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Therapeutic efficacy of quinapyramine compounds in *T. evansi* affected cattle

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Abstract
A total of ten (10) crossbred cattle suffering from clinical trypanosomiasis were confirmed by microscopic examination and treated with Quinapyramine compound of Sulphate and Chloride @ 4.4 mg/kg.b.wt, S/C, single dose along with supportive therapy. To assess the therapeutic efficacy of Quinapyramine compounds, blood and serum samples were collected on day 0 (pre-treatment), 3, 7 and 14 (post-treatment) for parasitological, haematological and biochemical examinations respectively. Affected cattle were recorded with haematological alterations (pre-treatment) viz. reduced Hb (7.94 g/dl ± 0.186), PCV (24.23% ± 0.567) and TEC (4.06 $\times 10^6$/µL ± 0.097) value, Leucopenia accompanied by Lymphocytopenia, Eosinophilia, Neutrophilia, Monocytosis and Thrombocytopenia. Similarly alterations in serum biochemical value (0 day pre treatment) of the affected animals were significantly decreased Glucose (33.97 mg/dl ±0.86), Total Protein (5.35 g/dl ± 0.052), Albumin (1.9 g/dl ± 0.053), Globulin (3.45 g/dl ± 0.083), A/G ratio (0.56 ± 0.027) and increased BUN (15.91 mg/dl ± 0.226), Creatinine (0.8 mg/dl ± 0.01 IU/L), ALT (34 ± 0.212 IU/L) and AST (122.89 ± 1.04). A gradual disappearance of clinical signs with no parasitemia microscopically was observed on 3rd day post treatment among all the affected cattle, along with a gradual restoration in the altered haemato-biochemical values on different post-treatment observation periods. Hence, it was inferred that anaemia and hypoglycaemia are two important pathological effects of trypanosomiasis affected cattle and Quinapyramine compound of Sulphate and Chloride was found to be effective against *T. evansi* infection in cattle.

Keywords: Quinapyramine sulphate and chloride, *Trypanosoma evansi*, cattle, anaemia, hypoglycemia

1. Introduction
Surra is caused by an important haemoflagellate protozoa; *Trypanosoma evansi* and pose a constraint to animal's health and productivity across the tropics and subtropics of world [1]. India is endemic to Trypanosomosis, with wide host range affecting both domestic and wild animals, where cattle, buffalo and camel act as reservoir hosts with subclinical form of disease, but often suffer clinically, when subjected to stress [2]. The acute form of the disease is characterized by high intermittent fever, anaemia, emaciation, loss of weight, lacrymation, oedema of dependent parts, reduced milk yield, corneal opacity, nervous signs and death may occur within 24 hours to post onset of clinical signs, whereas chronic form is characterized by loss of body condition with impaired reproductive performance [3-4]. The disease causes immunosuppression leading to failure of vaccination against other disease [4]. Looking into its importance, many researchers hit on vaccine development against the disease entity, but not a single promising experimental result to develop a vaccine could be obtained till date because of the capacity of parasite to modulate its own antigen termed as antigenic variation; ability of parasite to regularly switch its surface coat glycoprotein [3]. In India culling is not possible due to religious issues. So the only way left is early diagnosis and treatment with an effective drug. The disease entity has threatened the world and it has been now a challenge for many countries to control the infections. Drug resistance again renders an important role in treatment failure, which necessitates development of an effective drug. In Africa, the salts of three compounds viz., diminizine, homidium and isometamidium were used for control of animal trypanosomiasis, due to nonavailability of newer drugs [5]. While Indian veterinarian mostly prescribe three trypanocide specific drugs viz. diminazene aceturate, Isometamidium and Quinopyramine coumpounds [6-7]. Quinopyramine compounds are used for both prophylactic and therapeutic purposes. Though there were already previous reports claiming for Diminazene and Isometamidium to be effective against *T. evansi* [8], conflicting arises on efficacy on these drugs due to wide use and also brings a question mark on its ability to clear the trypanosomes from peripheral circulation.

So the present study focused on therapeutic efficacy of Quinopyramine compounds against naturally infected cattle with *T. evansi* through parasitological examination and haemato-biochemical alterations.

2. Materials and Methods

2.1 Sample size and study area

A total of ten (10) cross bred cattle naturally infected with Trypanosomiasis in and around the Durg district of Chhattisgarh, India were used for therapeutic study. Animals were recorded with history of inappetance or anorexia, fever, pallor mucous membrane and were confirmed for Trypanosomiasis through microscopic examination of stained blood smears. The study was conducted in the month of August 2018 with respect to availability of clinical cases. Since the incidence of infection is mostly post-rain; a favourable time for breeding of vectors [4]. Blood samples were collected in EDTA and clot activator tubes for harvesting serum for analysis of haematological and biochemical parameters respectively.

2.2 Parasitological examination

Blood smears were prepared immediately after each blood collection for detection of *Trypanosoma evansi* through microscopic examination. The blood smears were air-dried and fixed in methanol (99%), for 2–3 min, stained in field stain and examined at 100x magnification (oil immersion) for detection of *T. evansi* following standard protocols, as described by Murray *et al*. (1977) [9] and Paris *et al*. (1982) [10].

2.3 Haemato-biochemical examination

The EDTA blood samples collected from cattle (day 0; pre-treatment and day 3, day 7 and day 14; post-treatment) were analysed through automated haematological analyser (Mindray company, model BC-2800Vet) following standard protocols for Hb (gm/dl), PCV (%), TEC ($\times 10^6$ /µl), TLC ($\times 10^3$ /µl). Differential Leucocytes Count (DLC %) was performed following standard procedure [11]. The serum samples of cattle procured on day 0 (pre-treatment) and day 3, day 7 and day14 (post-treatment) were processed for analysis of Serum Glucose (mg/dl), Total serum Protein (gm/dl), Serum Albumin (gm/dl), Serum Globulin (gm/dl), A/G ratio, AST (IU/L), ALT (IU/L), Serum Urea (mg/dl) and Creatinine (mg/dl) using semi-auto analyser (diaSIL- 100, Systonics India Ltd) by standard procedure as per the literature supplied with biochemical kits (Biolab diagnostic pvt ltd., Maharashtra).

2.4 Therapeutic Efficacy

Animals were treated with Antrycide pro-salt (Quinapyramine injection; 4.4 mg/kg.b.wt, S/C, single dose) with supportive therapies. Therapeutic efficacy of Quinapyramine compounds was assessed on the basis of disappearance or amelioration of clinical signs, absence *of T. evansi* parasite in blood examination and haemato biochemical parameters on day 0 (pre-treatment), day 3, 7 and 14 (post-treatment day).

2.5 Statistical analysis

The results are presented as means ± SE for both the pre and post therapy values of different day. Analysis was carried out by using IBM SPSS software (version 20) for Duncan's Multiple Range Test (DMRT) and $P < 0.05$ was considered as statistically significant.

3. Results and Discussion

Microscopic examination of stained blood smears revealed slender and flagellated trypomastigote forms of *T. evansi* (Fig 1). The structure has already been described by Desquesnes *et al*. (2013) [12] and being an extracellular parasite can easily be identified in microscopic examination. Previous facts recite a low sensitivity of giemsa-stained thin blood smears equivalent to 10^5 trypanosomes ml^{-1}, due to which subclinical infection can't be detected, because of the periodically cryptic nature of parasitaemia [13]. To avoid this, advanced sensitive reliable test can be developed to detect the infection at field condition. After confirmation of clinical infection, all animals were treated with Quinapyamine and supportive therapy, where all treated cattle were found microscopically negative for parasite on 3rd day post treatment. The recorded fever before treatment ($104.56^{O}F \pm 0.16$) subsided to normal temperature might be due to administration of paracetamol injection. Usually when there is a parasitemia in body fluid, pyrogenic stimuli are released in blood and the temperature set point in the hypothalamus the body rises [14]. All the animals were having history of inappetance or anorexia, fever, pallor mucous membrane. Previously clinical signs like anaemia, poor body conditions, urticaria, edema and petechial hemorrhages of serous membranes were recorded by Reid *et al*., 2001 [15], Mijares *et al*., 2010 [16] and Padmaja, 2012 [17].

The haematological alteration in affected animal (pre-treatment day) included reduction in Hb, TEC, PCV, MCH, MCHC, TLC, lymphocyte and platelet, while an increase in oesinophil, neutrophil and monocyte was observed (Table 1). The haematological findings during the study are in the agreement of Sivajothi and Reddy (2017) [18] and except total leucocyte count is in agreement with Hussain *et al.* (2016) [19]. The anaemia in Trypanosomiasis is a catchy clinical finding of complex and multi factorial in origin, might be due to mechanical injury to RBC by the lashing movement of flagella and microtubule reinforced bodies of the parasite or might be due to adhesion of erythrocytes, platelets and reticulocytes to trypanosome surfaces via sialic acid receptors leading to membrane damages [20]. The recorded Leucopaenia might be due to ineffective or depressed granulopoiesis in the bone marrow [21]. The observed eosinophilia is a feature of parasitic infections and is associated with immediate-type hypersensitivity reactions. The lower mild thrombocytopenia, counts of WBC and lymphocytes might be due to the immunosuppressive actions of infecting parasite [22-23]. Often aggregation of platelets occurs along with severity of parasitemia [24]. The biochemical alteration in affected animal (pre-treatment day) include reduction in blood glucose, total protein, albumin, globumin and A/G ratio, while an increase in BUN, creatinine, AST and ALT was observed (Table 2). The findings are in agreement of Mishra *et al*. (2017) [25] except A/G ratio and Sivajothi *et al*. (2015) [26]. The recorded hypoglycaemia is due to excessive utilization of the blood glucose by trypanosomes for their metabolism. The recorded lower mean serum Albumin, Total Protein and Globulin might be due to increase hepatocellular damage arising in Trypanosomiasis infection [25]. The elevated values of ALT and AST enzymes might be due to tissue breakdown and inflammation in the host, particularly of the liver, heart, muscle and or due to lysed trypanosomes at different stages of the infection [26]. Increase in levels of serum creatinine might be due to damage to host tissues as well as renal and hepatic malfunction [27].

Animals were recorded with a correction in the haemato-biochemical alterations on 3rd, 7th and 14th day post-therapy. The significantly ($p<0.05$) anaemia got corrected through a substantial increase of Hb by the 14th day of post-treatment (9.06 g/dl ± 0.171) from 0 day of pre-treatment (7.94 g/dl ± 0.186), due to supportive therapy of Iron injection, vitamin B 12 and fluid therapies. The similar trend was also observed in altered PCV, MCH and MCHC which increased substantially and altered MCV substantially decreased by 3rd, 7th and normalised on 14th day of post treatment. But exception was observed in the altered TEC (4.06×106/µL ± 0.097), which increased by 7th day (4.27×10^6/µL ± 0.1) and normalised on 14th day (4.58×10^6/µL ± 0.094) of post-treatment, The recorded Leucocytopenia (TLC; 8.85×10^3/µL ± 0.127) and Thrombocytopenia (Platelet counts; 309.3×10^3/µL ± 3.56) in affected animals gradually got corrected substantially on 3rd, 7th day and normalised on 14th day post-treatment (TLC; 10.79×10^3/µL ± 0.167 and Platelet Counts; 358.2×10^3/µL ± 1.9). The alterations in White Blood Cells (WBC) were found corrected on 14th day post treatment with a similar trend, except monocyte corrected on 14 day post treatment (Table 1). The recorded biochemical alterations in all affected animals were also significantly ($p<0.05$) corrected by the 3rd, 7th and 14th day post treatment, where the recorded hypoglycemia on 0 day pre-treatment (Glucose: 33.97 mg/dl ± 0.86) substantially increased by 3th, 7th and restored to its normal value on 14th day (49.3 mg/dl ± 0.49) of post treatment. A similar trend was observation in Total Protein and Albumin, with a slight deviation in Globulin (3.45 g/dl ± 0.083) and A/G ratio (0.56 ± 0.027) normalised on 14 day of post treatment (Globulin; 3.74 g/dl ± 0.1 and A/G ratio 0.9 ± 0.049). The altered BUN (15.91 mg/dl ± 0.226) gradually decreased and returned to its normal value on 14th day of post treatment (12.07 mg/dl ± 0.22). A similar trend was also observed in AST and ALT, with a slight deviation in Creatinine (0.8 mg/dl ± 0.01; pre-treatment) significantly decreased on 7 day and normalised on 14 day of post treatment (0.65 mg/dl ± 0.01; Table 2).

The rise in TEC may be attributed to the trypanocidal effect of the drug leading to elimination of parasite from blood circulation thus significantly decreasing the mechanical destruction and reduced levels of parasitic toxins. Also there was a significant increase in blood glucose levels post treatment due to the fact reduction in consumers of glucose following elimination of parasite [28]. Overall the drug with supportive therapy was able to correct the altered haemato-biochemical value by 14th day of post treatment by Quinapyramine. The efficacy is in the agreement with Raina *et al*. (2000) [29] and Rajesh *et al.* (2010) [30]. Previously reports claims for quinapyramine @ 4.4 mg kgG1 b.wt. to have good therapeutic and prophylactic efficacy than other drugs [8]. Kumar *et al*., 2012 [1] recorded no parasitemia after 24 hrs of treatment in cows, treated with quinapyramine sulphate and chloride combination (Triquin). Previously Quinapyramine compounds were withdrawn from many areas after 1976 due to the emergence of resistance and again reintroduced in 1984 to treat *T. b. evansi* in camels and horses and are used till date [31-32]. So now it creates a question mark for efficacy of the drug to recover *T. evansi* affected animals, against which we found the drug effective, might be due to no proper diagnosis or use of the drug in the state of Chhattisgarh. Looking into the scenario, a new drug can be developed to cross over the emerging resistances. But the commercial pharmaceutical investors have been discouraged due to high costs of drug development and the low anticipated profit in developing countries. Looking into this, numbers of private international non-profit organisations are investing for the development of new therapeutic and prophylactic trypanocidal drugs [32]. However, no such resistance recorded in the state of Chhattisgarh and till a novel licensed new compound is available in the market, the rational and correct use Quinopyramine following a proper diagnosis is of paramount importance.

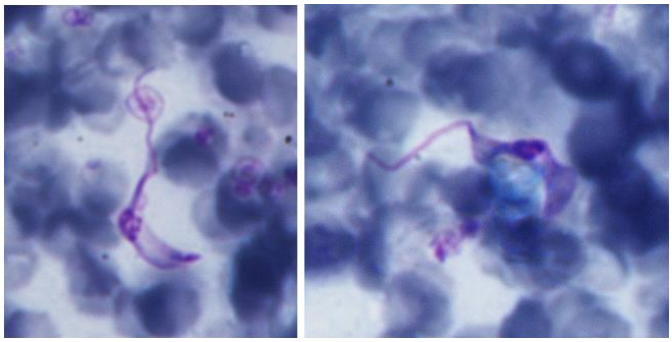

Fig 1: Microscopic view of *T. evansi* under 100x (oil immersion)

Table 1: Haematological values on different day of Pre and Post Treatment

Haematological Parameters	Pre-treatment	Post-treatment (Mean ± SE)		
	0 Day	3rd Day	7th Day	14th Day
Hb (g/dl)	7.94^{a}±0.186	8.14^{b}±0.186	8.42^{c}±0.187	9.06^{d}±0.171
TEC (×10^6/µL)	4.06^{a}±0.097	4.14^{a}±0.097	4.27^{b}±0.1	4.58^{c}±0.094
PCV (%)	24.23^{a}±0.567	24.64^{b}±0.577	25.2^{c}±0.583	29.93^{d}±0.55
MCV (fl)	59.69^{a}±0.218	59.46^{b}± 0.206	59.01^{c}± 0.205	58.76^{d}±0.209
MCH (pg)	19.56^{a}±0.083	19.65^{b}±0.079	19.72^{c}±0.078	19.78^{d}±0.09
MCHC (g/dl)	32.77^{a}±0.105	33.04^{b}±0.107	33.42^{c}±0.078	33.65^{d}±0.096
TLC (×10^3/µL)	8.85^{a}±0.127	9.23^{b}±0.132	9.73^{c}±0.125	10.79^{d}±0.167
Lymphocyte (%)	41.6^{a}±0.45	52.1^{b}±0.67	60.9^{c}±0.98	62.9^{d}±0.64
Eosinophil (%)	7.8^{a}±0.25	5.2^{b}±0.25	3.2^{c}±0.25	2.7^{d}±0.21
Neutrophils (%)	48.5^{a}±0.401	40.8^{b}±0.593	34.2^{c}±0.814	32.8^{d}±0.442
Monocyte (%)	2.1^{a}±0.314	1.9^{ab}±0.314	1.7^{ab}±0.26	1.6^{b}±0.221
Platelet (×10^3/µL)	309.3^{a}±3.56	324.2^{b}±3.119	339.2^{c}±2.79	358.2^{d}±1.9

Table 2: Biochemical Values on different Day of Pre and Post Treatment

Parameters with respect to drugs	Pre-treatment	Post-treatment		
	(Mean ± SE)			
	0 Day	3rd Day	7th Day	14th Day
Glucose (mg/dL)	33.97^{a}±0.86	41.43^{b}±0.6	48.08^{c}±0.53	49.3^{d}±0.49
Total Protein(g/dL)	5.35^{a}±0.052	6^{b}±0.053	6.56^{c}±0.058	7.04^{d}±0.042
Albumin (g/dl)	1.9^{a}±0.053	2.41^{b}±0.074	2.87^{c}±0.105	3.3^{d}±0.095
Globulin (g/dl)	3.45^{a}±0.083	3.59^{b}±0.1	3.69^{bc}±0.096	3.74^{c}±0.1
A/G ratio	0.56^{a}±0.027	0.68^{ab}±0.038	0.79^{bc}±0.047	0.9^{c}±0.049
BUN (mg/dL)	15.91^{a}±0.226	14.44^{b}±0.273	13.18^{c}±0.26	12.07^{d}±0.22
Creatinine (mg/dl)	0.8^{a}±0.01	0.76^{a}±0.01	0.73^{b}±0.011	0.65^{c}±0.01
AST (IU/L)	122.89^{a}±1.04	115.01^{b}±1.23	106.62^{c}±1.16	98.97^{d}±0.88
ALT (IU/L)	34^{a}±0.212	33.32^{b}±0.184	32.55^{c}±0.15	31.96^{d}±0.14

4. Conclusion

A significant hypoglycaemia and anaemia recorded is the catchy clinical findings of Trypanosomiasis. The drug Quinapyramine sulphate and chloride was very effective to clear the Trypanosomes from blood by the 3rd day of treatment. Specific treatment and supportive therapy resulted amelioration of clinical signs by 3rd day post treatment and altered haemato-biochemical parameters were restored to their normal level by 14th day of treatment.

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