Babesiacidal Drugs

See Table 1

Table 1. Babesiacidal drugs used in domestic animals

Economic Importance

Members of the genus *Babesia* occur throughout the world and may cause a wide range of clinical syndromes in most domestic animals and humans due to differences in virulence within each *Babesia* species. They are transmitted by hard ticks (Ixodidae) during blood meals, and may produce diseases in their hosts, which are characterized by an acute febrile reaction, jaundice, hemolytic anemia, hemoglobinuria and variable mortality. The babesiosis is of major economic importance in cattle because the majority of about 1.2 billion cattle in the world are potentially exposed to *Babesia* spp. because of the extensive husbandry methods employed in raising these animals. *Babesia* spp. infections may also occur by the frequent introduction of *Babesia*-free animals into *Babesia*-enzootic areas, and by introduction of tick vectors and *Babesia* spp. into clean zones. The greatest economic loss is due to *Babesia* spp. infections in cattle, particularly in the USA, Australia (State of Queensland), South Africa, and South America. Indigenous animals are normally protected from babesiosis in early life by premunition resulting from continuous reinfection. In regions with enzootic stability babesiasis is not a disease problem, and control measures are not necessary. In these zones calves are still protected by maternal antibodies which they had received through the colostrum. Subsequently the animals remain carriers by repeated natural infections.

Epizootiology and Enzootic Stability of Bovine Babesiasis

The idea of maintaining enzootic stability is to allow limited challenge of the parasite and the tick to cattle without producing disease or loss of production. The immune status of a herd can be monitored serologically, and in cases where more than 50% of cattle show no antibabesial serum titres the whole herd should be vaccinated. Thus, the efficient application of vaccination procedures depends considerably on the epizootiology of babesiasis, and involves knowledge of the complex interaction of the host, *Babesia* parasite, and vector. The aim of premunization (Premunization and Use of Antibabesial

Drugs (Chemoimmunization)) or immunization with live blood-derived vaccines of attenuated strains of *B. bovis* and *B. bigemina* is to maintain herd immunity, and thus the balance between host and vector. In various countries the idea of reestablishing areas of enzootic stability has strongly been supported, particularly after the introduction of so-called "tick-resistant" cattle, and the occurrence of increasing failures of chemical control measures.

Strategic Tick Control in Areas with Enzootic Instability of Babesiasis

Attempts at controlling babesiasis in districts with enzootic instability (i.e., where less than 90% of cattle show premunition) can be directed against the tick vector (for more details see control of ticks, and application techniques). There are one-host ticks (e.g., *Boophilus* spp.), two-host ticks, and three-host ticks (e.g., *Rhipicephalus* spp., *Haemaphysalis* spp.; *Ixodes ricinus*) which can be controlled by aggressive or strategic dipping (this latter method may involve three dippings in the dry season and is used for example in Australia) plus pasture improvement and/or pasture spelling at intervals of 8–10 weeks in summer or early autumn. Aggressive dipping is still imperative in areas where, in addition to babesiosis, East Coast fever, heart water due to *Cowdria ruminantium* infection and anaplasmosis (*Anaplasma centrale* and *A. marginale*) occur. This method involves acaricide administration at regular intervals, either throughout the year or during tick seasons, with the aim of eliminating the tick vector. The application of acaricide can be done in any of three ways. These may be (1) a plunge bath, communal dip, or dip on large farms, (2) a spray-race (system of pipes fitted with spraying nozzles) on large farms, or (3) a hand-spraying system consisting of a large water container and a hand-pump or small motor-pump. The strategic dipping system, i.e., administration of an acaricide at certain time intervals, may lead to temporarily unstable situations since transmission of *Babesia* spp. and *Anaplasma* spp. is not completely interrupted; in this case an additional vaccination against both organisms is advisable.

Tick Control in Livestock to Prevent Babesiosis

Today, the only conventional control measure against argasid and ixodid ticks is the use of acaricides for animals at risk. Pesticides belong to different chemical groups such as chlorinated hydrocarbons, organophosphates, carbamates, diamidines, synthetic pyrethroids, and avermectins. Drugs of these groups have different mode and site of actions. For instance the growth regulator **fluazuron** inhibits the chitin formation in ticks. Its effect results in reduced production of viable eggs in engorged females and may reduce pasture contamination.

Acaricidal control of vectors to protect animals from disease has been applied in many countries although with only limited success, as ticks rapidly developed resistance to pesticides and acaricides (Ectoparasitocidal Drugs, Arthropodicidal Drugs). However, acaracide treatment continues to be necessary although drug tolerance of ticks to most agents, except the macrolytic lactones, is common. In the field, there may occur tremendous economic losses due to breakdown of dipping systems in various regions, the increasing cost of acaricides often beyond the means of many farmers, and the lack of

veterinary infrastructure in many countries have made the eradication of tick vectors impossible.

Closantel used for the control of helminthic infections (Nematocidal Drugs, Animals, Nematocidal Drugs, Man, Trematodocidal Drugs) of sheep and cattle, and larval stages of nasal bot fly (*Oestrus ovis*) of sheep has been shown to have a marked effect also on fecundity and egg viability of ticks. The strongly plasma bound drug is ingested by ticks while feeding and probably affects their mitochondrial energy production by inhibiting oxidative phosphorylisation and thereby adenosin triphosphate synthesis. Thus closantel may play a role in tick control strategies, due to its effect on tick reproductive cycle being greatest at time of dosing. Current alternative control measures and their effective use in the field are still of minor importance. Biological control of ticks with living antagonists distributed by man to lower pest (parasite) populations may lead to their reduction and so to acceptable subclinical densities. In the field, however, the use of biological agents as formulations (products) of viruses, bacteria, fungus, protozoans (e.g., microsporidia), nematodes, and insects, or pheromones, are very much limited and less promising in their effects today. A more successful control measure against widely distributed *Boophilus* spp. and other tick species seems to be the immunisation of cattle with recently developed anti-tick vaccines. The antigens of interest against ticks are native or recombinant proteins located in the gut cells' plasmatic membrane. They are called " novel, concealed, or occult antigens" causing lesions in the tick's intestine thereby reducing the fecundity of ticks. Other putative antigens seem to be located in cells of the salivary glands preventing feeding of the ticks and thus depressing their fertility.

Control of Babesiosis by Various Application „Techniques of Acaricides

Acaricides can be applied to animals by different application techniques. When treating animals for external parasites it is important that agents not absorbed through the skin or from the digestive tract or parenteral injection be so applied that contact with the parasite will occur. Dips and sprays generally are suited for treating most animals (especially herds) except when temperatures are below freezing or extremely thirsty animals are to be treated. Systemic drugs, usually the organophosphates and macrocyclic lactones (ivermectin, moxidectin, doramectin, and eprinomectin) are applied as pour-ons, spot-ons, injectables, sprays and feed additives, or via dipping vats (tanks). These agents gain access to the host circulatory system and are then distributed throughout the body.

Dipping probably offers the best means and most cost effective method of tick control for cattle in tropical areas, and for dogs (is less frequently used for cats). Dipping with acaricides has the advantage of thorough coverage of the skin, coat, and head of cattle (if deep tanks are used). When using such agents caution must be exercised to prevent contaminating humans and their food supply and environment.

Premunization and Use of Antibabesial Drugs „(Chemoimmunization)

Bovines of an enzootic area commonly acquire a so-called infection-immunity or **premunition** against babesiosis in the first six months of life. As a result, most of the

cattle of enzootic areas are carriers of a few parasites and will therefore develop a certain degree of protective immunity against local *Babesia* strains without showing signs of disease. In contrast, elimination of the infection by curative agents is soon followed by loss of resistance to the parasite in most hosts. Cattle introduced from areas free of babesia or with parasites of different antigenic strains, may acquire babesiosis and die. **Premunization** (artificial induction of premunition) has allowed the introduction of quality cattle into enzootic areas of Australia, USA, Latin America, and elsewhere. Animals introduced are injected with blood from babesia carriers and monitored for the presence of fever and parasitemia. Soon after clinical signs are apparent, animals are treated with subcurative doses of diminazene aceturate or imidocarb dipropionate (Table 1), thereby killing enough parasites to prevent an outbreak of disease but allowing some surviving parasites to induce protective immunity to natural challenges in hosts. Animals can be injected simultaneously with a standardized dose (several million organisms of each species per animal) of *B. bigemina*, *B. bovis*, and *Anaplasma marginale* (*Rickettsia* species) derived from blood of donor bovines often splenectomized. They are then treated well timed with Imidocarb or with long-acting tetracyclines, which are active against both Babesia and Anaplasma. Premunization has several drawbacks. The main obstacles, like the occurrence of hemolytic disease in newborn calves (antibodies against erythrocyte isoantigens), transmission of other blood-born pathogens (e.g. leukosis virus), or storage and transportation problems of the `**vaccines**', have largely been overcome but some problems remain. Thus premunization prevents eradication of the parasites, may cause economic losses (outbreak of disease or occurrence of mortality in herds), may induce a variable resistance status in cattle, and is expensive. On the other hand there may be some advantages concerning premunization. Thus its application is still needed in large enzootic areas because refinements to the system of immunization with attenuated parasites are not yet satisfactory with regard to tolerability of vaccines. Occasionally there are adverse effects such as abortion, hemolytic neonatal disease, or induction of severe babesiosis. The safety of blood derived vaccines is not always guaranteed and transmission of other hematogenous infections cannot be absolutely excluded. This may also be true for the stability of vaccines. They may fail to induce strong herd immunity because of instability of vaccinal parasites or changes in selection of field strains, or prolongation of vaccine shelf life beyond expiration date. Intolerability of vaccines may be shock and disturbances of the blood clotting mechanisms, and calcium balance.

Chemotherapy of Babesiosis in Animals

The elimination of babesias (Table 1) in cattle or horses may play an important role for those animals which have a low-grade infection premunition. In these cases it must be guaranteed that carrier animals are free from infection before being imported into *Babesia*-free areas. However, when drugs are used therapeutically in endemic regions the aim is to promote clinical recovery only, and to allow some parasites to survive, reestablishing premunition. Thus, instead of the chemoimmunization programs (Premunization and Use of Antibabesial Drugs) that are used in districts with enzootic stability or instability, in countries where babesias are rare the so-called diagnosis-treatment method is employed. There are several drugs in use, all of which are

"oldtimers" and are more or less afflicted with adverse effects involving long withdrawal periods for meat and other edible tissues. Drugs commonly used in treating acute ovine or porcine babesiosis are quinuronium sulfate, imidocarb, and diminazene, which have sufficient efficacy against clinical attacks. Infections with *Babesia* spp. in sheep, goat, and swine must be treated with somewhat higher doses than those normally recommended in cattle. Repeated administration of drugs may be necessary to cure *B. ovis* infections (for details regarding activity and toxicity of antibabesial drugs see Table 1, Trypanocidal Drugs, Animals; for pharmacokinetics of diminazene diaceturate and ethidium bromide see Trypanocidal Drugs, Animals/Pharmacokinetics of Trypanocides and Chemical Residues in Edible Tissues and Milk). The effect of an antibabesial drug may vary and can be modified by the severity of the disease, the dosage used, the timing of treatment in the course of infection, and the length of time that the drug is present to affect the parasite. As a rule, large *Babesia* spp. are distinctly more susceptible to chemotherapeutic agents than are the small ones. In general, the latter respond variably to antibabesial drugs. **Sterilization of infection**, i.e., complete elimination of parasites, is usually not achieved with small *Babesia* spp. possibly due to adherence of parasites to capillary walls and consequent obstruction of blood flow. There may be differences in relation and metabolism between small and large *Babesia* spp., and as a result the target and biochemical mode of action of drugs differ. Recovery of ill animals can be achieved if specific and effective treatment is given prior to the onset of severe anemia or disorders of the nervous system, i.e., in the early course of infection. Prognosis is poor for those animals already showing cerebral signs; these are caused by clumps of parasitized erythrocytes blocking capillary blood vessels of cerebral cortex. In severe cases the aim of supportive treatment (e.g. blood transfusion, fluid therapy) is to reduce the occurrence of shock and disturbances of the blood clotting mechanisms and calcium balance.

Elimination of Babesia in Horses

Equine babesiasis is widespread; severe clinical disease and mortality may occur occasionally. Therefore, the elimination of carrier infection in horses being shipped from endemic zones to *Babesia*-free areas gains increasing importance. Various drugs may be used for clearing *Babesia caballi* infections. Amicarbalide (8.8 mg/kg body weight, x2, 24 h interval), imidocarb (1–2 mg/kg body weight, x2, 24 h interval), diminazene (5 mg/kg body weight, x2, 24 h interval), and phenamidine (8.8 mg/kg body weight, x2, 24 h interval) may show sufficient action. *B.equi* (small species) has recently been transferred to the genus *Theileria*.

Elimination of Babesia in Dogs and Cats

Canine babesiosis is becoming increasingly widespread in the USA, Europe, Africa (*B. canis*) and Asia (*B. gibsoni*). The disease can be treated with a few antibabesial drugs causing more or less toxic side effects, such as diminazene (which is not recommended for use in dogs by the manufacturer, Table 1), imidocarb, amicarbalide, phenamidine and trypan blue. *B. canis* may cause uncomplicated infections (fever, depression, acute hemolysis with a mild to severe anemia, pale mucous membranes, and splenomegaly), or complicated ones (coagulopathy, hepatopathy, immune-mediated hemolytic anemia, renal

failure, cerebral signs, pulmonary oedema, and shock). The specific therapy (if started too late, or in case of complicated infection per se) must be combined with supportive treatment (fluid infusion followed by blood transfusion, liver protectants, diuretics, vitamin B complexes, prednisolone). In general, drugs are distinctly less active against *B. gibsoni* than against *B. canis*. Relapses in *B. gibsoni* infections are common, and may also occur after administering markedly higher doses than those recommended. Thus, diminazene in doses of 7–10 mg/kg body weight only suppresses parasitemia, but these doses and even lower ones may cause severe side effects and occasionally mortality in dogs (Raether unpublished). *B. felis* infection, which may cause anemia and icterus in the domestic cat, has been reported to respond to trypan blue and quinuronium. These results are inconsistent with those of Potgieter who found that all known antibabesial drugs failed to affect *B. felis*; successful treatment was achieved in using primaquine diphosphate. Concerning differential diagnosis of feline babesiosis *Cytauxzoon felis* infection (*Theileria* species) should be considered; it may occur in North America and parasitizes lymphocytes and erythrocytes of cats.

Chemoprophylaxis of Babesiasis in Animals

The aim of chemoprophylaxis is to protect susceptible animals from clinical signs of babesiosis caused by natural tick infection, or to moderate the clinical course of infection in immunization programs (Premunization and Use of Antibabesial Drugs). The administration of drugs like **diminazene**, **imidocarb,** or **oxytetracycline** (Table 1) should allow the development of premunition. Imidocarb, which exhibits a fairly long effect on *Babesia* spp. in cattle (4–12 weeks at 2 mg/kg body weight, depending on *Babesia* species, and infection pressure), can also be used for short-term protection of susceptible animals after their introduction into *Babesia*-infected areas.

A single subcutaneous dose of 2.4 mg/kg body weight **imidocarb** may protect dogs from *B. canis* infections for about 4 weeks. However, controversy exists concerning the duration of its prophylactic efficacy. So in Beagle dogs experimentally infected with *B. canis* (merozoites), a single dose of 6mg/kg body weight resulted in a 2-week protection period only. In enzootic *Babesia* areas, dogs can also be protected by long acting acaricides applied in 4-day-intervals, or by application of an inactivated vaccine (Pirodog®, available in France, Switzerland). Although this vaccine allows *Babesia* infection under high infection conditions it may prevent infected dogs from mortality.

Resistance

Although malaria and babesiosis have many similarities, and their causative agents are related, resistance of Babesia and malaria parasites to drugs differs markedly. While resistance of *P. falciparum* to drugs has probably become the most important threat to effective control of malaria, drug resistance in large *Babesia* spp. seems to be a minor problem in the chemotherapy of babesiosis. Resistance to antibabesial drugs can be induced experimentally. Thus in vitro micro-titres tests (96-well flat-bottom plates) may be used to assess drug responsiveness of *B. bovis* or *B. bigemina* to various antibabesial compounds, thereby selecting drug-adapted lines by the presence of sub-inhibitory drug concentrations. Under field conditions drug resistance in *Babesia* spp. may emerge if

drugs are used prophylactically or in chemoimmunization programs. Using such dose regimes it is likely that subtherapeutic, low concentrations of the drug are in temporary or permanent contact with the parasites, thereby causing selection of drug-resistant organisms. However, it must be emphasized that the innate poor response of small *Babesia* spp. (e.g., *B. bovis*, *B. ovis*, *B. gibsoni*, *B. felis*, *B. microti*) to antibabesial drugs should be distinguished from an acquired drug resistance occasionally occurring in large babesias. Compared to the greater drug sensitivity of large *Babesia* spp., the varied action of drugs against small forms ("natural resistance") may well be connected with differences in their relation. Small species undergoing schizogony in lymphocytes (e.g. *B. microti*) appear in their fine structure very similar to *Theileria* spp. Molecular analyses of the small subunit ribosomal RNA genes (rDNA) suggest that small *Babesia* spp. may have a close relation to *Theileria* spp. There were a number of reasons why *B. equi* was transferred to the genus *Theileria*.

Chemotherapy of Human Babesiosis

Since the first description of human babesiosis in 1957 in a splenectomized patient in Yugoslavia there have been several case reports from the USA, Europe, and other countries on babesiosis in man. The acquisition of human babesiosis may depend on contact with subadult stages of certain *Ixodes* ticks, e.g. *I. dammini* (its main host is white-footed mouse, *Peromyscus leucopus*), and *I. ricinus* possibly transmitting *Babesia microti* (a rodent piroplasm) and *B. divergens* (a parasite of cattle), respectively. *B. gibsoni* is a parasite of dogs, and WA-1, a *B. gibsoni*-like piroplasm, has been documented in residents along the Pacific Coast of the USA, and may infect humans in Taiwan and South Africa too. The host (vector/tick) of WA-1 and its reservoir are still unknown. Although closely related to *B. gibsoni*, WA-1 should not infect dogs. However, it is highly pathogenic for most rodents. In humans WA-1 and *B. microti* may cause a similar course of infection and symptoms. Apparent **clinical signs** are parasitemia (intraerythrocytic parasites show characteristic tetrad forms), fever, rigors, cough, headache, vomiting, anorexia, and dark-colored urine. Spleen-intact humans infected with *B. microti* or WA-1 may well respond to a combination of **clindamycin** (macrolide antibiotic) and **quinine** (chinchona alkaloid, Table 1, Malariacidal Drugs/Malaria of Human) although quinine proved to be totally ineffective against *B. microti*. In many areas of Europe, the enzootic cycle of *B. microti* may obviously depend on uniquely mouse specific tick, *I. trianguliceps*. Possibly for that reason this species is not transmitted to humans, or its European strains are not pathogenic to humans. Reported cases of human babesiosis in Europe are due to *B. divergens* and chiefly occur in farmers and other persons frequently in contact with cattle. As a rule, *B. divergens* infections in man show rapid increasing parasitemia, and damage of large numbers of infected red cells causing massive hemoglobinuria, intravascular hemolysis and renal failure. Therefore an early start of specific treatment is important for any patients infected with *B. divergens*. The treatment of choice seems to be the immediate administration of clindamycin (adult dosage: 1.2 grams 2x/d IV or 600mg 3x/d PO × 7d) plus quinine (650mg 3x/d PO × 7d; all doses cited are from Medical Letter, 1995; pediatric dosage for both drugs see there). Chemotherapy is followed by a massive exchange transfusion to

reduce parasitemia, i.e., to remove physically large numbers of infected red cells and prevent extensive hemolysis and renal failure. Exchange transfusion may be used as an alternative or in addition to chemotherapy relying on relatively toxic drugs. However, this therapy with its attendant risks should be reserved for heavily parasitized and seriously ill patients only. Symptomatic and other supportive care should be associated with specific treatment. Clindamycin plus quinine treatment proved to be insufficient in immunosuppressed patients or in HIV infected ones. Therefore, in foudroyant infection courses massive blood exchange may be life saving or application of **atovaquone** as was recently shown.

Pentamidine isethionate (a trypanocide, see Trypanocidal Drugs, Man) has shown good activity against *B. microti* but failed to eliminate parasites from blood completely.

Diminazene aceturate (Table 1 and Trypanocidal Drugs, Animals), an aromatic diamidine like pentamidine and approved for use in animals only, has also been tested in humans. The drug was successful in treating a *B. microti* infection, which did not respond to therapy with oral chloroquine phosphate. The infection was eliminated, but the patient developed acute iodiopathic polyneuritis, probably related to the diminazene therapy.