# Sensitivity of Bovine *Trypanosoma vivax* Isolate Using Three Trypanocidal Drugs in Experimentally Induced Caprine Trypanosomosis

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Abstract: There were reports of widespread trypanocidal drugs resistant in the whole of the African continent as no newer trypanocides were available especially in Nigeria; hence bovine trypanosomosis still remains an obstacle to livestock production. A bovine isolate (Trypanosoma vivax) obtained from the field study conducted was used to intravenously inoculate a donor goat for cloning and subsequently used for drug sensitivity test. A set of fifteen susceptible goats for three different trypanocide dose regimens was studied over a period of three and half months to detect relapsed infection following the treatments. Homidium chloride, diminazene aceturate and isometamidium chloride were used for dosing goats infected with Trypanosoma vivax. Changes in the weekly mean body weight, packed cell volume, rectal temperature were recorded and analyzed using ANOVA. The results did not indicate any relapsed infection at all dose regimens used of Homidium chloride on Trypanosoma vivax. There was no change in the parameters that were studied. The Trypanosoma vivax isolate showed a relapsed infection after about two months post treatment with Diminazene aceturate (3.5mg/kgbwt) but not at the higher doses of 7.00mg and 10.5mg/kgbwt. Relapsed infection showed up earlier on animals treated with Isometamidium chloride. The use of trypanocides can at best supplement other approaches that include vector control and upgrading the efficacy of the available antitrypanosomal drugs.

Keywords: Sensitivity, bovine T.vivax, trypanocidal drugs, caprine trypanosomosis

#### 1. Introduction

African animal trypanosomosis has produced serious epidemics in Africa and is responsible for about 80% of Nigeria landscape being unsuitable for livestock production [1]. It is one of the tropical diseases for which newer and better drugs are required. Resistance to one or more of the trypanocidal drugs used in cattle has been reported in at least 13 countries of the sub-Sahara Africa [2]. It was reported that trypanocidal drug resistance is widespread in regions of Africa where drug pressure is high enough to select resistant strains [3].

Drug resistance in Trypanosomes is likely to occur as a result of drug pressure, immunocompetency of the host, inadequate dosing, cross resistance or use of mutagenic drugs [4].In the absence of an effective vaccine, trypanocidal drugs mainly Isometamidium chloride, Diminazene aceturate and Homidium chloride are the most commonly used veterinary products in sub-Saharan Africa [2].

Most of these trypanocides have been in use for over 5 decades and, not surprisingly, resistance of trypanosomes to them is inevitable [5]-[10]. The therapeutic and prophylactic use of trypanocidal drugs is as due to many limitations, including toxicity and the development resistance by the parasite [8]. Trypanosome resistance to trypanocides increase cost, reduces the efficiency of production and depletes the stock farmer of effective control tools[11]. The risk of environmental contamination increases due to progressive increase in frequency of use and dose rate of

drugs with declining effects also increased risk of toxicity from the use of large doses[11]. Resistance to each of the most commonly used trypanocides has emerged and continued to mar effective veterinary management of trypanosomosis in Africa and elsewhere [12],[3]. There is now further field and experimental evidence of diminished effectiveness and increased resistance of trypanosomes to suramin[13]-[16].Diminazene aceturate and Isometamidium chloride had been regarded as the best therapeutic and prophylactic trypanocides, diminazene aceturate was reputed as the only drug to which trypanosomes do not easily develop resistance because of its rapid elimination from the system when compared with the more persistent prophylactic drugs such as Isometamidium chloride [17]-[18]. Contrary to this view some field laboratory isolates and strains of Diminazene aceturate resistant trypanosomes had been reported and requiring up to 45mg/kg as the minimum dose to achieve a cure [19]-[20].Similarly, Isometamidium treatment failures and shortened prophylactic intervals have been attributed to drug resistant trypanosomes species[21]-[22].Homidium chloride used extensively as a prophylactic drug has been characterized by widespread development of resistant trypanosome strains[23].

## 2. Materials

**Trypanosome** – Bovine *T. vivax* was obtained from field studies used for trypanocides efficacy.

**Experimental goats-** A set of fifteen goats per drug were randomly categorized into a group of three for the drug

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efficacy trials. Each drug has three dose regimen and a group of positive and negative controls. Positive control group consist of three goats that were infected and not treated, negative control group were given a placebo treatment (not infected).

All experimentally infected and treated goats, and their controls were housed in a fly proof pens (nested pens), which were partitioned into three equal space for the different drugs trials.

Procurement of Trypanocides- Homidium chloride (Novidium<sup>R</sup>250mg/tablet) was purchased from the manufacturer Merial France with a batch no.A257461A.Mfd. 10/02/2005, ED.02/2010 and, purified and stable at  $28^{\circ}$ C.Isometamidium chloride (Trypamidium<sup>R</sup>1g) with lot no. Mfd.10/02/08, ED.03/2011, A257461A) and and Diminazene aceturate (Samorecide<sup>R</sup>23.6g) Animal care with Mfd.license no: 458/05/06 and ED. no 04/2011 having NAFDAC.REG.NO.04-6725.

**Methods-**A modified Multi dose protocol as described according to[24], 3 doses of each drug varying between e.g. 1.0 mg/kg- (3goats) -2.0 mg/kg (3goats), 3.0mg/kg(3goats) for Homidium chloride; 3.5mg/kg(3goats), 7.0mg/kg (3goats), 10.5 mg/kg (3goats) for Diminazene aceturate, 0.5mg/kg (3goats), 1..0mg/kg (3goats), 1.5mg/kg (3goats) for Isometamidium chloride, in addition to each dose regimen 6 goats for positive and negative controls thus making a total of 15 goats for experimental group.

Experimental goats were monitored twice weekly for parasitological and hematological examinations for over a period of three and a half months. Drug efficacy trials were conducted; three dose regimens were used for each of Homidium chloride (HDC), Isometamidium chloride (ISM) and Diminazene aceturate (DMZ). In each of the studies nine (9) infected and treated goats were used plus 6 for both positive and negative controls. Goats were randomly allocated into three groups. The first 3 groups were infected and treated, last two, one group was infected and untreated as positive control and the other one not infected and untreated as negative control group.

**Criterion of susceptibility or resistance of an isolate**-Trypanosome isolate was considered as drug sensitive if at least 2/3 of the treated goats cured, that is if they remain aparasitemic until the end of three and a half months observation period. If fewer than 2 goats cured then it was considered resistant to the dosage used. If, one goat dies prior to detection of parasitaemia, the isolate was considered as drug sensitive, if fewer than 2 of the remaining, it was considered resistant[24].

Weighing of experimental goats- All experimental goats were weighed using a personal scale model BR 9011 (calibrated in kilogrammes), with the aid of an assistant's taking his weight and then lifting the goat, hence the weight was deduced from the total weight. This was done in order to get accurate weight and to avoid drug under dosage and toxicity.

Handling of experimental goats and Ethical considerations- The ethical guidelines used during the course of study were those set by Biomedical Research involving animals as directed by the Medical Council for International Organizations of Medical Sciences (CIOMS), which includes good, clean and hygienic housing, good and adequate feeding, provision of clean water and humane handling of animals during sample collection, treatment and inoculations of trypanosomes into clean goats throughout the experiment. Valid approvals and ethical clearance were obtained from the Ministry of Livestock.

**Statistical Analysis -** All data generated were analyzed using EPINFO andSPSS 16.0and Graph pad Instat for Analysis of Variance (3x3) to determine association between variables.

# 3. Results

#### **Drug Resistance Studies**

Sensitivity of various doses of Homidium chloride on *T.vivax* isolate from Yola south local government area had indicated that the obtained isolate was sensitive to the three doses of the drug used, all the experimental treated goats survived till the end of the study and also negative control groups, while the positive control group of goats died before the termination of the study due to acute/chronic anemia.

Sensitivity of various doses of Diminazene aceturate (DMZ) of the isolate revealed a relapsed infection after treatments with 3.5 mg/kg/bw on the  $51^{\text{st}}$  (7.3wks) day post treatment (see goat no. 16) and the 2 goats in the same group revealed a relapsed infection on the  $60^{\text{th}}$  day (8.4wks) post treatment. Experimentally infected and treated goats with 10.5mg/kgbw DMZ did not show any relapsed infection throughout the study period, while all the goats in these two groups died before termination of the study. All the positive control group of goats died before the end of the first 30 days post treatment due to high level of parasitaemia.

Sensitivity of various doses of Isometamidium chloride (ISM) of the isolate had revealed an early relapse in the first week post treatment even with a very high dose of ISM (1.5mg/kgbw). Infact all the experimentally infected and treated groups with this drug (0.5mg/kgbw-1.0mg/kgbw), showed a relapsed infection within the 6<sup>th</sup> week post treatment. All the experimental goats were lost before the end of the study. Most of the goats in the negative control group survived nearly till the end of the experimental study. Goat ID. No.48 was lost as early as  $51^{st}$  (7.3 wks) day of the study due to acute pneumonia. The remaining was also lost before the end of the study period. Positive control group of animalsdiedbefore 72<sup>nd</sup> (10.3wks) day post treatment due to severe and progressive anemia. All of the experimentally infected (positive control) goats showed a progressive anemia characterized by facial oedema or puffy up syndrome, severe cachexia, scrotal oedema in males, coughing, diarrheoa, rough hair coat, bilateral ocular discharges, low PCV; continuous loss of weight and fluctuating high rectal temperatures, while the negative control experimental goats showed a regular increase in mean weekly body weight and increased PCV, fluctuating

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rectal temperature during the course of study. There was no cross infection between the positive / treated and negative control group that were kept together throughout the period of study. This had indicated that the pens were properly nested and had prevented all the biting flies and there was no mechanical transmission between the various treatment groups via injection during the course of study.

Results of treatment blocks with Homidium chloride(HDC) revealed that Mean weekly weight of experimental goats and their controls revealed that there was a gradual and continuous increase in the weight from 10.5kg to 16.5kg (Fig.1).The negative control had an exponential increase in the weekly weight gains from 18.0 to 24.0 kg (Fig.1).



Figure 1: Weight changes of goats treated with various dosages of homidium chloride

Positive control group had a persistent loss of weight and a survival rate of less than 16 weeks and the treated while negative controls survived for more than 18weeks (Fig.2). Mean PCV (%) of the experimentally infected and treated

goats with various doses of HDC had shown a regular increased in the % PCV (20.0- 26.0%), while the positive controls had a declined PCV from 20.0 14.0%.



Weeks Figure 2: PCV change of goats treated with homidium chloride

Mean rectal temperature in goats treated with various dosages of HDC had indicated a regular temperature change with little fluctuations of less than  $+_0.05^{\circ}C$  (38.8°C) except

for the positive control which recorded a mean rectal temperature of  $41.05^{\circ}$ C (Fig.3).



Figure 3: Temperature changes of goats treated with different dosages of homidium chloride

Experimentally infected and treated goats with Diminazene aceturate (DMZ) at various doses had shown a fluctuating increase or decrease in their weekly mean weights, while the positive control group revealed a continuous decreased in the

mean weight and until on the  $7^{th}$  week when it suddenly rose up and died on the  $8^{th}$ . The negative control group had an increased mean weight but died on the  $14^{th}$  week due to pneumonia (Fig.4).



Weeks Figure 4: Weight changes of goats treated with Diminazene aceturate

There was no statistical significant differences between those treated with 7.00 mg/kg as compared to the other groups (p>0.01).

Rectal temperature revealed a regular pattern of fluctuation till the end of the experiment or death of the experimental goats. Positive control group showed an increased in rectal temperature (Fig.5).



Figure 5: Temperature changes of goats treated with Diminazene aceturate

PCV of the experimental goats treated with various doses of DMZ had shown a fluctuating change in the PCV, while the negative control group had an increased in PCV but died on

the  $14^{th}$  week. The positive control group had a persistent declined in PCV and died on the  $9^{th}$  week of the study (Fig.6).

decreased in weight, the least weight gains was those of a

higher dosage of 1.5mg/kg (Fig.7). Negative control group



Figure 6: PCV changes of goats treated with diminazene aceturate

Results of the experimentally infected and treated goats with various doses of Isometamidium chloride (ISM) showed a

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showed an initial decrease but later gains weight considerably over the study period and survived till the end of the experiment while positive control group showed a continuous decline in weight gains. There was no statistical significant difference between those treated and their controls (p>0.01).



Weeks Figure 7: Weight changes of goats treated with Isometamidium chloride

PCV of the experimentally treated groups of goats with various doses of ISM had indicated a continuous but fluctuating decrease in their values. The negative control

group showed a drop in PCV initially but later recovered and had an increased in the parameter and died on the 14<sup>th</sup> week due to pneumonia (Fig.8).



Weeks Figure 8: PCV changes of goats treated with Isometamidium chloride

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Mean changes in rectal temperature treated with various doses of ISM had indicated a regular increase and constant fluctuations but higher than the negative control (Fig.9).



Weeks

Figure 9: Temperature changes of goats treated with Isometamidium chloride

### 4. Discussion

Drug resistance studies on the most prevalent isolate-Drug efficacy trials had revealed that there was no relapsed infection in the treatment groups with the various doses of Homidium chloride (HDC) in the present study which disagreed with the findings of the previous workers[25], who reported an early relapsed infections with 1.00mg/kgbw Homidium chloride and also resistant of trypanosomes to 7.00mg/kgbw diminazene aceturate, here it was noticed that the T.vivax isolate is very sensitive to the doses of diminazene aceturate at 7.00mg/kgbw and 10.5mg/kgbw but low survival rate occurred with the latter dose. This was indicated by the reversed in the various parameters measured during the period of study. The administration of trypanocidal drugs like Homidium chloride reversed the depression of parameters like mean weekly weight gains, PCVs and mean rectal temperatures. There was statistical significant difference between the dose of drug given and the measured parameter (p<0.05). In the present study, Homidium chloride treated group gained faster weight, increased PCVs, decreased in rectal temperatures to normal and higher Survival rate as opposed to works reported by [4] and [25]. This could be explained based on the fact that there was complete elimination of the T.vivax from the systemic circulation of the animal thus giving it permanent cure; hence the isolate was susceptible to the trypanocidal drug. The reduced weight gains, increased in rectal temperature and weight loss observed in the infected goats (positive control) agrees with the findings associated with trypanosomes infected animals [26]-[28].Sensitivity of various doses of diminazene aceturate had revealed relapsed infection after treatment with 3.5mg/kgbw as early as 51 days (7.3weeks) post treatment and the two goats in the same group showed a relapsed infection on the 60<sup>th</sup> day (8.1weeks). Relapsed infection with T.vivax had been reported as early as 14days post treatment [29], [4], [19]. Experimentally infected/treated goats with 7.00mg/kgbw survived throughout the period of the study with statistically significant difference (p<0.05) while those treated with 10.5mg/kgbw died before the termination of the experiment. It could be possibly explained due to toxic effects of the diminazene aceturate at a high dosage (10.5mg/kgbw). All those in the negative control group survived nearly the end of the study period but some mortality were recorded due to pneumonias and those in the positive control group were lost before the end of the first 30 days post treatment due to high level of parasitaemia.

Sensitivity of the *T.vivax* isolate to the various doses of Isometamidium chloride showed relapsed infection on the 1<sup>st</sup> week post treatment of experimental group of animals with 0.5mg/kgbw and also on the 2<sup>nd</sup> week for those treated with 1.00mg/kgbw and other group treated with higher doses of 1.5mg/kgbw on the 3<sup>rd</sup> week post treatment. The observation, that early breakthrough infection occurs in ISM treated animals are predominantly *T.vivax* concurs with the previous reports [30], [19]. Relapsed infections to doses as low as 0.25mg/kgbw has been reported [29], [31], [32]; and as high of 2.00mg/kgbw doses has been reported in Ethiopiaby [19],[5] recorded as high as 90% resistance in the trypanocidal drug treatment was due to isometamidium chloride drug failures which were mainly against *T.vivax* infections.[25] also reported about 81% of trypanocidal

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treatment failures were as a result of isometamidium chloride chemotherapeutic resistant.

Drug resistance studies revealed an increased and or decreased in the weekly weight gains of the group of goats infected by the T.vivax isolate and treated with all the doses of Homidium chloride (1.00mg/kgbw, 2.00mg/kgbw and 3.00mg/kgbw). This finding revealed an exponential increased in the mean weekly gains of all the goats treated with Homidium chloride. The result agrees with earlier reports of [33], [28] but disagreed with [34]. The difference could be explained based on the fact that the latter conducted their research in another set of animal species (canine) and the course of the disease is sub-acute while the former was in Caprine and it was chronic. The fact that the drug was effective in the treatment group at all doses. No relapsed infection because the parasite was sensitive and might have been not exposed to the drug. Increased in PCV as revealed in the present study, concurs with the findings of [28], but also disagreed with [4] and [8], the reason was that the latter conducted their study on dogs; the disease runs an acute infection. In the present study and that of [28] propounded the removal of the parasite from the peripheral circulation by the drug reverses the anemia. Mean rectal temperature revealed a decreased to normal, this agrees with reports of[35]. The best dosage that had higher increased in weekly weight, PCV, number of survivors and decreased to normal rectal temperature was 2.00mg/kgbw.

Sensitivity of T.vivax isolate showed a relapsed infection in the experimental group of goats treated with 3.5mg/kgbw but sensitive to higher doses of 7.00mg/kgbw and 10.5mg/kgbw. This could be seen in the parameters measured over period of time during the course of study. There was decreased in mean weekly weight, PCV, and a marked decreased in rectal temperature to normal values. This agrees with the studies conducted by [31], [4], [36][37]. Relapsed infection occurred on the  $50^{th}$  and  $60^{th}$  day post treatment with 3.5mg/kgbw.[29], reported early breakthrough infection within 2 weeks post treatment. The dose was not effective to clear the parasite, mortality occurred in the group treated with 10.5mg/kgbw of diminazene aceturate possibly due to toxicity but no relapsed infection in this group and the other of 7.00mg/kgbw. Only a remarkable increased in the mean weight gains, PCV, higher survivors and decreased to normal rectal temperature was recorded in the group 7.00mg/kgbw. This agrees with the works of [38], [32], [19], [39],[10].Reason was the migration of the parasite to where the drug could not reach. Response to and survival of treated animals experimentally infected cattle, sheep and goats have been reported[40], all infected and treated animals died before the end of the study as opposed to the present studies. T.vivax infection is reported to have been more resistant to Isometamidium chloride than T.congolense and T.vivax did produce more severe infections than T.congolense[41], our findings also agreed with the previous authors.

Breakthrough infections occurred in the group of experimental goats infected with *T.vivax* and treated with various dosages of Isometamidium chloride (0.5mg/kg; 1.00mgkg and 1.5mg/kg). This could be seen in the measured parameters used in the study. The mean weekly weight gains/loss, PCV, rectal temperature and survival rates

of the experimental goats. Relapsed infections in T. vivax infected and treated goats occurred within the first week post treatment with 0.5mg/kg, 2nd and 3rd week for 1.00mg/kgbw and 1.5mg/kgbw respectively. The result concurs with the previous work of[19], that resistant occurred even with higher doses of 2.00mg/kgbw Isometamidium chloride. Similar findings were reported by[30]. The findings disagreed with the report of [25] and [42]. Contrary to the study[42],reported findings of the present that Isometamidium chloride treated animals gained faster weight than the other trypanocides treated groups. The reason could be that the isolate of *T.vivax* used in that geographical area was very sensitive because of the variation in the different strains. Highest relapses occurred with Isometamidium chloride treated group, it could be that isometamidium chloride is a tissue depot drug, also T.vivax spent most of its time in the peripheral circulation and that the parasite must have developed some escaped mechanism to have avoided contact with the trypanocides[25].

Relapses occurred within the first week indicated that continuous exposure of the parasite to the concentration of the drug used, this showed that the drug pressure was very high. Low survivors in this group indicated that the parasite was not sensitive to the drug at therapeutic levels but rather could be used as chemoprophylaxis.[29] reported a relapse infection in goats treated with Isometamidium chloride (2.00mg/kgbw) as early as 2 weeks, and this is in accord with the present study.

# 5. Conclusion

It showed the presence of resistant *T.vivax* strains to a particular dosage of 3.5mg/kgbw diminazene aceturate and to all dosages of Isometamidium, hence it could only be useful for chemoprophylaxis in the management of bovine trypanosomosis and the best recommended drug for curative treatment of *T.vivax* is Homidium chloride at 2.00mg/kgbw and 7.00mg/kgbw of diminazene aceturate. This data obtained from the current studies indicated that the dose regimen could be used for managing bovine trypanosomosis in the field for an increased animal protein.

# 6. Recommendations

The need for a more effective trypanocide for *T.vivax* is essential for the control of the parasite. Furthermore, research in to the existing drugs is a prerequisite for their optimal usage in the overall effect of improving animal health and productivity through control of trypanosomosis. Also socio economic studies should be conducted to identify factors which influence the development of resistance to trypanocidal drugs in the state and the country at large. Chemotherapy is the main strategy used in the past and presently in the control of bovine trypanosomosis since there are no vaccinesavailable. The presence of quacks in administration of trypanocides to animals during treatments and lack of control on the purchase of trypanocides from any "open market" not minding the genuineness of the source and quality of drugs. Policies on the importation, sale and utilization of such drugs should be carefully controlled. Drug cross resistance studies should be carried out in various areas in order to have detailed sensitive isolate and the type of the

Volume 4 Issue 3, March 2015 <u>www.ijsr.net</u> Licensed Under Creative Commons Attribution CC BY trypanocide so as to have an effective control of the disease. Regular profile monitoring and evaluation of resistant strains in a given geographical area will provide information for rapid intervention.

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