Introduction:

Goats are one of the most domesticated small ruminants which are mainly used for production of milk, meat, wool, and leather particularly in arid, semi arid mountainous countries (Morand, 2004). Despite the major environmental changes, goats are still of considerable economic importance for the poor families.

In Republic of South Sudan, goats were reared for milk, meat and socially in marriage. Nilotic goat (true dwarf) is the major breed of Republic of South Sudan (Mason and Maule, 1960). These goats live scavengers in streets. Nevertheless Nilotic goats play a very important role in the rural economy. The Nilotic goats are distributed at the latitude 12° N in Republic of South Sudan specially around Nile, shanty, swampy and tsetse fly areas. They are found in Southern states of Yei, Torit and Latuka areas, Bari and Taposa (Atlas Animal Resource-Sudan 1994-1995).

It is well known that trypanosomosis is a vector-borne disease of humans and livestock. It is caused by a unicellular, flagellated protozoa of the genus trypanosoma, and it is a major health problem for domestic and wild life animals particularly in Africa, Asia and South America (Fernandez, *et al.,* 2009). Trypanosomosis in goats produces acute, subacute and chronic or subclinical forms. The most causative trypanosomes for goats are *T.evansi, T.vivax,* and *T. conglense* (Gutierrez, *et al.,* 2006).

Transmission of trypanosomes can occur through different routes; mainly cyclical transmission and is restricted to *Glossina* species only (Soulsby, 1982), mechanical transmission; materialized by two means,

firstly biting insects e.g *Tabanids* and *Stomoxys* and secondly through operating by contamination instruments (Vilenberg, 1998). Also transmission can occur by other means such as bites of vampire bats (Hoare, 1965). Venereal transmission in dourine of equines (Vilenberg, 1998). Moreover, congenital transmission from mother to the offspring through placenta while the feotus in the uterus or when bleeding occurs during birth. Carnivores were reported to be infected by ingesting meat or organs from infected animals as long as these are still sufficiently fresh to contain live trypanosome (penetration through the mucous membrane). Since sheep and goats herded together with camels, are likely to be infected with *T.evansi* (Ngerenwa, *et al.,*1993). It has been reported that goats may serve as a reservoir host of trypanosoma infection for the other animal species (Gutierrez, *et al.,* 2004). Abdalla and Elmalik (2002) studied the incidence of trypanosomosis in sedentary cattle at Umbenen and Abunaama areas (Singa area, Sinnar state, Sudan) and mentioned that possible source for trypanosomosis infection within the herds studied are sheep and goats. The control groups of goats which experimentally infected with *T.evansi* and *T. vivax* in the study of Youssif, (2005) about the Pharmacotoxicity of some trypanocidal drugs in food animals showed severe parasitaemia on days 7-10 post infection and animals died 9-11 days (*T.evansi*), while *T.vivax* showed severe parasitaemia on days 13-17 and death occurred on day 17 post infection. The clinical signs in *T.evansi* infection were hypothermia, frothy salivation, mucopurulent conjunctivitis and mucopurulent nasal discharge, decrease in appetite gradually until lost, severe diffuse alopecia, diarrhoea, depression, muscle tremors, convulsions and shivering, increase in respiratory rate, decrease in pulse rate and blood pressure, swollen lymph nodes, testes were swollen and hot, cachexia and recumbent with lateral kink of the neck then death.

In *T.vivax* the clinical signs were hypothermia, watery lacrimation, mucopurulent conjunctivitis and mucopurulent nasal discharge, frothy salivation, decrease in appetite until lost, watery yellowish diarrhea, muscle tremors, increase in respiratory rate and blood pressure, decrease in the pulse rate, cachexia, recumbent with lateral curvature of the neck and the death.

Generally four groups of anti-trypanosome were used: diamidines compounds, Aminophenanthridium compounds, Quinapyramine compounds and other compounds such as Melarsorpol, Cymelarsan (Arsenical compounds), Suramin, Samorin and Nitrovinylferan (Bywater, *et al.,* 1991). It is important to realize that drugs alone will not treat trypanosomosis because trypanosomosis overwhelm the immune system (Immunosuppressive). Treatment will be more effective in well fed and rested animals as chemotherapy stopping the multiplication of trypanosomes and this helps the immune system to overcome the infection (Osman, *et al.,* 1992). The control of trypanosomosis depends on two ways: the use of chemotherapy/chemoprophylaxis programs and vector control. However, the treatment/prophylactic programs is the current method going on because it is easier to eradicate the trypanosomes than the vectors (Brown, *et al.,* 1990).

Chapter one.

1. Literature Review:

1.1.*Trypanosoma evansi:*

Trypanosoma evansi belongs to the genus Trypanosoma, subgenus Trypanozoon (salivarian section) together with (i) *T. brucei brucei*, one of the agents of a disease called Nagana in livestock, and for which wild animals often act as a reservoir; Nagana is a complex of diseases due to a number of Trypanosoma species including mainly *T. brucei brucei, T. vivax*, and *T. congolense* which have a great impact on cattle breeding in Africa;(ii)*T. brucei rhodesiense* and *T. brucei gambiense* are responsible for Human African Trypanosomiasis (HAT) or sleeping sickness, to which 60 million people are exposed in 36 sub-Saharan African countries; 70,000 persons are thought to be infected and the disease is most often fatal in the absence of treatment;(iii)*Trypanosoma equiperdum*, which is sexually transmitted in Equidae and is responsible for a disease called dourine (Rodgers, 2009 and WHO, 1998).

The word “surra” comes from the India and means “rotten,” which qualifies the state of the animals after chronic evolution of the disease (Vittoz, 1995), this especially fits to the evolution of the disease in camels. *Trypanosoma evansi* and surra are found under various names; Hoare (1972) reviewed the literature and found the parasite under more than 30 names, while the disease was found under an even greater number of vernacular names (Stephen, 1986). In Venezuela: *T. equinum* or *T. venezuelense* was found to be the agents of Peste-Boba or Derrengadera (which means “limping”), in relation to nervous clinical signs in horses; in Argentina *T. hippicum* was found to be responsible for Mal de Caderas, in relation to the posterior paralysis of the legs, before

the single name of *T. evansi* was adopted; however the disease is still found under its local names world over such as Murrina in Central America (Stephen, 1986).

In Africa, for example, surra is found under the Arabic name Debab (El debab in Algeria) which means fly (linked to the vector) (Atarhouch *et al,*. 2003), and also Mbori in Sudan, Guifar or Dioufar in Chad, Menchaca (which means “emaciated” despite sufficient food provision) in Touareg populations of the Agadez area, Niger (Antoine-Moussiaux *et al,*. 2007), Yudleye or Yudle, which refers to an emaciated camel aimlessly moving or jolting forward, or even Dukhan or Salaf (or Salef) in Somali (Dirie and Abdurahman, 2003) or Tahaga and su-auru (Stephen, 1986). The parasite itself was found under various names: *T. soudanense*, *T. marocanum*, *T. aegyptum,* and *T. cameli* before the single taxon *T. evansi* was accepted (Hoare, 1972).

1.2.Origin:

Trypanosoma (Trypanozoon) evansi (Steel 1885) Balbiani, 1888, is the first pathogenic mammalian trypanosome to be described in the world, in 1880, by Griffith Evans, in the blood of Indian equines and dromedaries (Hoare, 1972). Its principal host is originally the camel but it is present in dromedaries, horses, and other Equidae as well as in a large range of other hosts.

Trypanosoma evansi is thought to be derived from *T. brucei brucei* (cyclically transmitted by tsetse flies), but it is no longer able to undergo its cycle in Glossina due to the loss of the maxicircles of kinetoplastic mitochondrial DNA (Borst *et al.,* 1987). When this phenomenon occurred is not known, and some authors even recently suggested that it might have occurred in several instances (Lai *et al.*, 2008). *Trypanosoma evansi* is mainly a parasite of camels *(Camelus dromedarius),* the host species in

which it probably early developed from *T. brucei brucei*. However, it is pathogenic in other Camelidae, such as the Bactrian camel *(Camelus bactrianus*). *Trypanosoma evansi* is highly pathogenic in Equidae, especially in horses (*Equus caballus*), and also in asses and donkeys *(Equus asinus)* together with their crossbreeds (mules), in which it is responsible for a sometimes acute disease, but most often chronic (Hoare, 1972).

In Africa *T. evansi* is present in all countries where camels are present, north of a line extending from Senegal (15° North) to Kenya (equator), above the tsetse belt; it is found not only in Mauritania, Morocco, Algeria, Tunisia, Libya, Egypt, Sudan, Eritrea, and Ethiopia, but also in the northern parts of Mali, Burkina Faso, Niger, Nigeria, Chad, Somalia, and Kenya (Hoare, 1972). Nowadays, its geographical distribution is continuous from the northern part of Africa through the Middle East to South-East Asia.

Although it is not possible to date the initial spread of *T. evansi* eastwards, the analysis of historical data suggests that surra was already present in India since time immemorial, at least VIII centuries B.C., and that livestock must have suffered from it in the absence of treatment (Hoare, 1972). It is present in sub-Saharan and Mediterranean climates but can be found in temperate areas as well as in arid deserts and semiarid steppes.

Dia and Desquesnes (2007), reported that *T.evansi* can infect cattle (*Bos taurus*) in Africa; however they are sometimes refractory to the infection, can affect pigs (*Sus scrofa*), domestic sheep (*Ovis aries),* and goats (*Capra hircus*). It is considered as nonpathogenic in the African buffalo (*Syncerus caffer*), in the serum of which a trypanolytic component was recently demonstrated (Reduth *et al.,* 1994). It is

occasionally found in domestic cats (*Felis domesticus*) (Tarello, 2005), and regularly in dogs *(Canis familiaris)*, which may act as sentinel animals as observed in the surroundings of slaughter houses, since they can acquire the infection when eating fresh raw meat from infected animal. To conclude, in Africa, *T. evansi* is mainly a parasite of camels, which act both as the main host and a reservoir; it is sometimes found in horses and dogs, in which the infection is most often fatal.

In the world *T. evansi* is found in host species introduced by humans, such as horses, cattle, buffaloes, sheep, and goats, but it has also been found in a very large range of local wild hosts. It is principally pathogenic in horses, sometimes with a very high prevalence, reaching 73% to 83% in the outbreaks reported from Brazil or Guyana (Desquesnes, 2004, Herrera *et al.,* 2004). It is found in water buffaloes with a prevalence reaching 40% in some instances (Herrera *et al.,* 2004, and Dávila *et al.,* 2003); however, in the past, clinical signs of trypanosomosis in buffalos have most often been reported in infections due to *T. vivax* (García *et al.,* 2006), rather than *T. evansi.* It has been reported in cattle with a prevalence of around 10% in Brazil, but there are no reports of pathogenic effects. *T. evansi* is regularly found in dogs, which are also infected by *T. cruzi*, and sometimes leishmania (Savani *et al.,* 2005). Several reports from Guyana mentioned ocular haemorrhages and death with cardiac signs (Desquesnes, 2004). Guinea pigs *(Cavia porcellus*) can harbour the parasite, specifically in Peru, where they are raised for meat.

T. evansi is continuously present eastwards, in the Arabian peninsula, including Saudi Arabia, Oman, the United Arab Emirates, Jordan, Israel, Lebanon, Syria, Iraq, and Turkey, and even with one occasional record in Bulgaria; it is present from Iran to Kasakhstan as

well as in Afghanistan and Pakistan (Desquesnes *et al.,* 2009). Hoare (1972), said that it is conceivable that surra was introduced beyond Africa by the ancient Egyptians since they used dromedaries in their military campaigns in Arabia, Mesopotamia, Persia, and Baluchistan.

Trypanosoma evansi is present in India, China, Mongolia, Russia (from Kuibyshev, 53°N, to the Caucasus, 44°N), Bhutan, Nepal, Myanmar, Laos, Vietnam, Cambodia, Thailand, Malaysia, the Philippines, and Indonesia (Luckins, 1988). Its presence was suspected in Papua New Guinea but was not confirmed (Reid *et al.,* 1999). It is so far absent from Australia (Reid, 2002).

The extension of *T. evansi* toward the West is more recent. It was introduced into Latin America in the fifteenth century with the Arabian horses belonging to the Spanish conquistadores (Hoare, 1965). It was described for the first time on the Island of Marajo (Amazon estuary) in 1827, and was further observed in Paraguay (1847) in Pantanal, Brazil (1850), and Mato Grosso, Brazil (1860), before spreading into Bolivia, Venezuela, Guyana, and Colombia; it is present in Central America up to Mexico (Hoare, 1972). Nowadays, epizootics due to *T. evansi* are described periodically from Argentina to Panama (Wells, 1984), a geographical distribution related to the vampire bat *Desmodus rotundus*, a new host-vector reservoir of the parasite (Hoare, 1972).

Trypanosoma evansi recently arrived in the Canary Islands (Spain) where it has been regularly observed since 1995 (Gutierrez *et al.,*1998); it is thought to have been imported there by illegal introduction of camels from enzootic countries such as Mauritania or Morocco.

Toward the North, *T. evansi* was recently introduced on the Spanish mainland, in the Province of Alicante, where an outbreak occurred in a mixed camel and horse farm (Tamarit *et al.,* 2010). It was also introduced

into France, in 2006, in a single epizootic focus in camels imported from the Canary Islands (Desquesnes *et al.,* 2009). These incursions into Europe should lead the sanitary authorities to include *T. evansi* among the animal health conditions for international trading of live animals within the European Union and other countries; thus, new procedures including diagnosis, curative or preventive treatment and quarantine should be established to ensure the status of these animals (Gutierrez *et al.,* 2010).

1.3.Transmission:

In the subgenus Trypanozoon, mechanical transmission of *T. brucei spp*. was described both through contamination by sucking flies and through serial biting action by biting insects such as *Tabanids* and *Stomoxes* (Mihok *et al.,* 1995), including tsetse as mechanical vectors (Roberts *et al.,*1989). In the particular case of *Trypanosoma evansi,* due to a loss of genetic material, the parasite can no longer undergo its cycle in tsetse flies, thus it is mainly mechanically transmitted by biting insects, which probably selected parasites presenting the best ability for such transmission. For this reason, *T. evansi* spread outside the tsetse belt in Africa, towards the Middle East and Southern Asia, and was exported with livestock to Latin America, and even to Australia and Europe (Hoare, 1972), although in the latter cases, early eradication was possible.

It is not only the transmission of *T. evansi* that is different from that of the other African trypanosomes, but also its capacity to invade a host's tissues (such as *T. equiperdum*). The most pathogenic African livestock trypanosomes, *T. congolense* and *T. vivax*, known as blood parasites, exhibit a direct relation between pathogenic effects and the presence of parasites in the blood. Although *T. evansi* can exhibit very high parasitaemia, especially in camels, horses, and dogs (and even occasionally cattle and buffaloes), it must be considered as both a blood

and tissue parasite, due to its ability to invade the nervous system, not only in horses and dogs but also in cattle, buffaloes, and pigs (Holland *et al.,* 2003). When the parasite is in very low numbers (although able to induce immunosuppressive effects), or when it is absent from the host blood stream (although present in the nervous system), identification of the etiological agent and evaluation of its pathogenic effects and impact are especially difficult. For these reasons, medical and economic impacts of *T. evansi* have most often been underestimated (Hoare, 1972).

1.4.Diagnosis:

Due to the absence of pathognomonic signs, clinical examination is of little help in the diagnosis of animal trypanosomosis (Losos, 1986). Definitive diagnosis of the disease is based on the identification of the trypanosomes in the blood samples of animals, using parasitological methods (Itard, 1989). Microscopic examination of fresh blood samples may be carried out on wet-blood films. The parasites are identified by their motility in the wet films, examined using a clear-background or phase-contrast illumination. Preparation and examination of thin and thick blood films stained by Giemsa, May-Grunwald-Giemsa, Stevenel blue or methylene blue staining techniques, have been described. Specific diagnosis of trypanosome species is possible on stained blood films using trypanosome morphological characteristics (Itard,1989). In cases of low parasitaemia, infection may not be detected by wet, thin and thick film methods. Therefore, the techniques of concentrating trypanosomes by centrifugation of a whole blood sample or separation of the trypanosomes by filtration or erythocyte lysis are adopted to improve the efficiency of diagnosis (Baker, 1970). The blood is concentrated in heparinized capillary tubes after centrifugation in the haematocrit centrifugation technique (HCT); Woo, (1971) and the buffy coat method (Murray *et al.*,

1977). After centrifugation, the capillary tube in HCT is mounted on glass sides with immersion oil covering the buffy coat-plasma junction, which is examined for trypanosomes. The capillary tubes in BCM are cut with a diamond pencil at the buffy coat-plasma junction and the content at the junction is smeared on a glass side and is examined as a wet film (Murray *et al.*, 1977).

The miniature anion-exchange centrifugation method (mAEC), separates the trypanosomes from the erythrocytes on a DEAE column, the elute containing trypanosomes is centrifuged and the sediment examined by wet film method (Lumsden *et al.*,1979). The silicone centrifugation method (SCM), separates the trypanosomes after layering of the blood on silicone fluid (Ogbunude and Magaji, 1982). The erythrocyte lysis centrifugation method (LCM), Itard, (1989) involves the lysis of erythrocytes by mixing heparinized blood with twice the volume of distilled water, after which the fluid's osmolarity is balanced with a hypertonic solution, centrifuged and the sediment examined by wet film method. The wet, thin and thick film methods were considered poor diagnostic tools for animal trypanosomosis (Kalu and Agu, 1984), when compared with the concentration methods (Kalu *et al.*, 1986). The HCT was less sensitive than the BCM (Paris *et al.*, 1982). The superiority of BCM over HCT and other concentration methods was enhanced by the phase-contrast facility (Murray *et al.*, 1977; Paris *et al.*, 1982). Also, BCM is a more rapid and practicable supplement to HCT (Kalu *et al.*, 1986). The HCT has been reported to be less sensitive than the mAEC method (Lumsden *et al.*, 1981).

Laboratory animal inoculation (Itard, 1989) using blood, lymph, oedema or tissue fluid, provides an excellent technique for detection of trypanosome species in the subgenus Trypanozoon, but is less sensitive

with other trypanosome species (Kalu *et al.,* 1986). The sample is inoculated subcutaneously or intraperitoneally into rats or mice for *T. congolense, T. evansi* and *T. brucei*, or intrascrotally into rabbits for *T.equiperdum* (Itard, 1989). The incubation period varies from 5 to 85 days. Mouse inoculation cannot be carried out routinely in the field, but it has been reported to be more sensitive than HCT and has a lower detection limit of three parasites per ml of blood for *T. evansi* infection (Le *et al.*, 2000).

Seroimmunological techniques such as the mercuric chloride test, formol gel method, IgM titration by precipitation-diffusion, indirect fluorescent antibody test, enzyme-linked immunosorbent assay (ELISA), complement fixation test, agglutination test and passive haemagglutination test have been indicated as being applicable in the diagnosis of trypanosomosis (Itard, 1989). Among these techniques, only ELISA has been used in epidemiological surveys of trypanosomosis (Desquesnes *et al.*, 1999). The antigen ELISA was considered unsuitable for reliable detection of trypanosomal antigens (Rebeski *et al.*, 1999), because the trypanosome species specificity's were poor (Eisler *et al.*, 1998) and required improvement (Rebeski *et al.*, 1999). The technique is less sensitive than BCM (Doko *et al.*, 1997). Its sensitivity was less than 50% in primary trypanosome infections, but the sensitivity was high in repeated or chronic infections (Mattioli and Faye, 1996), aparasitaemic chronic infections (Kanwe *et al.*, 1992) and mixed infections (Anosa *et al.*, 1993). The estimated sensitivity of *T. congolense* antigen-based ELISA was greater than 96% (Rebeski *et al.*, 2000). A sandwich-ELISA was highly sensitive for the detection of antigen in the blood of *T evansi*-infected cattle (Swarnkar *et al.,* 1993). Antigen ELISAs are 4-5.5 times more sensitive than BCM in the diagnosis of sub-patent infections

(Masake *et al.*, 1995) and more sensitive and specific than antibody ELISAs in the diagnosis of latent *T. evans*i infection of buffaloes and horses (Singh *et al.*, 1995). In a survey, an ELISA for trypanosome antibody detection gave a prevalence of 81.7%, whereas BCM was less sensitive with a prevalence of 15% (Desquesnes *et al.*, 1999). An ELISA to detect antibodies against *T. evansi* appeared to be sensitive and specific (Tuntasuvan *et al.*, 1996). Other antibody detection methods already in use, include direct card agglutination tests and indirect card agglutination tests (Latex); Verloo, (2000), with specificity's of 95% and 82% respectively. An indirect latex agglutination test (Suratex) has been developed for detecting circulating trypanosomal antigens in latent infections, which cannot be detected by parasitological techniques (Nantulya and Diall, 1998). Double immunodiffusion and counter-immunoelectrophoresis tests are not effective for detection of trypanosomal antigens (Swarnkar *et al.*, 1993).

Techniques using polymerase chain reactions (PCR) have been used in surveys of trypanosome infection in cattle in Zambia (Katakura *et al.*, 1997). The parasitological (HCT, BCM) and PCR techniques have approximately the same sensitivities for detection of *T. vivax* infections in cattle (Desquesnes, 1997). However, some workers reported that PCR proved consistently more sensitive than parasitological techniques (Almeida *et al.*, 1997), especially in antigenaemic but aparasitaemic animals (Majiwa *et al.*, 1994). The need for improvement in the PCR technique has led to the consideration of dipstick assays and tests (Rebeski *et al.*, 1999). There is already a dipstick colloidal dye immunoassay used in the field (Kashiwazaki *et al.*, 1994)

1.5.Clinical signs in goats and sheep:

Natural infection is generally considered as mild or asymptomatic in sheep (Boehringer and Prosen, 1961). In some cases, experimental infections can even fail, but in others they can lead to clinical signs, mainly fever (40°C), lack of appetite, and anaemia; during hyperthermia, modification of behaviour such as exhaustion or sudden aggressiveness has been observed; anaemia can recede after 2 months; parasitaemia is generally low (105 parasites/mL) and decreases until undetectable for several months; however, under certain circumstances such as food restriction or transport stress, parasites can relapse into the blood and clinical signs reappear (Desquesnes, 1997). In experimental infection of Yankasa sheep with a Nigerian isolate of *T. evansi*, acute and chronic evolutions were observed, with fever, pale mucous membrane, epiphora, loss of appetite, emaciation, dullness, and rough haired coat; in acute evolution the animals died within 2 weeks; postmortem observation indicated enlargement of the spleen and lymph nodes (Audu *et al.,* 1999).

Goats are also most often of low susceptibility (Jacquiet *et al.,* 1993); thus in experimental infections with a camel isolate from the Canary Islands they showed mild symptoms with a few episodes of fever in early infection and arthritis in the next 6 months; although low, parasitaemia remained persistent (Gutierrez *et al.,* 2004). In the Philippines, experimental infection led to the observation of fluctuating fever, progressive emaciation, anaemia, coughing, testicular enlargement, and diarrhoea but not in all animals (Dargantes *et al.,* 2005). However, other reports mention moderate (Ngeranwa *et al.,* 1993) but sometimes severe or fatal infections with fever, lachrymation, salivation, loss of appetite, and nervous symptoms (shivering and convulsion) followed by hypothermia and death (Youssif *et al.,* 2008). Ocular lesions have also

been recorded (Morales *et al.,* 2006). Finally, the susceptibility of goats seems to be occasionally high in some reports, but, under natural conditions, most of the reports mention mild clinical signs due to *T. evansi* in goats (Gutierrez *et al.,* 2006).

As sheep and goats are not regular hosts of *T. evansi*, based on the reports available, it is difficult to decide on their susceptibility.

1.6.Drugs Resistance:

Is defined as a loss of sensitivity by a strain of an organism to a compound to which it had previously been susceptible (Vilenberg, 1998).

It would appear, from field observations, that whatever trypanocidal drugs are used on a regular basis, sooner or later strains of trypanosomes resistant to these drugs are bound to arise. That drug resistance is a major impediment to the effective control of trypanosomiasis and thus to improved livestock production in Africa, has long been recognized. Recent reports have shown that, at least in three countries (Nigeria, Kenya and Uganda), drug resistance has assumed some significance, and in Central Africa, indications of reduced drug sensitivity by trypanosomes have been reported (Peregrine *et al.*, 1988).

1.7. Drug Resistance in Sudanese Trypanosomes

Mohamed-Ahmed *et al*. (1992) reported multiple drug resistant in South Darfur-Sudan. Sensitivities of 16 *T. evansi* for suramin in a 10-day-*in vitro* assay varied within a 124-fold range. The *in vitro* results were confirmed by infection/treatment experiments in mice. Sensitivities *in vitro* for quinapyramine varied within a 166-fold range. In mice, the least sensitive isolates were not cured with dosages up to 10 mg/kg quinapyramine. Based on *in vitro* results, all the 16 *T. evansi* strain

isolates appeared to be susceptible to isometamidium. El Rayah, *et al*. (1998) reported that molecular karyotyping by pulsed field gel electrophoresis was used to characterize *Trypanosoma evansi* isolates. Ten *T. evansi* isolates from camels were collected in Eastern and Western Sudan. Isolates from Eastern Sudan which were kept under continuous prophylactic treatment with quinapyramine (Trypacide®), were found to bear a single pattern and belonged to one karyotype group.

From Western Sudan where trypanosomosis management was done by individual treatment of proven parasitaemic cases, isolates with diverse karyotype patterns were obtained. This study concluded that the occurrence of karyotype homogeneity amongst *T. evansi* isolates from field situations where antitrypanosomal compounds have been used may infer the existence of drug-resistance (El Rayah, *et al*., 1999).

1.8.Chemotherapy

The control of African animal trypanosomiasis is based on two broad strategies, using chemotherapeutic agents to treat infected animals and to control the vector. In generally, however, the chemotherapeutic approach is much more widely used than vector control because it is easier to treat the trypanosomes than control the flies (Leeflang and Ilemobade, 1971).

Drug control of animal trypanosomiasis relies essentially on three drugs, namely: Homidium (Homidium chloride=Novidium; and Homidium bromide= Ethidium), Diminazene aceturate (Berenil) and Isometamidium chloride (Samorin, Trypamidium). Quinapyramine sulphate (Antricide) has been reintroduced because of the need to especially combat camel trypanosomosis (Fairlamb *et al*., 1992). After the introduction of isometamidium in 1961 (Berg *et al.,* 1961) the

manufacture of new trypanocidal drugs has made little progress. It is estimated that in Africa 25-30 million doses of trypanocidal drugs are used annually in the treatment of animal trypanosomosis, but the population of animals at risk indicated that ten times these figure were necessary (Kristjanson, *et al.,*1999). The former figures are based on single-dose treatment. Although restrictive, the single dose treatment requirement is particularly suited to the nomadic situation in the field, but sedentary herds may receive 3 to 4 times treatment a year (Peregrine, 1994).

The seasonal movement of livestock into areas infested by tsetse flies, by livestock owners wanting to take advantage of pasture and water, requires that animals be protected if severe stock losses are to be averted. Such protection is often achieved by chemotherapy which can make the difference between small losses that allow a reasonable productivity and severe losses which can be crippling. If stock are to be kept permanently in such areas, however, chemotherapy as a strategy will succeed or fail depending on whether the tsetse in the area are the riverine or savanna species (MacLennan, 1970). Also it has been shown by MacLennan (1970) that the trypanosome infection rate of riverine tsetse is low (between 1 and 10%) and that the trypanosomiasis transmitted by riverine tsetse is usually less pathogenic than that transmitted by savanna tsetse. Furthermore, the density of riverine tsetse, for example *Glossina palpalis palpalis*, is usually of a low order and is confined to riverine courses and in vegetation along streams. However savanna tsetse, for example *Glossina morsitans submorsitans,* usually has a high density and is widely distributed in the savanna zone within specific belts. Thus, the chemotherapeutic approach is more successful in those areas infested by riverine tsetse than in those infested by savanna tsetse. As early as 1956

Professor Hill, then at the University of Ibadan, showed that Zebu cattle can be maintained under light to moderate trypanosomiasis risk for an extended period without ill effects by careful monitoring and treatment of affected animals (Hill, 1956).

Chemotherapy is very effective in the control of sporadic trypanosomiasis due to mechanical transmission, seasonal fly dispersal and scattered tsetse foci. In 1971 an unusual outbreak of trypanosomiasis occurred on the Shika (now National Animal Production Research Institute [NAPRI]) livestock farm (Leeflang and Ilemobade, 1971). The trypanosomiasis was believed to have been transmitted by dispersed flies and maintained by mechanical transmission. Although only a small percentage of cattle on the farm was proved infected, it was believed that, trypanosomiasis being an occult disease, many more animals were also infected. Trypanocidal treatment of all animals resulted in the eradication of trypanosomiasis on the area. Raising livestock in reclamation areas is a kin to the situation where the density of the flies is sufficiently low to allow livestock to be raised under a regime of chemotherapy. This has led to better land utilization. Cattle passing through fly belts can often be protected by chemotherapeutic means. Also, animals returning from the dry-season grazing areas infested with tsetse to tsetse-free wet-season grazing zones often perform better when they are treated against possible trypanosome infection. The usefulness of chemotherapy is limited in the field because cattle in contact with tsetse flies are liable to re-infection. If chemotherapy is to be successful, the need for regular monitoring of the trypanosomiasis risk cannot be overemphasized. It is essential to know at which point drug intervention would be appropriate, which species of trypanosome is prevalent and its drug sensitivities.

Chemotherapy on a wide scale requires a thorough knowledge of the prevalent trypanosomes and their sensitivity to drugs. In Nigeria, for instance, *T. vivax* is generally more susceptible to Berenil than is *T. congolense*. Consequently, the use of either Homidium or Berenil is dictated by which of the two species predominates in a given area or season. In order, therefore, to determine the prevalence of trypanosomes, a sensitive diagnostic tool is essential. Unfortunately, the diagnostic tools available are limited in their sensitivity to detect trypanosomes. Hence the absence of trypanosomes, therefore, may not necessarily imply that an animal is not infected (Jones-Davies, 1968).

1.9.Measures aimed at combating drug resistance in the field

The following measures are aimed at combating drug resistance in trypanosomes in the field.

1.9.1. Change of drugs:

When drug resistance became a problem following wide-spread use of antrycide in the early 1950s, the obvious thing to do was to change drugs especially since the phenanthridinium compounds had arrived on the market. This was the case in Nigeria (Clover, 1965) and in Kenya (Whiteside, 1960), where homidium compounds were introduced and used extensively. In Nigeria for instance, the homidium compounds were used widely between 1954 and 1965 and were then withdrawn from general use for two years following widespread drug resistance by *T. congolense* (Jones-Davies and Folkers, 1966; Na-Isa, 1967; Folkers *et al.,* 1968) and replaced by Berenil which had been introduced into the market by 1955 and isometamidium (Samorin) which was introduced in 1961. A similar fate soon befell Berenil in Nigeria (MacLennan and Jones-Davies, 1967; Jones-Davies, 1968). The extent to which a change of drugs can be effected, however, will depend on the drugs available on the market. The

last drug to be introduced to the market was Cymelarsan which was introduced in 1983 for prophylaxis. This, therefore, called for the evolution of a new treatment strategy. In the meantime, Whiteside (1962) had introduced the concept of sanative treatment.

1.9.2. Sanative treatment:

The concept of sanative treatment prescribes the use of a pair of trypanocides (e.g. Berenil and Homidium) which are chemically unrelated and, therefore, are unlikely to induce cross-resistance. One of the pair is used until resistant strains of trypanosomes appear and then the second is substituted and used until the resistant strains have disappeared from cattle and tsetse (Whiteside, 1962). In Nigeria, while this technique was not used, a similar approach was adopted in 1965 when widespread resistance of *T. congolense* to homidium compounds dictated a change. Initially Berenil was used for two years, but strains of *T. vivax* resistant to Berenil soon appeared in the field, thus requiring a change. The evidence was that *T. vivax* was uniformly susceptible to Homidium treatment while *T. congolense* was not and that *T. vivax* was less sensitive to Berenil treatment than was *T. congolense.* It was therefore decided that Homidium be used when *T. vivax* was the prevalent trypanosome and Berenil used when *T. congolense* predominated.

This treatment regime eventually became the trypanosomiasis drug policy of the Northern Region of Nigeria. This arrangement was found to be more suitable than the Whiteside sanative-pair concept because it has been demonstrated that the resistant nature of trypanosomes was unaffected by passage through tsetse (Gray and Roberts, 1968) or wildlife (Gray and Roberts, 1971). The drug policy prescribed that each of the two curative drugs be used for six months of the year when a species of trypanosomes sensitive to the drug was predominant. For example, *T.*

vivax was found to be generally susceptible to homidium compounds and was the predominant species in cattle when they were withdrawn to the wet-season grazing areas; whereas *T. congolense* was generally susceptible to Berenil and was the predominant species in cattle during the dry season when cattle were moved to pastureland in the tsetse belts of the south. This treatment regime was effective for almost ten years before isolates of *T. congolense* and *T. vivax* with multiple resistance to curative trypanocides were isolated and subsequently found to be widespread (Ilemobade, 1979). Since there was no drug to fall back upon, the only recourse was to increase the dose of the available trypanocides.

1.9.3. Increased dosage:

When trypanocides were first introduced in the market there was some question as to whether sufficient laboratory and field trials had been carried out to justify increased dosages of the drugs recommended for field use by manufacturers. Obviously, because of competition and the pressure for new drugs, manufacturers could not, in the absence of strict registration requirements, wait for extensive trials before launching new trypanocides. That this could be an important consideration was underlined by Davey (1957). However, the recommended increased dosage of trypanocides did not appear to offer a solution as shown by MacLennan and Na-Isa (1970), Leeflang *et al*. (1977) and Ilemobade (1979).

1.9.4. Repetitive treatments:

Repeated treatments of drug-resistant isolates of trypanosomes (*T. vivax* and *T. congolense*) have been tried. While they were found to be effective, field applications appeared impractical because of the need for effective monitoring to ensure that animals were treated soon after relapse (Leeflang, 1978; Ilemobade and Na-Isa, 1981).

The use of complexes was tried with isometamidium chloride-dextran complex, based on the early work of Williamson (1957). A complex can be used at a high enough dosage without the attendant toxic reactions, to cure resistant strains. Initial results have, however, been disappointing (Aliu and Sannusi, 1979).

1.10.Antibiotics:

Antibiotics are substances produced by micro-organisms which inhibit the growth of bacteria (Alexander,1976). The first useful antibiotic was penicillin, and the astonishing success of this substance stimulate an intensive such for other antibiotics; only a few of those discovered have proved clinically useful. None of the commoner antibiotics such as penicillin, streptomycin or chlorophenicol is active against African trypanosomes.

Alexander (1985) mentioned that nitrofurazone derivatives have an effect on muco-cutaneous leishmaniasis. The same author also mentioned that Tetracycline group has an act on certain protozoa such as an *anaplasma* and *thileria* in addition to anti-bacterial effect. Youssif , (2005) studied the toxicity and efficacy of Oxytetracycline in goats infected with *T.evansi* and found that single dosage of 20mg, 50mg and 100mg/kg, or 20mg/kg weekly for three weeks and 20mg/kg twice a week for two weeks are toleratable and the parasiteamia became mild until the end of the experiment in contrast to infected untreated animals which died 10-11 days post infection. Youssif, (2005) also studied the toxicity and efficacy of cymelarsan and Oxytetracycline combination in Nubian goats infected experimentally with *T.evansi* and found that the half therapeutic dose and their combination did succeed to overcome the parasitaemia while single intramuscular injection of cymelarsan (half therapeutic dose) and Oxytetracycline (two and half therapeutic dose) or

cymelarsan (half therapeutic dose) and Oxytetracyline (therapeutic dose) twice a week for two weeks cleared the parasitaemia without relapse. Among the aminoglycoside antibiotics, paromomycin has been shown to be effective against some protozoa and cestodes (Chamber and Sande, 1996). The cost of paromomycin is low, making it a particular good drug candidate in countries that carry a burden of high parasitic infection rates. While paromomycin is out of use as an antibacterial, it is marketed as an oral treatment for amoebiasis and giardiasis. Paromomycin is also used in combination therapy as a topical treatment for cutaneous leishmaniasis (EL-On J *et al*., 2007). Recently, paromomycin was licensed as a treatment for visceral leishmaniasis, the most severe form of leishmaniasis (Davidson *et al*., 2009). Recent data have demonstrated that mitochondrial translation is essential for both the procyclic and the bloodstream form of *Trypanosoma brucei* and that consequently mitochondrial protein synthesis may represent an important drug target throughout the life cycle of trypanosomes (Cristodero *et al.,* 2010).

Ekanem and Johnson (2003) Studied antimicrobial drug Oxytetracycline-HCl against the infections of the protozoan parasite *Trypanosoma brucei* which causes the disease African Trypanosomosis. Oxytetracycline-HCl was used to treat rats infected with the disease at early and late stages of infections. Prophylactic administration was also carried out. The results showed that prophylactic treatment only did not inhibit the proliferation of the parasite but with continued administration kept parasitaemia low. Both prophylactic and early stage treatment of the infection extended the lifespan of the animals. The study revealed that early stage treatment and prophylactics at high dosage of 30mg/kg and 40mg/kg extended the life span of the animals. In the case of the

prophylactic treatment very low parasitaemia with almost total clearance of parasite in the system was observed.

1.10.1.Sulphonamides:

The Sulphonamides are one of the oldest groups of antimicrobial compounds still in use today. Sulphanilamide , an amide of sulfunilic acid, was the first sulphonamide used clinically. It was derived from the azo dye prontosil, and all other sulphonamides produced since have structurally resembled it. Sulphonamides have been in clinical use for 50 years, and wide spread resistance has develop against some of them. All sulphonamides are derivatives of sulphanilamide (structurally similar to para-aminobenzoic acid) which was in 1940 the first sulphonamide discovered to have antimicrobial activity. Many structural derivatives of sulphanilamide with differing pharmacokinetic and antimicrobial spectrums have been used in veterinary medicine to treat microbial infections of the respiratory, urinary, gastrointestinal, and central nervous systems. Susceptible organisms include many bacteria, coccidia, chlamydia and protozoal organisms, including *Toxoplasma spp*. Sulphonamides are white crystalline powders that are weak organic acids, are relatively insoluble in water. Sulponamides are more soluble in alkaline than in neutral or acidic PH. Sulphonamides do not significantly affect the solubility of each other which has important clinical considerations in the excretion of parent compound and any metabolites. Three sulphonamides formulated in solution together allow increased efficacy without a significant increased risk of adverse effects (Prescott and Baggot, 1993: Bevill, 1988).

1.10.2.Sulphadimidine:

Sulphadimidine, like many sulphonamides, has been utilized for decades in veterinary medicine. Sulphadimidine has been formulated for use in drinking water (Church *et al.,* 1979) and as a feed additive, an extended- release bolus, and an IV preparation. Sulphadimidine has been marketed by itself and in combination with other antimicrobials, such as other sulphonamides, tylosin, chlortetracycline and procaine penicillin G. The basic pharmacokinetic parameters of sulpadimidine in cattle have been reported by Bevill *et al.*(1977) and Nouws *et al.*(1988). The sustained-release formulation has been reported to achieve therapeutic blood level (50 *ug/ml*) within 6-12 hours after oral administration and to maintain or exceed that level for 2-5 days after dosing. Clearance of sulphadimidine and its metabolites in cattle are age and dose dependent (Nouws *et al.,* 1986; Lapka *et al.,* 1980).

1.10.2.1.Mode of action:

For sulphonamide to be therapeutically effective, organisms must intracellularly synthesize their own folic acid. Sulphonamides are antimetabolites, interfering with the normal production of RNA, protein synthesis, and microbial replication mechanisms. Sulphonamides inhabit intermediary metabolism by interfering with the production of folic acid, while the diaminopyrimidines interfere in later steps of this metabolic cascade by arresting the production of tetrahydrofolic acid (THFA). Sulphonamides used in the absence of diaminopyrimidines are bacteriostatic. The existing folic acid supply within the susceptible organisms must be consumed before any metabolic effects can begin, which usually occurs within 4-6 hours after administration (Prescott and Baggot, 1993).

Para-aminobenzoic acid (PABA), pteridines, glutamic acid, and the enzyme dihydropterate synthase interact to form hydropteroic acid, the intermediate precursor to dihydrofolic acid. Dihydropteroic acid is enzymatically converted to dihydrofolic acid by dihydrofolate synthase, followed by another enzymatic conversion of dihydrofolic acid to tetrahydrofolic acid (THFA) via dihydrofolate reductase (DHFR). Tetrahydrofolic acid continues on in this pathway to permit RNA production and bacterial production. Sulpanilamide, and all sulphonamides, inhibit the biosynthesis of folic acid by being mistakenly substituted for PABA. However, there are sufficient structural differences between the sulphonamides and PABA to not allow the conversion to dihydropteroic acid, hence inhibiting bacterial synthesis. Folic acid can be restored by flooding the system with excess PABA. Sulphonamides have little effect on those microbial organisms that, like mammalian cells, can utilize performed folic acid (Prescott and Baggot, 1993: Bevill, 1988).

1.10.2.2.Uses of Sulphadimidine:

The spectrum of activity for the sulphonamides is broad, affecting gram-positive, gram-negative and many protozoal organisms, and is bacteriostatic rather than bactericidal. Combining sulphonamides with diaminopyrimidines has markedly increased the spectrum of activity and the most common sulphonamide preparation used in veterinary antimicrobial therapy today. *In vitro* susceptibility patterns of many pathogens (Van Duijkeren *et al,*.1994) and more specifically *Salmonella spp* that affect the horse have been recently reported. Sulphonamides are used to treat infections of the CNS, respiratory tract, gastrointestinal tract and in particular the urinary tract (Prescott and Baggot, 1993).

1.10.2.3. Side effects:

Sulphonamides induced toxicoses may be classified as nonimmunologic or immunologic in etiology. A retrospective evaluation of dermal adverse reactions due to trimethoprim-sulphonamide combinations used in male dog and cats has been presented by Noli *et al.*(1995).

1.10.3.Gentamicin

Gentamicin is an aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms. However, gentamicin is not used for *Neisseria gonorrhoeae, Neisseria meningitidis* or *Legionella pneumophila.* Gentamicin is also ototoxic and nephrotoxic, with this toxicity remaining a major problem in clinical use (Moulds *et al.,* 2010).

1.10.3.1.Mode of action:

Active against a wide range of human and animal bacterial infections, mostly Gram-negative bacteria including *Pseudomonas, Proteus, Serratia*, and the Gram-positive *Staphylococcus* (Lexi-company). Gentamicin is not used for *Neisseria gonorrhoeae, Neisseria meningitidis* or *Legionella pneumophila* bacterial infections (because of the risk of the patient going into shock from lipid A endotoxin found in certain Gram-negative organisms). Gentamicin is also useful against *Yersinia pestis,* its relatives, and *Francisella tularensis* (the organism responsible for Tularemia seen often in hunters or trappers (Goljan, 2011). Some *Enterobacteriaceae, Pseudomonas spp., Enterococci, Staphylococcus aureus* and other *Staphylococci* are resistant to Gentamicin sulfate, USP to varying degrees.

As predicted by allometric principles, on a mL/min/kg basis, gentamicin clearance decreases as body weight increases (Brown *et al.,* 1985). This also strongly suggests that dosages must be reduced in the face of renal dysfunction. Recovery of gentamicin in the urine has been reported to be 91±28% within first 24 hours in sheep (Brown *et al.,*1986). The disposition of gentamicin in equine plasma synovial fluid and lymph has also been reported (Anderson *et al.,*1995). Gentamicin is accumulated in renal proximal tubules to concentrations several-fold higher than in serum or any other tissue in every species investigated (Schentag and Jusko, 1977). There is some information on the use of gentamicin in sheep and goats. Elsheikh *et al.*(1997) dosed male Nubian goats and male desert sheep with 3mg/kg gentamicin IV and found no significance differences volume of distribution, clearance, and elimination half-lives between the species.

1.10.3.2.Use of gentamicin:

Gentamicin is produced by the fermentation *of Micromonospora purpurea*. It was discovered in 1963 by Weinstein, *et al*. (1963) at Schering Corporation in Bloomfield, N.J. working with source material (soil samples).

It was initially used as a topical treatment for burns at the Atlanta and San Antonio burn units and was introduced into usage in 1971. It remains a main stay for use in sepsis. Gentamicin is also used in molecular biology research as an antibacterial agent in tissue and cell culture, to prevent contamination of sterile cultures. It is synthesized by *Micromonospora,* a genus of Gram-positive bacteria widely present in the environment (water and soil). To highlight their specific biological origins, gentamicin and other related antibiotics produced by this genus (verdamicin, mutamicin, sisomicin, netilmicin, retymicin) generally have

their spellings ending in ~micin and not in ~mycin. Gentamicin is a bactericidal antibiotic that works by binding the 30S subunit of the bacterial ribosome, interrupting protein synthesis. Like all aminoglycosides, when gentamicin is given orally, it is not systemically active. This is because it is not absorbed to any appreciable extent from the small intestine. It is administered intravenously, intramuscularly or topically to treat infections. It appears to be completely eliminated unchanged in the urine. Urine must be collected for many days to recover all of a given dose because the drug binds avidly to certain tissues. *E. coli* has shown some resistance to gentamicin, despite being Gram-negative. Reluctance to use gentamicin for empirical therapy has led to increased use of alternative broad-spectrum antibiotics, which some experts suggest has led to the prevalence of antibiotic-resistant bacterial infections and other so-called "superbugs" (Moulds *et al.,* 2010). Gentamicin is one of the few heat-stable antibiotics that remain active even after autoclaving, which makes it particularly useful in the preparation of some microbiological growth media. It is used during orthopaedic surgery when high temperatures are required for the setting of cements e.g hip displacement (Hendricks *et al.,* 2004).

1.10.3.3. Side effects:

These aminoglycosides are toxic to the sensory cells of the ear, but they vary greatly in their relative effects on hearing versus balance. Gentamicin is a vestibulotoxin, and can cause permanent loss of equilibrioception, caused by damage to the vestibular apparatus of the inner ear, usually if taken at high doses or for prolonged periods of time, but there are well documented cases in which gentamicin completely destroyed the vestibular apparatus after three to five days. A small number of affected individuals have a normally harmless mutation in

their mitochondrial RNA (m1555 A>G), that allows the gentamicin to affect their cells. The cells of the ear are particularly sensitive to this, sometimes causing complete hearing loss. However, gentamicin is sometimes used intentionally for this purpose in severe Ménière's disease, to disable the vestibular apparatus. These side effects are most common when the drug is administered via drops directly (Moulds *et al.,* 2010).

Gentamicin can also be highly nephrotoxic, particularly if multiple doses accumulate over a course of treatment. For this reason gentamicin is usually dosed by ideal body weight. Various formulae exist for calculating gentamicin dosage. Also trough and peak serum levels of gentamicin are monitored during treatment, generally before and after the third dose is infused. Gentamicin, like other aminoglycosides, causes nephrotoxicity by inhibiting protein synthesis in renal cells. This mechanism specifically causes necrosis of cells in the proximal tubule, resulting in acute tubular necrosis which can lead to acute renal failure (Sundin, *et al.*, 2001).

Side effects of gentamicin toxicity vary from patient to patient. These effects may become apparent shortly after or up to months after gentamicin is administered. A number of factors and determinants should be taken into account when using gentamicin, including differentiation between empirical and directed therapy which will affect dosage and treatment period (Moulds *et al.,* 2010). Many medical practitioners freely administer gentamicin as an antibiotic without advising patients of the severe and permanent potential ramifications of its use.

1.10.4.Tetracycline:

The tetracycline antibiotics were isolated from various species of *streptomyces* in the late 1940s and early 1950s. Since that time, many

semisynthetics structural modifications have been made on the tetracycline molecule to yield other tetracyclines with differing pharmacokinetic properties and antimicrobial activities. The tetracyclines are a group of four-ringed amphoteric compounds that differ by specific chemical substitutions at different points on the rings. As a group, the tetracyclines are acidic, hygrocopic compounds in aqueous solutions and easily form salts with acids and bases, which are how they are commonly marketed. The most common salt form is the hydrochloride formulation, however, as is the case with oxytetracycline, combining the base compound with certain carriers will result in prolonged serum and tissue half-lives (Suzuka *et al.,* 1966).

1.10.5.Oxytetracycline Long Acting (Oxy-LA):

The clinical usefulness of Oxytetracycline has been studied in most domestic species of animals in recent years. Oxytetracycline has been used to treat ehrlicchiosis in dogs (Adawa *et al.,* 1992) and in horses (Palmer *et al.,*1992). A long acting formulation of oxytetracycline administered intramuscularly with piroxicam was found to be effective in treating canine ehrlicchiosis, while the piroxicam minimized the pain and swelling associated with oxytetracycline injections. The study by Palmer *et al.*(1992) also found that low-dose oxytetracycline given once instead of twice daily (administered intravenously) was effective in eliminating *Ehrlichia risticii* in horses. Use of a long acting formulation particularly in food animals has the main advantage of obtaining clinically useful sustained serum and tissue concentration for long periods of time (3-5 days) without frequent dosing (Nouws *et al.,*1990).

1.10.5.1.Mode of action

Tetracycline binds to the 30S subunit of microbial ribosomes. It inhibits protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome. After binding to the ribosomes, the tetracyclines interfere with the binding of aminoacyl-tRNA to the messenger RNA molecule/ribosome complex, thereby interfering with bacterial protein synthesis in growing or multiplying organisms. Tetracyclines have much less affinity for mammalian ribosomes, but some amount of inhibition does occur in mammals given tetracycline . Tetracyclines are bacteriostatic and broad spectrum at therapeutic concentrations (Gales and Folkers, 1953).

1.10.5.2.Uses of tetracycline.

The tetracyclines are broad-spectrum antibiotics and as a class, inhibit the growth of a wide variety of bacteria, protozoa and many intracellular organisms such as mycoplasma, chlamydia and rickettsia (Prescott and Baggot, 1993). Differences in antimicrobial spectrum of the tetracyclines in *vivo* result mainly from differences in lipid solubility. Tetracycline is also used as a biomarker in wildlife to detect consumption of medicine- or vaccine-containing baits (Olson *et al.,* 2000).

1.10.5.3.Side effects:

Numerous side effects have been reported in tetracyclines, such as gastrointestinal upset that results from irritation of the stomach and the upper small intestine where the bulk of the tetracyclines is absorbed after the oral administration. Hepatotoxicity may result from accumulation of tetracyclines when they are not eliminated quickly enough by the kidneys or by administration of frequent and large doses above recommended

therapeutic dosages. In mice tetracycline induced toxicosis resulted in increased transaminases, alkaline phosphatase, urea and total conjugated bilirubin, in addition to decreased cholesterol (Bocker *et al.,* 1982). Tooth mottling or discoloration occurs when tetracyclines are administered during pregnancy when tooth development is occurring or when administered during the first postnatal month. The discoloration is related to the chelating of tetracyclines to the calcium deposits in the development of teeth (Moffit *et al.,* 1974).

1.10.6.Mechanisms of Resistance:

Bacteria usually acquire resistance to tetracycline from horizontal transfer of a gene that either encodes an efflux pump or a ribosomal protection protein. Efflux pumps actively eject tetracycline from the cell, preventing the buildup of an inhibitory concentration of tetracycline in the cytoplasm (Chopra *et al.,* 2001). Ribosomal protection proteins interact with the ribosome and dislodge tetracycline from the ribosome, allowing for translation to continue (Connell *et al.,* 2003).

Chapter two

2. Materials and Methods

2.1. Experimental Animals:

Thirty nine (39) Nubian goats of both sexes aged 1-3 years and weighing 13-20 kg were purchased from White Nile state (Rebek) local markets . They were housed in a Fly-proof barn.

2.2. Animal accommodation:

All animals were housed at the College of Veterinary Medicine, Sudan University of Science and Technology (SUST), Hilla Kuku. They were supplied with limited concentrates (Kenana concentrate) and grain *Sorghum vulagarae* (Abo-70), provided with running water access and minerals adlibitum twice a day. The daily movement of animals within flies-proof barn assured contact between all groups. Animals were allowed to acclimatize for one month before the commencement of experiments.

2.3. Pre-infection screening of the animals (Acclimatization period):

All animals were carefully examined for blood parasites, internal and external parasites then treated with Ivermectin 1% (Hebei Yuanzheng, China) against internal and external parasites, administered subcutaneously at a dose of 1ml/50kg body weight. Dewormed with Albendazole 2.5% (Jordon Vet & Agri. Med, Amman) for treatment of internal parasites, administered orally at a dose of 1ml/5kg body weight and Diclosol (Diclazuril, Pharma Swede. Egypt) as anticoccidosis administered orally at a dose of 1mg/10kg body weight. The animals were also treated with Penivex Complex (Procaine Benzyle Penicillin, S.a. Taragonia, Spain) at a dose of 0.6ml/10kg body weight intramuscularly against pulmonary diseases. Animals were divided

randomly into subgroups each consist of three goats. Six animals were chosen randomly and divided into two subgroups and used as control groups for all the experimental groups, and divided as control negative and control positive. Control negative (subgroup 1) was untreated and uninfected while control positive (subgroup 2) was untreated and infected with *T.evansi*. The remaining experimental subgroups (3-13) were all infected with *T.evansi*.

2.4.The classifications of experimental groups and their subgroups.

Exp. (1):2.4.1. Efficacy of Sulphadimidine (sulphamethazine) in Nubian goats infected experimentally with *Trypanasoma evansi,* and consisted of three subgroups as follows:

2.4.1.1.Subgroup (3) infected and treated with single half recommended dose of Sulphadimidine administered intramuscularly (100mg/kg of body weight).

2.4.1.2.Subgroup (4) infected and treated with single recommended dose of Sulphadimidine administered intramuscularly (200mg/kg of body weight).

2.4.1.3.Subgroup (5) infected and treated with single double recommended dose of Sulphadimidine administered intramuscularly (400mg/kg of body weight).

Exp.(2):2.4.2. Efficacy of Gentamicin in Nubian goats infected experimentally with *Trypanasoma evansi,* and consist of three subgroups as follows:

2.4.2.1.Subgroup (6) infected and treated with single half recommended dose of Gentamicin administered intramuscularly (2mg/kg of body weight).

2.4.2.2.Subgroup (7) infected and treated with single recommended dose of Gentamicin administered intramuscularly (4mg/kg of body weight).

2.4.2.3.Subgroup (8) infected and treated with single double recommended dose of Gentamicin administered intramuscularly (8mg/kg of body weight).

Exp. (3): 2.4.3. Efficacy of Oxytetracycline in Nubian goats infected experimentally with *Trypanasoma evansi,* and consisted of one subgroups as follows:

2.4.3.1.Subgroup (9) infected and treated with single recommended dose of Oxytetracycline (20mg/kg of body weight) administered intramuscularly.

Exp. (4):2.4.4. Efficacy of Sulphadimidine and Gentamicin combination in Nubian goats infected experimentally with *Trypanasoma evansi,* and consisted of two subgroups as follows:

2.4.4.1.Subgroup (10) infected and treated with single recommended dose of combination of Sulphadimidine (200mg/kg of body weight) and Gentamicin (4mg/kg of body weight) administered intramuscularly.

2.4.4.2.Subgroup (11) infected and treated with single double recommended dose of combination of Sulphadimidine (400mg/kg of body weight) and Gentamicin (8mg/kg of body weight) administered intramuscularly.

Exp. (5):2.4.5. Efficacy of combination of Sulphadimidine, Gentamicin and Oxytetracycline in Nubian goats infected experimentally with *Trypanasoma evansi,* and consisted of two subgroups as follows:

2.4.5.1.Subgroup (12) infected and treated with single recommended dose of combination of Sulphadimidine (200mg/kg of body weight) and Oxytetracycline (20mg/kg of body weight) administered intramuscularly.

2.4.5.2.Subgroup (13) infected and treated with single recommended dose of combination of Gentamicin (4mg/kg of body weight) and Oxytetracycline (20mg/kg of body weight) administered intramuscularly.

2.5. Treatment:

All the infected groups (except positive control) were treated immediately after the appearance of the parasite in the blood.

2.6. Drugs:

2.6.1. Gentamycin 20% injection (Univet, Ireland).

2.6.2. Sulphadimidine Sodium 33.3% injection (Iterchemie Werken, Holland).

2.6.3. Oxytetracycline Long Acting (OXY-LA) 20% injection Hebei Yuanzheng, China.

2.7.The Parasite and infection

Albino rats of two months old, weighing 230 gm, were inoculated intraperitoneally with 0.2 ml camel's blood containing 3-6 parasite/field, this camel was infected naturally with *T.evansi* stock Gad tryp (1) which was isolated from El-gaderif state (Eastern-Sudan). When parasitaemia developed in rats, two donor goats were injected on jugular vein with 1ml from rat's blood containing $5x10^5$parasites, which were identified in the

laboratory at College of Veterinary Medicine, Sudan University of Science and Technology based on their morphological character according to the method of (Hoare, 1972). After development of parasitaemia in donor goats, the experimental goats (2-13) except negative control group were injected intravenously with 1ml blood from donor goats containing 5 x 10^5 parasites as count using modified scoring method (Ismail, 1988). The parasites were activated by adding phosphate buffered saline with glucose (PSG) before inoculation. At each peak of parasitaemia, 2ml from infected blood of donor goats was collected through jugular vein puncture by the use of 5ml disposable syringes and harvested into ethylene diamine tetraacetic acid (EDTA) vaccum containers mixed with phosphate buffered saline with glucose (PSG, PH 8.0, in 10% glycerol), then drawn into capillaries tubes and cryopreserved in liquid nitrogen L.N (-196 C^0) until needed (Cunningham *et al.,* 1963).

2.8.Techniques used for blood collection:

Blood samples for parasitological, heamatological and biochemical investigations were collected daily for duration of 65 days in case of parasitaemia investigation and every (3) days for duration of 65 days for heamatological and biochemical investigations. Blood was obtained through jugular vein puncture using 5ml disposable syringes, 2ml of collected blood was harvested to ethylene diamine tetraacetic acid (EDTA) containers for parasitological and heamatological investigations for Hb, RBCs count, PCV, MCV, MCH, MCHC, WBCs count and differential white blood cells count. 3ml from blood for serum samples was collected into plain vacuum containers, left for 3-4 hours at room temperature then separated by using Germany centrifuge (Zentrifugen, D.78532.Tuttlingen) with 3000 rounds/5minutes and the clear serum was harvested and kept at -20C^0 in vacuum container tubes (HNTE-Jordan)

for the measurement of glucose, total proteins, albumin, globulin, GOT and urea.

2.9.Investigations.

All animals both experimental and control groups were examined daily for the followings:

2.9.1.General body condition:

All infected animals were inspected several times a day during the experimental period for physical changes and clinical signs. The control animals were also observed for any abnormalities.

2.10. Parasite detection:

All infected and infected-treated animals were bled daily for duration of sixty five (65) days, 2ml blood was collected from jugular vein puncture into tubes contained ethylene diamine tetraacetic acid (EDTA). Parasite detection was conducted using the following methods:

2.10.1. Wet blood film:

A drop of fresh blood from the infected (control positive) and infected-treated animals was placed on slide, covered with 22x22 mm cover slip and examined microscopically using x10 eye pieces and x40 objective lens as wet preparation looking for parasite (Hoare, 1972; Soulsby, 1986). The wet preparation was carefully screened and all parasites in wet film (>30 fields). The results were reported as number of parasite per preparation, per field and then converted to number of parasites per cubic millimeter (mm^3) according to Ismail, (1988), expressed as $log_{10}$the parasitaemia curves were drawn. Blood examined for parasites daily for duration of 65 days (9 weeks).

2.10.2.Buffy coat technique:

When the parasite was absent or in very low numbers (Kendrick, 1968) in the wet film, the Buffy coat technique was used to increase the probability of parasite detection as described by Woo (1970) and modified by Murray *et al.* (1977) in the following procedures : One heparinised capillary tube was filled with blood from experimental animals and sealed at one end with "plasticel". The sealed capillary tubes were centrifuged in micro-capillary centrifuge for 4 minutes at 12,000 (rpm) (Woo, 1971). The centrifuged capillary tubes were cut immediately below the junction of the red blood cells and white blood cells (buffy coat) using diamond pencil. The buffy coat and some of plasma was placed on a clean slide and covered with *22* x *22* cover glass and examined microscopically as a Buffy coat wet preparation Murray, (1977). When parasitaemia was detected in the wet mount, parasites were counted in the wet preparations or in haemocytometers as below.

2.10.3.Parasite count using haemocytometers:

When parasite counts were 1/field or more, counting in haemocytometer was used to confirm the number of parasite per mm^3 using the method of Paris *et al.* (1982).

2.11.Clinical parameters:

Clinical parameters such as rectal temperature, respiratory rate, pulse rate and heart rate were also recorded. Rectal temperature was measured by digital thermometer recorded as degrees centigrade C^0. Respiratory rate was taken from the chest using the stethoscope and recorded as inspiration/minute. Pulse rate was taken from femoral artery using stethoscope and recorded as thrills/minute. Heart rate was taken from chest using stethoscope and recorded as beats/minute. All these clinical

parameters were recorded every three days from both experimental and control groups animals for duration of 65 days.

2.12. Haematological examinations:

2.12.1. Haemoglobin concentration (Hb):

Haemoglobin concentration was measured using commercial kits (Muslcosj-Saudi Arabia for Laboratory Limited). Haemoglobin values in both experimental and control animals were measured every three days throughout the study period using haemoglobin method (Schalm *et al.,* 2000). The principle was determination of haemoglobin which is converted into cyanmethaemoglobin under the influence of potassium ferricyanide and potassium cyanide. For the test preparation 49ml from distilled water was added to 1ml of concentrated Drabkin's reagent to form Drabkin's working solution, then 5ml from working solution was used for zero adjustment of Colorimeter and another 5ml from the same Drabkin's working solution was added to 20µl blood with EDTA as anticoagulant mixed and measured with optical density (OD 540nm) using Colorimeter (WPA, Cambridge, UK). Also 5ml from Drabkin's standard was measured for reaching to the formula:

$$\frac{\text{Absorbance of sample}}{Absorbance\ of\ standard} x15\ g/dl.$$

Results were expressed as g/dl.

2.12.2.Packed Cell Volume (PCV %):

EDTA coated capillary tubes were filled to more than ¾ of its volume then closed the one end of capillary tubes with plasticeal and centrifuged in micro-capillary haematocrit centrifuge (Germany Industrial Corporation, Taiwan) for 4 minutes at 12,000 rpm . The PCV value was determined as a percentage of total blood volume measure by using

Reading Device (Remi Motors Ltd, Mumbai-India). Results were expressed as percentage (%).

2.13. Blood cells count:

Red blood cells (RBCs) and White blood cells (WBCs) were counted using the method of Schalm *et al.* (2000) with minor modification of Ismail (1988).The working dilutions for RBCs were prepared in Eppendorf tubes in suitable volumes to reach a final dilution of 1:200 or 1:400 and their duplicates as dictated by the concentration of RBCs.The blood sample for WBCs was diluted 1:20 or 1:40 and their duplicates . Haemocytometer chambers (improved Neubar Germany) for both cells count was filled and incubated in humid containers for 3-5 minutes to allow the cells to settle. The blood cells were counted using light microscope x10 eye-piece and x 40 objective lenses. Thereafter, multiplication was done by using the haemocytometer correction factor and dilution factor to give the number of the cells per mm^6 for RBCs and per mm^3 for WBCs.

2.14. Differential white blood cells count:

The thin and thick blood smears were prepared from freshly collected whole blood from control, infected and infected-treated animals every three days, stained by Giemsa stain (Jain, 1986) for differential white blood cells and parasite morphological studies. A small drop of blood was dipped on glass slide, dry and fixed with 10% alcohol then stained with Giemsa then subjected under oil x100 eye-piece microscope for detection of neutrophils, eosinophils, basophils, lymphocytes and monocytes.

2.14.1. Erythrocyte indices:

The mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and the mean corpuscular haemoglobin

concentration (MCHC) were calculated from the PCV, RBC and Hb, using the method of Schalm *et al.* (2000).

Following formula were used for calculations:

$$\text{MCV}=\frac{\text{PCV}\ \%}{RBCs\ x10^{6}/\text{mm}^{3}}\,x100\ (fl).$$

$$\text{MCHC}=\frac{\text{Hb g/dl}}{PCV\ \%}\ (g/\text{dl}).$$

$$\text{MCH}=\frac{\text{PCV}\ \%}{RBCs\ x10^{6}/\text{mm}^{3}}\ (pg).$$

2.15. Serobiochemical examinations:

Serum samples were collected every three days till the end of the experiments and kept at -20℃ until needed for biochemical analysis. All biochemical analysis were performed at the College of Veterinary Medicine, Sudan University of Science and Technology using colorimeter (WPA, Cambridge, UK) and Spectrophotometer (Jenway Ltd, UK). The following biochemical parameters were investigated .

2.15.1.Serum total proteins:

Serum total proteins were measured using commercial kits (Fortress Diagnostics Limited, United Kingdom). The values of total proteins were measured using Colorimeter (WPA, Cambridge, U.K) at the optical density 540 nm. The test principle used Copper ions react in alkaline solution, with protein peptide bonds to give a purple colored burette complex. The amount of complex formed is directly proportional to the amount of protein in the specimen, Tietz, (1995) and Henry, (1974). The reagent for total proteins was Burette Method –ready to use.

The calculation was performed:

$$\frac{\text{Absorbance of sample}}{Absorbance\ of\ standard} x\ Standard\ concentration\ g/dl$$

Results were expressed as g/dl.

2.15.2.Serum albumin:

Serum albumin was measured using commercial kits (Fortress Diagnostics Limited, United Kingdom). The test was used for quantity determination of albumin in serum. Serum albumin binds with the bromocresol green indicator in an acid medium to form a green (BCG) Bromocresol Green complex, the amount of which produced is directly proportional to the albumin concentration present in the sample, (Young, 2000) and Grant, (1987). The measurement was done by using Colorimeter (WPA, Cambridge, UK) at the optical density 580 nm, then calculated as albumin concentration:

$$\frac{\text{Absorbance of sample}}{Absorbance\ of\ standard} x\ Standard\ concentration\ g/dl$$

Results were expressed as g/dl

2.15.3.Serum glucose:

Serum glucose was measured using commercial kits (Fortress Diagnostics Limited, United Kingdom), using Colorimeter (WPA, Cambridge, UK) at the optical density 540 nm. Test was done as enzymatic indicator, and based on the Trinder reaction quantified by the formation of a pink quinoneimine dye. In this reaction glucose is determined after enzymatic oxidation in presence of glucose oxidase. The hydrogen peroxide formed is catalyzed by peroxidase and react with phenol and 4-aminoantipyrine to form the dye indicator as described by

Barham and Trinder, (1972). The glucose concentration was calculated as : $\frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} x\ Standard\ concentration\ g/dl$

Results were expressed as g/dl.

2.15.4.Serum urea:

Serum urea was measured using commercial kits (Medical Device Safety Services, Germany). The measurement of urea was performed primarily either by a condensation reaction using diacetyl monoxime or by enzymatic hydrolysis of urea by urease to produce ammonia. The diacetyl monoxime method was first proposed by Fearon, (1939) and modifications of this colorimetric method are in wide use. The use of urease in determinations was introduced by Marshall, (1913) who measured the liberated ammonia by titration with an acid. Vitro urea endpoint reagents uses the modified Berthelot reaction that describes urea is hydrolyzed by urease to form ammonium and carbonate. In alkaline medium, the ammonium ions react with the salicylate and hypochlorite to form a green colored indophenol (2.2 dicarboxylindophenol). The measurement was done by using Spectrophotometer (Jenway limited, U.K) at the optical density 630 nm.The calculation was done as: Urea concentration:

$$\frac{\text{Absorbance of sample}}{Absorbance\ of\ standard} x\ Standard\ value\ mg/dl$$

Results were expressed as mg/dl

2.15.5.Serum Glutamate Oxaloacetate Transaminase (GOT):

Serum GOT (AST) was measured using commercial kits (Medical Device Safety Services, Germany). The first kinetic determination of Aspartate aminotransferase (AST/GOT) activity in serum using a coupled

reaction of malate dehydrogenase (MDH) and NADH (Karmen *et al.,* 1955). This assay system was critically evaluated and optimized (Henry, 1964). A modification of this method incorporates lactate dehydrogenase into ASTassay mixtures in order to accelerate the lag phase by exhaustion of endogenous ketoacids. The amino group is enzymatically transferred by AST present in the sample from the aspartate to the carbon atom of 2-oxoglutarate yielding oxaloacetate and L-glutamate. Oxaloacetate is reduced to malate by MDH present in the reagent with simultaneous oxidation of the NADH to NAD. The measurement was done by the use of Spectrophotometer (Jenway limited, U.K) at optical density 340 nm and calculated as U/I=1746 x 340 nm/min (U/l).

Results were expressed as U/l

2.15.6. Globulins:

Globulin is a generic term used to describe a set of sixty proteins including the antibodies or gamma globulin and protein-carbohydrate compounds known as glycoprotein. There are four basic groups of globulin proteins known as the alpha-1, alpha-2, beta and gamma proteins.These are used to help transport proteins through the lipoproteins and assisting the blood in clotting. They also act as plasma cells which indicate whether there is an antibody deficiency in the blood stream. The level of these proteins is measured against the levels of albumin (Total proteins g/dl- albumin g/dl=globulins g/dl) (Davey *et al.,* 1972). Results were expressed as g/dl.

2.16. Statistical analysis.

All data were computerized using MSTAT- C program (Michgan State University), for the analysis of variance and for mean separation version 10.

Chapter three

3.Results:

3.1. Efficacy of Sulphadimidine in Nubian goats infected experimentally with *Trypanosoma evansi.*

3.1.1.Clinical signs and morbidity:

All goats of group 2 (control positive) died on week 3 post-infection by showing lack of appetite, weight loss, emaciation, recumbency and death, while goats of (group 3) which infected with *T. evansi* and treated with sulphadimidine (100mg/kg body weight) showed lack of appetite, weight loss, emaciation and isolation from group, recumbency, mucus nasal discharges, conjunctivitis, high limb paralysis, convulsion and lateral curvature of the neck. These animals were slaughtered on week 4 post treatment in moribund condition. No clinical signs and morbidity were shown by goats of group 4 and 5.

3.1.2.Clinical Parameters.

The clinical parameters in Nubian goats experimentally infected with *T.evansi* and treated with sulphadimidine are presented in table (3-1). There were no significant changes were observed in the body temperature, respiratory rate, pulse rate and heart rate compared to the control group (1). But insignificant slight increase (0.4-0.8℃) in body temperature was observed in groups (2, 3, 4 and 5) and in respiratory rate in group 3.

Table (3-1) Clinical parameters in Nubian goats infected with *T.evansi* and treated with Sulphadimidine Mean±SE.

Groups	Temperature ℃	Respiratory rate (inspiration/min)	Pulse rate (thrills/min)	Heart rate (beats/min)
Group 1	38.3 ± 0.26^{a}	32.4 ± 0.17^{a}	80.2 ± 0.54^{a}	92.7 ± 0.51^{a}
Group 2	39.1 ± 0.29^{a}	34.4 ± 0.20^{a}	78.6 ± 0.57^{a}	87.5 ± 0.50^{a}
Group 3	39.0 ± 0.24^{a}	41.0 ± 0.26^{a}	79.6 ± 0.50^{a}	93.0 ± 0.53^{a}
Group 4	38.7 ± 0.23^{a}	31.9 ± 0.25^{a}	85.9 ± 0.50^{a}	108 ± 0.61^{a}
Group 5	38.9 ± 0.27^{a}	30.0 ± 0.16^{a}	83.1 ± 0.58^{a}	99 ± 0.50^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$.

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

3.1.3.Haematological parameters:

The haematological parameters in Nubian goats experimentally infected with *T.evansi* and treated with sulphadimidine are shown in table (3-2). There were no significant changes recorded for red blood cells (RBCs) count, packed cell volume (PCV), haemoglobin (Hb) concentration, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) when compared with the control group (1). But there were insignificant decreases in the values of RBCs, PCV and Hb concentration in all infected and treated groups (2, 3, 4 and 5) and were not returned to the control values, also MCH and MCV showed insignificant decreases in their values specially in group 4 and 5.

Table (3-2) Haematological parameters in Nubian goats experimentally infected with *T. evansi* and treated With Sulphadimidine Mean±SE

Groups	RBCs ($x10^6/mm^3$)	PCV (%)	Hemoglobin (g/dl)	MCV (Fl)	MCH (Pg)	MCHC (g/dl)
Group 1	7.39 ± 0.03^a	26.1 ± 0.19^a	9.42 ± 0.05^a	61.6 ± 0.20^a	5.54 ± 0.05^a	34.3 ± 0.26^a
Group 2	5.43 ± 0.02^a	21.0 ± 0.16^a	9.40 ± 0.05^a	59.0 ± 0.18^a	4.16 ± 0.03^a	44.7 ± 0.23^a
Group 3	6.90 ± 0.02^a	19.9 ± 0.15^a	7.38 ± 0.03^a	65.8 ± 0.19^a	5.16 ± 0.03^a	36.5 ± 0.26^a
Group 4	5.09 ± 0.02^a	19.8 ± 0.15^a	7.08 ± 0.02^a	48.1 ± 0.11^a	2.90 ± 0.01^a	40.5 ± 0.27^a
Group 5	4.96 ± 0.02^a	20.8 ± 0.16^a	6.82 ± 0.02^a	55.7 ± 0.13^a	2.98 ± 0.01^a	36.8 ± 0.27^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

3.1.4.White blood cells count:

The white blood cells in Nubian goats experimentally infected with *T.evansi* and treated with sulphadimidine are presented in table (3-3). No significant changes in the total white blood cells count (WBCs), neutrophils, basophils, eosinophils, monocytes and lymphocytes in all experimental groups compared to the control group. But significant increase ($p \leq 0.05$) in the monocytes was deserrved in group 4. There were insignificant slight increases in the total white blood cells count, (group 5) and neutrophils (group 4 and 5) and the lymphocytes (group 3 and 5) compared to control group 1.

Table (3-3) White blood cells count in Nubian goats experimentally infected with *T.evansi* and treated with Sulphadimidine Mean±SE

Groups	WBCs $(x10^{3}/mm^{3})$	Neutrophils (mm^{3})	lymphocytes (mm^{3})	Monocytes (mm^{3})	Basophils (mm^{3})	Eosinophils (mm^{3})
Group 1	6.40 ± 0.04^{a}	0.77 ± 0.03^{a}	5.45 ± 0.03^{a}	0.84 ± 0.04^{a}	0.05 ± 0.00^{a}	0.23 ± 0.01^{a}
Group 2	6.73 ± 0.03^{a}	0.52 ± 0.02^{a}	5.55 ± 0.03^{a}	1.84 ± 0.01^{a}	0.09 ± 0.00^{a}	0.07 ± 0.00^{a}
Group 3	6.10 ± 0.04^{a}	0.50 ± 0.02^{a}	6.24 ± 0.04^{a}	2.66 ± 0.01^{a}	0.34 ± 0.01^{a}	0.45 ± 0.02^{a}
Group 4	6.34 ± 0.03^{a}	1.10 ± 0.03^{a}	5.52 ± 0.03^{a}	4.05 ± 0.02^{b}	0 ± 0.00^{a}	0.90 ± 0.04^{a}
Group 5	7.44 ± 0.05^{a}	1.55 ± 0.04^{a}	7.89 ± 0.05^{a}	2.42 ± 0.01^{a}	0.05 ± 0.00^{a}	0.31 ± 0.01^{a}

Note: Different letters in one column showed the significant changes (a,b,c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

3.1.5.Serobiochemical parameters:

The serobiochemical parameters in Nubian goats experimentally infected with *T.evansi* and treated with sulphadimidine are given in table (3-4). There were significant decrease ($p \leq 0.05$) in serum glucose and albumin and a significant increase in serum urea in all experimental groups (2-5) compared to the control group 1. Significant increase in the activities of (GOT) was recorded in groups 2 and 3. A significant increase in the serum concentration of globulins was also observed in group 3. No significant changes were recorded for serum total proteins for all experimental groups compared to control group 1.

Table (3-4) Serobiochemical parameters in Nubian goats experimentally infected with *T.evansi* and treated with Sulphadimidine Mean±SE

Groups	Glucose (g/dl)	Total proteins (g/dl)	Albumin (g/dl)	Globulins (g/dl)	Urea (mg/dl)	GOT (U/l)
Group 1	74.1±0.37^{a}	8.50±0.08^{a}	5.49±0.05^{a}	3.01±0.01^{a}	55.9±0.24^{a}	217±1.23^{a}
Group 2	58.8±0.35^{b}	7.14±0.05^{a}	3.62±0.02^{b}	3.52±0.02^{a}	88.4±0.27^{b}	251±1.24^{b}
Group 3	53.9±0.35^{b}	7.48±0.06^{a}	2.05±0.00^{c}	5.43±0.02^{b}	96.9±0.28^{b}	255±1.25^{b}
Group 4	54.7±0.38^{b}	8.44±0.08^{a}	3.46±0.01^{b}	4.98±0.02^{a}	74.5±0.25^{b}	224±1.22^{a}
Group 5	56.3±0.36^{b}	8.06±0.06^{a}	3.71±0.02^{b}	4.35±0.02^{a}	71.8±0.24^{b}	213±1.21^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

3.1.6.The efficacy of sulphadimidine:

The efficacy of sulphadimidine in Nubian goats experimentally infected with *T.evansi* was shown in table (3-5). Parasitaemia in group 2 started to appear in week 1 and reach the maximum on week 2 then start to decline and the animals were died with week 3 post-infection.

However, the parasitaemia in group 3 followed the same pattern as in group 2 for the first and second week but a harsh peak was noticed in week 4 and the animals were slaughtered in moribund condition. Groups 4 and 5 followed the same criteria as in group 2, then the peripheral blood was cleared from the parasites from week 4 in both groups.

Table (3-5): Efficacy of Sulphadimidine in Nubian goats infected experimentally with *T.evansi* Mean±SE using wet smear method.

Groups/Weeks	1	2	3	4	5	6	7	8	9
Group 1	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a
Group 2	0.5 ± 0.03^b	0.93 ± 0.03^b	0.28 ± 0.02^a	Animals were died					
Group 3	0.1 ± 0.01^a	1.38 ± 0.04^b	0.76 ± 0.01^a	2.3 ± 0.03^b	Animals were slaughtered in moribund condition				
Group 4	0.56 ± 0.03^b	1.96 ± 0.04^b	0.43 ± 0.02^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a
Group 5	0.56 ± 0.03^b	1.96 ± 0.04^b	0.43 ± 0.02^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a

Note: Different letters in one column showed significant changes (a,b,c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

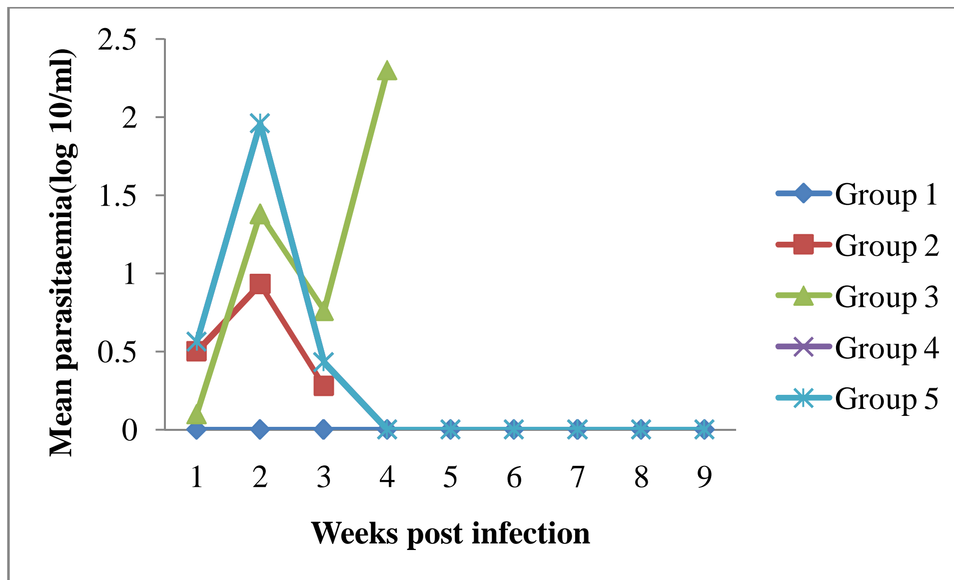
Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

Figure (3-1): Efficacy of Sulphadimidine in Nubian goats infected experimentally with *T.evansi* using wet smear method (Parasitaemia Mean±SE)



Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 3 infected and treated with sulphadimidine (100mg/kg b.w)

Group 4 infected and treated with sulphadimidine (200mg/kg b.w)

Group 5 infected and treated with sulphadimidine (400mg/kg b.w)

3.2. Efficacy of Gentamicin in Nubian goats infected experimentally with *Trypanosoma evansi:*

3.2.1.Clinical Signs and Morbidy:

All goats of group 2 (control positive) died on week 3 post-infection by showing lack of appetite, weight loss, emaciation, recumbency and death. All goats of group 6 were slaughtered on week 4 post-treatment in moribund condition showing emaciation, recumbency, mucopurulent nasal discharges and conjunctivitis. No clinical signs were shown by goats of group (7 and 8).

3.2.2. Clinical Parameters:

The clinical parameters in Nubian goats infected with *T.evansi* and treated with Gentamicin were shown in table (3-6). Results showed that there were no significant changes in the rectal body temperature, respiratory rate, pulse rate and the heart rate in any of the tested groups (2-8) compared with control group (1).

Table (3-6) Clinical parameters in Nubian goats infected with *T.evansi* and treated with different doses of Gentamicin Mean±SE

Groups	Temperature °C	Respiratory rate (inspiration/min)	Pulse rate (thrills/min)	Heart rate (beats/min)
Group 1	38.3 ± 0.26^{a}	32.4 ± 0.27^{a}	80.2 ± 0.34^{a}	92.7 ± 0.37^{a}
Group 2	39.1 ± 0.29^{a}	34.4 ± 0.26^{a}	78.6 ± 0.30^{a}	87.5 ± 0.36^{a}
Group 6	38.7 ± 0.24^{a}	36.9 ± 0.27^{a}	71.6 ± 0.25^{a}	76.6 ± 0.28^{a}
Group 7	38.3 ± 0.26^{a}	38.2 ± 0.23^{a}	84.8 ± 0.35^{a}	106 ± 0.42^{a}
Group 8	38.8 ± 0.23^{a}	35.7 ± 0.22^{a}	86.1 ± 0.36^{a}	102 ± 0.40^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

3.2.3.Haematological parameters:

The haematological parameters in Nubian goats infected with *T.evansi* and treated with Gentamicin are shown in table (3-7). Results showed no significant changes in the RBCs count, PCV, Hb, MCV, MCH and MCHC. But, it was noticed that there were insignificant decrease in the RBCs count and PCV in all treated and infected groups compared to the control negative group. In addition the haemoglobin (Hb) concentration and the MCH were insignifantly decreased specially in goats of group 7 and 8.

Table (3-7) Haematological parameters in Nubian goats infected with *T.evansi* and treated with different doses of Gentamicin Mean±SE

Groups	RBCs ($x10^{6}/mm^{3}$)	PCV (%)	Hemaglobin (g/dl)	MCV (Fl)	MCH (Pg)	MCHC (g/dl)
Group 1	7.39 ± 0.03^{a}	26.1 ± 0.18^{a}	9.42 ± 0.03^{a}	61.6 ± 0.20^{a}	5.54 ± 0.05^{a}	34.3 ± 0.26^{a}
Group 2	5.43 ± 0.02^{a}	21.1 ± 0.16^{a}	9.40 ± 0.02^{a}	59.0 ± 0.28^{a}	4.16 ± 0.04^{a}	44.7 ± 0.27^{a}
Group 6	5.55 ± 0.02^{a}	19.3 ± 0.14^{a}	9.11 ± 0.05^{a}	70.1 ± 0.29^{a}	4.94 ± 0.06^{a}	50.8 ± 0.28^{a}
Group 7	4.20 ± 0.01^{a}	19.9 ± 0.15^{a}	7.12 ± 0.02^{a}	69.5 ± 0.17^{a}	3.48 ± 0.02^{a}	39.1 ± 0.27^{a}
Group 8	4.15 ± 0.01^{a}	20.3 ± 0.17^{a}	6.74 ± 0.02^{a}	58.9 ± 0.27^{a}	3.17 ± 0.02^{a}	40.4 ± 0.27^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

3.2.4.White blood cells count:

The results of the white blood cells count (WBCs) and the differential white blood cells count in Nubian goats experimentally infected with *T.evansi* and treated with different doses of Gentamicin are shown in table (3-8). No significant changes were observed in the WBCs count, neutrophils, monocytes, basophils and eosinophils in any of the tested animals compared to the control negative. Significant increase in the lymphocytes count was observed specially in group 7 and 8.

Table (3-8) White blood cells count in Nubian goats infected with *T.evansi* and treated with different doses of Gentamicin Mean±SE

Groups	WBCs ($x10^3/mm^3$)	Neutrophils (mm^3)	Lymphocytes (mm^3)	Monocytes (mm^3)	Basophils (mm^3)	Eosinophils (mm^3)
Group 1	6.40 ± 0.05^a	0.77 ± 0.01^a	5.45 ± 0.05^a	0.84 ± 0.04^a	0.05 ± 0.00^a	0.23 ± 0.01^a
Group 2	6.73 ± 0.06^a	0.52 ± 0.01^a	5.55 ± 0.05^a	1.84 ± 0.08^a	0.09 ± 0.00^a	0.07 ± 0.00^a
Group 6	6.81 ± 0.04^a	0.76 ± 0.01^a	5.95 ± 0.07^a	1.49 ± 0.07^a	0.11 ± 0.00^a	0.38 ± 0.02^a
Group 7	6.55 ± 0.05^a	1.00 ± 0.04^a	9.81 ± 0.08^b	1.68 ± 0.07^a	0.05 ± 0.00^a	0.15 ± 0.00^a
Group 8	6.65 ± 0.06^a	1.16 ± 0.05^a	13.0 ± 0.09^b	1.55 ± 0.07^a	0 ± 0.00^a	0.29 ± 0.01^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

3.2.5.Serobiochemical parameters:

The results of the biochemical serum changes in Nubian goats experimentally infected with *T.evansi* and treated with different doses of Gentamicin are shown in table (3-9). Significant decreases in serum glucose concentrations were observed, while significant increases in serum urea concentrations and GOT activity were observed in the tested groups compared to that of the control negative group. No significant changes were observed for the concentrations of serum total proteins, albumin and globulins. There were significant differences in total proteins (groups 2-8), albumin (groups 2, 7 and 8) and increases in the globulins concentrations (groups 7 and 8) in all experimental groups were noticed.

Table (3-9) Serobiochemical parameters in Nubian goats infected with *T.evansi* and treated with Different doses of Gentamicin Mean±SE

Groups	Glucose (g/dl)	Total proteins (g/dl)	Albumin (g/dl)	Globulins (g/dl)	Urea (mg/dl)	GOT (U/l)
Group 1	74.1 ± 0.37^{a}	8.50 ± 0.08^{a}	5.49 ± 0.04^{a}	3.01 ± 0.01^{a}	55.9 ± 0.24^{a}	217 ± 1.23^{a}
Group 2	58.8 ± 0.27^{b}	7.14 ± 0.02^{a}	3.62 ± 0.03^{a}	3.52 ± 0.03^{a}	88.4 ± 0.32^{b}	251 ± 1.27^{b}
Group 6	65.3 ± 0.27^{b}	7.06 ± 0.02^{a}	5.30 ± 0.04^{a}	1.76 ± 0.01^{a}	111 ± 0.44^{b}	262 ± 1.27^{b}
Group 7	44.2 ± 0.21^{c}	7.37 ± 0.03^{a}	3.22 ± 0.03^{a}	4.15 ± 0.03^{a}	72.0 ± 0.27^{b}	234 ± 1.25^{b}
Group 8	55.4 ± 0.22^{b}	7.58 ± 0.04^{a}	3.30 ± 0.02^{a}	4.28 ± 0.03^{a}	80.3 ± 0.35^{b}	251 ± 1.23^{b}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

3.2.6.The efficacy of gentamicin:

The efficacy of gentamicin in Nubian goats experimentally infected with *T.evansi* and treated with different doses of Gentamicin is presented in table (3-10). The half recommended dose of gentamicin (group 6) failed to decrease the parasitaemia in the peripheral blood of the infected goats and the animals by week 4 post treatment were slaughtered in moribund condition. Infected goats which received single recommended dose of gentamicin decrease the parasitaemia from week 5, 6 and 7 post-treatment, then the parasite was cleared thereafter. Also the single double recommended dose follow the same pattern as group 7 but, the blood was cleared of the parasite from week 7 to the end of the experiment.

Table (3-10): Efficacy of Gentamicin in Nubian goats infected experimentally with *T.evansi* using wet smear method Mean±SE

Groups/Weeks	1	2	3	4	5	6	7	8	9
Group 1	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$
Group 2	$0.5±0.07^{b}$	$0.93±0.03^{b}$	$0.28±0.04^{a}$	Animals were died					
Group 6	$0.5±0.01^{b}$	$0.7±0.02^{b}$	$0.47±0.06^{b}$	$1.3±0.00^{b}$	Animals were slaughtered in moribund condition				
Group 7	$0.1±0.01^{a}$	$0.96±0.03^{b}$	$0.57±0.08^{b}$	$0.86±0.02^{b}$	$0.28±0.04^{a}$	$0.28±0.04^{a}$	$0.28±0.04^{a}$	$0±0.0^{a}$	$0±0.0^{a}$
Group 8	$0.5±0.01^{b}$	$1.77±0.05^{c}$	$1.44±0.04^{c}$	$1±0.04^{b}$	$0.14±0.02^{a}$	$0.57±0.08^{b}$	$0±0.0^{a}$	$0±0.0^{a}$	$0±0.0^{a}$

Note: Different letters in one column showed the significant changes (a, b, c) at $p≤0.05$

Keys:

Group 1 uninfected and untreated (control negative)

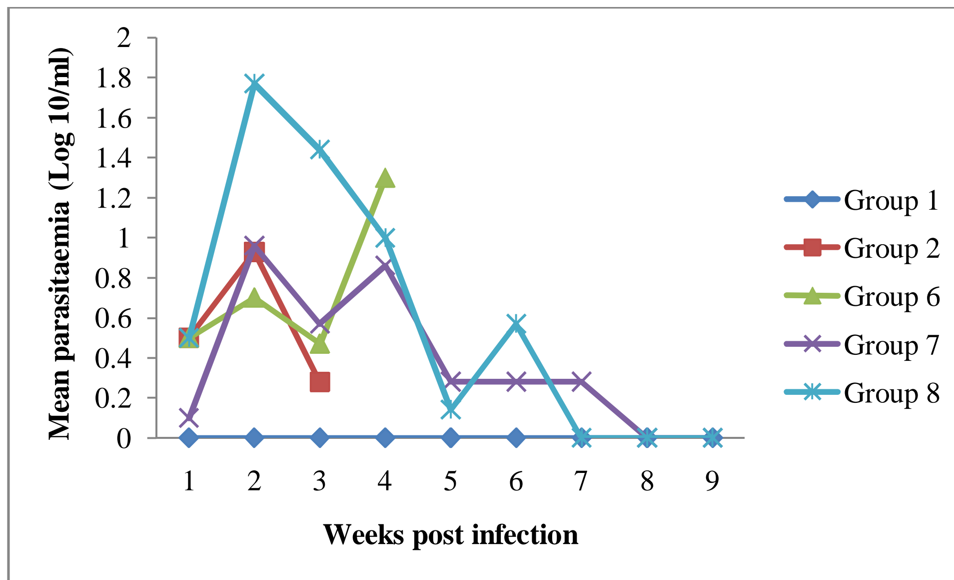
Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

Figure (3-2): Efficacy of Gentamicin in Nubian goats infected experimentally with *T.evansi* using wet smear method (Parasitaemia Mean±SE)



Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 6 infected and treated with gentamicin (2mg/kg b.w)

Group 7 infected and treated with gentamicin (4mg/kg b.w)

Group 8 infected and treated with gentamicin (8mg/kg b.w)

3.5. Efficacy of Oxytetracycline in Nubian goats experimentally infected with *T.evansi:*

3.5.1.Clinical signs and morbidity:

No clinical signs and morbidy were observed for group 9 (infected and treated with single dose of oxy 20mg/kg b.w) post-treatment.

3.5.2.Clinical Parameters:

The clinical parameters in Nubian goats experimentally infected with *T.evansi* and treated with oxytetracycline (20mg/kg at single dose) are shown in table (3-11). No significant changes were recorded for the temperature, respiratory rate, pulse rate and heart rate in any of the experimental animals.

Table (3-11) Clinical parameters in Nubian Goats infected experimentally with *T.evansi* and treated with Oxytetracycline Mean±SE

Groups	Temperature °C	Respiratory rate (inspiration/min)	Pulse rate (thrills/min)	Heart rate (beats/min)
Group 1	38.3 ± 0.26^{a}	32.4 ± 0.27^{a}	80.2 ± 0.34^{a}	92.7 ± 0.29^{a}
Group 2	39.1 ± 0.26^{a}	34.4 ± 0.26^{a}	78.6 ± 0.27^{a}	87.5 ± 0.27^{a}
Group 9	38.8 ± 0.27^{a}	29.8 ± 0.25^{a}	83.5 ± 0.29^{a}	104 ± 0.42^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

3.5.3.Haematological parameters:

The haematological parameters in Nubian goats experimentally infected with *T.evansi* and treated with oxytetracycline at single dose (20mg/kg b,w) are shown in table (3-12). Results showed significant decreases in the RBCs count and in the MCH in group 9 ($p \leq 0.05$). While no significant changes were observed for the PCV, MCV and the MCHC in the experimental animals. However, slight insignificant decreases in Hb concentration and PCV of goats in group 9 were observed.

Table (3-12) Haematological parameters in Nubian goats infected with *T.evansi* and treated with Oxytetracycline Mean±SE

Groups	RBCs ($x10^{6/}mm^3$)	PCV (%)	Hemaglobin (g/dl)	MCV (Fl)	MCH (Pg)	MCHC (g/dl)
Group 1	7.39 ± 0.04^a	26.1 ± 0.18^a	9.42 ± 0.05^a	61.6 ± 0.20^a	5.54 ± 0.03^a	34.3 ± 0.26^a
Group 2	5.43 ± 0.03^b	21.1 ± 0.16^a	9.40 ± 0.04^a	59.0 ± 0.18^a	4.16 ± 0.02^a	44.7 ± 0.23^a
Group 9	4.84 ± 0.02^b	19.5 ± 0.18^a	7.35 ± 0.03^a	49.0 ± 0.12^a	1.92 ± 0.01^b	40.2 ± 0.22^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

3.5.4.White blood cells count:

The white blood cells (WBCs) count in Nubian goats experimentally infected with *T.evansi* and treated with oxytetracycline (20mg/kg b.w) are shown in table (3-13). No significant changes were observed in WBCs, basophils and eosinophils count in any of the experimental animals (group 9). While significant increases in the blood counts of the neutrophils, lymphocytes and monocytes in this group were observed.

Table (3-13) White blood cells count in Nubian goats experimentally infected with *T.evansi* and treated with Oxytetracycline Mean±SE

Groups	WBCs ($x10^{3/}mm^3$)	Neutrophils (mm^3)	Lymphocytes (mm^3)	Monocytes (mm^3)	Basophils (mm^3)	Eosinophils (mm^3)
Group 1	6.40 ± 0.04^{a}	0.77 ± 0.01^{a}	5.45 ± 0.02^{a}	0.84 ± 0.01^{a}	0.05 ± 0.00^{a}	0.23 ± 0.01^{a}
Group 2	6.73 ± 0.04^{a}	0.52 ± 0.02^{a}	5.55 ± 0.02^{a}	1.84 ± 0.01^{a}	0.09 ± 0.00^{a}	0.07 ± 0.00^{a}
Group 9	7.95 ± 0.05^{a}	1.26 ± 0.01^{b}	9.44 ± 0.04^{ab}	2.80 ± 0.02^{b}	0.02 ± 0.00^{a}	0.59 ± 0.02^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

3.5.5.Serobiochemical parameters:

The biochemical parameters in Nubian goats experimentally infected with *T.evansi* and treated with oxytetracycline at a dose (20mg/kg b.w) are shown in table (3-14). There was significant decrease in the level of serum glucose concentration and albumin levels ($p \leq 0.05$) in group 9 and significant increases in the serum concentration of globulins and urea were also noticed compared to control groups.

Table (3-14) Serobiochemical parameters in Nubian goats infected with *T.evansi* and treated with Oxytetracycline Mean±SE

Groups	Glucose (g/dl)	Total proteins (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Urea (mg/dl)	GOT (U/l)
Group 1	74.1 ± 0.27^{a}	8.50 ± 0.05^{a}	5.49 ± 0.04^{a}	3.01 ± 0.01^{b}	55.9 ± 0.24^{a}	217 ± 1.23^{a}
Group 2	58.8 ± 0.27^{b}	7.14 ± 0.04^{a}	3.62 ± 0.01^{b}	3.52 ± 0.01^{b}	88.4 ± 0.28^{b}	251 ± 1.21^{b}
Group 9	50.6 ± 0.20^{b}	7.68 ± 0.03^{a}	3.56 ± 0.01^{b}	4.12 ± 0.02^{b}	68.0 ± 0.22^{b}	219 ± 1.23^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

3.5.6.The efficacy of oxytetracycline:

The efficacy of oxytetracycline in Nubian goats experimentally infected with *T.evansi* and treated with (20mg/kg b.w) was shown in table (3-15). The parasitaemia was cleared from the peripheral blood of goats in group 9 at week 4 and thereafter.

Table (3-15): Efficacy of Oxytetracycline in Nubian goats infected experimentally with *T.evansi* Mean±SE using wet smear method.

Groups/Weeks	1	2	3	4	5	6	7	8	9
Group 1	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a
Group 2	0.5 ± 0.03^b	0.93 ± 0.03^b	0.28 ± 0.02^b	Animals were died					
Group 9	0.54 ± 0.04^b	0.94 ± 0.03^b	0.43 ± 0.03^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

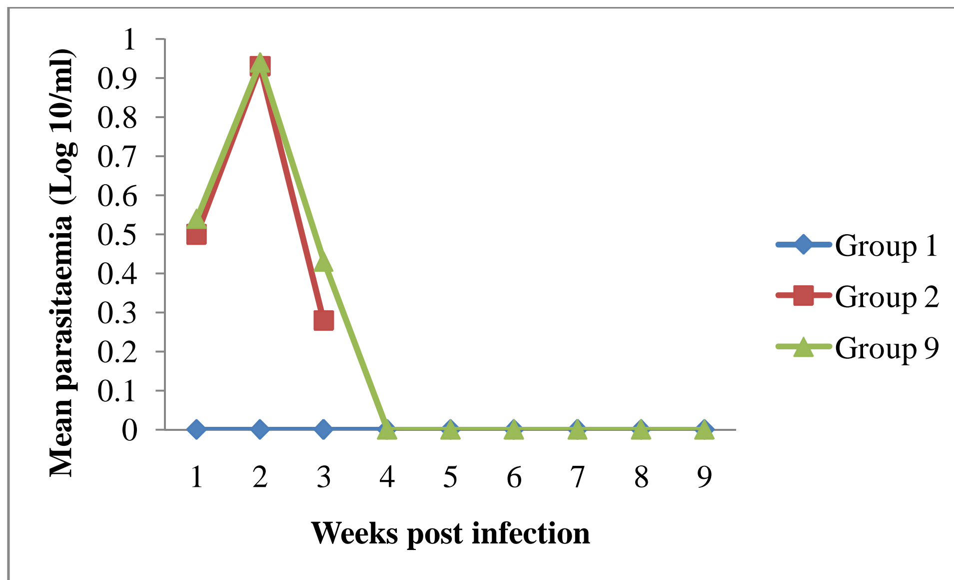
Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

Figure (3-3): Efficacy of Oxytetracycline in Nubian goats infected experimentally with *T.evansi* using wet smear method (parasitaemia Mean±SE)



Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 9 infected and treated with oxytetracycline (20mg/kg b.w)

3.6. Efficacy of the combination between Sulphadimidine and Gentamicin in Nubian goats infected experimentally with *Trypanosoma evansi:*

3.6.1.Clinical Signs and morbidity:

No clinical signs and morbidity were recorded for experimental treated group 10 and 11.

3.6.2.Clinical Parameters:

The clinical parameters in Nubian goats infected with *T.evansi* and treated with combination of sulphadimidine and gentamicin were shown in table (3-16). There were no significant changes observed between tested groups and the control negative for the rectal temperature, respiratory rate, pulse rate and heart rate.

Table (3-16) Clinical parameters in Nubian goats infected with *T.evansi* and treated with combination of Sulphadimidine and Gentamicin Mean±SE

Groups	Temperature °C	Respiratory rate (inspiration/min)	Pulse rate (thrills/min)	Heart rate (beats/min)
Group 1	38.3±0. 26[a]	32.4±0. 27[a]	80.2±0. 24[a]	92.7±0. 21[a]
Group 2	39.1±0. 29[a]	34.4±0. 26[a]	78.6±0. 27[a]	87.5±0. 27[a]
Group 10	39.0±0. 20[a]	26.3±0. 19[a]	87.4±0. 27[a]	106±0. 72[a]
Group 11	39.1±0. 19[a]	34.4±0. 26[a]	78.6±0. 26[a]	87.5±0. 47[a]

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

3.6.3.Haematological parameters:

The haematological parameters in Nubian goats infected with *T.evansi* and treated with combination of sulphadimidine and gentamicin are shown in table (3-17). There were no significant changes appeared between the tested groups and the control negative. Although there were no significant changes but it was noticed that there were insignificant decreases in the RBCs count, PCV and the MCH.

Table (3-17) Hematological parameters in Nubian goats infected with *T.evansi* and treated with combination of Sulphadimidine and Gentamicin Mean±SE

Groups	RBCs $(x10^{6/}mm^{3})$	PCV (%)	Hemaglobin (g/dl)	MCV (Fl)	MCH (Pg)	MCHC (g/dl)
Group 1	7.39±0. 03^{a}	26.1±0. 13^{a}	9.42±0. 03^{a}	61.6±0. 20^{a}	5.54±0. 03^{a}	34.3±0. 26^{a}
Group 2	5.43±0. 04^{a}	21.1±0. 16^{a}	9.40±0. 03^{a}	59.0±0. 28^{a}	4.16±0. 02^{a}	44.7±0. 26^{a}
Group 10	4.43±0. 02^{a}	20.9±0. 15^{a}	7.73±0. 05^{a}	65.6±0. 28^{a}	3.67±0. 02^{a}	41.1±0. 27^{a}
Group 11	5.43±0. 03^{a}	21.1±0. 16^{a}	9.40±0. 04^{a}	59.0±0. 28^{a}	4.16±0. 03^{a}	44.7±0. 29^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

3.6.4.White blood cells count:

The white blood cells (WBCs) count and the differential white blood cells count in Nubian goats infected with *T.evansi* and treated with combination of sulphadimidine and gentamicin are presented in table (3-18). Results showed that there were no significant changes in the WBCs count, basophils and eosinophils. The neutrophils, lymphocytes and monocytes were increased significantly in group (10) compared to the control negative group.

Table(3-18) White blood cells in Nubian goats infected with *T.evansi* and treated with Combination of Sulphadimidine and Gentamicin Mean±SE

Groups	WBCs ($x10^{3}/mm^{3}$)	Neutrophils (mm^{3})	Lymphocytes (mm^{3})	Monocytes (mm^{3})	Basophils (mm^{3})	Eosinophils (mm^{3})
Group 1	6.40 ± 0.03^{a}	0.77 ± 0.02^{a}	5.45 ± 0.04^{a}	0.84 ± 0.04^{a}	0.05 ± 0.00^{a}	0.23 ± 0.01^{a}
Group 2	6.73 ± 0.04^{a}	0.52 ± 0.02^{a}	5.55 ± 0.05^{a}	1.84 ± 0.02^{b}	0.09 ± 0.00^{a}	0.07 ± 0.00^{a}
Group 10	7.14 ± 0.04^{a}	0.82 ± 0.03^{b}	10.9 ± 0.09^{b}	3.33 ± 0.05^{b}	0.04 ± 0.00^{a}	0.27 ± 0.01^{a}
Group 11	6.73 ± 0.04^{a}	0.52 ± 0.02^{a}	5.55 ± 0.05^{a}	0.84 ± 0.04^{a}	0.09 ± 0.00^{a}	0.07 ± 0.00^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

3.6.5.Serobiochemical parameters:

The biochemical parameters in Nubian goats infected with *T.evansi* and treated with combination of sulphadimidine and gentamicin are shown in table (3-19). There were significant decrease in glucose serum concentrations ($p \leq 0.05$), and significant increase ($p \leq 0.05$) in albumin, globulin, urea and GOT values in group 10 and 11compared to the control negative group.

Table (3-19) Serobiochemical parameters in Nubian goats infected with *T.evansi* and treated with combination of Sulphadimidine and Gentamicin Mean±SE

Groups	Glucose (g/dl)	Total proteins (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Urea (mg/dl)	GOT (U/l)
Group 1	74.1 ± 0.23^{a}	8.50 ± 0.06^{a}	5.49 ± 0.04^{a}	3.01 ± 0.01^{b}	55.9 ± 0.24^{a}	217 ± 1.23^{a}
Group 2	58.8 ± 0.27^{b}	7.14 ± 0.05^{a}	3.62 ± 0.01^{b}	3.52 ± 0.02^{b}	88.4 ± 0.23^{b}	251 ± 1.29^{b}
Group 10	51.8 ± 0.25^{b}	7.00 ± 0.03^{a}	3.23 ± 0.02^{b}	3.77 ± 0.01^{b}	73.1 ± 0.22^{b}	239 ± 1.27^{b}
Group 11	58.9 ± 0.27^{b}	7.14 ± 0.03^{a}	3.62 ± 0.02^{b}	3.52 ± 0.01^{b}	88.4 ± 0.29^{b}	251 ± 1.21^{b}

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

3.6.6.The efficacy of combination of sulphadimidine and gentamicin:

The efficacy of combination of sulphadimidine and gentamicin in Nubian goats experimentally infected with *T.evansi* is shown in table (3-20). The parasitaemia was significantly decreased in goats of group 10 and 11 at week 5 and 6, then disappeared completely at week 7, 8 and 9 post-treatment.

Table.(3-20): Efficacy of combination of Sulphadimidine and Gentamicin in Nubian goats infected experimentally with *T.evansi* using wet smear method mean±SE

Groups/Weeks	1	2	3	4	5	6	7	8	9
Group 1	0 ± 0.0^a	$0 \pm 0\ 0^a$	0 ± 0.0^a	$0 \pm 0\ 0^a$	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a
Group 2	0.5 ± 0.07^b	0.93 ± 0.03^b	0.28 ± 0.04^b	Animals were died					
Group 10	0 ± 0.0^a	0.97 ± 0.04^b	1.76 ± 0.05^c	0.61 ± 0.08^{bc}	0.18 ± 0.02^b	0.57 ± 0.08^b	0.28 ± 0.04^a	0.28 ± 0.04^a	0 ± 0.0^a
Group 11	0.5 ± 0.07^b	0.93 ± 0.03^b	0.28 ± 0.04^b	0.14 ± 0.02^b	0.14 ± 0.02^a	0.14 ± 0.02^a	0 ± 0.0^a	0 ± 0.0^a	0 ± 0.0^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

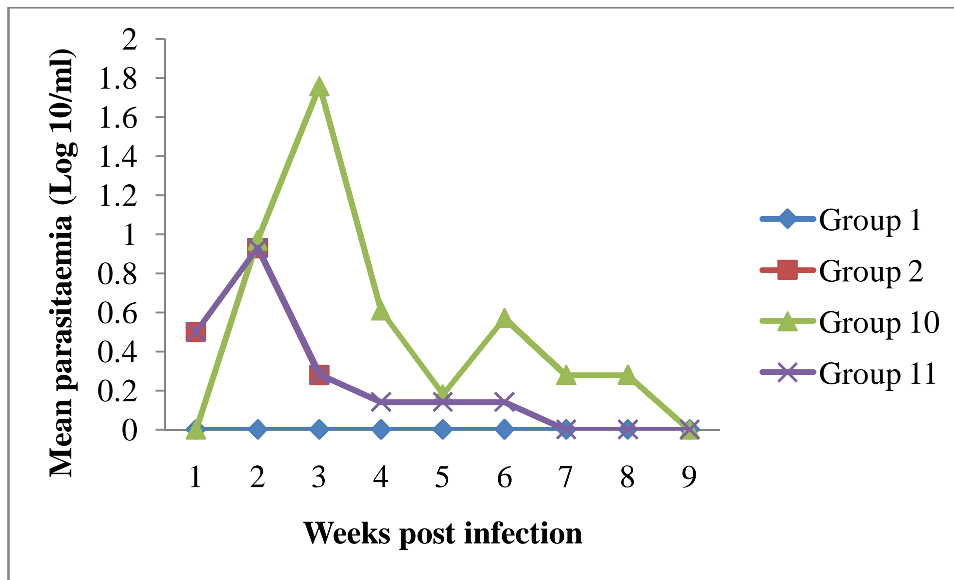
Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

Figure (3-4): Efficacy of Sulphadimidine and Gentamicin combination in Nubian goats infected experimentally with *T.evansi* using wet smear method (Parasitaemia Mean±SE)



Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 10 infected and treated with sulphadimidine (200mg/kg b.w) + Gentamicin (4mg/kg b.w)

Group 11 infected and treated with sulphadimidine (400mg/kg b.w) + Gentamicin (8mg/kg b.w)

3.7. Efficacy of Sulphadimidine, Gentamicin, Oxytetracycline combination in Nubian goats infected experimentally with *Trypanasoma evansi:*

3.7.1.Clinical signs and morbidity:

No clinical signs were recorded for group 12 and 13 post-treatment.

3.7.2.Clinical Parameters:

The clinical parameters in Nubian goats experimentally infected with *T.evansi* and treated with sulphadimidine, gentamicin and oxytetracycline combination are shown in table (3-21). No significant changes were observed for the rectal temperature, respiratory rate, pulse rate and heart rate in the infected and the infected-treated goats compared to the control negative group.

Table (3-21) Clinical parameters in Nubian goats infected with *T.evansi* and treated with combination of Oxytetracycline with Sulphadimidine and GentamicinMean±SE

Group	Temperature °C	Respiratory rate (inspiration/min)	Pulse rate (thrills/min)	Heart rate (beats/min)
Group 1	38.3 ± 0.26^{a}	32.4 ± 0.27^{a}	80.2 ± 0.44^{a}	92.7 ± 0.51^{a}
Group 2	39.1 ± 0.29^{a}	34.4 ± 0.26^{a}	78.6 ± 0.37^{a}	87.5 ± 0.47^{a}
Group 12	38.8 ± 0.28^{a}	29.8 ± 0.25^{a}	83.5 ± 0.49^{a}	104 ± 0.52^{a}
Group 13	39.0 ± 0.21^{a}	33.9 ± 0.24^{a}	85.9 ± 0.50^{a}	102 ± 0.53^{a}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

3.7.3.Haematological parameters:

The haematological parameters in Nubian goats experimentally infected with *T.evansi* and treated with combination of sulphadimidine, gentamicin and oxytetracycline are shown in table (3-22). There were no significant changes were recorded for the RBCs count, PCV, haemoglobin concentration(Hb) and the red blood cells (RBCs) indices. Although there were no significant changes but decreases in the RBCs count, PCV, haemoglobin concentration, MCH and the MCV were noticed in infected and infected-treated groups (12 and 13).

Table (3-22) Haematological parameters in Nubian goats infected with *T.evansi* and treated with combination of Oxytetracycline with Sulphadimidine and Gentamicin Mean±SE

Groups	RBCs ($x10^{6/}mm^3$)	PCV (%)	Hemaglobin (g/dl)	MCV (Fl)	MCH (Pg)	MCHC (g/dl)
Group 1	7.39±0. 03^a	26.1±0. 18^a	9.42±0. 04^a	61.6±0. 20^a	5.54±0. 03^a	34.3±0. 26^a
Group 2	5.43±0. 04^a	21.1±0. 16^a	9.40±0. 05^a	59.0±0. 18^a	4.16±0. 02^a	44.7±0. 23^a
Group 12	4.84±0. 02^a	19.5±0. 18^a	7.35±0. 03^a	49.0±0. 22^a	1.92±0. 01^a	40.2±0. 22^a
Group 13	4.00±0. 02^a	19.4±0. 18^a	7.19±0. 02^a	62.0±0. 22^a	2.42±0. 01^a	40.0±0. 21^a

Note: Different letters in one column showed the significant changes (a, b, c) at p≤0.05

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

3.7.4.White blood cells count:

The white blood cells and the differential white blood cells count in Nubian goats experimentally infected with *T.evansi* and treated with combination of oxytetracycline with sulphadimidine and gentamicin are shown in table (3-23). No significant changes were observed in the tested groups for the WBC counts, basophils and eosinophils in group 12 and 13, while significant increases were observed for the neutrophils in group (12), lymphocytes and monocytes in group 12 and 13 compared to the control group 1.

Table (3-23) White blood cells count in Nubian goats infected with *T.evansi* and treated with combination of Oxytetracycline with Sulphadimidine and Gentamicin Mean±SE

Groups	WBCs $(x10^3/mm^3)$	Neutrophils (mm^3)	Lymphocytes (mm^3)	Monocytes (mm^3)	Basophils (mm^3)	Eosinophils (mm^3)
Group 1	6.40 ± 0.05^a	0.77 ± 0.03^a	5.45 ± 0.02^a	0.84 ± 0.04^a	0.05 ± 0.00^a	0.23 ± 0.01^a
Group 2	6.73 ± 0.03^a	0.52 ± 0.02^a	5.55 ± 0.03^a	1.84 ± 0.02^b	0.09 ± 0.00^a	0.07 ± 0.00^a
Group 12	7.95 ± 0.04^a	1.26 ± 0.01^b	9.44 ± 0.04^{ab}	2.80 ± 0.02^b	0.02 ± 0.00^a	0.59 ± 0.02^a
Group 13	6.39 ± 0.04^a	0.99 ± 0.01^a	10.5 ± 0.07^{ab}	1.33 ± 0.01^b	0.07 ± 0.00^a	0.19 ± 0.01^a

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

3.7.5.Serobiochemical parameters:

The biochemical parameters in Nubian goats experimentally infected with *T.evansi* and treated with combination of oxytetracycline with sulphadimidine and gentamicin are shown in table (3-24). Significant decreases were recorded in glucose and albumin serum concentration in group (12 and 13) while significant increases in the globulins in group (12 and 13) and urea serum concentration and in the serum activity of GOT in group 13 only were observed.

Table (3-24) Serobiochemical parameters in Nubian goats infected with *T.evansi* and treated with combination of Oxytetracycline with Sulphadimidine and Gentamicin Mean±SE

Groups	Glucose (g/dl)	Total proteins (g/dl)	Albumin (g/dl)	Globulins (g/dl)	Urea (mg/dl)	GOT (U/l)
Group 1	74.1 ± 0.27^{a}	8.50 ± 0.05^{a}	5.49 ± 0.04^{a}	3.01 ± 0.01^{b}	55.9 ± 0.24^{a}	217 ± 1.23^{a}
Group 2	58.8 ± 0.27^{b}	7.14 ± 0.02^{a}	3.62 ± 0.02^{b}	3.52 ± 0.02^{b}	88.4 ± 0.22^{b}	251 ± 1.29^{b}
Group 12	50.6 ± 0.20^{b}	7.68 ± 0.05^{a}	3.56 ± 0.02^{b}	4.12 ± 0.01^{b}	68.0 ± 0.19^{a}	219 ± 1.23^{a}
Group 13	49.7 ± 0.16^{b}	7.29 ± 0.04^{a}	3.06 ± 0.01^{b}	4.23 ± 0.02^{b}	70.4 ± 0.20^{b}	242 ± 1.29^{b}

Note: Different letters in one column showed the significant changes (a, b, c) at $p\leq0.05$

Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

3.7.6.The efficacy of combination of oxytetracycline, sulphadimidine and gentamicin:

The efficacy of the combination of oxytetracycline, sulphadimidine and gentamicin in Nubian goats experimentally infected with *T.evansi* is shown in table (3-25). Results showed that single recommended oxytetracycline + sulphadimidine cleared the parasite from peripheral blood from week 4 to the end of the experiments. while single recommended combination of oxytetracycline + gentamicin cleared the parasitaemia of the peripheral blood from week 8 to the end of the experiment.

Table (3-25): Efficacy of Sulphadimidine, Gentamicin, Oxytetracycline and and their combination in Nubian goats infected experimentally with *T.evansi* using wet smear method Mean±SE

Groups	1	2	3	4	5	6	7	8	9
Group 1	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$
Group 2	$0.5±0.02^b$	$0.93±0.03^b$	$0.28±0.04^a$	Animals were died					
Group 12	$0.54±0.03^b$	$0.94±0.03^b$	$0.43±0.02^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$	$0±0.0^a$
Group 13	$0.1±0.01^a$	$1.5±0.02^b$	$1.16±0.04^b$	$0.94±0.03^b$	$0.24±0.03^b$	$0.43±0.04^b$	$0.14±0.02^b$	$0±0.0^a$	$0±0.0^a$

Note: Different letters in one column showed the significant changes (a, b, c) at $p \leq 0.05$

Keys:

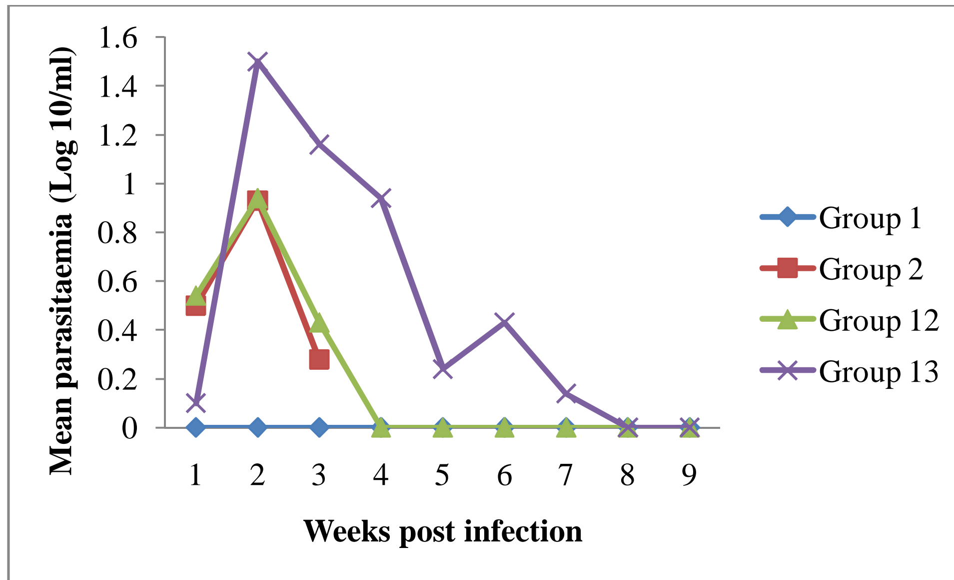
Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

Figure (3-5): Efficacy of Sulphadimidine, Gentamicin, Oxytetracycline and their combination in Nubian goats infected experimentally with *T.evansi* using wet smear method (Parasitaemia Mean±SE)



Keys:

Group 1 uninfected and untreated (control negative)

Group 2 infected and untreated (control positive)

Group 12 infected and treated with sulphadimidine (200mg/kg b.w) + oxytetracycline(20mg/kg b.w)

Group 13 infected and treated with gentamicin (4mg/kg b.w) + oxytetracycline (20mg/kg b.w)

Table (3-26) Summary of the results:

Drugs and control groups	Groups	Number of animals	Number of Dead animals	Time of death or slaughter	Clinical signs
Control -ve	1	3	-	-	No
Control+ve	2	3	3	week 3 post-infection	present
Sulpadimidine	3	3	3	week 4 post-treatment	present
	4	3	-	-	No
	5	3	-	-	No
Gentamicin	6	3	3	Week 4 post-treatment	present
	7	3	-	-	No
	8	3	-	-	No
Oxytetracycline	9	3	-	-	No
Sulphadimidine + Gentamicin	10	3	-	-	No
	11	3	-	-	No
Sulphadimidine + Gentamicin + Oxytetracycline	12	3	-	-	No
	13	3	-	-	No

Chapter four

Discussion:

Parasitic diseases have an enormous health, social and economic impact and are a particular problem in tropical regions of the world. Diseases caused by protozoa are the cause of most parasite related morbidity and mortality. The global burden of these diseases is exacerbated by the lack of vaccines, making safe and effective drugs vital to their prevention and treatment. Unfortunately, where drugs are available, their usefulness is being increasing threatened by parasite drug resistance. Trypanosomosis is a disease caused by various species of the genus trypanosome affect man and animal, resulting in an enormous morbidity and mortality. This effect reflected on pastoralism, migration, social and economical impacts on animals herders, populations and governments.

The objectives of the present study were to investigate the efficacies of Gentamicin, Sulphadimidine, Oxytetracycline and their combinations in Nubian goats infected experimentally with *T.evansi.*

Sheep and goats are extensively used as model laboratory animals for various pathological and pharmacological studies of *T.evansi* (Dargantes *et al.,* 2005, Youssif, 2005). Parasitism is a specific type of interaction between two organisms that have many features in common with other infections processes, but host-parasite interactions often operate over a longer time-scale than those seen with other pathogens. This extended process results in significant host parasite

interaction at the cellular and organismal level (Stephen *et al.,* 2007). The same author also mentioned that parasites inhabit a wide range of habitats within their hosts, as some parasites will inhabit only one site and others move to various site within the body throughout their life cycle in order to aid transmission and evasion of host immune attack.

Drug resistance emerged as a real problem facing the treatment of animal trypanosomiasis (Elrayah *et al.,* 1999) and this forcing towards the need for newer drugs to be used as trypanocidal agents. Katzung (2007) mentioned the use of antibiotics in the treatments of protozoans, for example tetracycline and doxycycline were found to be active against malaria and toxoplasmosis.

In this study the parasitaemia in all infected groups started to appear in week 1 and reach the maximum on weeks 2, and on weeks 3 post infection. Youssif *et al.* (2008) studied the efficacy and toxicity of Cymerlarsan in Nubian goats infected experimentally with *T. evansi* and found that the parasite was detected in the peripheral blood of goats was mild on days 4-5 and moderate on day 6 and severe on days 7-10 until the animal died on days 9-11 post infection. Dargie *et al.*(1979); Murray and Dexter, (1988), mentioned that peaks of the parasitaemic waves are usually high within this acute period. The animals that progress into the chronic phase usually have lower parasitaemia (Anosa, 1988). The chronic phase is characterized by low transient parasitaemia or aparasitaemia. Death may occur at any phase of the disease or the animal may recover naturally (Uzoigwe, 1986). The disappearance and resurgence of parasitaemia at different intervals of the experimental monitoring may be as a result of

dynamic of antigenic variation activity of parasites as earlier reported by Jones and Mickinell, (1984).

All goats of group 2 (control positive) died on week 3 post-infection by showing lack of appetite, weight loss, emaciation, recumbency and death. Manuel *et al.* (1998) mentioned that nervous signs may occur in infections involving *T. brucei* subspecies and *T. evansi*, and include ataxia, circling movement, inco-ordination, aimless running, staggering gait, head pressing and banging, paraplegia, paralysis and prostration. *T. simiae* infected pigs may die within a few hours, presenting as the severest and quickest form of trypanosomosis, with signs of fever, increased respiration, dullness, stiff and unsteady gait and cutaneous hyperaemia (Losos, 1986).

In the present study single half recommended dose of sulphadimidine failed to eliminate the parasite from the peripheral blood and on week 4 when the parasitaemia reach the peak the animals were slaughtered in moribund condition due to clinical signs as in group 2 (control positive). When the drug was given at single recommended or double recommended dose animals survived and the peripheral blood was cleared from the parasite since week 4 to the end of experiment. Stephen *et al*. (2007) mentioned that folic acid is an important co-factor in all living cells, and bacteria and protozoa are unable to take up exogenous folate and must synthesize it themselves. This is carried out in a series of reactions involving first the synthesis of dihydropteroic acid from one molecule each of pteridine and P-aminobenzoic acid (PABA). Glutamic acid is then added to form dihydrofolic acid (DHF), which is reduced by dihydrofolate reductase

(DHFR) to tetrahydrofolate (THF). Mammalian cells do not make their own DHF, instead they take it up from dietary nutrient and convert to THF using DHFR. Stephen *et al.* (2007) also mentioned that sulphonamides are structural analogues of PABA. They competitively inhibit the incorporation of PABA into dihydropteroic acid and there is some evidence for their incorporation into false folate analogues, which inhibit subsequent metabolism.

The efficacy of gentamicin at single half recommended dose failed to free the peripheral blood from the parasite and the animals died on week 4 when the parasitaemia reach the peak and the animals were died. Single recommended dose of the drug cleared the peripheral blood of the parasite since week 8 till the end of the experiment. Single double recommended dose of the drug cleared the parasite from the peripheral blood on week 7 and the animals survived till week 9 the end of the experimental period.

Katzung (2007) mentioned that the aminoglycosides include streptomicin, neomicin, kanamicin, amikacin, gentamicin, tobramicin, sisomicin, netilmicin and others and are used most widely against gram-negative enterocbacteria, especially in bacteraemia and sepsis, in combination with vancomycin or penicillin for endocarditis, and for treatment of tuberculosis. Also Katzung (2007) mentioned that the mechanism of aminoglycosides are irreversible inhibitors of protein synthesis, and inside the cell, aminoglycosides bind to specific 30S-subunit ribosomal proteins and the protein synthesis is inhibited in at last three ways: Interference with the initiation complex of peptide formation, misreading of mRNA, which causes incorporation of

incorrect amino acid into the peptide resulting in a nonfunctional or toxic protein and breakup of polysomes into nonfunctional monosomes.

The efficacy of oxytetracycline at single recommended dose succeeded to eliminate the parasite from the peripheral blood at week 4 and all the animals were survived until the end of the experiment. Rang *et al.*(2009) mentioned that tetracyclines are broad –spectrum antibiotics. The group includes tetracycline, oxytetracycline, demeclocycline, lymecycline, doxycycline and minocycline. Also Rang *et al.*(2009) mentioned that tetracyclines are bacteriostatic inhibitors of protein synthesis and accumulated intracellularly and binds bacterial ribosomal subunit (30S). The drug interferes with the binding of aminoacyl-t RNA to the A site on the ribosomal complex. This blocking action prevents alignment of the aminoacycl-t RNA anticodons with mRNA and peptide bond synthesis is inhibited. Mascochaw *et al.* (2006) mentioned that minocycline impedes African trypanosome invasion of the brain in a murine model that daily administration of minocycline impedes the penetration of leucocytes and trypanosomes into the brain parenchyma of *T. brucei-brucei* infected mice, and the loss of weight occurring during infection was not observed after treatment and those mice also survived longer than non-treated mice with minocycline. Minocycline and other tetracyclines antibiotics have been used in combination therapy against other parasitic diseases.

Vallachira and Usha (2014) mentioned that the trypanocidal action of quinapyramine is mainly due the inhibition of growth and

cell division of the organism. While the aromatic diamidines bind to DNA causing it to unbind and denature, this result in vacoulation and alterations in cytoplasm composition of the protozoa. Diminazene aceturate which is active against trypanosomes acts by binding to DNA containing organ cells, first in the kinetoplast followed by macromolecules.

Trypanosomiasis (*T.cruzi*) in dogs also treated by antibiotics such as Nitrofurones and nitromidazole (Riviere and Papich, 2009). Sulphonamides also used for the treatment of protozoal diseases especially coccidiosis in birds and animals. This may be the first trail to use a folate inhibitor in treatment of trypanosomiasis.

Erythrocytic schizonts of all human malaria parasites, Azithromycin, clindamycin and fluroquinolones are also used in treatment of malaria, tetracycline and erythromycin for treatment of intestinal amoebiasis, and spiramycin for treatment of primary toxoplasmosis acquired during pregnancy. Bywater *et al.*(1991) mentioned treatment of anaplasmosis by tetracyclines. Although the mode of action of antibiotics in treatment of protozoan till now is not clearly understood, but we believe that it acts to a certain level as its mode of action on bacteria and other microorganisms. Aminoglycosides and tetracyclines used in this study may act through inhibition of protein synthesis. But in all situations also another unknown mechanisms for these antibiotics to act on the trypanosome are yet unknown.

The efficacy of the combination of single recommended dose of gentamycin and sulphadimidine eliminate the parasite on week 9,

while the single double recommended dose of gentamycin and sulphadimidine eliminate the parasite on week 7 and the animals were survived till the end of the experiment. The efficacy of the combination of single recommended dose of oxytetracycline and gentamycin eliminated the parasite from the peripheral blood on week 8 while the single recommended dose of oxytetracycline and sulphadimidine eliminate the parasite on week 4 and the animals were survived till the end of the experiment.

Riviere and Papich (2009) described many drug combinations used in treatment of protozoal diseases, such as treatment of *Sarcocystis neurona* in horses (pyremethamine + sulphadizine), *Neuspora caninum* in dogs (pyremmethamine + sulphadizine), *Toxoplasma gondii* in dogs and cats (pyremmethamine + sulphadizine), *Eimeria sp* and *Isospora sp* in dogs and cats (ormetoprim + sulphadizine) also (trimethoprim + sulphadiazine) and coccidiosis in cats also treated by combination of (Amprolium + sulphadimethoxine).

Bywater *et al.* (1991) in multi-drug therapy it sometimes happens that the response seen is less than the sum of the component responses, in which case there has been antagonism between the drugs used. Antagonism can sometimes be explained on the basis of one drug interfering with or even reversing the action of the other i,e. It is often dependent on a mechanism involving pharmacological or physiological incompatibility. The use of a mixture which contains a bacteriostatic sulphonamide and bactericidal antibiotic exemplifies this possibility is that penicillin achieves its greatest antibacterial effect when the organism is multiplying rapidly. A sulphonamide

arrest cell division and so reduces the usefulness of the antibiotic. Antibiotics are generally used alone, but may on occasion be prescribed in combination. Combining two antibiotics may result in synergism, indifference or antagonism. In case of synergism, neutral inhibition is achieved at concentrations below that for each agent alone and may prove advantageous in treating relatively insusceptible infections (penicillin + gentamicin), another advantage is that it may enable the use of toxic agents where dose reduction is possible (amphotericin B + 5-flucylosine), another advantage is to prevent resistance emerging during treatment (fusidic + flucloxacillin), but the most common reason for using combined therapy is in treatment of confirmed or suspected mixed infection where a single agent alone will fail to cover all pathogenic organisms (metronidazole + aminoglycosides or a broad spectrum cephalosporins). Finally in cases who are seriously ill and about when uncertainty exists concerning the microbiological nature of the infection (Denyer *et al.,* 2004).

Stephen *et al.*(2007) mentioned that all pathogenic protozoa are heterotrophs, using carbohydrates or amino acids as their major source of carbon and energy and some parasitic protozoa utilize oxygen to generate energy through oxidative phosphorylation, but many protozoan lack mitochondria or have mitochondria that do not function like those in mammalian cells, and a results many parasites exhibit fermentative metabolism that functions even in the presence of oxygen. The same author also mentioned that the protozoan parasites possessing unique organelles such as kinetoplasts and hydrogenosomes and many intermediate metabolites or precursors

such as lipids, amino acids and nucleotides are actively scavenged from their environment, which means that the membrane of the parasite protozoa is rich intransporter. Secretion of haemolysins, cytolysins, proteolytic enzymes, toxins, antigenic and immuno-modulatory molecules that reduce host immune response also occurs in pathogenic protozoa.

No clinical signs were shown by the groups infected with *T. evansi* and treated with gentamicin, oxytetracycline combination with gentamicin and sulphadimidine or single recommended oxytetracycline.

Clinical parameters in this study showed no significant changes were recorded for the temperature, respiratory rate, pulse rate and heart rate in any of the experimental animals, although, there was slight insignificant increase in the temperature in goats of groups 2 and 9 infected and infected treated with Oxytetracycline. Body temperature varies according to the phases of the disease. Fiennes, (1970), Valera *et al.*(2005) and Akinwale *et al.* (2006) noticed that febrile changes in trypanosomosis could be demonstrated by plotting three-day average peak, with regular intervals each lasting for 2-3 days. A period following a temperature peak when *trypanosomes* were being destroyed in very large numbers is termed cold crisis (Fiennes, 1970). Youssif (2000) revealed that hyperthermia and hypothermia in goats infected with *T.vivax* is controversial. Increase in heart rate was observed in *T.vivax* infected goats (Ugochukwu, 1986). Youssif (2005) recorded the decrease in pulse rate and respiratory rate in

T.vivax infected goats. While Anosa and Isoun (1980) reported increase in respiratory rate in cattle infected with *T.vivax.*

There were no significant changes were recorded for haematological parameters in this study for the RBCs count, PCV, haemoglobin concentration and the red blood cells indices. But, decreases in the RBCs count and Hb concentration, PCV, MCH and the MCV were noticed specially in infected and treated groups compared to the control group. This coincide with findings of Saror, (1980); Sekoni *et al.* (1990) and Silva *et al.* (1995) in *T.vivax* and *T.congolense* infections in goats and cattle and Sharma *et al.*(2000) in *T.evansi* infection in Barbari goats, the decrease in PCV might be correlated with the decrease in total red blood cells count or due to haemodilution while the decrease in Hb concentration may be due to the decrease in PCV and RBCs count. The decrease in the above mentioned parameters indicate the state of anaemia in the infected groups (Sharma *et al.,* 2000). This anaemia might be due to the haemolysis such as proteases, phospholipases and nueramidases induced by trypanosomes (Soulsby, 1982), haemodilution which is a state when the fluid content of blood is increased and this results into lowered concentration of the formed elements. Trypanosomes may cause direct mechanical injury to erythrocytes and other cells by the lashing action of their powerful flagella and microtubule-reinforced bodies (Vickerman and Tetley, 1978), after adhering to the tissue (Banks, 1979).

Serobiochemical parameters in this study showed significant decreases in serum glucose concentration in the tested groups

compared to that of the control negative, this agree with Kadima *et al.*(2000) that reported hypoglycaemia may occurred at the periods of high parasitaemia or at the terminal stage in cattle with acute *T.vivax* infection but did not occur in chronically infected cattle. Decrease of serum glucose was noticed in sheep infected with *T.congolense* or *T.brucei* (Taiwo *et al*., 2007). while significant increases were observed in serum urea concentration and GOT activity in the tested groups compared to that of the control negative, this agree with Steven and Micheal, (2002) mentioned that GOT is a common marker of hepatocytes damage, but muscle damage, haemolysis and other processes also increase serum GOT activity. Youssif (2005) reported the increase of GOT activity in Nubian goats infected with *T.evansi*. The increase of serum urea agree with (Cheesbrough, 1998). A decreasing GFR (Glomerular Filtration rate) is the best indicator of renal insufficiency, and since UN (urea nitrogen) and CT (creatinine) are both freely filtered by the glomerulus they are the analysts most commonly used to estimate GFR. As the GFR decreases plasma UN and CT increase, however GFR must be reduced by 75% before UN and CT increase in blood plasma. Because azotemia is not evident until 75% of nephron are no longer functioning adequately, and because the ability to concentrate urine is best after 66% of nephons are compromised.

Azotemia and dilute urine or polyurea caused by renal failure are not detected until a large portion of the total renal mass is compromised. Therefore, they are not early indicators of renal failure. These percentages indicate the tremendous reserve of renal function,

since only 25% of total renal mass is needed to excrete sufficient nitrogenous waste to prevent azotemia, and only 33% is needed to concentrate urine and preserve the body's fluid volume (Thrall *et al.,* 2012).

The same author also mentioned that decreased plasma UN is uncommon. A decreased serum UN implies decreased production of urea, either due to hepatic failure or post systemic shunt. The same author mentioned that dehydration, hypovolumia and shock are non renal factors that increase serum UN and CT, while gastrointestinal haemorrhage increase the UN only, but non renal factors that increase the serum CT only are none creatinine chromogens, oxyglobin, glucose ketones, carrotines, uric acid, vitamins A and C. No significant changes were observed for the concentration of serum total proteins, albumin and globulins. No significant changes were recorded for serum total proteins for all experimental groups. But non suspected decrease was observed in total proteins of goats in groups 2 and 3 that infected and treated with sulphadimidine. Ghada, (2005) reported an increase of total proteins in goats infected with *T.vivax.* Similarly, Tabel *et al*., (1980) recorded an increase of total proteins and albumin in sheep infected with *T.congolense*. Adeiza *et al*., (2008) recorded decrease of total proteins in sheep and goats infected with *T.congolense, T.vivax* and *T.brucei.* A significant decrease in the serum concentration of globulins was observed in group 3. Significant decreases were observed also in albumin serum concentration of goats infected and treated with combination of gentamicin and sulphadimidine. A decrease of albumin and elevation of globulins in

sheep, goats and cattle infected with *T.congolense* and *T.vivax* was reported by Anosa and Isoun, (1976).

Thrall *et al.*(2012) mentioned that an increased concentration of serum albumin is seen only with dehydration. Decreased serum albumin is seen with glomerular diseases and is also seen with diseases in gastrointestinal, liver and cardiovascular system.

In this study there were no significant changes in the total white blood cells count, neutrophils, eosinophils, monocytes, basophils and lymphocytes in all experimental groups compared to the control group. But significant increase in the monocytes in group 4 that treated with sulphadimidine. Also there were an increases in the total white blood cells count, neutrophils, monocytes, and lymphocytes in all experimental groups. Taylor and Authei, (2003) reported increase in phagocytosis of leukocytes, platelets in animals infected with *T.congolense* and *T.vivax.* Goosssens *et al.* (1998) also revealed increase in WBCs count in chronic phase in sheep infected with *T.congolense.* Total leukocyte counts may drop by 30 to 50% in trypanosomes infected animals; the initial decrease is due mainly to an absolute decrease in T-cell, eosinophils, lymphocytes and neutrophils (Wellde, 1983 and Anosa, 1988b). In contrast, monocytes may have a transient increase. Macrophages, neutrophils and eosinophils are able to destroy opsonized trypanosomes and to remove circulating immune complexes (Taylor and Authei, 2003).

In the present study it was noticed that combination of (Gentamicin (bacteriacidal) + Sulphadimidine (bacteriostatic) and Gentamicin + Oxytetracycline (bacteriostatic) exhibited weak or no

synergism, but results force towards antagonism. However, the use of the combinations of two bacteriostatics drugs revealed positive synergetic action (sulphadimidine + oxytetracycline).

The present study concluded that treatment of trypanosomiasis with gentamicin (4-8mg/kg body weight), sulphadimidine (200-400mg/kg body weight) and combination of oxytetracycline at (20mg/kg body weight) and sulphadimidine (200mg/kg body weight) were succeeded in elimination of the parasite from the peripheral blood of the animal without any serious adverse effects on the vital organs, and the animals were survived for 65 days post infection.

The present study recommended the use of sulphadimidine, gentamicin and oxytetracycline alone or a combination of sulphadimidine with oxytetracycline for elimination of the parasite from the blood as development for new treatment strategies.

Further studies are needed to highlights on the mode of actions of these antibiotics on the trypanosome.

Comparison studies between the efficacy of conventional trypanosides and the antibiotics and their combinations used in the present study should be performed.

Another studies should be done to confirm the activities of these antibiotics and their combination in large population in natural and experimentally infected animals.

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Appendix:

Drugs available for treatment of African animal trypanosomiasis (adapted from Finelle, 1973).

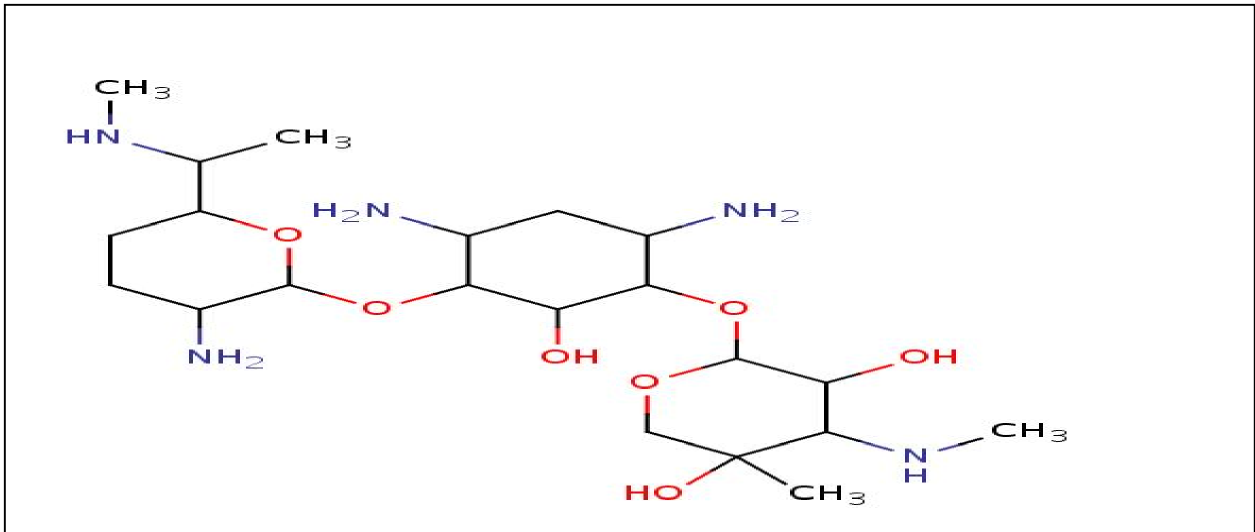
Drug	Trade Name	Activity		Toxic Effect			Treatment of Relapses
		Highly affective on	**Less effective on**	**Good Tolerance**	**Possible local Reaction**	**Possible General Reaction**	
Homidium chloride	Novidium	*T. vivax*		Cattle	Horses	Horses	Diminazine
		T. congolense		Goats			Isometamidium
				Sheep			
Homidium	Ethidium	*T .vivax*		Cattle			
		T. congolense		Goats			Isometamidium
				Sheep			
Diminazine aceturate		*T. .congolense*	*T. brucei*	Cattle	Horses	Horses	Homidium
	Berenil	*T. vivax*	*T .evansi*	Goats		Camels	Isometamidium
				Sheep			
Isometamidium chloride	Samorin	*T. vivax*	*T .brucei*	Cattle	Cattle	Cattle	Diminazine
	Trypamidium	*T. congolense*		Goats			
				Sheep			
				Camel			

Quinapyramine Sulphate	Antrycide	*T. congolense*		Cattle	Horses	Cattle	Homidium
		T. vivax		Goat,			Isometamidium
		T. brucei		Sheep			Diminazine
		T .evansi		Camel			

Spread of Drug Resistance In Africa (adapted from Finelle, 1973).

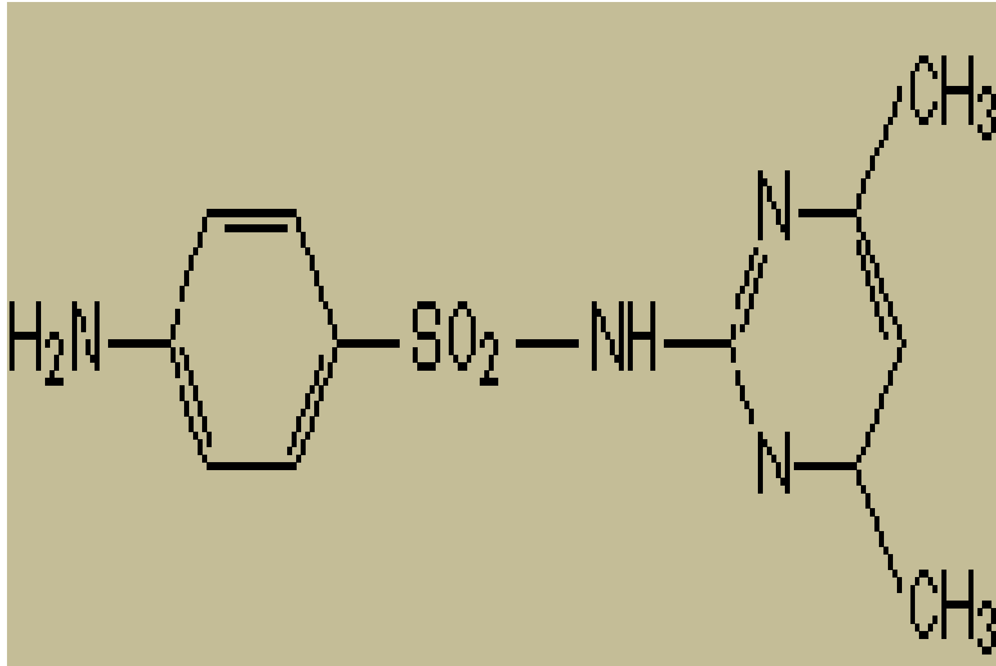
Subregion	Country	Trypanocides in current use to which parasite resistance has developed	Manufacturers recommended dose (mg/kg)	Species of trypanosomes	References
West Africa	Nigeria	Diminazine Aceturate	3.5	*T. congolense*	MacLennan & Jones-Davies (1967)
		(Berenil)		*T .vivax*	Jones-Davies (1967)
					MacLennan & Na-Isa. (1970)
					Leeflang *et al* (1977)
					Ilemobade (1979)
		Homidium Chloride (Novidium)	0.1	*T .congolense*	Jones-Davies (1968)
					Folkers (1966)
					Jones-Davies (1968)
					Folkers *et al* (1958)
				T. vivax	Ilemobade & Buys (1970)
					Gray 6 Roberts (1971)

					Leeflang *et al* (1977)
					Ilemobade (1979)
		Isometamidium Chloride	0.5	*T. congolense*	Na-Isa (1967)
		(Samorin)		*T. vivax.*	Ilemobade (1979)
East Africa	Kenya	Diminazine-Aceturate	3.5	*T. congolense*	Whiteside (1963)
					Gitatha (1979)
	Uganda	Homidium Chloride	1.0	*T. vivax*	Rottcher & Schililnger (1984)
		Isometamidium Chloride	0.5	*T. vivax*	Mwambu & Mayende (1971)
				T .vivax	
Southern Africa	Zimbabwe	Isometamidium Chloride	0.5	*T. congolense*	Boyt (1971)
					Lewis & Thomson (1974)

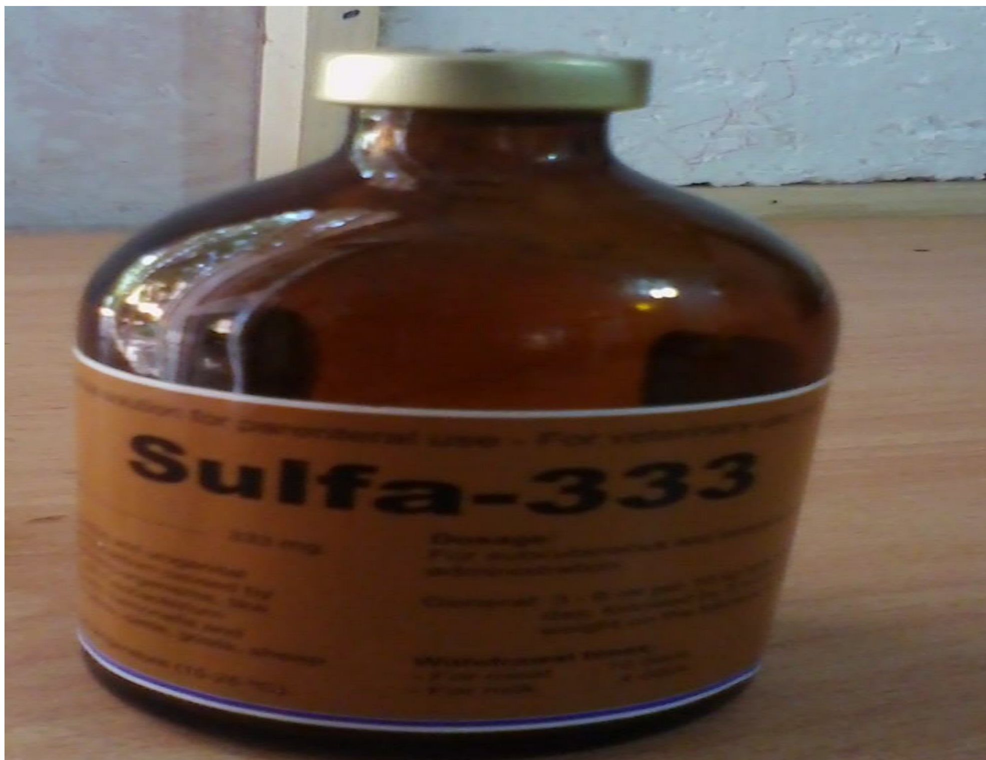


Chemical structure of gentamicin.

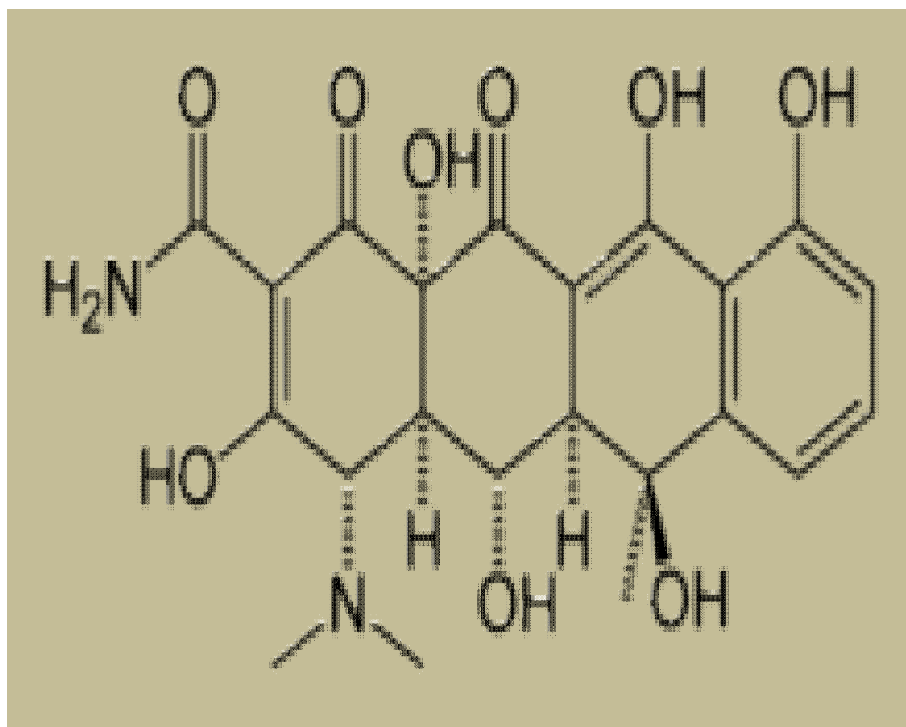
Gentamicin 20% injection 100ml



Chemical Structure of Sulphadimidine



Sulpadimidine 33.3% injection 100ml



Chemical structure of Oxytetracycline

Oxytetracycline Long-Acting 20% injection 100ml.

Parasitaemia estimation (Ismail, 1988):

1-2 parasite/preparation=…………………………………..…$1x10^2$

3-4 parasite/preparation=……………………………………..$5x10^2$

5-6 parasite/preparation=……………………………………..$1x10^3$

7-8 parasite/preparation =…………………………….….$5x10^3$

9-10 parasite/preparation=………………………………..…$1x10^4$

1-3 parasite/field =…………………………………………$1x10^4$

4-5 parasite/field=…………………………………………..$5x10^4$

Haemocytometer Work:

6-8 parasite/field=……………………………………………$1x10^5$

9-10 parasite/field=…………………………………………..$5x10^5$

11-20 parasite/field=…………………………………………..$7.5x10^5$

>50 parasite/field=…………………………………………..$5x10^6$

Note:

-Parasite/preparation means number of parasite in whole slide (not less than 30 fields).

-Parasite/field means number of parasite in each microscopic field.