellaria

body surface, which is underlaid by *musculature* consisting of several layers: the outer circular, intermediate longitudinal and inner diagonal muscles (Erhardová-Kotrlá 1971; Trailović et al. 2015).

The anterior end of the fluke is slightly pointed, while the posterior margin is widely rounded. In the anterior half of the body, two muscular suckers are localized; the *oral sucker* surrounding the mouth opening is usually connected with oral cavity and allows sucking of blood (*hematophagy*). The *ventral sucker* (*acetabulum*) is localized on the ventral side in the first third of the body, 3–4 mm from the oral sucker and serves as attachment organ (Erhardová-Kotrlá 1971).

Internal organs of mature hermaphrodic flukes are present in the parenchyma. The *digestive system* with well-developed oral sucker and the sac-like intestine are differentiated already in the rediae. It is formed by mouth surrounded by the oral sucker, passing to buccal cavity, following by short muscular pharynx and oesophagus. It is bifurcated into two branched intestinal systems, largely extended into many diverticula, which continued along the whole body length (Fig. 1.1) (Erhardová-Kotrlá 1971; Špakulová et al. 2003). The suckers and pharynx contain numerous receptory cells (Erhardová-Kotrlá 1971). Abundantly branched intestine is blindly terminated in the parenchyma and creates a thin epithelium (*gastrodermis*) with the ability of absorption and secretion (Stiles and Hassall 1895 c.i. 2001).

Giant liver fluke has protonephridial *excretory system*, which forms network of excretory canals opened to the outside of body through terminal excretory pore. Basic structures of the excretory system are flame cells deposited in the parenchyma. The *nervous system* of *F. magna* consists of a paired nerve ganglion and nerve cords (longitudinal and transverse) extending throughout the fluke body (Erhardová-Kotrlá 1971).

Adult flukes of *F. magna* are characterized by the presence of male and female reproductive systems in each individual (Fig. 1.1). Sexually mature flukes have one common *genital pore* for both reproductive systems, which is median and immediately pre-acetabular. *Male reproductive organs* consist of two branched *testes* localized closer to the body centre and *vas deferens* opening into the *bursa cirri*. The walls of the *vas deferens* pass into the *vesicula seminalis* and then in the *pars prostatica*. The copulatory organ (ejaculatory duct) terminates in short *cirrus*. Testes are placed side by side almost in the entire second third of the body, but usually one testis may be slightly above the other (Erhardová-Kotrlá 1971).

Female reproductive system consists of lobulated and branched *ovarium*, which is pretesticular, situated slightly to the right side. The *oviduct* surrounded by the Mehlis' gland lies in the middle, and is connected with the *transverse vitelline ducts*. The short Laurer's canal extends from the oviduct. Widely branched *vitellarium* is localized only on the ventral side of the digestive system, and vitelline fields fill lateral regions of body from level of acetabulum to posterior body end. *Oviduct* continues by ball-shaped *uterus* placed in the first third of the body, proceeding to the *bursa cirri* and short *metraterm*.

Uterus is usually filled with a large number of eggs, which possess typical *operculum* on an apical pole (Erhardová-Kotrlá 1971). The peculiar appendage localized opposite the opercular end of the egg is present in variable forms on practically all eggs removed from liver pseudocysts filled with flukes. This appendage is present only on approximately 20 % of eggs normally passed from the final hosts (Swales 1935). The overall length of eggs is 109–175 μm, width is 81–117 μm, depending on the type of the final host and course of infection. The eggs are oval or slightly widened in the centre, yellow or yellowish-brown in colour. They are covered by shell, which is approximately 3.0 μm thick and smooth; however, the germ and vitelline cells are visible through the translucent surface (Swales 1935; Campbell 1961; Erhardová-Kotrlá 1971).

1.3 Life Cycle

The complete life cycle of *F. magna* was described by Swales in 1935. The details of all developmental stages of the life cycle were later specified by Erhardová-Kotrlá (1971). Giant liver fluke has complex life cycle with four stages (Fig. 1.2). The first developmental stage takes place in external environmental conditions, including the phase after dissemination of eggs within the host's faeces into water environment and their development to miracidium. The second stage involves the development of different larval stages (sporocysts, mother and daughter rediae) within the intermediate hosts (aquatic snails). In the third stage, metacercariae develop after release of cercariae from intermediate host in the humid external environment. The fourth stage begins after the ingestion of infective metacercariae by final hosts (e.g. cervids or other ruminants), and continues up to the maturity of adult flukes and production of eggs.

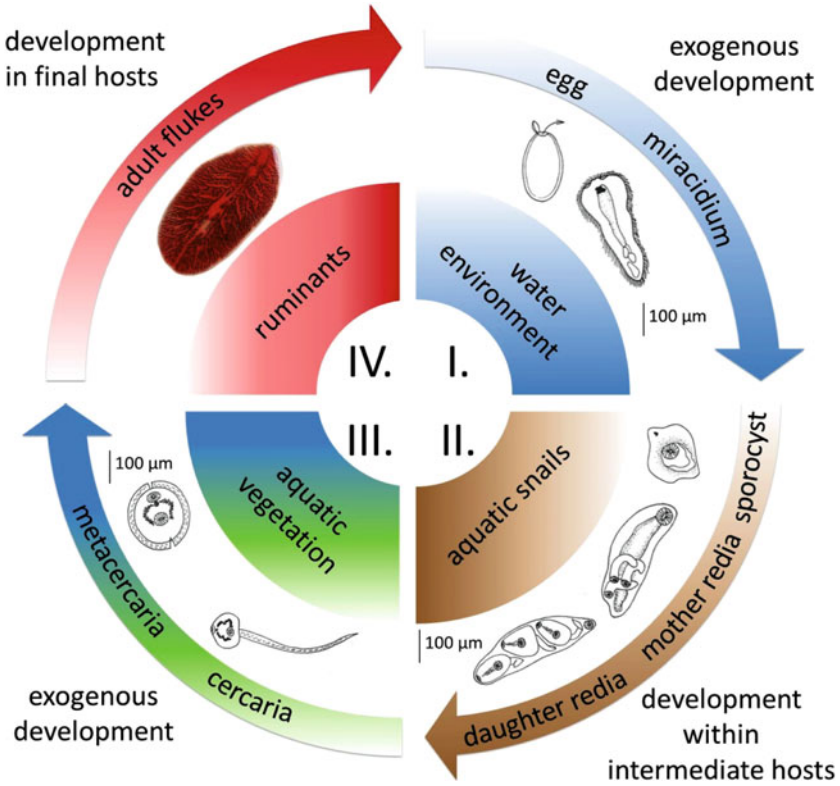

Fig. 1.2 The life cycle of *F. magna* (*Drawings of larval stages* M. Špakulová)

First stage: exogenous development Adult flukes are usually localized in the liver pseudocysts of final hosts, in particular in definitive type of hosts (for details see 1.4 and 1.5). Mature flukes may release up to 4,000 thick-walled operculated *eggs* per day (Swales 1935). The eggs are released with bile into the intestine and leave host's organism along with faeces (Erhardová-Kotrlá 1971). In mature eggs, the process of embryonation results in formation of larval stage, *miracidium*. Complete embryonation takes approximately 35 days (Swales 1935), but this time varies considerably with changes in temperature and moisture (Pybus 2001). In general, the reduction of the temperature prolongs the development (Erhardová-Kotrlá 1971). Low temperatures (<20 °C) retard development, while high temperatures (>34 °C) lead to abnormalities in embryonation and an inability to hatch (Campbell 1961).

In external environmental conditions, a fully developed ciliated larva miracidium hatches from egg by opening the operculum and is released into the water environment during 2–4 weeks (Schwartz et al. 1993). The growing miracidium produces proteolytic enzymes that liberate the egg operculum and allow hatching (Pybus et al. 1991).

Free-living miracidia are fast moving stages, which actively seek intermediate snail hosts and penetrate into the snail's body under the mantle fold on the posterior part of the pulmonary sac (Swales 1935). The penetration into the aquatic snails is facilitated by the secretion of apical gland situated in the anterior part of miracidium. One miracidium has already fully developed six sensory organs, which are connected with the central ganglion (Erhardová-Kotrlá 1971). Miracidia display positive phototaxis and have strong affinity for mucus of lymnaeid snails (Campbell 1961; Erhardová-Kotrlá 1971). If miracidia do not penetrate into the suitable intermediate host, they gradually lose their energy and die. They can survive in humid environment from 10–16 h (Erhardová 1961) up to 1–2 days (Pybus 2001).

Second stage: development within intermediate hosts The development within the intermediate host (or multiplication phase) begins by the creation of new larval stage, *sporocyst*. Miracidia can migrate through the snail's body away from the penetration site. Therefore, sporocysts can sometimes be found in various sites; in the shell cavity or in the shell, in the foot of snail, near the digestive system or in pulmonary cavity. However, they have never been found in the hepatopancreas and kidney (Erhardová-Kotrlá 1971). Transformation of miracidia into the sporocyst takes about 8–10 h after the penetration (Swales 1935; Erhardová 1961; Schwartz et al. 1993). In the stage of sporocyst, only muscular pharynx, buccal cavity and rudimentary oesophagus are developed; no other internal organs are evolved. Sporocysts are able to form two types of rediae, which enter the snail's tissue (Schwartz et al. 1993).

At first, sporocysts change their form and develop into *mother rediae*. Each sporocyst usually contains only one mother redia and 4–6 germ cells. Mother rediae elongate their body, actively move and escape from sporocysts by rupturing their wall. They have completely developed digestive organs; mouth, very large muscular pharynx, oesophagus and gut. Mother rediae migrate through the tissue of the snail; they can be found mainly in the kidney, female reproductive organs, pulmonary cavity and near the anal pore. Each mother redia contains 4–6 light-yellow coloured *daughter rediae* (Erhardová 1961), which gradually develop in growing mother rediae. They have very similar digestive system comparing to mother rediae, involving mouth, pharynx, oesophagus and gut. Smaller muscular pharynx of daughter rediae is differential feature from mother rediae. The shape of body of daughter redia is divided into two parts; the anterior is larger and wider, while the posterior one is shorter and narrower. Within each daughter redia, the next larval stage (*cercaria*) develops in various numbers; the highest number is usually six cercariae in one daughter redia (Erhardová-Kotrlá 1971). An apparent difference between mother and daughter rediae is the retention of the strong collar in the anterior part of the redia. In daughter rediae containing cercariae, no indication of collar is observed, while in mother rediae, it is formed by a simple fold in the wall, probably as a result of growing and stretching cercariae (Swales 1935).

Third stage: exogenous development The cercariae emerge from the daughter rediae and they usually migrate into the hepatopancreas and reproductive organs of snails, where they complete their development. Mature cercariae represent free-living larval stage, which persist in external environment after leaving snail.

They are very active inside the daughter rediae, where they have been formed. The light-yellow coloured cercariae are very similar by their body construction with adult stages of fluke; anterior portion is heart-shaped and wide, while the posterior one represents one long tail. Their digestive system is formed by mouth, muscular pharynx, short oesophagus, intestine bifurcated into two branches and caecum. Some kind of excretory system and rudimentary basis of reproductive organs are also developed (Swales 1935; Erhardová-Kotrlá 1971).

After the complex of multiplication processes in the intermediate host, several larval generations are produced during approximately 2.5 months. As a result, about 1,000 cercariae are released from infected snail (Swales 1935; Erhardová 1961). Development in snails depends mainly on physical conditions (e.g. temperature, moisture etc.), and type or species of intermediate hosts (Pybus 2001). Finally, the cercariae move from the snail's tissue back into the water, migrate a short distance, encyst on the surface of an aquatic vegetation and develop into the *metacercariae* (Schwartz et al. 1993). Metacercariae represent the stage infectious for final hosts; they remain infectious during 2–2.5 months fixed on submergent or emergent vegetation, particularly in cold water. The dark-brown metacercariae are covered by the wall, which is formed by two layers; thinner inner and thicker outer (Erhardová-Kotrlá 1971; Schwartz et al. 1993). Metacercariae-infected herbage may be ingested by domestic or free-living ruminants (Foreyt and Parish 1990), mainly in two primary transmission periods, in the late summer and fall, and in the spring (Erhardová-Kotrlá 1971).

Fourth stage: development in the final hosts After ingestion of metacercariae, activated larva penetrates the intestinal wall of its final host, migrate along the ventral aspect of the peritoneal cavity, and then penetrates the liver through the Glisson's capsule, where they slowly grow and develop into adults (Pybus 2001). In final hosts, flukes mature approximately 30 weeks after infection (Foreyt and Todd 1976a). Localization of flukes depends on the type of the final host (definitive, aberrant, dead-end; for details see Chap. 3). In definitive host, *F. magna* occurs in thin-walled fibrous pseudocysts within the liver parenchyma usually in pairs, but occasionally also in higher numbers (Foreyt et al. 1977; Schwartz et al. 1993; Pybus 2001). Hermaphroditic helminths in general prefer cross-fertilization; however, self-fertilization may occur in absence of available partner (Šnábel et al. 1996).

In dead-end hosts, thick-walled encapsulation of flukes was observed, while for aberrant hosts, excessive wandering of immature flukes and lack of encapsulation are typical. Single immature fluke may migrate through the hepatic parenchyma up to one year before becoming encapsulated with other fluke (Foreyt et al. 1977; Mulvey et al. 1991). Such immature flukes may migrate aimlessly and destructively through the organs of abdominal or thoracic cavities. Prepatent period of *F. magna* in ruminants ranges from three (Erhardová-Kotrlá 1971) to seven months (Swales 1935; Foreyt and Todd 1976a). Adult flukes survive in liver of final hosts at least five years (Erhardová-Kotrlá 1971).

1.4 Clinical Signs

Clinical signs caused by *F. magna* infection strongly depend on the type of final host (definitive, aberrant, dead-end; for details see Chap. 3). Infection in the definitive hosts (e.g. white-tailed deer, wapiti, red deer etc.) is usually well tolerated (except for young animals, or animals of lower fitness) and *F. magna* is not considered as a serious pathogen in these cervids (Swales 1935; Griffiths 1962; Foreyt and Todd 1976a). However, some clinical signs, such as lethargy, poor appetite, anorexia, anemia, depression and weight loss, may occur (Foreyt 1992, 1996a). In occasional cases, fascioloidosis can lead to death of definitive host, as was reported e.g. in naturally infected white-tailed deer (Pursglove et al. 1977), red deer (Balbo et al. 1987), and also in experimentally infected wapiti (Foreyt 1996b) or mule deer (Foreyt 1992).

Contrary to definitive hosts, infections in aberrant (e.g. sheep, goat, roe deer) and dead-end hosts (e.g. cattle, moose, sika deer) display different clinical signs and may more often cause a lethal effect. The course of infection in these types of hosts could also be subclinical and coprological examinations may not provide reliable results (Foreyt and Todd 1976b; Stromberg et al. 1983). For instance, goats, sheep and llama apparently did not exhibit initial clinical signs of infection, but in some cases, infected animals show signs of lethargy and weakness shortly before death (Foreyt 1990, 1996a). Mortality usually occurs within 4–6 months post-infection (Swales 1935; Erhardová-Kotrlá and Blažek 1970; Erhardová-Kotrlá 1971; Foreyt and Leathers 1980), and may be associated with acute peritonitis before or after migrating larvae reach the liver. Since fascioloidosis in domestic ruminants may cause significant economic losses, monitoring of farmed animals and compliance of preventive measures are highly important in order to prevent infections in cattle, sheep and goats (Lanfranchi et al. 1985).

1.5 Pathology

Pathological changes caused by *F. magna* infection also depend on the type of its ruminant hosts, with different tolerance to fascioloidosis (Pybus 2001). In definitive hosts, fibrous encapsulated pseudocysts of sedentary adult flukes (Fig. 1.3), which lead to pathological enlargement of the liver, are typical. The liver has usually rounded margins and fibrous tags on the serosa (Pybus 2001). An enlarged grey liver with irregular grooves, fibrin and scattered diffuse foci of black pigment on the surface, a lot of different cystic spaces filled with brownish mucous fluid, and changes in the liver tissue typical for cirrhosis, were also observed (Karamon et al. 2015). Perivascular inflammation is generally not detectable (Foreyt and Todd 1979).

The infected liver is predominantly characterized by primary lesions associated with mechanical damage due to migrating immature flukes. After flukes'

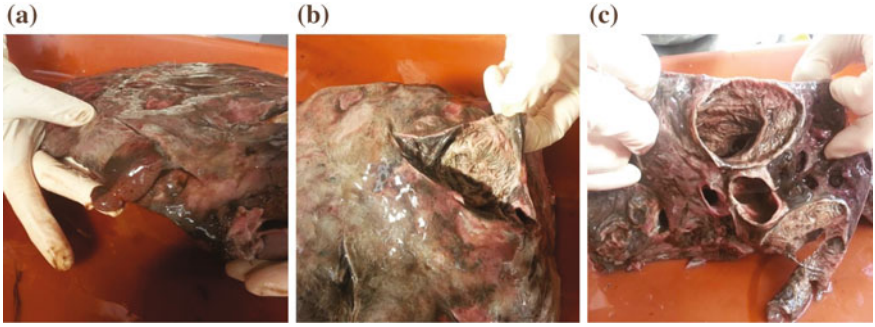

Fig. 1.3 **a** adult *F. magna* in liver of infected red deer from Danube floodplain forests, Slovakia; **b** pathological changes of infected liver; **c** details on fibrous capsules in the liver parenchyma (*Photos* M. Špakulová and E. Bazsalovicsová)

consumption of blood and its components, particularly erythrocytes, streaks of black pigment may be seen. They occur in abdominal or thoracic organs, especially in the liver. Black pigment accumulates in hepatic cells either on the serosal surface or throughout the liver parenchyma (Swales 1935; Pybus 2001). Black spots of different size may be visible on the omentum, peritoneum, pleura and cranial part of lungs (Karamon et al. 2015). Black or dark-green pigment belongs to the group of hematins and is produced in the intestine of immature and adult flukes as a by-product of feeding on blood (Campbell 1960; Blažek and Gilka 1970). The presence of hematin is typical only for giant liver fluke; there is no evidence of its occurrence in parasitic infections caused by other flukes (Chroust 1987).

Thin-walled pseudocysts usually arise as a result of an immune defense mechanism against the migration of young flukes throughout the hepatic parenchyma and are filled with a dark-green liquid. With the gradual development of capsule around the flukes, the surrounding liver parenchyma is destroyed due to pressure atrophy (Swales 1935, 1936). Capsules are of host origin and are an apparent attempt to prevent further migration of flukes within the liver parenchyma (Pybus 2001).

Cysts with adult flukes are situated in the liver parenchyma and are opened to the biliary system (Conboy and Stromberg 1991). Giant liver flukes usually occur in pairs (Erhardová-Kotrlá 1971), although in some cases more than two flukes can be present in one pseudocyst (Špakulová et al. 2003). The size of pseudocysts is variable (average size 50–100 mm); it depends on the amount of accumulated fluid and detritus, but also on the number and size of flukes enclosed in cyst (Swales 1935, 1936).

In aberrant hosts, pathological changes are mainly characterized by excessive wandering of immature flukes and lack of encapsulation. In addition to necrosis throughout the liver, perforation of the hepatic capsule or penetration into various abdominal and pleural organs (most frequently lungs) may also occur (Foreyt and Todd 1976b; Foreyt and Leathers 1980). In dead-end hosts, fibrosis and thick-walled encapsulation of flukes was observed. In some cases, even chronic

calcification of pseudocysts may occur (Pybus 2001). The presence of black pigmentation of various tissues is one of the initial macroscopical diagnostic markers of *F. magna* infections in this type of hosts (Špakulová et al. 2003). Higher number of flukes and prolonged infections cause more extensive histopathological changes in liver parenchyma of infected ruminants (Pybus 2001).

1.6 Therapeutic Treatment

Therapeutic treatment of fascioloidosis in domestic ruminants is feasible as a part of on-going individual herd management programs (Pybus 2001). An important role plays the way of housing animals in farms, pasture rotation and the frequency of animals in pastures, improvement of animal zoo-hygienic conditions and general animal welfare. Therefore, the treatment of domestic ruminants appears to be more effective due to possibility to control the dosage and administration of anthelmintic drugs. It is fully copying the knowledge on pharmacological anthelmintic treatment of liver fluke *Fasciola hepatica* (Trematoda; Fasciolidae), species which is closely related to *F. magna* (Mas-Coma 2005). Due to this fact, pharmacological treatment, as known for *F. hepatica* (Fairweather and Boray 1999), was adopted in treatment of *F. magna*. However, *F. magna* infections are in most cases difficult to treat because flukes are not localized directly in the bile ducts as in *F. hepatica* infections. As a result, most anthelmintic drugs effective against *F. hepatica* do not work well against *F. magna* (Foreyt and Todd 1976b).

Treatment of *F. magna* in free-living ruminants differs from that of domestic ones. Anthelmintic drugs are administrated to animals through the feeding mixtures in winter seasons. In such cases, an exact dose of anthelmintics can not be controlled and treatment of cervids is mostly unfeasible (Pybus 2001). The main reason is that mixing of drugs with salt might limit the amount of mixture that can be eaten in one visit to the feeding table by the dominant deer, and leaving enough to treat the inferior ones (Janicki et al. 2005). Direct treatment of cervids is possible only in situations of their translocations from enzootic areas to husbandry (Pybus 2001). Natural populations of cervids are largely difficult to treat due to inability of drugs to penetrate into liver pseudocysts (Rajský et al. 2002). The side effect of treatment is presence of drugs in muscles or other tissues of cervids, what is often less desirable than drug-free animal with good tolerance of fascioloidosis. Table 1.2 summarizes data on anthelmintic drugs used in fascioloidosis treatment of free-living and domestic ruminants in North America and Europe.

In the long-term history of fascioloidosis treatment, several groups of anthelmintics with different type of agents were administrated in veterinary and husbandry practices (see Table 1.2 and references therein). Some anthelmintic groups were proved to be effective against mature and immature stages of *F. magna* in different type of final hosts (Foreyt and Todd 1974; Balbo et al. 1987; Qureshi et al. 1989). High level of efficacy (63–100 %) was detected for *triclabendazole* (*benzimidazoles*) with best results against both forms of flukes (adult and immature) in

Table 1.2 Summary of anthelmintic drugs used in fascioloidosis treatment of free-living and domestic ruminants

Group of anthelmintics	Agent	Molecular formula	Dose mg/kg	Efficacy %	Against A/I	Final host	References
Benzimidazoles	Triclabendazole	$C_{14}H_9Cl_3N_2OS$	10	100	A, I	White-tailed deer	Qureshi et al. (1989)
			11	63	A, I	White-tailed deer	Qureshi et al. (1994)
			50–60	98	A	Rocky Mountain elk	Pybus et al. (1991)
			50–60	90	I	Rocky Mountain elk	Pybus et al. (1991)
			6–12	77–88	A, I	Cattle	Craig and Huey (1984)
			20	99	I	Goat	Foreyt (1989)
	Albendazole	$C_{12}H_{15}N_3O_2S$	11–54	38	A, I	White-tailed deer	Foreyt and Drawe (1978)
			5–17	82–84	A	White-tailed deer	Qureshi et al. (1990)
			17–46	67	A	White-tailed deer	Foreyt and Drawe (1985)
			17–46	89	I	White-tailed deer	Foreyt and Drawe (1985)
			5–15	70	n.i.	Sheep	Stromberg et al. (1983)
			15–45	94–99	n.i.	Cattle	Ronald et al. (1979)
Salicylanilides	Rafoxanide	$C_{19}H_{11}Cl_2I_2NO_3$	12–25	75	I	White-tailed deer	Foreyt and Todd (1976b)
			10	n.i.	A	Red deer	Balbo et al. (1987)
			15	98	n.i.	Roe deer	Chroust (1987)
			10–15	100	A, I	Cattle	Foreyt and Todd (1974)
	Oxyclozanide	$C_{13}H_6C_{15}NO_3$	13–29	100	A	White-tailed deer	Foreyt and Todd (1973)
			7–15	27	A, I	Cattle	Foreyt and Todd (1974)
	Closantel	$C_{22}H_{14}Cl_2I_2N_2O_2$	7.5–15	94–98	A, I	Sheep	Stromberg et al. (1985)
Sulphonamides	Clorsulon	$C_8H_8Cl_3N_3O_4S_2$	12–30	92	A	White-tailed deer	Foreyt and Drawe (1985)
			12–30	80	I	White-tailed deer	Foreyt and Drawe (1985)
			21	75–100	I	Cattle	Foreyt (1988)
			21	92	I	Sheep	Foreyt (1988)

(continued)

Table 1.2 (continued)

Group of anthelmintics	Agent	Molecular formula	Dose mg/kg	Efficacy %	Against A/I	Final host	References
Halogenated phenols	Hexachlorophene	$C_{13}H_6Cl_6O_2$	12–26	50	A	White-tailed deer	Foreyt and Todd (1976b)
			12–26	0	I	White-tailed deer	Foreyt and Todd (1976b)
	Nitroxynil	$C_7H_3IN_2O_3$	11–24	0	A	White-tailed deer	Foreyt and Todd (1976b)
			11–24	50	I	White-tailed deer	Foreyt and Todd (1976b)
	Bithionolsulfoxide	$C_{12}H_6Cl_4O_3S$	40–50	100	A	Cattle	Chroustová et al. (1980)
Phenoxyalkanes	Diamphenetide	$C_{20}H_{24}N_2O_5$	255–280	0	A, I	White-tailed deer	Foreyt and Todd (1976b)
			140	n.i.	A, I	Red deer	Balbo et al. (1987)

A adult *F. magna*, *I* immature *F. magna*, *n.i.* not indicated in the respective literature

white-tailed deer, Rocky Mountain elk and cattle (see Table 1.2 and references therein). Consequently, several authors recommended triclabendazole as the best choice for fascioloidosis treatment (Craig and Huey 1984; Foreyt 1989; Pybus et al. 1991; Qureshi et al. 1989, 1994). Slightly lower efficacy (38–99 %) was observed for *albendazole* (*benzimidazoles*), which was applied for fascioloidosis treatment in white-tailed deer, sheep and cattle (see Table 1.2 and references therein).

According to the other studies on fascioloidosis therapy *salicylanilides* and *sulphonamides* were also highly effective in free-living and domestic ruminants (Table 1.2). *Rafoxanide* (salicylanilides) has high efficacy (100 %) against both forms in cattle (Foreyt and Todd 1974) and was also effective against giant liver flukes in free-living ruminants, e.g. white-tailed deer (75 %; Foreyt and Todd 1976b) and roe deer (98 %; Chroust 1987). *Clorsulon* (sulphonamides) is active mainly against immature flukes parasitizing cattle and sheep (Foreyt 1988), with rather high efficacy (80–92 %) against adult and immature flukes infecting white-tailed deer (Foreyt and Drawe 1985).

Out of *halogenated phenols*, *hexachlorophene* and *bithionolsulfoxide* were proved to be effective against adult flukes in white-tailed deer and cattle, respectively (Foreyt and Todd 1976b; Chroustová et al. 1980). *Nitroxynil* was efficient only against immature flukes in white-tailed deer (Foreyt and Todd 1976b). *Diamphenethide* (*phenoxyalkanes*) fed in medicated pellets effectively controlled *F. magna* infection in captive red deer (Balbo et al. 1987); however, authors did not declare exact efficacy of the drug. In contrast, diamphenethide used in higher dose was not effective either in adults or in immature flukes in white-tailed deer (Foreyt and Todd 1976b).

Until recently, nothing has been known about the metabolism of anthelmintics in *F. magna*. The latest study of Prchal et al. (2015) was focused on determination of the activities of drug-metabolism enzymes in *F. magna* and the metabolism of selected benzimidazoles (triclabendazole, albendazole, mebendazole) and salicylanilides (rafoxanide, closantel), which are commonly used to control fascioloidosis. Specific activities of several drug-metabolizing enzymes (e.g. peroxidase, catalase, glutathione peroxidase, flavine monooxygenase, UDP-glucosyl transferase etc.) were found in subcellular fractions.

The results showed that giant liver fluke is able to oxidize albendazole and reduce mebendazole in vitro; however, it can not oxidize triclabendazole. Ex vivo cultivation of living adult flukes with anthelmintics confirmed the ability of parasites to oxidize albendazole to albendazole sulphoxide and to reduce mebendazole. Concerning the salicylanilides, no metabolites of rafoxanide and closantel formed by *F. magna* were detected. It was concluded, that *F. magna* possess the active xenobiotic-metabolizing system, but it is not able to mediate sufficient protection against anthelmintic drugs (Prchal et al. 2015).

Comparing to other veterinary important parasitoses, fascioloidosis is responsible for generally lower economic consequences. Probably due to this fact, no specific pharmacological therapeutics are available till now. Therefore, preventive measures are of high importance. Particularly high risk represents the feeding with hay from meadows, where are commonly found either infected free-living

ruminants or aquatic snails, intermediate hosts of *F. magna*. The suitable alternatives seem to be timely reduction of parasite spreading by physical methods (e.g. drainage or drying of pastures), application of molluscicides to grassland or introduction of competitive species of snails, which eliminate intermediate hosts in habitat (Novobilský and Koudela 2005).

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