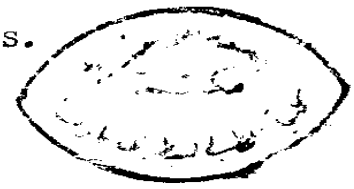
BIOCHEMICAL STUDY ON THE EFFECT OF ORAL ANTIBILHARZIAL DRUGS ON LIVER AND KIDNEY FUNCTIONS IN RATS.



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TO

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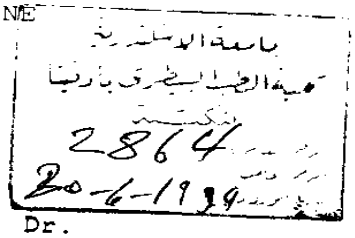

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قرار لجنة الحكم والمناقشـــــــة

قررت لجنة الحكم والمناقشة ترشيح السيد ط.ب/ رأفت أحمد الرمادى للحصول علـــى درجـة الماجستير فـى العلوم الطبية البيطرية (كيمياء حيوية وأكلينيكيـــــة)

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"CONTENTS"
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INTRODUCTION

Schistosomiasis is considered as one of the most important public health problems in tropical and subtropical countries including Egypt. The most recent estimate of the prevalence of schistosomiasis was 200 million cases, further 600 million live constantly at risk to be infested .(W.H.O., 1980).

After the construction of the High Dam the incidence of schistosomiasis has been expected to increase in these years and the fore - coming ones. (W.H.O., 1980).

This is due to the fact that the total agricultural area has been increased and the basin irrigation is replaced by the perennial ones. (Hammoda 1971).

Schistosomiasis is endemic in Egypt and it's headed the list of communicable diseases, where 50 - 60% of the population in area irrigated perennially, are infested while about 5 - 10 % are infested in areas irrigated by the basin system (Hilal, 1968).

In Africa, a conservative estimate places the number of infested individuals at present to be about 70 million and those under risk to be about 100 million or more (Mousa,1974).

The disease affects the mental, physical and genital development of childrens and greatly diminishes the productive power in adults (Kamel, 1977).

There are multiply evidences to indicate that there is an etiological relationship between cancer of bladder and bilharziasis haematobion infestation (Hashem et al., 1961).

Statistical reports showed that schistosomiasis is directly or indirectly responsible for the death of 25% of the inhibitants of Egypt (Nagaty et al., 1960).

Infestation with schistosoma mansoni causes marked histopathological changes in the liver of mice and human patients including enzymes activities which may be due to hepatic functional derangement (Sadun, et al., 1969).

Proteinuria is the most common manifestion of glomerular lesions in S. mansoni and the schistosomal glomerulopathy which could progress to renal failure (Barsoum, et al., 1977).

The schistosomocidal drugs which had been developed during the last years were namely :-

(A) Antimonials Compounds :-

The experimental animals treated with tarter emetic showed toxic effect on the Red Blood corpsules and liver parenchyma and Haemolytic anemia will develope , and also produced serious alterations as anaphylactic reaction, shock and sudden death, (Halawani, 1964).

The toxicity of these compounds is due to interference with cellular metabolism not only in liver but also in kidney by combined action with the sulphydryl group of respiratory enzymes. (Bueding & Schiller 1968).

(B) Non - Antimonials Compounds :-

Hycanthone., it could produce an acute hepatonecrosis and death occur during 2-5 days (Rollo, 1980).

Hycanthone resulted biochemical and morphological changes in liver of mice and rats even after small doses (Schuster et al., 1973 and Saad et al., 1978).

Hycanthone considered as a hepatotoxic drug and produced hepatocellular carcinoma in several experimental animals sometimes inducing jaundice and in some patients causing

sever hepatic injury with subsequent death (Katz, 1977).

This drug has teratogenic and embryolethal effect for mice and for rabbits on certain days of gestation period (Moore; 1972 & Sieber et al., 1975).

Niridazole (Ambilhar), it's considered a potant carcinogenic drug and can produce sever liver and kidney damage in experimental animals in the therapeutic doses (Garrattini, 1977 and Bulary & Shubik, 1978).

Metrifonate (Bilarcil), it's an organophosphorus inhibator of cholinesterase and by this way its effect on the worm but produced a liver cirrhosis after long duration in experimental animals (Hass, 1970).

Our choice drugs in this study are oxamniquine (vansil) and praziquantel (Biltricid).

These druge are recomonded recently for treatment of schistosomiasis in human patients .

AIM OF THE PRESENT WORK

The aim of the present work is to study the effect of oral, antibilharzial drugs represented by Oxamniquine (vansil) and praziquantel (Biltricid) on liver and kidney function tests in rats.

Moreover, to evaluate the changes that may take place from drugs administration at different time intervals.

It is hoped that this investigation may be used as helpful guide to clincians in treatment of schistosomiasis.

OXAMNIQUINE (VANSIL)

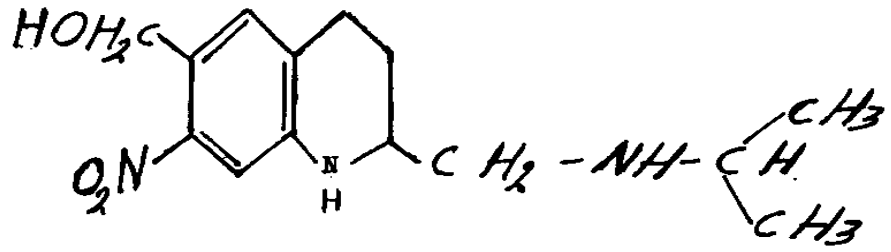
Oxamniquine is a drug which has been developed from the lucanthone series by Pfizer limited, Sandwich , Kent U.K.

It is prepared from compound U.K. 3883 (Pfizer) by microbiological hydroxylation in the presence of the fungus Asperigillus sclerotiorum. It is an active substance against S.mansoni (Foster,1973).

Chemistry :

The active substance of oxamniquine is 6- hydroxymethyl -2- isopropylaminomethyl -7- nitro - 1,2,3,4, 4- tetrahydroquinoline .

Structural Formula :-



It is soluble in methanol, acetone and chlorform , but sparingly soluble in water (Foster, 1973). The drug is metabolized by the liver as is elimenated by the kidneys.

Abd-Rabbo et al., (1977) gave oxamniquine in Egypt, they obtained a cure rate of 78.4% after three monthes with a total dose of 40 mg/kg B.W. in divided doses over two or three days.

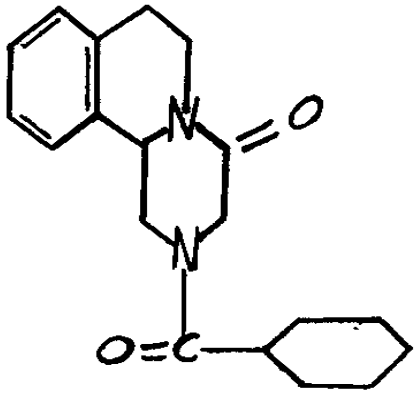
Abaza et al., (1978) using oxamniquine in chemotherapy of schistosomal colonic polyposis showed a good response as regard reduction in the size of ploypi with secondary correction of anaemia and hypo albuminaemia. Rollo, (1980) found that oxamniquine therapeutic dose was ranged from 15 - 60 mg/kg given orally and over 1-3 day.

Foster, (1973) recorded that this drug has a bad effects on the liver, and the drug has no evidence of teratogenic effects in a dose up to 400 mg/Kg in rats and rabbits. And also reported that high doses of oxamniquine (750 mg/kg) led to a decrease in red and white blood cells counts and to liver alterations in mice. While a dose of 120 mg/kg administered to mice for 3 consecutive days showed no toxicity, where 300 mg/kg day produced histochemical changes in the liver without morphological abnormality .

PRAZIQUANTEL

(BILITRICID)

Praziquantel is a new broad spectrum schistosomicide drug, chemically it is known to be 2- cyclohexyl- carbonyl- 1,2,3, 6,7,11b- hexahydro- 4 H-pyrazino-(2,1- a) isoquinoline-4 - one with structural formula $C_{19}H_{24}N_2O_2$ and molecular weight 312.4 (Andrews , 1981).



It is present in a colorless, crystalline powder, bitter in taste, and melts at 136- 140 C° .

It is soluble in chloroform, dimethyl-sulfoxide and ethanol, but sparingly soluble in water.(*Biltricid®) Bayer AG, 1972).

The maximum serum concentration of praziquantel were reached within 30 minutes to 1 hour after oral administration in all species(Steiner and Grabe, 1976) .

Within only 24 hours following oral administartion praziquatel was found to be eliminated in the form of its metabolites mainly in the urine (Steiner et al., 1976).

In the urine of treated rats, dogs and monkeys(Diekman & Buhring 1976), noticed that the the metabolites of praziquantel were conjugates of glucuronic or sulphuric acid.

Renal excretion of the given dose was found to be 80%-85% of it within 4 days, 90% of which was eliminated in the first day (Patzschke et al.,1979).

Excretion of praziquantel into the milk was studied in a group of lactating women and indicated that the drug is not secreted,but passively equilibrated between serum and milk (Putter, 1979).

The praziquantel drug did not reveal any undesired pharmaco dynamic action(Frohberg and Schencking, 1981).
It's therapeutic effect was compared to other antischistosomal drugs , where provied to be more effective(katz et al. 1979).

From the results of many clinical studies it has been concluded that , with respect to population based on chemotherapy, a single oral dose of 1X40 mg/kg is the most suitable for s. haematobium and s. mansoni while 2X30 mg/kg given on one day is recommended for s. japanicum infections(Da silva, et al., 1981).

Andrews(1981) reported that, from correlative studies, a single oral dose of 20 mg/ kg should be therapeutically effective in human.

In experimental studies, the acute toxicity in dogs could not be evaluated owing to the emetic effect of higher doses of the compound in this species (Von-Eberstein & Frohberg, 1974).

In mice, high dose of 1200 mg/kg produced no marked or prolonged adverse symptomes but only slight somnolence of the animals. (Machemer & Fork , 1978).Only with high sublethal doses of the drug, some neuro and psychopharmcological effects could be elicited in mice, rabbits and cats.
(Gleich and Frohberg, 1976), recorded that praziquantel

had no embryotoxic or teratogenic effects in rats, while in adult rabbits, maternal toxic effects like salivation and diarrhoea were observed.

Praziquantel when given to healthy rats in oral doses comparable to the humentherapeutic dose, failed to reveal any clinically relevant effects on peripheral nervous system, cardio vascular system , central nervous system, organs innervated by autonomic nervous system, blood clotting and renal function. The results of carcinogenicity studies with oral doses of 100 and 250mg/kg praziquantel given once weekly to syrian hamesters for 80 weeks and to rats for 104 weeks, respectively, showed that there was no indication of a carcinogenic potential(Mohr,1982 a and b)

Davis et al., (1981) Using three different dose regimens (1X30, 1X40 & 2X 20 mg/kg) showed that success rates were maximal after a single dose of 40 mg/kg. On the other hand, Oyediran et al.,(1981) and Diallo etal., (1981) using the same dose regimens, concluded that there were no statistically significant difference in efficacy between the three dose schedules.

Omer(1981), showed that there was no significiant

difference in the success of therapy as regards dosage , he noticed that the therapy with a dose of 1 X 40 mg/kg gave the better results .

LIVER FUNCTION.

The liver is considered to be the main organ responsible for the biosynthesis, uptake and degradation of a number of biological materials in blood including proteins and enzymes .

Liver function may,therefore, be reflected to some extent on the levels or the activities of these circulating biochemical compounds in serum.Schistosomal infection of the liver results in cirrhosis characterized by fibrosis and absence of parenchymal regeneration (Salah, 1962).

Liver supports the intermediary metabolism of all food stuff, it's the major nucleus of synthetic, catabolic and detoxifing activities in the body, it is crucial in the excretion of heme pigments and through it's kupffer cells,it participates in the immune response i.e the liver is a complex organ which performs many of metabolic function .

Many tests have been based on the hundreds of reactions occuring in the liver .

Going through the literature, oxamniquine and praziquantel have the following effects on the liver function tests:

I. SERUM TRANSAMINASES.

These tests are now an in dispensible part of diagnosis this is especially true in the case of hepatic disease. Serum glutamic oxal acetic **transaminase** (SGOT) or aspartate amino transferase (AS.T) is an enzyme that catalyses the reversible transfer of amino group from glutamic to oxal acetic. It's present in large quantities in liver,skeletal muscle ., . kidney, cerebral tissues, pancreas, spleen and lung in order that occurance. And the **serum level** of the enzyme .increases whenever these tissues are acutely destroyes and elevation occurs due to release of enzyme from damaged cells. Very high values are found with hepatocellular necrosis(Sherloek, 1975),Serum glutamic pyruvic transaminase (SGPT) or alanine amino transferase (AL.T); is a cytosol enzyme that catalyses the reversible transfer of an amino

group from glutamic to pyruvic acid.

This enzyme is also present in liver and although the absolute amount is less compared with (AS.T), a greater proportion is present in liver compared with heart and skeletal muscles.

A serum increase is therefore more specific for liver damage than (AS.T)(Sherlock, 1975) (AL.T)is found nearly exclusively in the cytoplasm of hepatic cells and the increase in it's serum activity reflects inflammation of the liver better than all other enzymes, this test is now used in preference to the SGOT assay particularly for screening purposes (Kruse, 1977 Ellis., 1978 and Popper, 1979).

AL.T assay is very sensetive and is thus of special value for the early detection of hepatitis and reflect the progress of liver inflammation. Measurment must be made early for the high value may-be normalized within a week of the onset.

The patient may develop fatal acute hepatic necrosis inspite of falling transaminase values. Continued elevation

suggests a chronic hepatitis, but results must be taken in conjunction with the patients serum bilirubin and gama globulin levels,

Normally, the ratio of SGOT/SGPT is 1 or more except in viral or infective hepatitis, where in the ratio is less than 1(De Ritis etal., 1957). Transaminase are helpful in screening for liver ingury due to drugs(Wroblewski 1959). Moveover, Williams , 1966 and Sadun, , et al, 1969), found that changes in enzymes activities in blood serum have been frequantly reported in bilharziasis, elevation of serum glutamic oxal acetic transaminase and serum glutamic pyruvic transaminase in infected mice. Saif et al.,1964b)and Ghanem et al.,1970);stated that, with the advanced of the bilharziasis disease, marked increase in serum glutamic oxal acetic transaminase .

Antimonialis compounds result in a significant rise of transaminase (Abdallah et al., 1964 and El-said et al., 1967). Abdallah et al., 1971) Also, observed a significant elevation of transaminase level reaching to the maximum level during the first week and returned within 2-4 weeks after

treatment with hycanthone. Pedro et al.,(1973) recorded that oxamniquine did not affect serum transaminases .

Leopold etal.,(1978) and Wegner, (1979)reported that from 112 individuals of healthy volunteers, only 12 significant variants were detected of serum transaminases., They recorded that such changes might occured as an incidental observation .

In post - hepatic and chlangiolitic type of jaundice, the enzymes level show modest elevation (usually less than 300 u/ml), in patients with cirrhosis, there is a 60% to 70% incidence of elevated SGOT level(also below 300 u/ml) the incidence and degree of SGPT elevation is less (Zimmerman 1966) .In hepatology AL T is now used in preference to AS T assay.(kruse, 1977; Ellis, 1978 and popper , 1979).

The AS T assay is mainly used in hepatology together with the AL T value to obtain the so-called de ritis quotient(AS T/AL T). Which is of particular value in differential diagnosis (Ellis,1978).

II- SERUM LACTAIC DEHYDROGEASE (LDH)

" L D H "

Its aglycolytic enzyme which catalyzes the interconversion of lactate and pyruvate this enzyme is present almost in all tissues, body fluids and also in blood cells .

The possible explanations of increased LDH, in bilharzial hepatic fibrosis is the rise rate of release from liver cells in advanced stages of the disease .

Although the pathological losions in hepatic bilharziasis is mainly mesonchymal, yet, minor degenerative changes do occur in the hepatic cells in the territory of the fibrosed portal tracts (Erfan, et al.,(1957) and Salah,(1962); Ghanem, et al (1970 a) and El- Hawary, et al., 1970), suggestes that the occurance of high serum lactic dehydrogenase (LDH) activity and LDH4 isoenzyme is due to that s. infection which could alter the cell membrane permeability leading to leakage of the enzyme from the cytoplasm, where it's mainly locted , to the plasma.

Altered cells membrane permeability contributes to the increased level of LDH release from the liver cells.(wieme

and Demeulenaere, 1970) also, said that the enzyme is liberated from disintergrating liver cells.

This elevation of LDH in bilharzial hepatic fibrosis are faced by the results of wilkinson(1962) that the elevation of serum LDH in virus hepatitis is relatively mild if compared with the rise in the level of AL T and AS T in advanced bilharzial hepatic fibrosis, the elevation of serum LDH activity is due to the inability of the liver to inactivate the enzyme(Ghanem et al., 1970) but LDH clearance was not changed in the hepatectomized animal (Greenberg and Harper; 1960).

An extrahepatic factor which might explained the elevation of LDH activity in advanced cases of bilharzial hepatic fibrosis is the skeletal muscles.This observation was based on the results of striking muscle wasting in these cases and on the finding of Mansour et al., (1965) that myopathy occurs in mice infested with S. mansoni.

Ghanem etal., (1970) reported that in bilharzial hepatic fibrosis, serum LDH activity remained parctically within the normal range. In the presence of ascitis the mean value was slightly increased and the difference was not statistically

significant.

This report in bilharzial hepatic fibrosis is in aggreement with that reported by wu and Sung(1962)in other types of liver cirrhosis . Serum LDH was reported to be insensitive index of hepatocellular damage.However its value lies in the early detection of liver malignancy (Ghanem et al., 1970). Sherlock(1975) said that LDH is a relatively insensetive index of hepatocellular injury .

Farid et al., (1972), concluded that there is decrease in serum lactate dehydrogenase activity following antimonialis use in these patients treated with tartar emetic and bilharcid and this due to effect of drugs on liver tissues.

Abdel- Meguid,et al.(1975), reported that oxamniquine has no important changes on liver function tests included lactate dehydrogenase.

leopold et al.,(1978) , reported that serum level of lactic dehydrogenase showed no change in response to praziquantel treatment five isoenzyme , could be demonstrated by electrophoresis .

Isoenzyme separtion has greatly improved the diagnostic specificity of LDH (Lanter , 1970) thus the cardiac isoenzyme activity increase with myocardial infarction.

(Wroblewski and Gregory 1960).

While the hepatic isoenzyme activity is raised in destructive liver diseases (wieme & Demeulenaere, 1970).

Shata,(1982) showed that serum level of LDH increases in some cases of tubular cell affections .

III SERUM CHOLINESTERASE

Cholinesterases, Esterases are enzymes which catalyze the hydrolysis of esters to their components acids and alcohols.

The cholinesterases are more or less specifically active in hydrolyzing esters of choline.

These are found in form of acetycholinesterase(acetylcholin acetylhydrolase or cholinesterase (acylcholine - acylhydrolase) formerly known as true cholinesterase and other is pseudocholinesterase, respectively.

Acetyl cholinesterase is the predominant acetylcholine decomposing enzyme of nervous tissues and erythrocytes , whereas cholinesterase predominates in the blood plasma of most species (Augustinsson, 1948).

Acetyl cholinesterase and cholinesterase are found mainly in the microsomes but also in the nuclear and mitochondrial fractions of broken liver cells preparations.The cholinesterases have not been highly purified a part from the horse serum enzyme, which has been purified 6,000 times.

Adams (1949) has studied the specificity of the enzymes.

Butyrylcholine is hydrolyzed at only 1-2% of the rate of acetylcholine by acetylcholinesterase, with cholinesterase the reverse was found, butyrylcholine was hydrolyzed at twice the rate of acetylcholine.

Berry (1960) deduced that three separate cholinesterases occured in human serum, but Bernshohn et al., (1961 and 1962) found seven bands of activity in starch gel electropherograms and six in rat serum, serum cholinesterase is lowered in most forms of liver disease. The enzyme is a mucoprotein migrating with the α_2 - globulins and is synthesized in the liver.

(Saif et al., 1964 b,Khattab, et al., 1967 and Ghanem et al., 1970), They noticed that during hepatic schistosomiasis, the cholinesterase level is low and this reducing may be due to hepatic functional derangement.

In liver cirrhosis due to schistosomiasis a number of workers have found, that low levels of cholinesterase occur.Kaufman (1954) found that from 28 patients with liver cirrhosis due to schistosomiasis, 24 patients had low levels.

Hargreaves et al., (1961) found that in random blood samples only 35% in the cirrhotic group had a low cholinesterase level.

Williams et al., (1957) found depressed cholinesterase activity in 11 of 25 cases of benign biliary obstruction and 6 of 7 cases of malignant biliary obstruction.

Serum cholinesterase activity is depressed in a number of condition e.g liver disorders exposure to certain toxic elements and drugs and malignancy (Young et al., 1972) and Kanjaris et al., 1979).

Cholinesterase level is lowered during administration, the schistosomcidal drug named Niridazole to rats, Barnard, (1946) and shagei, 1969), and this depression in (CHE) level during Niridazol administration may be due to the that cholinesteras is an iron containing enzyme and as Niridazole is an iron - depleting drug (Salah et al., 1970) record that Niridazole have a direct inhibitory action on cholinesterase.

(shagei, 1969, Al-Mallah et al., 1977 and Ibrahim , 1984) obsereved that, cholinesterase level in the serum of

rats reduced during and after Niridazole administration.

El-Gohary, et al., (1982) they reported that, Astiban or metrofonate in it's full dose, led to a significant drop of (CHE) level., they attributed, the changes of CHE level, that it may be due to partly releated to the toxic effects of these drugs on the liver cells.

Friedheim, 1954, Abdel -Wahab et al., 1964, Hammouda 1971 and Plestina 1972, They recorded that Antimonialis compound has inhibitory action on cholinesterase activity and the maximum drop in CHE was observed one to 24 hours from the end of treatment because these drugs are an organo-phosphorus compound which has an inhibitory action on CHE.

Wegner, (1979) demonestrated that there is no any detectable changes in CHE, level following praziquantel administration.

The alteration of serum enzyme levels may point to inability of the liver to inactivate the enzyme, an altered cell membrane premeability or unknown metabolic defect.

IV SERUM CERULOPLASMIN

This is the term applied to a hetrogenous copper - containing fraction of the serum α_2 - globulins, which was once belived to play a role in copper transport (Latner , 1975).

Ceruloplasmin, is a blue copper - containing protein of plasma, had been reported to have oxidase activity in vitro to wards many substrates. (Holmberg & Laurell 1951) they observed activity to wards, P-phenylene diamine, quinol, catechol, dihydroxy phenyl alanine, adrenaline and ascorbic acid.

Curzon,(1960)and Levine,(1960)noticed that 5-hydroxytryptamine and some releated hydroxy indoles are oxidized in vitro by ceruloplasmin.ceruloplasmin has the following properties :-

It has a copper content of 0.32% a molecular weight of about 151000, eight atoms of Cu per molecule, an isoelectric point of about 4.4, and absorption peak at 605 nm. Human ceruloplasmin isolated from cohnfraction IV-I was found to yeild a single precipitin line on agar gel micro immuno electrophoresis, and a single band that is postive to both the

amido black and oxidase stains following starch gel electrophoresis.

The adult normal concentration of ceruloplasmin in serum as determined by, immuno chemical analysis, ranged from 23-44 mg/ 100ml. This range is only higher slightly than that obtained by spectrophotometric determination.

It is now known to function as the enzyme which oxidizes Fe^{+2} to Fe^{+3}, helping in transport Fe across the intestinal wall, enabling the Fe to bind with apotransferrin, forming transferrin, and also helping to mobilize Fe from storage tissues.

It has been proposed that the name ceruloplasmin can be replaced by serum ferroxidase, the low levels of ceruloplasmin found in wilson's disease. (Henry, et al., 1974).

Evans & wideranders (1967), they demonestereted that ceruloplasmin is an α_2 - glycoprotein, containing nearly 90% of copper in serum of rats or human being.

Gitlin and Scheinberg (1952) observed that ceruloplasmin level showed sharply decrease in hepatolenticular degeneration and this reduction may be due to defect in copper Metabolism.

Curzon and O-Reilly (1960), demonesterated that ceruloplasmin oxidize ferrous to ferric ions.

Curzon, (1961) demonestereted that there is releqtion - ship between ceruloplasmin -iron and " cytochrome-oxidase - system" .

Osaki et al., 1966, they recorded that ceruloplasmin is considered a ring between copper and iron metabolism.

Osaki et al., 1971, they pastulated that ceruloplasmin is rate limiting factor in the mobilization of iron by the liver.

Liver is the main storing site for copper in the body (Thompson et al., 1970).Increased copper or ceruloplamin level in the blood in the liver diseases has been reported by many investigators, (Gubler, et al., 1952; Abdel - Aal, et al ., 1970 and El-Nabawi, et al., 1970).

In bilharzial hepatosplenomegalic patients there is increasing in the ceruloplasmin level in the earlier stage of the disease but there is decreasing in ceruloplasmin level was found tc be slight in the majority of cases .

(Ghanem, et el., 1975). The increased amount of copper in certain tissues (e.g brain, liver, Kidneys) of patients with wilson's (hepatolenticular degeneration) is frequnatly accompanied by subnormal ceruloplasmin (and copper)concentration. The abnormal tissues deposite are belived to results from impairment of the capacity for in coprating exogenous copper into this non diffusible complex. due to geneticially determined defect in synthesis of certain specific globulins subnormal ceruloplasmin concentration have been observed in apparaently normal relatives of patients with wilson's disease (Latner, 1975).

Ibrahim, (1984,)demonestereted that the level of ceruloplasmin showed a significant increase after Ambilhar administeration and the results was related to the highly significant decrease in the plasma iron.

This increasing in the ceruloplasmin level was demonesterated by Osaki et al., 1971) who demonestereted that ceruloplasmin was the rate limiting factor in the mobilization of iron by the liver.

Also Lee et al., (1968) explained that ceruloplasmin was required for the release of iron from liver reticulo-endothelial cells to plasma. and this is essential for conversion of ferrous to ferric ions (Fe^{+2}) to (Fe^{+3}) (Ferroxidase activity and Finally the formation of Fe $(III)_2$- Transferrin.

V SERUM PROTEINS

It's claimed that 90 - 95% of plasma proteins are synthesized by the liver.

(Miller et al., 1951) reported that the liver plays an important role in the production of plasma proteins, and observed that the liver synthesized practically all of the plasma fibrinogen, the albumin fraction and probably more than 80% of globulin fraction. Some gamma globulins, however, are produced by lymphoid tissues.

An apparent reduction of serum albumin is found in several pathological conditions including various diseases of the liver, this may be due to inereased capillary permeability or expansion of extra cellular space, resulting in the presence of an increased proportion of albumin in extravascular compartment.

(Martin & Neubergar(1957), it may be also caused by increased albumin catabolism, the mormal quantity being reduced.

(Ragab, 1956) reported hypo-proteinaemia in 90% of bilharzial hepatic patients, on the other hand (Sowidan 1962) stated that serum proteins are higher than normal .

Ismail, et al., 1957; Ramirez, et al., 1961, Mousa, et al., 1976 and Saleh, et al., (1976), they recorded that there is an alterations in serum proteins as a host respons to infection have frequantly been observed in experimental animals and patients.

(Erfan et al., 1957; El-Hawary et al., 1971; Ghanem et al., 1977a) they reported the following conclusion that serum albumin was found to be significantly decreased in hepatosplenic schistosomiasis and highly significantly decreased in advanced ascitic group compared to control one and the Hypoalbuminaemia may be attributed to protein malnutrition.

Levine & Hoyt (1950) Observed that there is an proportional correlation between the serum albumin and the cholinesterase levels.

(Ismail and Sidkey 1962) found the total serum proteins show gradual increase as the condition progresses to late stage.

(Ghanem et al., 1970 b), reported that an evident decrease in the level of total serum proteins as the disease advances to the stage of shurnken liver in cases having serum bilirubin values exceeding 1.2 mg% and the authers stressed the beneficial effect of high coloric regime observed in some bilharzial patients who had low total serum protein values.

Serum protein abnormalities are of value clinically in indicating the presence of diseases.

Alpha 1 and Alpha 2 and beta globulins remains within the normal range in bilharzial heaptic cases (Ghanem et al.,1970b) The gamma globulin has been reported to increase in bilharzial hepatic fibrosis due to simple reflection of reticuloendothelial activity activity (Awny 1962; Abdel Ghaffar and Shoeb 1962).

Ismail and Sidky (1962) stressed the early incidence of hypergamma globulinemia and stated that it was the only early abnormality causing increase of erythrocyte sedimentation rate and turbidity and that this hypergamma globulinemia showed progressive increase in different stages of bilharzial hepatic fibrosis.

Ghanem et al.,(1970a) reported hypergamma globinemia in 68.5% of non ascitic and in 72.7% of ascitic bilharzial cases.

The level remained almost the same in the hepatomegalic splenomegalic stage, then showed a decline in cases with shrunken liver. Low total protein levels are usually associated with low albumin levels, which are usually accompined by a smaller change in globulins. Also albumin level may be caused by increased loss of albumin in the urine, decreased formation in the liver, or insufficient protein intake, (Kornglod; 1966).

Further more, Clarkson, (1966) and Bierer, (1969) recorded that, both alpha and beta globulins are produced by the liver alone.

In advanced stages of the disease, albumin is decreased and the globulins are increased, in the early stages of acute hepatitis, examination indicate the protein levels to be normal, Bauer, (1982b). Also Shank et al., (1968) recorded that, the decrease in albumin fraction may be due to a drastically decreased appetite, where no water or food consumed.

Galalet al., (1971) recorded that, there is decrease in serum albumin level following antimonialis use in their experimental animals treated with tartar emetic and this due to the toxic effect of these drugs on the liver cells.

Shoeb et al., (1971), noticed significant difference between serum albumin and globulin values before and 2 weeks after treatment with hycanthone.

Nash et al., (1982) state that the total protein level showed decrease in most the patients after the treatment with praziquantel, and this may be due to low amount formed by the liver due to the effect of praziquantel on liver cells .

El-Rooby et al., (1963) and El-Rooby, (1967) , stated that after antibilharzial treatment a significant rise in serum albumin occurs in hepatosplenic cases with pretreatment marked diarrhoea with some decrease in globulins.

And they attributed such albumin rise to the improvement of a malabsorption state of bilharzial origin.

VI BILIRUBIN

Bilirubin is one of the end products of haemoglobin break down in the body and is excreted by the liver via the bile, and it's a bile pigment normally present in blood, it's formed in the cells of the reticulothelial system.

In qualitative and quantitative analysis, the term bilirubin is applied to the unconguated bilirubin (Mallory & Evelyn, 1937).

The level of total bilirubin in human is normally from 0.5 to 1.4mg dl. levels above 2.5 mg/dl usually produce jaundice since biliary and cholangiolar unite implication is rare and late in pure bilharzial hepatic fibrosis, the bilirubin would be expected to rise only in terminal and complicated cases (Ismail & Sidky, 1962).

El-Mofty & Khattab, (1962), Cheever, (1965) and Schiller, et al., (1973), they reported that infection with schistosoma mansoni causes marked histopathological changes in the livers of mice and human patients , and they noticed that the bilirubin level remain normal untill very

late stage in the disease when fibrosis involved the liver completely and cirrhosis occur.

Jaundice has been classified by Ducci (1947) into prehepatic, hepatic and post hepatic.

The prehepatic includes hamolytic jaundice, Gilberts disease and hepatic dysfunction, in this type, the serum bilirubin is mainly indirect or unconjugated without bilirubin in urine.

Post - hepatic jaundice means the obstructive jaundice, the serum bilirubin in which is of the direct type and appears in urine, the hepatic jaundice has been further classification, it is divided into two types, hepato cellular, and hepato canalicular (cholangiolitic) Ducci,(1947)

The hepato cellular one occur due to injury to liver parenchyma (viral hepatitis).

Cirrhosis and toxic hepatitis) in this type there is increase in the direct bilirubin in serum and presence of bilirubin in the urine (zimmerman, 1966).

The hepato canalicular type is the second type of the hepatic jaundice, it has called cholangiolitic, the jaundice appears bacause bilirubin regurgitates to the blood through defects in the cholangioles.

This type of jaundice is commonly seen with certain drug reactions (chloropromazine, methyltestosterone) also occurs as a result of viral hepatitis or it may be idiopathic (zimmerman, 1966).

Elevated concentration in serum are of clinical importance in the diagnosis and evaluation of liver damage.

It was shown that bilirubin present in serum in three forms, as free bilirubin and as the mono- and diglucuronide compounds.

All three are loosely bound to serum albumin.

Bilirubin is in soluble in water unless bound to albumin - react slowly the diazo reagent and requires the presence of alcohol

Serum bilirubin is also elevated in a number of diseases of bones and liver, haemolytic and obstructive jaundice or hepatotoxic drugs (william et al., 1969 and Bauer et al., 1974).

Schuster et al., (1973) and Saad et al., (1978) recorded that Hycanthone was shown to produce biochemical and morphological alterations in the liver of mice and rats even after smoll doses, and serum bilirubin level was elevated.

Katz, (1977) reported that hyeanthone has to be considered a hepatotoxic drug and sometimes inducing jaundice.

Gibel et al., (1973) reported necosis of liver and cirrhosis after long duration of Metrifonate in take and produce jaundice in experimental animals.

Basmy, et al., (1969) suggested that, the Niridazol (Ambilhar) affect on liver function in man only in case of advanced hepatic fibrosis and serum bilirubin level was elevated.

(Leopold et al., 1978 and wegner, 1979) they recorded that, they did not observed change in serum bilirubin

after praziquantel treatment, in healthy volunteers.

On the other hand Davis et al., 1979 and Da Silva et al., 1981, they did not observed change in serum bilrubin after praziquantel treatment in the infected cases.

KIDNEY FUNCTION :-

The kidneys perform a series of functions, they excrete the end products of protein metabolism (urea, uric acid and creatinine) and about half the water eleminated from the body.

They maintain and regulate the composition of essential blood constituents, maintain the internal composition of the body to be compatible with life and help to preserve normal acid- base balance of the body fluids.

Renal function tests generally estimate an average performance of the total kidney.

A very large number of renal function tests have been done for this purpose.

From these tests are:-

I UREA LEVEL IN SERUM :

Urea is the main end product of protein catabolism, the liver is the sole site of urea formation as it's the only organ that contains all the enzymes necessary for urea biosynthesis through successive stages of deamination of amino acids, the formation of ammonia, the incorporation of this ammonia into the Krebs with the resultant formation of urea.

After urea is formed in the liver, it passes into the blood and is excreted in the urine.

Urea diffuses freely through capillary walls and cell membranes.

It is present in virtually identical concentration per unit of water in extracellular and intracellular fluids i.e plasma, serum , cerebrospinal fluids, saliva and intestinal secretions.

BUN depends upon the relation ship between urea production (protein ingestion and catabolism) and urea excretion; the minor amount of urea destroyed by microorganisms in the

intestinal tract may be disregarded. (Davidsohn and Henery 1974).

Urea is excreted mainly by the Kindeys.

It's through to be cleared at the glomerulus, but partly diffuse back to the blood during the tubular reabsorption of water(White et al., 1976).

The nitrogenous content of urea constitutes nearly about 50% of the total molecular weight.

The normal value of blood urea varies from 9-15 mg/dl. The range of normal values may be greater depending on age, sex and diet.

It has been also reported that the concentration is higher during the day than during the night. (White et al., 1976).

Blood urea nitrogen increase in nephritis, prostatic obstruction, renal insufficiency, and decrease in acute yellow atrophy of liver, liver cirrhosis and pregnancy.

Blood urea concentration does not began to increase

untill glomerular filtration has fallen below 50% (White et al., 1976).

In contrast to serum creatinine levels which vary at a minimum with the protein intake. (Zilva & Pannall 1979) obtained a 400% variation in serum urea levels and this due to the differences in protein intake .

Bueding & Schiller (1968), pastulated that, Antimonialis compounds resulted in renal damage and they observed a significant increase in serum urea following treatment.

Shafel et al., (1971) recorded that, Bilharcid has no toxic side effect on kindey function tests and no significant change in serum urea level following treatment.

Basuny et al.,(1969) suggested that no important change in serum urea level following Niridazole administration, and has no toxic side effects on Kidneys functions .

Thamm, (1960) and Abdallah et al.,(1965) suggested that, following Metrifonate intake for long duration, a renal damage will developed and the urea level showed a significant rise.

Siongok et al., 1975, reported that oxamniquine has no important effect on renal functions and no significant elevation in serum urea level after oxamniquine administration.

In healthy volunteers, leopold et al., (1978) revealed significant change in serum urea in some individuals. following praziquantel administration .

Da Silva et al., (1981), they did not found any detectable changes in the serum level of urea after praziquantel treatment.

I CREATININE LEVEL IN SERUM

Creatinine is derived from the metabolism of tissue creatine and so it is not affected by diet. The synthesis of creatine and parts of two amino acids (arginine and methionine).

Guanidoacetate (glycocyamine) is formed by transamidination primarily in the Kidneys; this is a reversible reaction mediated by transamidinase which is subject to feed back inhibition of dietary creatine.

Glycocyamine is then methylated with a second reaction requiring transmethylase and activated methionine in the liver to form creatine.

Creatine in the free state and as phosphocreatine is distributed from liver via blood to muscle and brain with trace amounts in the urine.

Phosphocreatine exists in high concentration, especially in muscle, where it is an important form of high - energy phosphate storage.

The dehydration of creatine results in a ringed compound creatinine which is readily excreated from the body by the Kindey. It is found in the plasma of adult animals in low quantities, in young growing animals it is found in higher quantities.

Creatinine is highly diffusible substance and is evently distributed in the body water.

The measurement of creatinine level in serum yeild the same diagnostic and prognostic inflammation concerning renal function as that obtained by the meaurment of urea nitrogen.

The determination of creatinine provides more accurate inflammation creatinine is cleared by the Kidney at the glomerular filteration rate (Davidsohn and Henery, 1974).

The concenreation of creatinine in the blood like that urea,will increase with decreased Kidney function, and the main use of estimation of serum creatinine is in the assessment of Kidney function (Taussky, 1954; Hudson and Rappoport 1968).

Plasma levels depend largely on glomerular function , while urinary concentration depend almost entirely on tubular function (Zilva & pannall, 1979).

Creatinine is the least variable nitrogenous constituent of blood. Normal values for serum in man are in the range of 0.5 to 1.2 mg/dl. in early nephritis, values of 2 to 4 mg/dl are noted, while in chronic haemorrhagic nephritis with uraemia values of 4 to 35 mg/dl may be obtained (White et al.,1976).

Creatinine concentration in the serum of bilharzial patients showed in significant variation except in the group of patients with ascitis who showed a significant decrease from normal levels, while non significant changes in creatinine , concentration were observed in patients with cancer bladder of bilharzial etiology compared with that found in serum of Normal subjects(Ekramaz.Khafagy, et al., 1976).

Bauer, (1982 a), reported that, creatinine concentration in the serum may be relatively higher than that of urea in obstruction of urinary Tract.

And in chronic nephritis, Hudson and Rappoport , (1968)

recorded that, the creatinine concentration will increase with decreased Kidney function.

Barsoum et al., (1977), pastulated that schistosomal glomerulo pathy could progress to renal failure.

Talaat et al., (1966), observed a significiant increase in endogenous creatinine following Antimonialis compound administration. Basmy, et al., (1969) pastulated that Niridazole has no important effect on serum creatinine level.

Shafei, (1979), reported that, following oxamniquine administration, No significant alteration in serum creatinine level.

Wegner, (1979) pastulated that following praziquantel administration, No any detectable changes in serum creatinine level .

NATERIALS

A) ANIMALS USED:

In the present work, 54 healty male albino rats were used , "to avoid the possible sex related".

- Their weights ranged from " 140 - 210 gms "
- The rats were obtained from the unit of the Vet. Med. Zag. Univ. experimental animals of the Vet.Med. zag. Univ.

The rats were divided into three groups were 18 for each.

The rats were caged together under the same environmental condition and kept in hygienic seperate boxes throughout the experimental period.

They were maintained on ration composed of barly grains, bread and milk.

Water were provided ad libitum.

Experimental animals were divided into three main groups:

Group 1: 18 male albino rats, were given saline only and kept as a control group.

Group2: Composed of 18 male albino rats, they were received the total recommended theraputic dose of oxamniquine (vansil) (42mg/ 200 gms body weight) divided into 3 successive days and given orally through stomach tube .

GROUP 3: Consisted of 18 male albine rats, given the total recommended therapeutic dose of praziquantel (Biltricid) 42 mg/200 gm body weight of rats, given orally at once as single dose.

Each group were subdivided into 3 subgroups each one of these subgroups were 6 rats and they were equal in number and had the same average weight. After the passage of 24 hours from the finished of the both drugs administration. Six rats from each different groups were taken and were anthesitized by ethyl ether through inhalation, after that the blood samples were collected from eye plexus of rats through narrow capillary tube prepared for it, and the blood sample was collected in a dried and clean centrifuge tube, allowed to coagulate, incubated for 2 hours at 37C°. Then centrifuged at 3000 r. p. m for 15 minutes.

The clear non hemolyzed sera were kept in ice-cooled sterile.

labelled glass vials and were subjected for determination of different biochemical parameters .

B) DRUGS USED

1) OXAMNIQUINE (VANSIL)

The drug was used in our experiment was a capsule form (250 mg) and drug was administrated orally through stomach tube after suspensing it in a distilled water, and this according to (Andrade, et al., 1981) at a total dose level of 42mg/200 gm B.W and this dose was divided into 3 successive days. This dose was approximately equivalent to adult human dose 40 mg/kg b.w (Abd-Rabbo et al., (1977).

Extrapolated to rats by the method of Pagets and Barnes (1964) for interspecies conversion scheme of the dose.

2) **PRAZIQUANTEL (BILTRICID)**

It is present in the form of tablet each of 600 mg and the total recommended dose for rats was 42mg/for rats weighted 200 gm, this dose was approximately equivalent to adult human dose 40 mg/kg body weigh as a single oral dose(according to Davis et al., 1981) extrapolated to the rats,calculated by the method of Pagets and Barnes (1964) for interspecies conversion of dose .

For rats, the drug was administrated orally through stomach tube after being powdered in a morter and dissolved in 5% aquous starch solution, according to (Xiao et al., 1985).

" METHODS "

1- SERUM TRANSAMINASES

Serum glutamic oxaloacetic(S.G.OT) and serum glulamic pyruvic transaminases(SGPT):

Serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase activities were estimated colorimetrically after Reitman and Frankel,(1957).

PRINCIPLE:-

The method is based on that, the pyruvate formed by glutamic pyruvic transaminase reacts with 2,4 dinitro phenyl hydrazine (DPNH) to give a brown coloured hydrazone which can be measured colorimetrically at 520 nm.

Also the oxaloacetic acid formed by glutamic oxal acetic transaminase decaboxylates spontaneously to pyruvate which is again measured as hydrazone .

REAGENTS:-

1) Phosphate buffer solution(PH.7.4) 11.3 gm of dry anhydrous Na_2 Hpo $_4$ and 2.7 gm of dry anhydrous KH_2po_4 in litre of distilled water, checked with a pH meter .

2) SGOT substrate solution: 13.3 gm of Dl- aspartic acid were dissolved in the N- sodium hydroxide and produced a solution with a PH 7.4. 0.146 gm of ∝- ketoglutaric acid was add and dissolved by adding N. sodium hydroxide the PH was then adjusted to 7.4 and completed to 500ml with phosphate buffer and kept at- 5C°.

3) SGPT substrate solution: 9 gm of alanine were dissolved in 90 ml of distilled water with the addition of N- sodium hydroxide to adjusted the PH to 7.4, 0.146 gm of ∝- keto glutaric acid was dissolved by adding N- sod.hydroxide and completed to 500 ml with phosphate buffer and stored at - 15C°.

- Stock pyruvate standard:

220 mg of sodium pyruvate were dissolved in 100ml of phosphate buffer solution PH 7.4 .

4) Working pyruvate standard solution:-

The stock standard pyruvate was diluted (1 in 5) with phosphate buffer, stored at -15C°. This solution was prepared freshly each week .

5) Colouring agent solution:

19.8 mg of dinitrophenyl hydrazine (0.099 m mol /l) were dissolved in 10 ml conc. Hcl and completed to 100 ml with distilled water and kept in a brown bottle at room temperature.

6) stopping reaction agent solution:-
16 gm of sodium hydroxide (0.4N) were dissolved in a liter of distilled water.

procedure for S. GOT:-

Test:- 0.5 ml of S.GOT substrate and 0.1 ml of non hemolysed serum were mixed and incubated at 37C° for 60 minutes exactly.

The tube was removed from the bath and immediately 0.5 ml of dinitrophenylhydrazine was added and mixed well

Control:- 0.5 ml of S.GOT substrate was mixed with 0.5 ml of dinitrophenylhydrazine and then 0.1 ml of serum was added.

Standard: 0.1 ml of working pyruvate was mixed with 0.4 ml of S. GOT substrate add o.1 ml of distilled water and 0.5 ml dinitrophenylhydrazine.

Blank: 0.5 ml of SGOT substrate was mixed with 0.1 ml of distilled water and 0.5 ml of dinitrophenylhydrazine.

Dinitrophenylhydrazine was allowed to react in all tubes for 20 minutes at room temperature, then 5 ml of 0.4 N.sodium hydroxide was added to each tube mixed well and then measured after 10 minutes at 520 nm .

CALCULATION:-

The pyruvate found in the serum is responsible for the difference between test and control (T-C).

The pyruvate in 0.1 ml of working standard (0.4 μm) produces the difference between standard and blank(S-B). so pyruvate formed in 60 minutes by 0.1 ml of serum is

$$\frac{T - C}{S - B} \times 0.4\ \mu \text{ mole}$$

Thus the pyruvate formed minute litre of serum is

$$\frac{T - C}{S - B} \times 0.4 \times \frac{1}{60} \times \frac{1000}{0.1} = \frac{T - C}{S - B} \times 67\ \mu \text{ mole}$$

T = Test , C = control, S = standard,

B = Blank

Procedure Of SGPT:-

The same procedure of SGOT except that, the SGOT substrate must be substituted SGPT substrate and the incubation of the test tube is reduced to 30 minutes only.

Calculation:-

The pyruvate formed in 30 minutes by 0.1 ml serum is $\frac{T - C}{S - B} \times 0.4$ µmol thus the pyruvate formed.

minute litre of serum is :-

$$\frac{T - C}{S - B} \times 0.4 \times \frac{1}{30} \times \frac{1000}{0.1} = \frac{T - C}{S - B} \times 133 \text{ µ mole.}$$

The calculated pyruvate for SGOT and S GPT were also converted to i.u/ litre by reference to the following table.

The relation of μ mole of pyruvate per min, per litre in the colorimetric reaction to internatianal units

Calculated pyruvate μmole per min/Litre	GOT result in I.U/l	GPT result in I.U/L	Calculated pyruvate μmole per min/litre	GPT result in I.U/L
2	2	1	56	24
4	3	2	58	25
6	5	2	60	29
8	6	3	62	27
10	7	4	64	29
12	9	4	66	30
14	11	5	68	31
16	13	6	70	33
18	15	7	72	34
20	17	7	74	35
22	19	8	76	36
23	20	8	78	37
24	21	9	80	38
26	23	9	82	39
28	25	10	84	40
30	27	11	86	42
32	29	12	88	44

34	31	I3	90	46
36	33	14	92	48
38	35	15	94	50
40	37	16	96	52
42	39	17	98	54
44	41	18	100	56
46	44	19	102	60
48	47	20		
50	51	21		
52	55	22		
54	60	23		

2) SERUM LACTIC DEHYDROGENASE (LDH)

Lactate dehydrogenase (LDH) enzyme was measured colorimetrically using the method reported by Wootton(1982)

Principle:-

The method depends on the reduction of pyruvate by the incubation with the enzyme solution in the presence of reduced co enzyme nicotinamide adenine dinucleotide. The reaction is stopped by adding dinitro phenyl hydrazine solution which reacts with remaining pyruvate forming a hydrazone.

The amount of unreacted pyruvate is found by measuring the brown colour produced when the hydrazone is made alkaline .

Reagents:-

1) Phosphate buffer pH (7.4) prepared as in buffer of SGOT. 11.3 gm of anhydrous disodium hydrogen phosphate and 2.7 9m of anhydrous potassium dihydrogen phosphate per litre in water .

2) Stock sodium pyruvate(37.5 mmol/l) 415 mg of sod. pyruvate were dissolved in 100 ml of phosphate buffer

3) Working sodium pyruvate buffered substrate (0.75 m mol/l)
Stock pyruvate solution were diluted 1 in 50 with phosphate buffer 1ml of stock solution was diluted in 50 ml of buffer
N.B: Freshly diluted solution was prepared daily just before use.

4) Reduced nicotinamide adenine dinucleotide (NADH). 10 mg of NADH per 1 ml of phosphate buffer was make and freshly prepared solution must be prepared daily.

5) 2,4 dinitrophenylhydrazine (DNPH) (2m mol/l). 400 mg of 2,4 dinitrophenylhydrazine were dissolved in 85 ml of concentrated hydrochloric acid. Make up to 1 litre with water and was stored in dark bottle.

6) Sod. hydroxide 0.4 mol./l·16 gm of sod. hydroxide per litre in distilled water .

Procedure :-

Test: 1ml buffered substrate was mixed with 0.05 ml of serum , the reaction was started by adding 0.1 ml of NADH solution.

The tube was incubated in a water bath, adjusted to 37°C for 15 minutes after which 1 ml of dinitrophenylhydrazine solution was added

and mixed well.

Control:- 1 ml of buffered substrate, 0.15 ml of buffer and 1 ml of DNPH also added .

Blank: 1.15 ml of buffer and 1 ml of DNPH. All tubes allowed to stand at room temperature for 20 minites .

Then 10 ml of 0.4 mol/l sod. hydroxide was added to each tube, after 10 minutes, the developing coloure was compared at 5 10 nm.

Calculation:

The control tube contains 0.75 μmol of pyruvate. The amount of pyruvate which has reacted is

$$\frac{C - T}{C - B} \times 0.75\ \mu\text{mol}$$

This is the effect of the enzyme in 0.1 ml of serum acting for 15 minutes .

The pyruvate reacting/minute/litre of serum is

$$\frac{C - T}{C - B} \times 0.75 \times \frac{1}{15} \times \frac{1000}{0.05}$$

$$\text{Enzyme activity} = \frac{C - T}{C - B} \times 1000$$

If the result is greater than 800 i.u/l, dilute serum 1 in 5 with phosphate buffer and repeat the estimation.

3) CHOLINESTERASE

Cholinesterase activiity was measured following the methods of Biggs et al.,(1958)

PRINCIPLE:

The methods depends on the change in the absorbance of bromo thymol blue colour after incubation with acetyl choline bromide at 37C° For 30 minutes the,Ku of cholinesterase activity was measured by reference to calibration curve .

Reagents:-

1) Stock buffer.

1.361 gm Potassium dihydrogen phosphate,12.37 gm sodium barbitons and 175.35 gm sodium chloride/1 in water.

2) Stock buffer- indicator solution.

100 mgof bromothymol blue was dissolved in 2 ml/2mol/1 sodium hydroxide solution and washed into a litre flask with 150 ml stock buffer solution and was diluted to about 950 ml with water .

PH was adjusted to 8.0 by adding approximately 16ml of 500 m mpl/1 hydrochloric acid and diluted to a liter

3) Working buffer-indicator solution.

47.6 ml of stock solution were diluted to 100 ml with distilled water .

4) Substrate, 156 gm acetylcholine bromide/1.in water.

5) Acetic acid, 150 m mol/1 was diluted 1 to 10 for used and the solution was kept at 4C° .

Technique:-

To 4.6 ml of working buffer indicator solution, o.1 ml serum and 0.2 ml of substrate were added .

- The contents of the tube were mixed well and were read at 620 nm.

- The tube contents were incubated at 37C° for 30 min. and read again.

To obtain a calibration curve prepare a series of dilutions as follows.

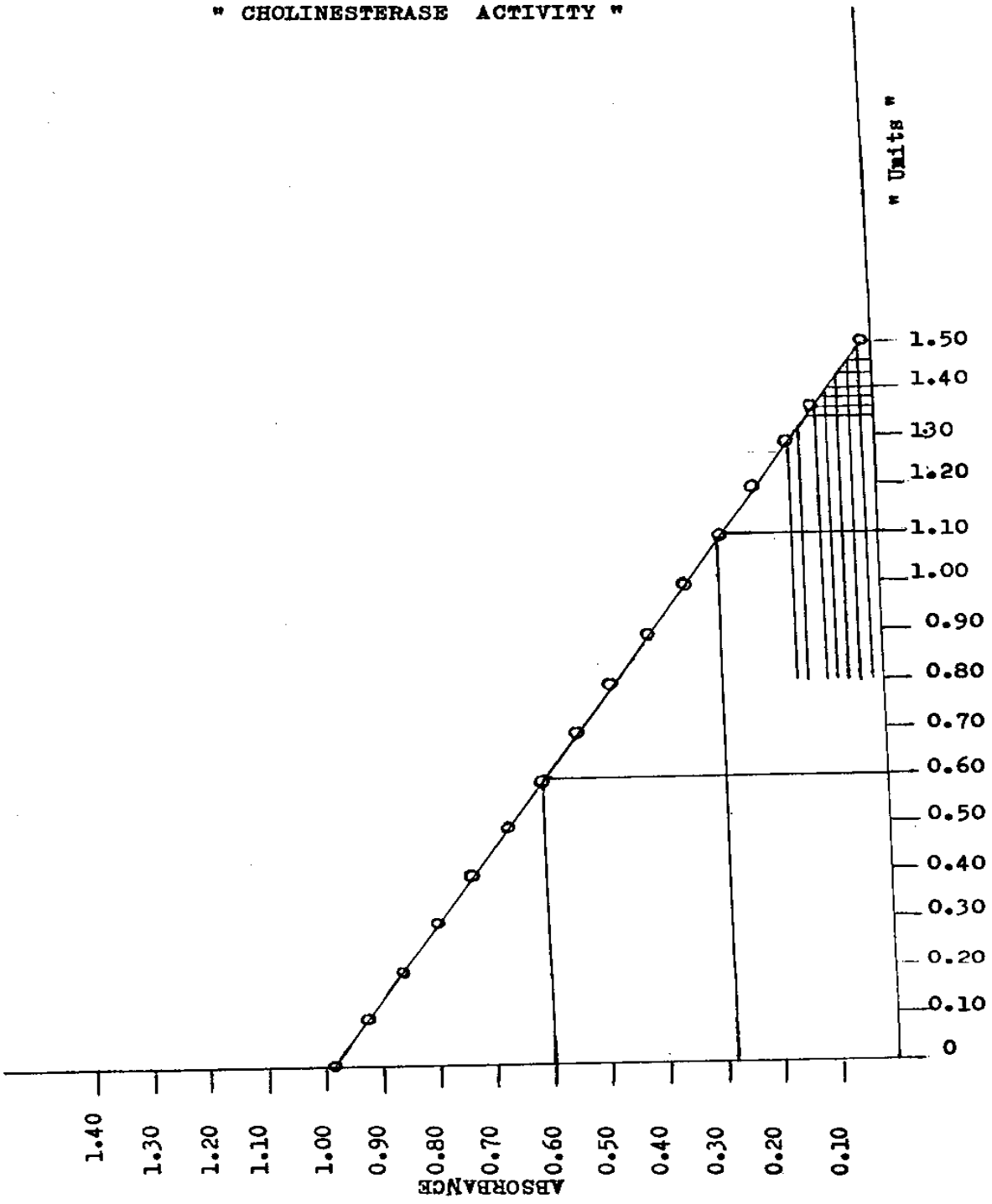
Serum cholinesterase Ku/l	0	1.0	2.0	3.0	4.0	5.0
Acetic acid((ml)	0	3	6	9	12	15
Water (ml)	15	12	9	6	3	0

A series of tubes containing 2 ml of stock buffer indicator solution were set up.

1.4 ml water, 0.1 ml pooled normal sera and 1ml of each of the above dilution were added.

Reading at 620 nm and plot the reading to obtain a Standard curve from which the units of serum cholinesterase can be read .

" CHOLINESTERASE ACTIVITY "



4) CERULOPLASMIN

Methods for quantitative estimation of ceruloplasmin in serum have been based on its blue colour.
Enzyme activity has been measured in terms of international units for p- phenylenediamine on the assumption that the coloured product obtained as a result of the oxidation is " Bandrowsk is base " a timer of p- phenylenediamine.

For measuring the enzymatic activity of ceruloplasmin with o- dianisidine dihydrochloride (4,4-diamino-3,3- dimethoxy- biphenyl) as substrate. This reagent, which requires no purification on the commerically available material and is stable in aqueous solution is converted into a yellowish brown.

Ceruloplasmine was determined colorimeterically and this according to (Schosinsky, et al., 1974).-

Reagents:-

1) Acetic buffer solution, pH 5, ionic strength 0.1.

In a 1000-ml volumetric flask, the following materials were added and mixed , 990 ml of water, 13.608 gm of sodium acetate.

$\cdot 3H_2O$ (J.T.Baker chemical Co., A R grade) and 2.6 ml of glacial acetic acid (Mallinekrodt chemical works, AR grade).

The pH was measured with a pH meter and if necessary, the PH was adjusted to 5.0 by addition of 0.1 mol/litre sodium hydroxide or glacial acetic acid .

Filled to the mark with water, and was mixed well and stored at 4C°.

2) Sulphuric acid,9 mol litre.
was added slowly with mixing, concentrated sulfuric acid (Mallinckrodt chemical works, AR grade) to an equal volum of water.

3) O. Dianisidine dihydrochloride, 7.88 m mol/l.
in a 100-ml volumetric flask, 250 mg of O.dianisidine dihydrochloride (sigma chemical co., purified crystal grade) were placed, water was added to the mark, and mixed well untill completely dissolved .

In a brown glass reagent jar, the reagent was stored in the refrigator at 4C°.

Procedure:

1) 0.75 ml of acetate buffer and 0.05 ml of serum were

pipetted into two tubes(for each sample), one of it marked " 5min " and the other " 15min " .

2) The tubes were placed in 30C° water bath.

3) Allowed 5 min for temperature equilibration.

4) 0.2 ml of substrate(O. dianisidine dihydrochlordide reagent) was added, after it was incubated at 30C° before used.

In each tube, the timer was starting at the first substrate addition .

5) After exactly 5 min, the " 5 min " tube was removed from the water bath .

6) 2.0 ml of 9 M sufuric acid were added and mixed immediately.

7) After exatly 15 min, the " 15 min " tube was removed from the water bath and 2.0 ml of 9 M sulfuric acid were added and mixed immediately .

8) The absorbance of the purplished solution was measured at 540 nm.

N.B - Distilled water was used as blank.

Calculation

The enzymatic activity of ceruloplasmin is expressed in international units, in terms of substrate consumed.

Ceruloplasmin oxidase activity $=(A_{15}-A_5) \times 6.25 \times 10^{-1}$ μ /mol

- A_{15} and A_5 are the measured absorbance of the "15 min" and "5 min" solutions, respectively.

The factor 6.25×10^{-1} was obtained as follow.

Conc. of substrated oxidized =

$$\frac{\text{absorbance} \times 3 \times 20}{(9.6 \times 10)\ \mu \text{ mol/ml per minute}}$$

Where 9.6 = molar absorptivity of coloured solution in terms of substrate consumed

($ml\ \mu\ mol^{-1}\ Cm^{-1}$) (17); 3.0 = correction factor for final measured solution volume.

20 = Correction for serum volume used (0.05ml); and

10 = incubation time (min) .

(5) SERUM TOTAL PROTEINS

The total serum proteins were determined colorimeterically according to the method of Weichselbaum (1946) in the serum, in the first diluted with isotonic sodium chloride solution and the proteins are then determined by the biuret reagent in which the peptide bonds of protein (-NH- co-) reacts with copper solution to give a violet colouration.

Reagents :

1) Sodium chloride (0.9%)

   9 mg of sodium chlordide were dissolved in 1000 ml of dist. water.

2) Stock biuret reagent (weichselbaum 1946)

   45 gm of sodium potassium tartarte were dissolved in 400ml of 0.2N sodium hydroxide,

   15 gm of copper sulphate ($Cu\ So_4 . 5H_2O$) were added and dissolved by stirring, then 5 gm of potassium iodide were added and made up to volume of 1 liter with 0.2 N HaoH.

3) Working biuret reagent

50 ml of stock biuret reagent were dilured to 250 ml with 0.2 N NaoH solution containing 50 gm of potassium iodide / litre .

4) Standard protein solution

1 gm of Armcur's crystalline bovine albumin was dissolved in water and made up 100 ml.

For use in the method, 10 ml of this solution were diluted to 100 ml with water (1 ml = 0.001 gm of albumin).

Procedure :

0.1 ml serum was pipetted into a test tube, 4.9 ml saline and 5 ml of working biuret reagent were added.

For standard, 0.1ml standard protein was placed in test tubs, 4.9 ml saline and 5ml of working biuret were placed in a test tube, the content of each tube were mixed well and placed in water bath (37°C) for 10 minutes; after cooling, the developing violet colour was measured at 530 nm.

Calculation :

$$\text{Protein in gm/dl serum} = \frac{\text{Reading of test}}{\text{Reading of standard}} \times 0.5$$

(6) SERUM ALBUMIN

Serum albumin was determined colorimeterically by dye - binding method as described by Bartholomev and Delancy (1966).

Reagents :-

a) N.Sodium citrate .

234 gm of sodium citrate were dissolved in dist. water and made up to 1 litre.

b) M-citric acid

210 gm of citric acid were dissolved in dist. water and made up to 1 litre.

c) 0.01 M bromocresol green.

0.0698 gm of bromocresol green was dissolved in 9.8 ml of 0.1 N NaoH and made up to 100 ml.

d) Buffer indicater reagent :

To about 800 ml of water, 17.3 ml of N. sodium citrate, 32.7 ml of M. citric acid and 6 ml of 0.07 M, bromo- cresol green were added, mixed well and diluted to 1 litre.

The PH was adjusted to 3.8., if necessary with a drop of citrate or acid. the reagent was stored at + 4°c.

e) Standard .

Bovine albumin was in different concentration 6,4;3,2 and 1 gm dl.

Procedure :

4 ml of buffer indicator and 0.02 ml of serum were mixed and measured at 637 W.L. against blank of buffer indicator.

Calculation :

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} = \frac{\text{Concentration of standard}}{\text{Concentration of unknown}}$$

(7) SERUM GLOBULIN

Globulins value were determined by substracting the albumin value from the total protein in the same sample according to Coles (1974).

(8) SERUM BILIRUBIN

The serum bilirubin was determined by a direct method (Jackson and Hernandez 1956 and Jackson 1961). Involves diluting serum with phosphate buffer and was measured the absorbance at 450 and 575 nm.

Reagents :-

15 M phosphate buffer (PH. 7.6): 7.65 gm $Na_2 Hpo_4$ were dissolved in 1 litre of dist, water and 3 drops of chloroform added as preservative .

Procedure :

1) 1.2 ml of phosphate buffer were pipetted and 40 µl of serum were added to the buffer in the cuvette.
2) measured at two wave length, the first at 450 nm and the second was 575 nm.
3) Phosphate buffer was used as blank in both wave lengths

Calculation :-

$$\text{Bilirubin mg/dl} = \left(A_{450} - A_{575} \right) \times 70 = \%$$

9) **SERUM UREA**

Urea was determined colorimeterically by Nessler method. (Cited in Practical Clinical Biochemistry. Varley, 1976)

PRINCIPLE

The sample was incubated with urease, which converted urea into ammonia.

After protein had been precipited, the colour produced when the ammonia was treated with Nessler's reagent was compared with the colour produced under the same condition by a standard urea solution also was treated with urease.

REAGENTS:-

1) Isotonic sodium sulphate:

30 gm. $Na_2 \cdot So_4 \cdot 10H_2O$ or 13.2 gm anhydrous $Na_2\ So_4$ per litre in water.

2) Urease solution.

a- 5 gm of jack been meal were shaken with 100 ml of 70% glycerol and was allowed to stand at room temperature.

over night and was centrifuged or filtered through Hyflo supercel. if kept in a refrigator, the solution will keep its activity for 2-3 months .

Or b- 1 tablet of British drug houses.

urease was crushed in 5ml of 30% (V/V ethanol), it must be freshly prepared every 2-3 days and shaked before use .

3) Standard urea solution.

100 mg of vaccum dried urea per 100 ml in water, it preserved with a drop of chloroform and Kept in the cold.

4) Zinic sulphate

10 gm of crystalline zine sulphate ($Zn\ So_4 . 7H_2O$) per 100 ml in water.

5) Sodium hydroxide 0.5 N.

This must be accurately prepared and cheeked against the zinc sulphate . 10 ml of zinc sulphate was taken and diluted to about 50 ml with water and few drop of ph. ph indicator were added and run in sodium hydroxide from a burette 10.8 - 11.2 ml, which should be required to produced a permanent pink colour.

6) Iodine solution:

2 gm of iodine were dissolved in a solution of 3 gm pot.

iodide in 15 water was make up to 100 ml.

7) Nessler reagent .

11.3 gm of iodine crystal were weighted on a rough balance in a solution of 15 gm of potassium iodide in 10 ml were dissolved of water.

Most this solution was added to 15 gm. of mercury in a glass stoppered reagent bottle.

The mixture was kept for cooling in water and was shaked untill the supernantant liquid had lost nearly all its colour, it was filtered into a 100 ml. volumetric flask and was tested by a drop of 1% starch.

If no colour was obtained, more of the iodine solution was added till a drop of the mixture was gave a faint reaction with starch, the total solution was diluted to 100 ml. and poured into 485 ml. of 10% sodium hydroxide, if the solution was turbid it should be filtered or allowed to settle before used and should be kept in a bottle with rupper stopper. It gives best result when aged .

Did not distributed the brown deposit which settles out in the bottom of the bottle .

Methods:

1) Test.

Into centrifuge tube, 4.4 ml of isotonic sodium sulphate, 0.1 ml of serum and 0.1 ml of urease solution were added.

2) Standard :

Into centrifuge tube, 4.4 ml of isotonic sodium sulphate, 0.1 ml of standard urea solution (100 mg per 100 ml) and 0.1 ml of urease solution were added.

3) Blank .

Into centrifuge tube, 4.5 ml of isotonic sodium sulphate and 0.1 ml of urase solution were added.

Technique :

The tubes were stoppered with rubber plugs , and the Contents were mixed and incubated at 37°C for 20 min . 0.2 ml of zinc sulphate and 0.2 ml of 0.5 N sodium hydroxide were added and with very through mixed after each addition and the tubes were centrifuged.

3 ml of each supernatant had been taken into test tubes and 2 ml of distilled water and one drop of iodine solution (to prevent clouding) were added.

When we were ready to measured the optical densities, each tube was taken in turn, and 1 ml of Nessler's reagent was added mixed and the contents were poured immediately into the cuvette of the instrument.

The optical density was read off at once before turbidity developed the colour was compared at 489 nm.

$$\text{blood urea (mg / 100ml)} = \frac{T - B}{S - B} \times 100$$

(10) SERUM CREATININE.

Creatinine was estimated colorimeterically according to (jackson,1975).

PRINCIPLE

The method depend on the chemical reaction betweem alkaline picrate and serum creatinine, the developing yellow red colour was measured colorimetrically at 520nm.

Reagents:

1) Sulphuric acid,. 0.42 N

1 litre distilled water was added approximately to 2 litre volumetric flask and cautiously was added exactly 4.7ml concentrated H_2SO_4 and mixed well and cooling at room temperature and was diluted to the mark with distilled water .

2) Sodium tungstate solution 5%(Wt/vol)25 gm of sodium tungstate(Na_2 Wo_4 -2 H_2O were dissolved in water and diluted to 500 ml.

3) Stock creatinine solution 1 mg/ml:0.100 gm creatinine (available from National Baureau of standards)was dissolved precisely in 0.1 N Hel and diluted to 100 ml in a volumetric flask .

4) Creatinine working standards,(2.0 mg/dl and 6.0 mg/dl.) 20 ml and 50 ml of stock solution were transfered respectively to 1 litre volumetric flask.
5.0 ml Hcl was added and diluted to mark with water.

5) Picric acid, 1% (wt / vol):129 gm moist picric acid (special clinical analysis quality)were dissolved in 1 litre warm distilled water, allowed the solution to cooling at room temperature and the volume was exactly to 1 litre and was stored in amber bottle .

6) sodium hydroxide, 2.5 N, 10% (wt / vol):100 gm, NaoH were weighted into 1-litre volumetric flask and was diluted to mark with distilled water.

Procedure :-

1) In a centrifuge tube, 0.2 ml serum were added precisely.

2) 1.6 ml 0.42 N H_2 So_4 and 0.2 ml 5% sodium tungstate were added to the same centrifuge tube.

3) The contents were mixed well and centrifuged for 10 min at 2000 r.P.m .

4) Fresh alkaline picrate reagent was freshly prepared by combined 1 vol 10% NaoH and 5 vol 1% picric acid.

5) 1 ml of supernatant was transfered to second tube.

6) 0.4 ml fresh alkaline picrate solution was added.

7) Waited was exactly 16 min. and because many tubes were analyzed, the steps (6) and (7) were performed with 3o second intervales between each .

8) Reading had been performed against blank at 520 nm .

Calculation :

$$\frac{\text{Value of standard}}{\text{A standard}} \times \text{A unknown} = \text{mg/dl creatinine}$$

STATISTICAL ANALYSIS

The data obtained in this study representing the different variables, were statistically analysed according to the methods described by sendcor (1955).

Showing :

1- Sample Mean ($\bar{x}$).

2- Sample standard error of the mean (S.E.M).

3- Sample minimum and maximum (range).

Test for significance between two average were made by calculating "t" value where the calculated "t" was compared to the tabulated.

"t" at the respective degree of freedom (D.F).

LISTS OF TABLES AND FIGURES

The results of biochemical analysis including liver and kidney function tests for rats serum treated with antibilharzial drugs are shown in the following tables :-

Table 1 :

Shows the statistical analysis for glutamic oxal acetic transaminase in rats serum ofter administration with oral antibilharzial drugs at different time intervals.

Table 2 :

Records the statistical analysis for glutamic pyruvic transmainase in rats serum post administration with oral antibilharzial drugs at different times.

Table 3 :

Represents the statistical analysis for lactate dehydrogenase in rats serum following administration with oral antibilharzial drugs at different time intervals .

Table 4 :

Demonstrates the statistical analysis for cholinesterase

in rats serum after administration with oral antibilharzial drugs at different time intervals .

Table 5 :

Summarises the statistical analysis for ceruloplasmin in rats serum post administration with oral antibilharzial drugs at different time intervals .

Table 6 :

Illustrates the statistical analysis for total protein in rats serum following administration with oral antibilharzial drugs at different times .

Table 7 :

Shows the statistical analysis for albumin in rats serum after administration with oral antibilharzial drugs at different time intervals .

Table 8 :

Summarises the statistical analysis for globulinsin rats serum following administration with oral antibilharzial drugs at different time intervals.

Table 9 :

Represents the statistical analysis for albumin-globulin ratio in rats serum post administration with oral antibilharzial drugs at different time intervals .

Table 10 :

Illustrates the statistical analysis for bilirubin in rats serum after administration with oral antibilharzial drugs at different times .

Table 11 :

Shows the statistical analysis for urea in rats serum following administration with oral antibilharzial drugs at different time intervals .

Table 12 :

Summarises the statistical analysis for creatinine in rats serum post administration with oral antibilharzial drugs at different times intervals .

Table 1 :

Glutamic oxal acetic transaminase (G.OT) i.u/l activity in serum of rats treated with oral antibilharizal drugs and their control at different intervals.

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	44.83 ± 1.67 (39.0 - 51.0)	* 49.33 ± 0.62 (47.0 - 51.0)	46.5 ± 1.40 (42.5 - 51.0)
2 Weeks	45.17 ± 1.91 (39.0 - 51.0)	44.83 ± 1.67 (39.0 - 51.0)	44.75 ± 1.49 (39.0 - 49.0)
4 weeks	45.83 ± 1.79 (40.0 - 51.0)	45.92 ± 1.8 (39.0 - 51.0)	45.33 ± 1.76 (40.0 - 51.0)

* Significance at level ≤ 0.05

Table 2 :

Glutamic pyruvic transaminase (GPT) i.u/l activity in serum of rats treated with oral antiblharzial drugs and their control at different intervals

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	15.92 ± 0.97 (13.5 - 19.5)	19.75 * ± 1.12 (15.0 - 23.5)	16.75 ± 1.75 (13.5 - 23.5)
2 weeks	16.67 ± 0.69 (14.5 - 19.0)	16.17 ± 1.4 (13.0 - 20.5)	16.0 ± 1.43 (13.5 - 20.5)
4 weeks	16.17 ± 1.004 (13.5 - 19.5)	16.67 ± 1.22 (13.5 - 21.5)	16.75 ± 1.49 (13.0 - 22.0)

* Significance at level 0.05

Table 3 :

Lactate dehydrogenase (LDH). i.u/l activity in serum of rats treated with oral antibilharzial drugs and their control at different intervals .

Groups / Time	Control group	Oxamniquine treated group.	Praziquantel treated group
24 hours	503.78 ± 24.49 (431.8 - 590.9)	496.22 ± 10.44 (465.9 - 522.7)	498.48 ± 22.36 (443.2 - 593.2)
2 weeks	488.64 ± 15.52 (420.5 - 522.7)	486.74 ± 21.44 (397.7 - 545.5	487.5 ±32 .95 (363.6 - 595.5)
4 weeks	488.65 ± 10.98 (443.2 522.8)	487.5 ± 8.27 (454.6- 511.4)	488.64 ± 24.19 (420.5 - 590.9)

Table 4 :

Cholinesterase (CHE) u/l activity in serum of rats treated with oral antibilharzial drugs and their control at different intervals .

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	1.42 ± 0.011 (1.38 - 1.46)	1.38 ± 0.013 (1.36 - 1.43)	1.39 ± 0.018 (1.34 - 1.46)
2 weeks	1.39 ± 0.012 (1.36 - 1.42)	1.40 ± 0.025 (1.32 - 1.46)	1.40 ± 0.001 (1.37 - 1.43)
4 weeks	1.41 ± 0.017 (1.37 - 1.45)	1.42 ± 0.013 (1.38 - 1.46)	1.42 ± 0.001 (1.38 - 1.45)

Table 5 :

Ceruloplasmin u/l level in serum of rats treated with oral antibilharizal drugs and their control at different intervals .

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	41.67 ± 4.17 (25 - 56.25)	49.48 ± 6.17 (25 - 68.75)	46.88 ± 6.60 (25 - 68.75)
2 weeks	43.18 ± 5.38 (25 - 62.5)	46.88 ± 4.77 (37.5 - 68.75)	43.75 ± 3.61 (31.25 - 56.25)
4 weeks	44.79 ± 5.21 (25 - 62.5)	45.83 ± 5.02 (31.25 - 62.5)	46.35 ± 3.82 (34.38-56.3)

Table 6 :

Total proteins(g/dl) in serum of rats treated with oral antibiharzial drugs and their control at different intervals .

Groups / Time	control group	Oxaminquine treated group	praziquantel treated group
24 hours	6.18 ± 0.12 (5.80 - 6.50)	5.95 ± 0.09 (5.7 - 6.2)	5.83 ± 0.08 (5.6 - 6.0)
2 weeks	6.02 ± 0.16 (5.50 - 6.50)	6.17 ± 0.17 (5.6 - 6.6)	6.17 ± 0.14 (5.5 - 6.5)
4 weeks	5.97 ± 0.21 (5.20 - 6.60)	6.12 ± 0.17 (5.5 - 6.7)	6.15 ± 0.18 (5.5 - 6.8)

Table 7 :

Albumin (g/dl) in serum of rats treated with orol anti-biharzial drugs and their Control at different intervals .

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	3.48 ± 0.17 (3.2 - 4.2)	3.2 ± 0.10 (3.0 - 3.5)	3.25 ± 0.13 (2.7 - 3.6)
2 weeks	3.52 ± 0.13 (3.20 - 4.00)	3.6 ± 0.10 (3.2 - 3.9)	3.67 ± 0.12 (3.2 - 4.0)
4 weeks	3.57 ± 0.07 (3.3 - 3.8)	3.7 ± 0.05 (3.5 - 3.8)	3.75 ± 0.12 (3.3 - 4.0)

Table 8 :

Globulin (g/dl) in serum of rats treated with oral antibilharzial drugs and their control at different intervals

Groups / Time	Control group	Oxamniquine treated group	praziquantel treated group
24 hours	2.7 ± 0.19 (2.10 - 3.3)	2.75 ± 0.18 (2.2 - 3.2)	2.58 ± 0.17 (2.1 - 3.3)
2 weeks	2.5 ± 0.12 (2.2 - 2.8)	2.53 ± 0.16 (2.1 - 3.0)	2.50 ± 0.20 (1.7 - 3.1)
4 weeks	2.4 ± 0.18 (1.70 - 2.80)	2.42 ± 0.18 (1.7 - 2.9)	2.4 ± 0.18 (1.6 - 2.8)

Table 9 :

Albumin/Globulin ratio in serum of rats treated with oral antibilharzial drugs and their Control at different intervals .

Groups / Time	Control group	Oxamniquine trated group	Praziquantel treated group
24hours	1.35 ± 0.16 (0.97 - 1.83)	1.21 ± 0.12 (0.94 - 1.59)	1.3 ± 0.12 (0.82 - 1.67)
2 weeks	1.43 ± 0.09 (1.14 - 1.82)	1.47 ± 0.11 (1.17 - 1.86)	1.53 ± 0.17 (1.03 - 2.24)
4 weeks	1.53 ± 0.13 (1.29 - 2.06)	1.59 ± 0.15 (1.29 - 2.24)	1.63 ± 0.18 (1.25 - 2.44)

Table 10 :

Bilirubin (mg/dl) in serum,of rats treated with oral antibilharzial drugs and their control at different intervals.

Groups / Time	Control group	Oxamniquine treated group	Praziquantel treated group
24 hours	0.43 ± 0.05 (0.3 - 0.6)	** 0.67 ± 0.07 (0.49 - 0.84)	0.53 ± 0.05 (0.35 - 0.7)
2 weeks	0.43 ± 0.04 (0.35 - 0.63)	* 0.62 ± 0.09 (0.35 - 0.98)	0.50 ± 0.05 (0.35 - 0.63)
4 weeks	0.46 ± 0.04 (0.35 - 0.56)	0.57 ± 0.07 (0.35 - 0.84)	0.51 ± 0.03 (0.42 - 0.63)

* Significance at level ≤ 0.05

** highly significance at level ≤ 0.01 .

Table 11 :

Urea (mg/dl) in serum of rats treated with oral antibilharzial drugs and their Control at different intervals .

Groups / Time	Control group	Oxamniquine treated group	praziquantel treated group
24 hours	26.53 ± 1.67 (20.4 - 30.6)	28.77 ± 2.12 (18.4 - 32.65)	27.96 ± 1.91 (20.4 - 32.7)
2 weeks	29.52 ± 0.94 (26.5 - 32.65)	28.30 ± 1.6 (24.5 - 34.7)	30.07 ± 2.85 (19.18 - 36.7)
4 weeks	24.69 ± 2.18 (18.4 - 32.65)	25.58 ± 2.22 (20.4 - 32.7)	25.17 ± 1.8 (18.4 - 30.6)

Table 12 :

Creatinine (mg/dl) in serum of rats treated with oral antibilharzial drugs and their control at different intervals.

Groups / Time	Control group	Oxamniquine treated group	Praziquanted treated group
24 hours	0.71 ± 0.06 (0.53 - 0.89)	0.81 ± 0.09 (0.53 - 1.06)	0.82 ± 0.05 (0.69 - 0.98)
2 weeks	0.76 ± 0.08 (0.53 - 1.12)	0.71 ± 0.07 (0.53 - 0.97)	0.75 ± 0.06 (0.56 - 1.004)
4 weeks	0.71 ± 0.07 (0.53 - 0.97)	0.81 ± 0.15 (0.53 - 1.40)	0.75 ± 0.09 (0.53 - 1.12)

LIST OF GRAPHS :

Graph 1 :

Shows the glutamic oxal acetic transaminase activity in serum of rats following administration with oral antiblharzial drugs at different time intervals .

Graph 2 :

Records the glutamic pyruvic transaminase activity in serum of rats post administration with oral antibilharzial drugs at different time intervals .

Graph 3 :

Represents the lactate dehydrogenase activity in serum of rats after administration with oral antibilharzial drugs at different times .

Graph 4 :

Summarises the cholinesterase activity in serum of rats following administration with oral antibilharzial drugs at different time intervals .

Graph 5 :

Demonstrates the ceruloplasmin level in serum of rats after administration with oral antibilharzial drugs at different time intervals .

Graph 6 :

Shows the total protein level in serum of rats post administration with oral antibilharzial drugs at different time intervals .

Graph 7 :

Illustrates the albumin level in serum of rats after administration with oral antibilharzial drugs at different time intervals .

Graph 8 :

Summarises the globulins level in rats serum post administration with oral antibilharzial drugs at different times intervals.

Graph 9 :

Represents the albumin / globulin ratio in serum of rats following administration with oral antibilharzial drugs at different time intervals .

Graph 10 :

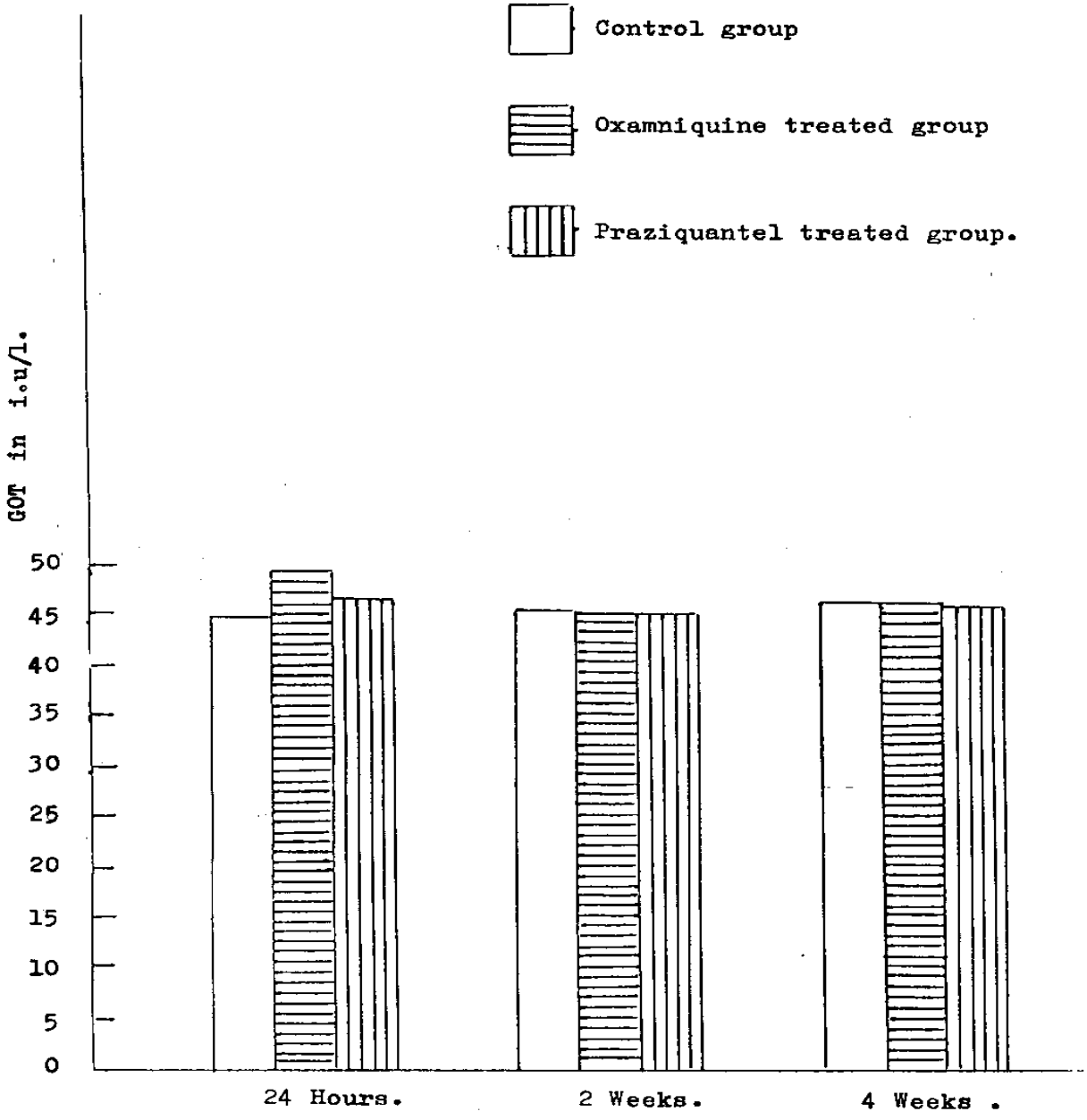
Shows the bilirubin level in serum of rats post administration with oral antibilharzial drugs at different time intervals .

Graph 11 :

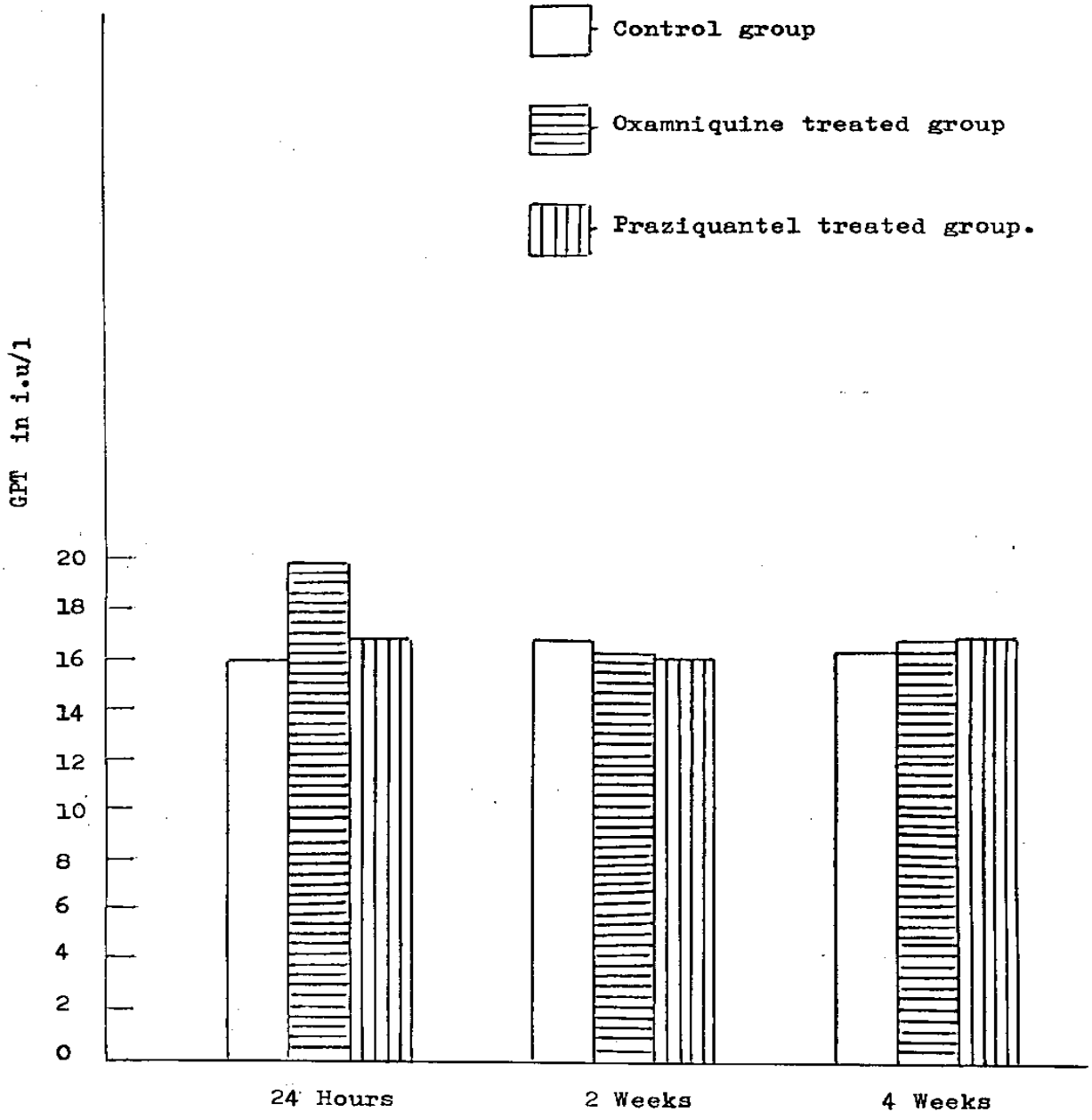
Represents the urea level in rats serum after administration with oral antibilharzial drugs at different time intervals .

Graph 12 :

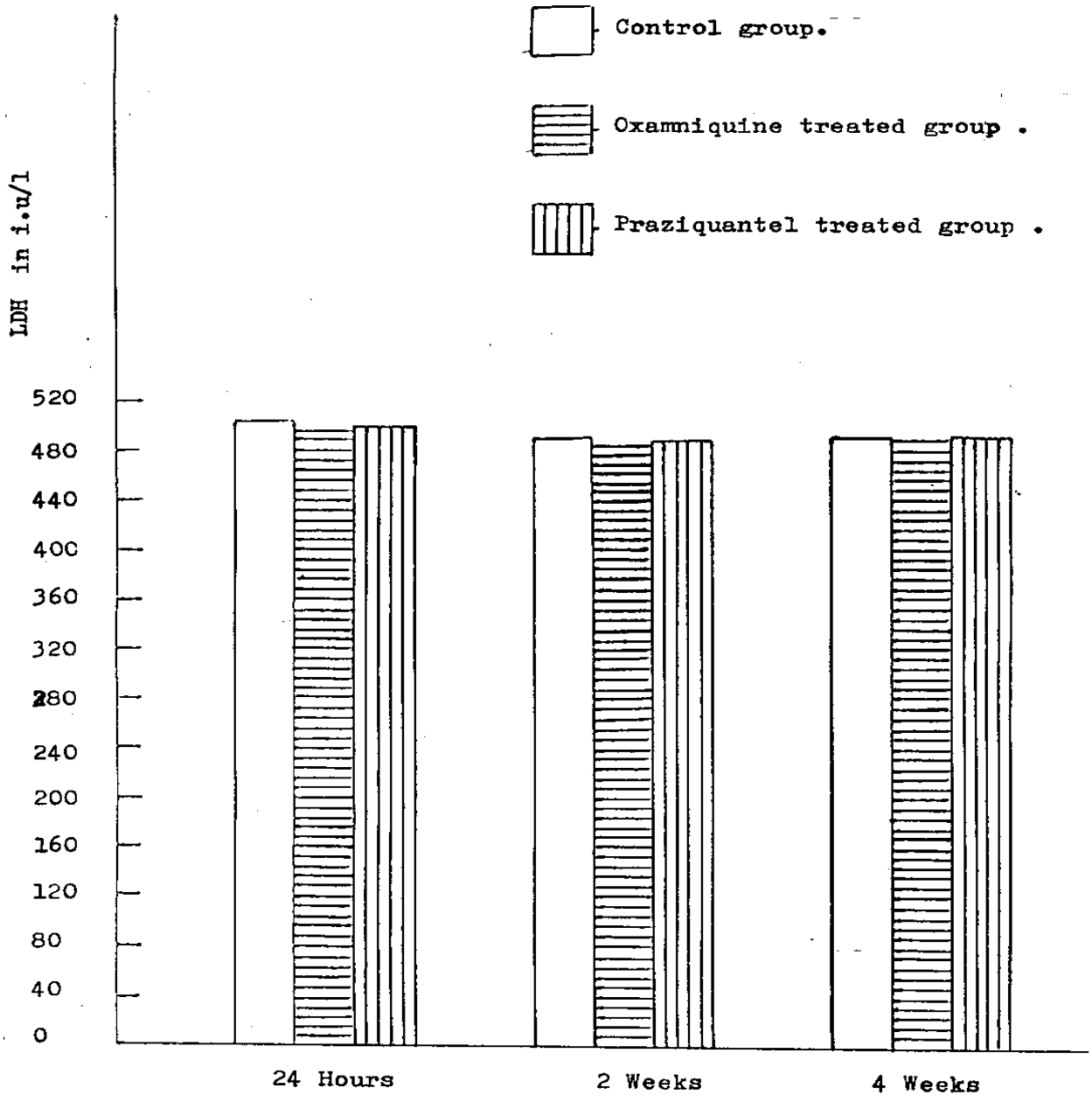
Illustrates the creatinine level in serum of rats following administration with oral antibilharzial drugs at different time intervals .



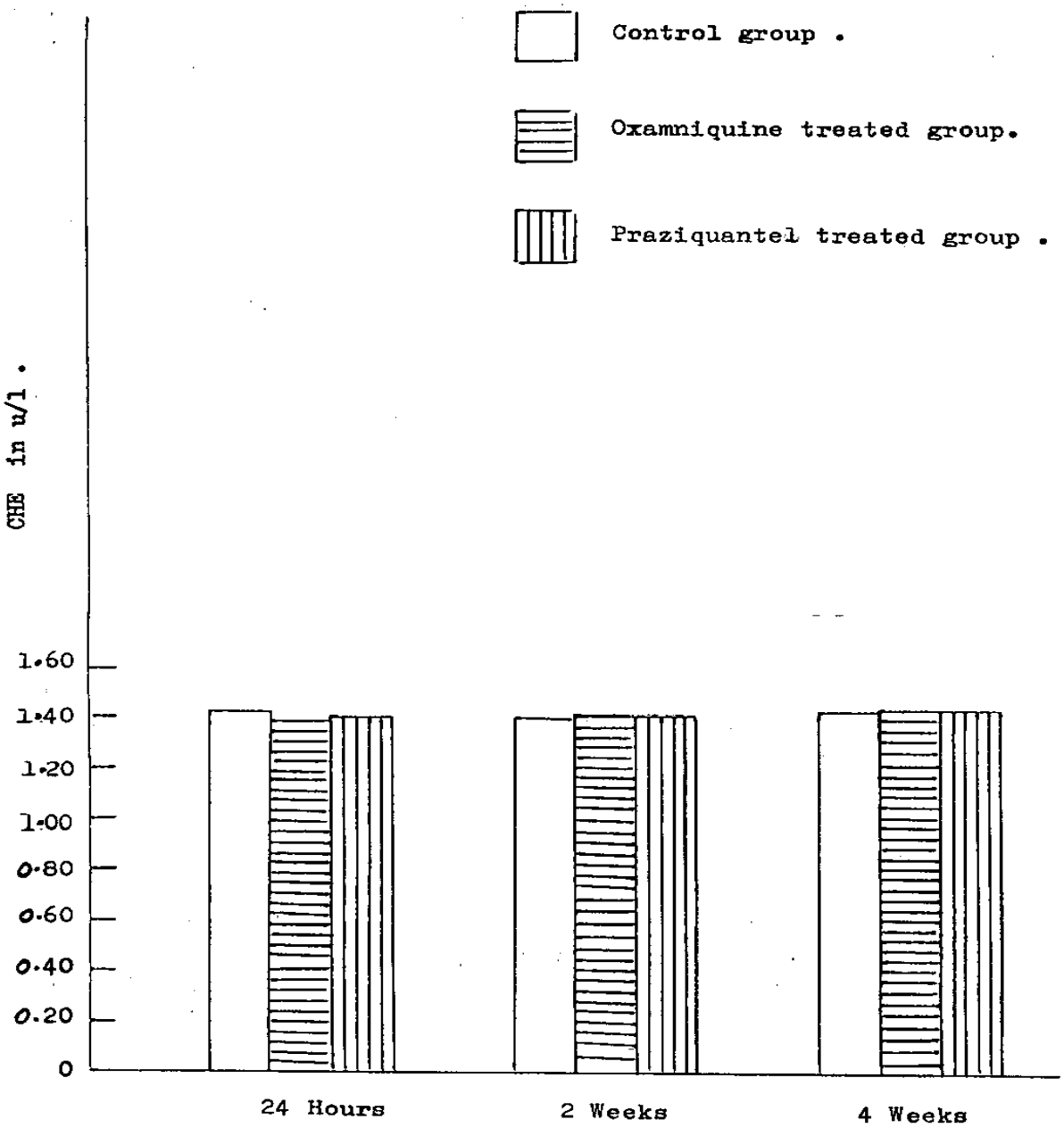
Graph (1) Glutamic oxal acetic transaminase activity in blood serum of rats administered with oral antibilharzial drugs .



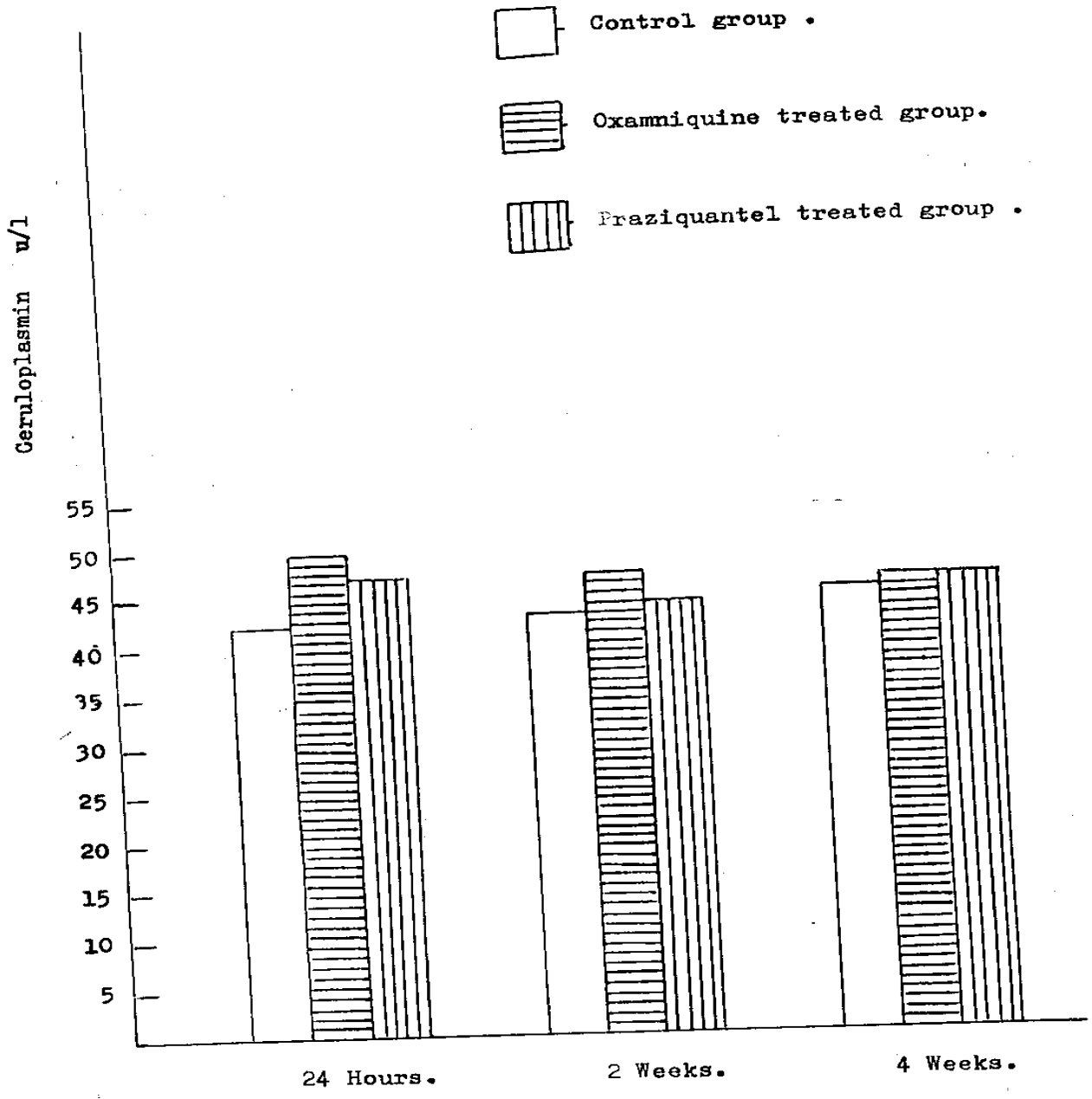
Graph (2) Glutamic pyruvic transaminase activity in blood serum of rats administered with oral antibilharzial drugs .



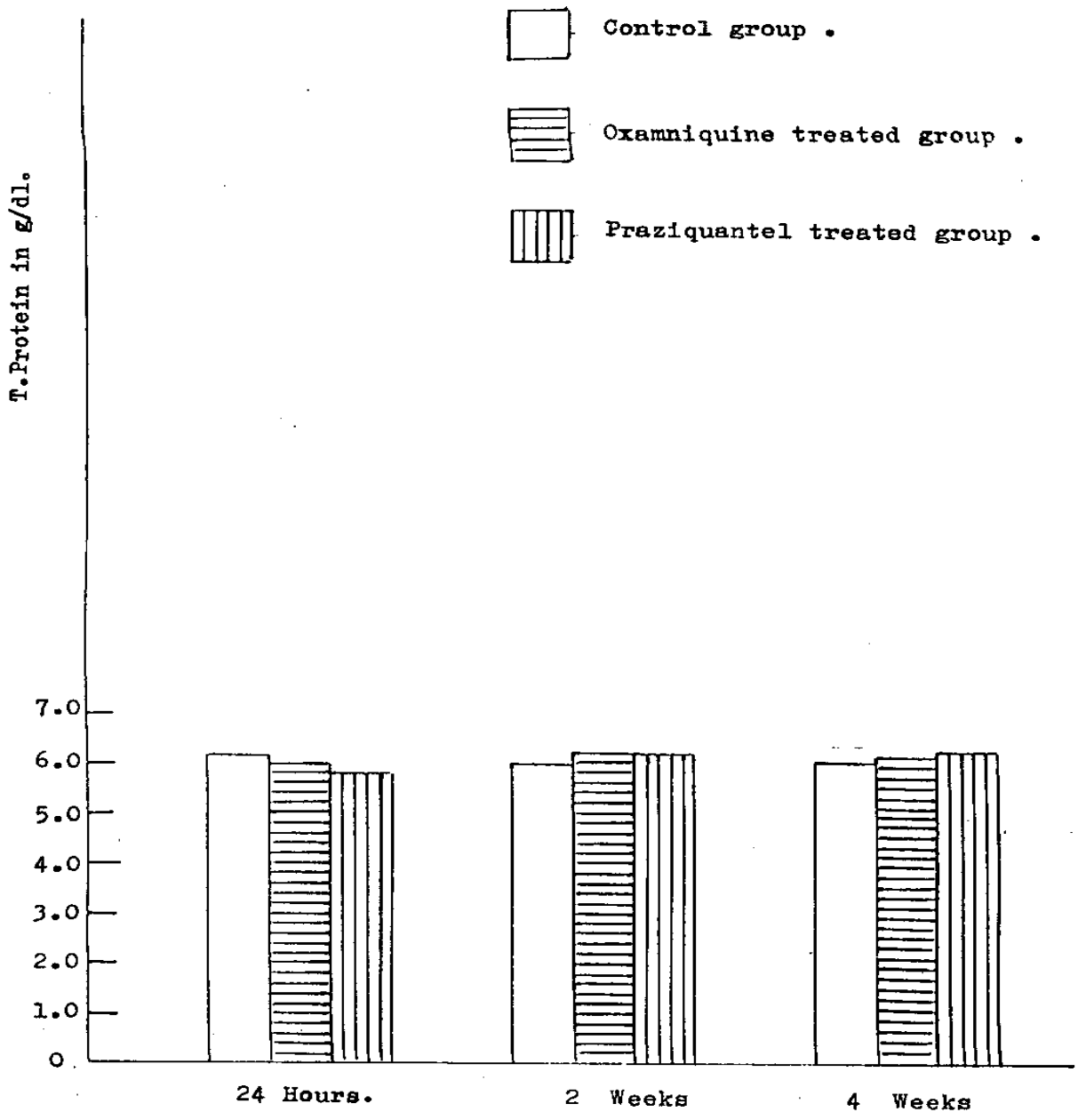
Graph (3) Lactate dehydrogenase activity in blood serum of rats administered with oral antibilharzial drugs.



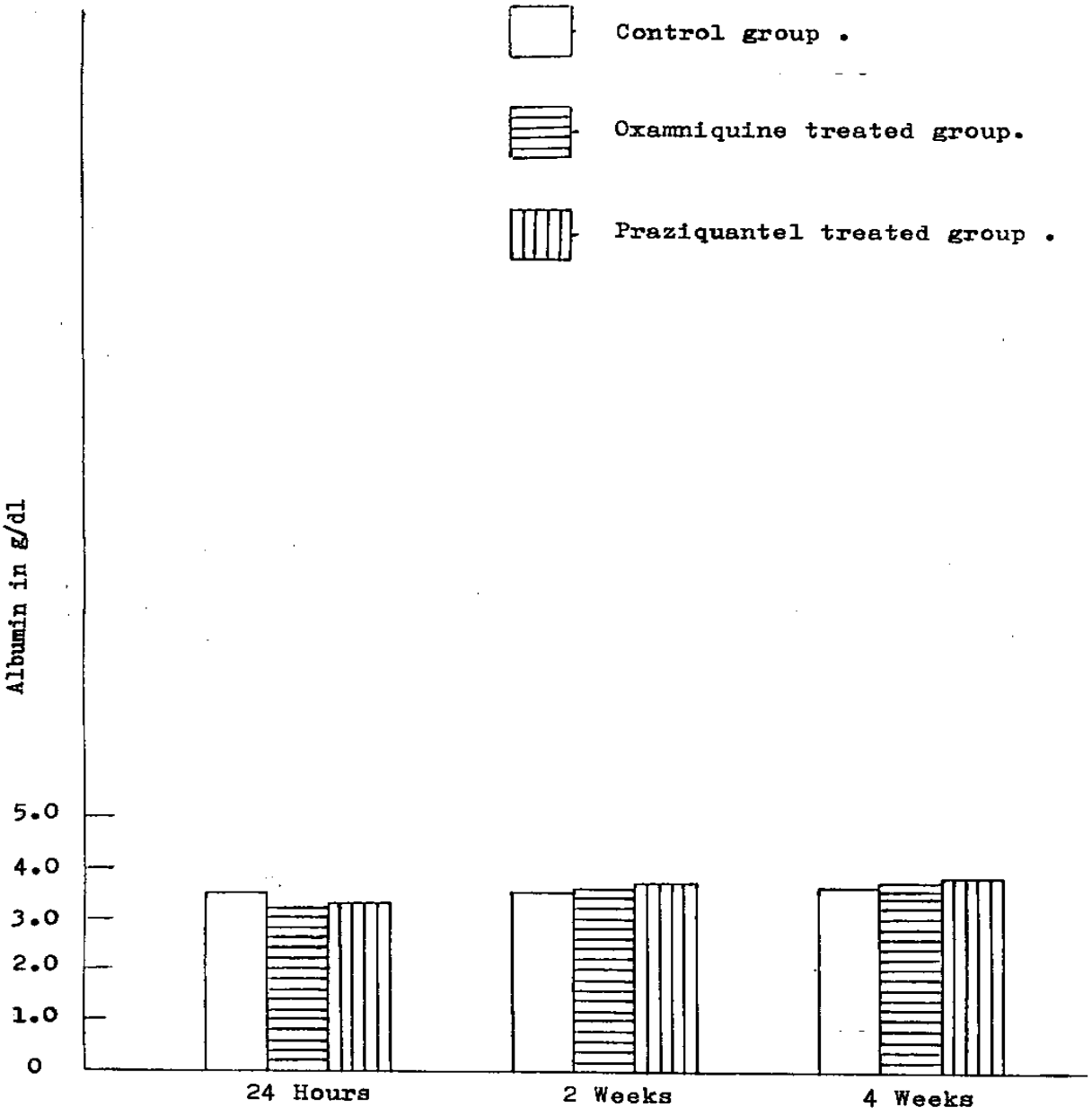
Graph (4) Cholinesterase activity in blood serum of rats administered with oral antibilharzial drugs .



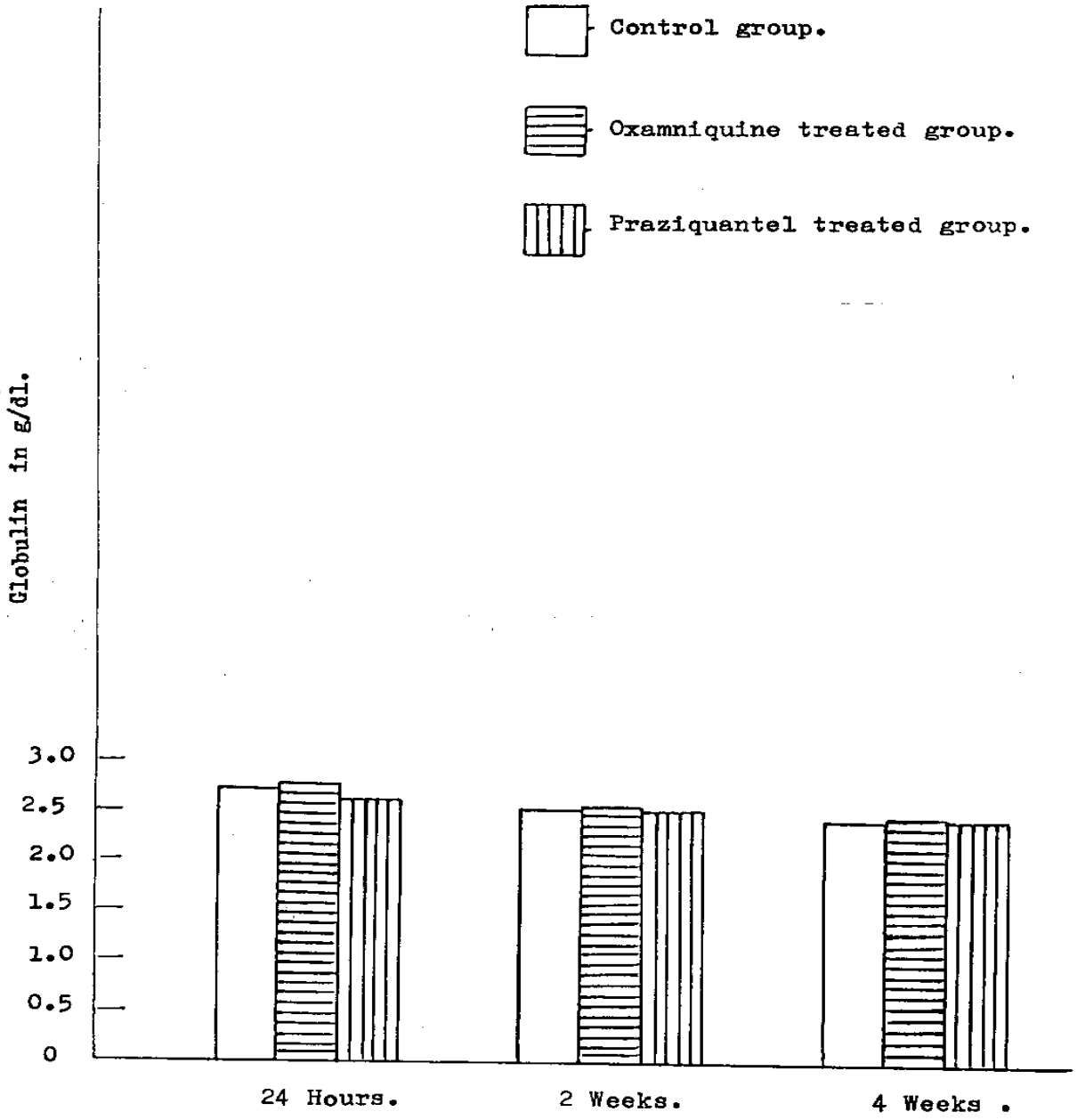
Graph (5) Ceruloplasmin level in blood serum of rats administered with oral antibilharzial drugs.



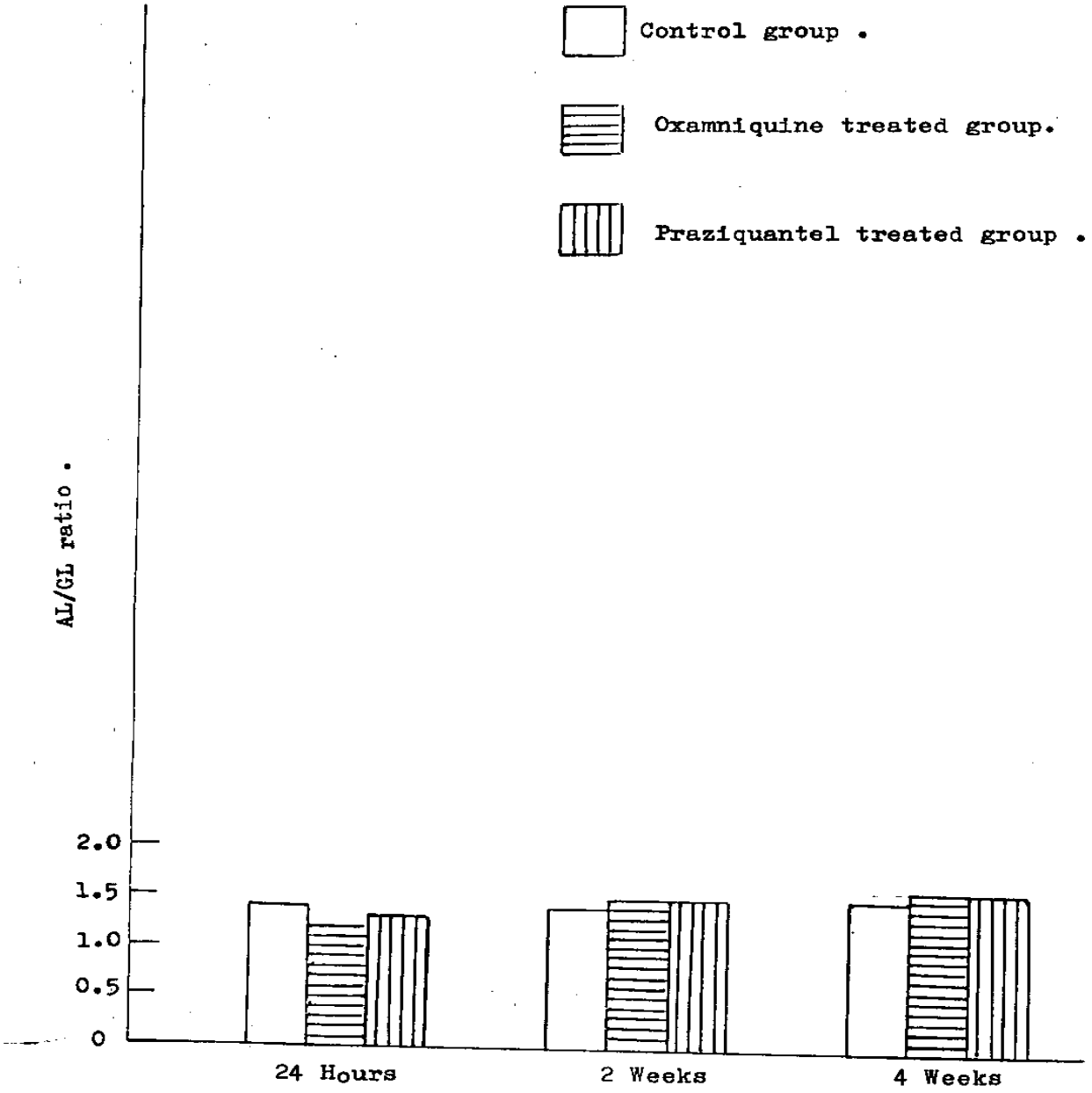
Graph (6) Total protein level in blood serum of rats administered with oral antibilharzial drugs .



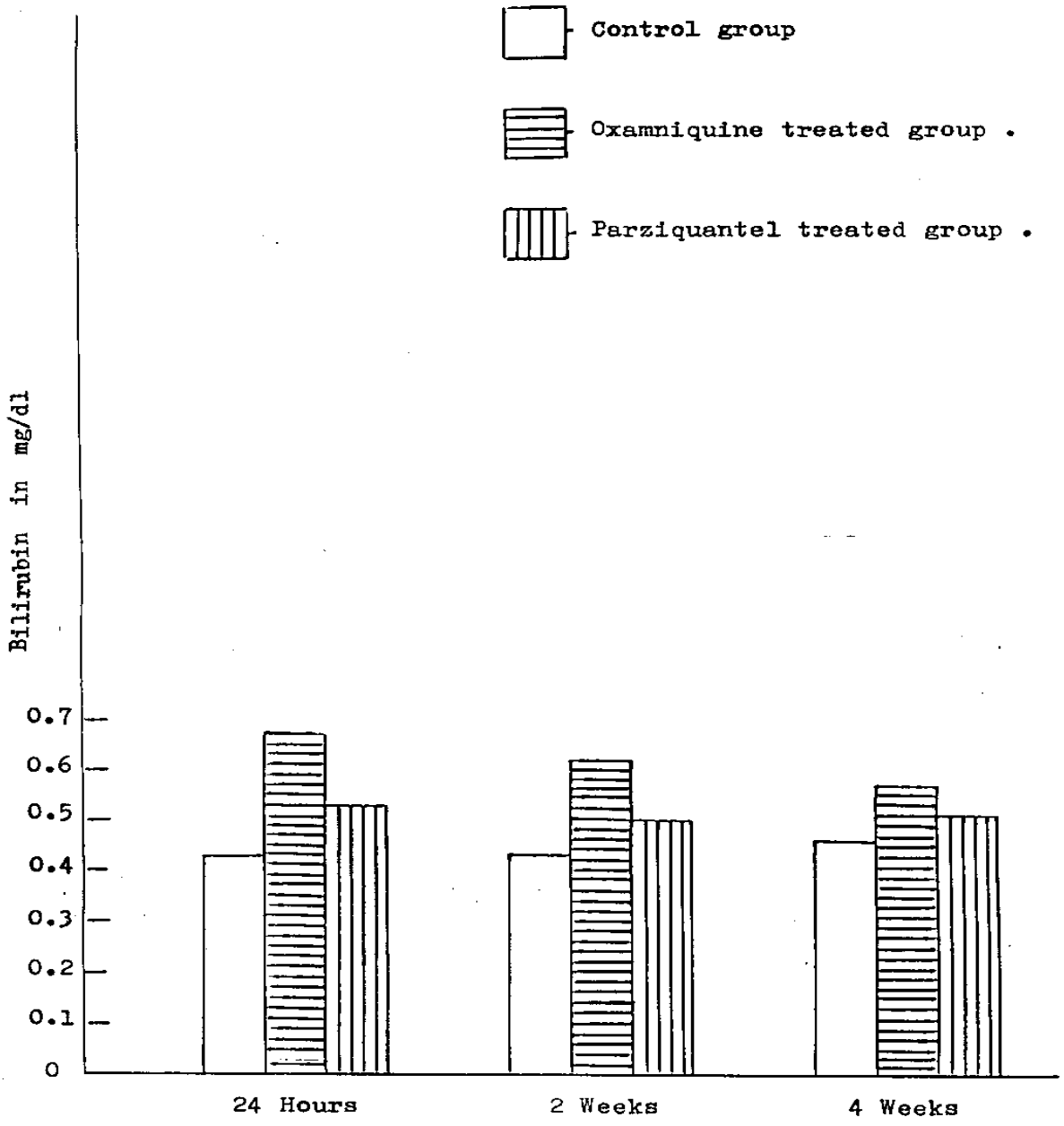
Graph (7) Albumin level in blood serum of rats administered with oral antibilharzial drugs.



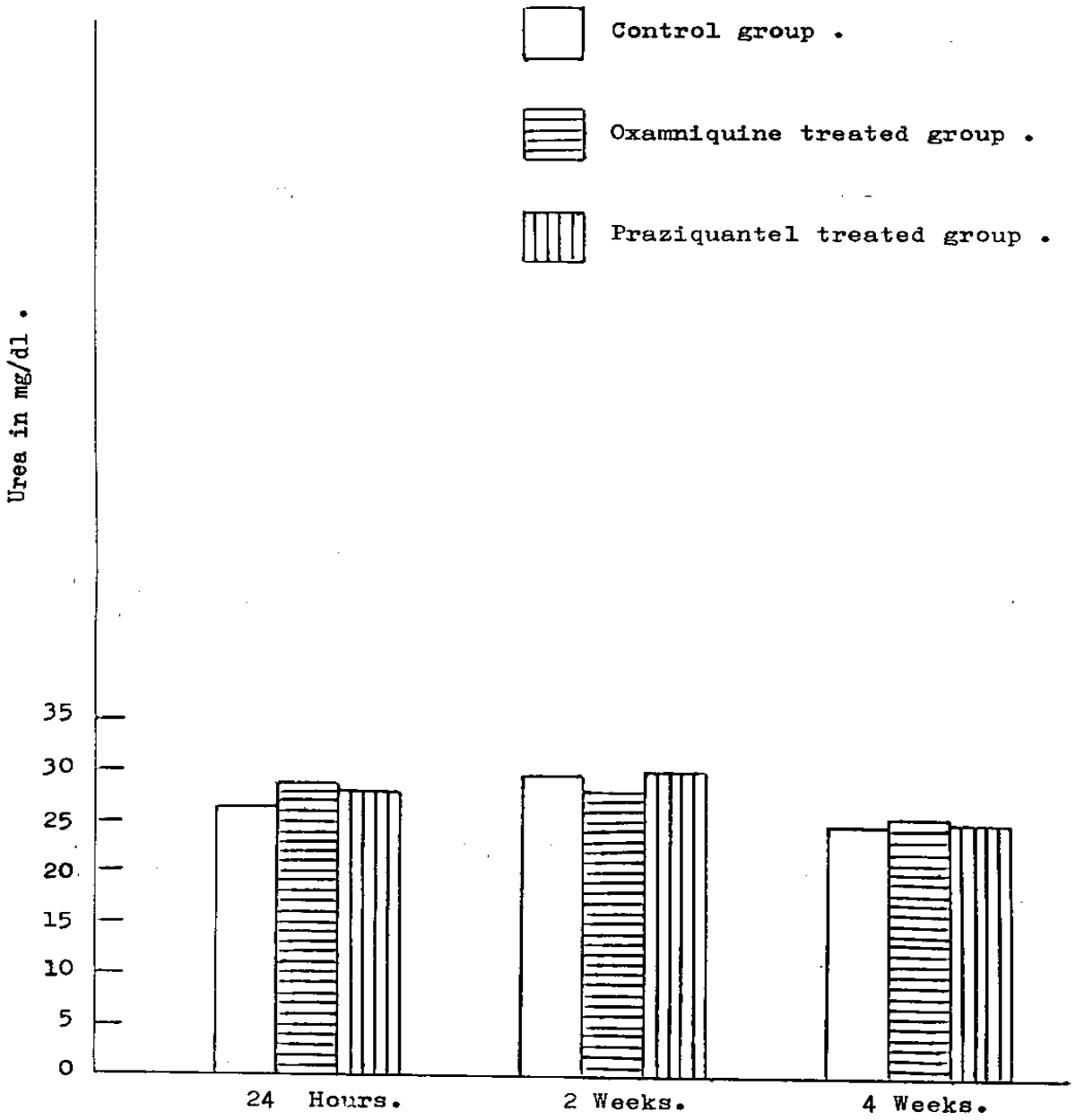
Graph (8) Globulins level in blood serum of rats administered with oral antibilharzial drugs.



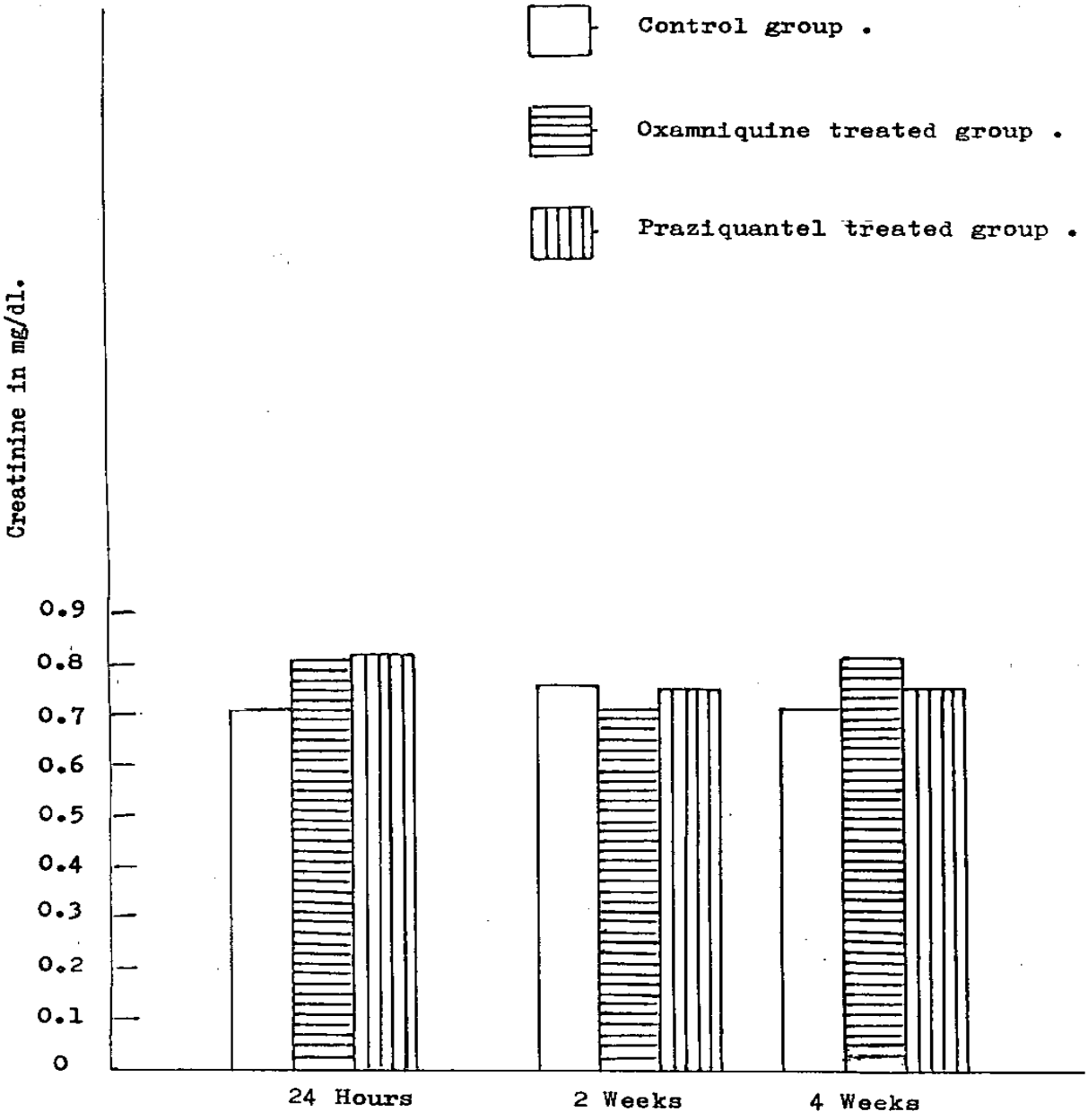
Graph (9) Albumin / Globulins ratio in blood of rats administered with oral antibilharzial drugs.



Graph (10) Bilirubin level in blood serum of rats administered with oral antibilharzial drugs.



Graph (11) urea level in blood serum of rats administered with oral antibilharzial drugs .



Graph (12) Creatinine level in blood serum of rats administered with oral antibilharzial drugs.

" DISCUSSION "

The aim of treating schistosomiasis is to prevent further tissue damage particularly liver and kidney which are commenly affected by a disease.

The ideal drug must give a chance to tissue repair without adding the burden of its toxic effect .

A) EFFECTS OF Oxamniquine(Vansil) and Praziquanyel(Biltricid) on liver function tests:-

The liver is particularly concerned with drug metabolism especially those given orally.

Sherlock, (1981) revealed that the drug testing must alaways includes pre and post treatment evaluation of serum bilirubin and level of transaminases .

In the present work, the effect of schistosomocidal drugs, Oxamniquine and Praziquantel on liver function were evaluated by determination of serum levels of transaminases, lactic dehydrogenase, cholinesterase, ceruloplasmin, total protein and their fractions and bilirubin .

1- **TRANSAMINASES** :

In the present study, our results revelaed that the activity of aspartate aminotransferase(AS T) (SGOT) in the control group after 24 hours, 2 weeks and 4 weeks were 44.83 ± 1.67, 45.17 ± 1.91 and 45.83 ± 1.79 i.u/l respectively.

The results after oral administration with Oxamniquine were 49.33 ± 0.62, 44.83± 1.67 and 45.92 ±1.8 i.u/l at 24 hours, 2 weeks and 4 weeks respectively.

While praziquantel administration at 24hours, 2 weeks and 4 weeks showed a levels of 46.5 ± 1.40, 44.75 ±1.49 and 45.33 ±1.76 i.u/l (Table, 1).

Meanwhile the activities of alanine aminotransferase (AL T) (S.G.P.T) in control group were 15.92 ±0.97, 16.67 ± 0.69 and 16.17 ±1.004 i.u/l at 24 hours, 2 weeks and 4 weeks respectively.

The results after administration with Oxamniquine were 19.75 ± 1.12, 16.17±1.4 and 16.67±1.22 i.u/l at 24 hours 2 weeks and 4 weeks respectively .

While, the levels in Praziquantel treated group were 16.75 ± 1.75, 16.0 ±1.43, and 16.75 ±1.49 i.u/l at 24 hours, 2weeks and 4 weeks (Table, 2).

In this investigation a significiant increase in (S.G.O.T) and S.G.P.T) was detected only after 24 hours in Oxamniquine treated group(Fig.1 and 2).

This is consistent with the results obtained by Da-silva et al., (1975), Eyakuse & Rugemalila (1978) and Siongok et al., (1978); they reported an elevation in transaminases following the treatment with Oxamniquine.

Sherlock(1981) reported that serum transaminases are most useful indicators of hepato-cellular damage and their determination are helpful in screening for liver injury due to drugs.

The significant increase in the serum transaminases levels following Oxamniquine administration may be due to that primary effect of the drug directly upon hepatocytes and this biochemical changes observed are indicative of liver injury induced by the drug which causes a definite injury to liver

parenchyma and also produced a mild histopathological changes in the liver and then the transaminases enzymes is liberated from disintergrating liver cells.

Omer (1978) and Bassily et el., (1978) revealed that the elevation in transaminases may appears a state as one week after treatment with praziquantel.

On the other hand, Davis et al., (1981), recorded no significant decrease in transaminase activity following treatment with praziquantel regardless of the dose.

In our work, a non significant increase in transaminases was observed after treatment with praziquantel, (Fig. 1 and 2)

This was agreed with the results obtained by Pedro et al., (1973); Davis et al., (1979); Ishizaki et al., (1979) Oyediran et al., (1981); Diallo et al., (1981); Nash et al., (1982); Sidhom, (1985) and El-Shinnawy, (1985).

Katz et al., (1979) and Diallo et al., (1981), Observed an elevation of serum transaminases activity one day post treatment with praziquantel and became normal on the 5 th day.

Andrews et al., (1980) reported transient elevation of plasma (SGOT) and (SGPT) a day after treatment with praziquantel, as similar rise in uninfested animals was not observed.

From this study it is clear that the oxamniquine exerts significant rise in S.G.O. T and S.G.P.T one day after drug administration, followed by its normal level. Mean while the praziquantel has no effect on the serum transaminases .

2- **SERUM LACTATE DEHYDROGENASE** :

Our results concerned the level of lactate dehydrogenase activity in the control group (untreated one) were 503.8 ± 24.5, 488.6± 15.5 and 488.7±10.9 i.u./l at 24 hours, 2 weeks and 4 weeks respectively.

The results obtained post the Oxamniquine treated were found 496.2 ± 10.4, 486.7± 21.4 and 487.5±8.3 i.u/l at 24hours, 2 weeks and 4 weeks respectively.

At the same times, the result after praziquantel administrated were, 498.5 ± 22.4, 487.5± 32.9 and 488.6 ±24.2 i.u/l (Table,3) . A medical record from Pfizer Co. Medical report,(1982) reported that minor and transient abnormalities in laboratory data have been observed after treatment with Oxamniquine which is not considered to be drug releated and were of no clinical significance, they included rare instances of mild to moderate liver enzyme elevation but there was no evidence of hepato toxicity in severe hepatosplenic involvement. There was evidence, however of liver abnormalities in animals with the female rat being uniquely sensitive to relatively low doses .

In the present work, non significant decrease in the level of LDH activity was detected at 24 hours post Oxamniquine treatment and non significant alteration(decreasing) at 2 weeks and 4 weeks(Fig., 3).

Our results is in aggreement with the observation of Koura et al., (1975)

On the other hand, a non significant decrease in the level of LDH activity was detected at 24 hours post praziquantel treatment and non significant changes were occured at 2 and 4 weeks(Fig.,3) and our results in consistent with the results obtained by Wegner,(1979) who reported that lactic dehydrogenase value revealed no clinical relevant deviation following treatment .

Also, Da silva et al., (1981) and Ambroise & Goullier, (1981), they reported that serum level,of lactic dehydrogenase showed no change response to praziquantel treatment.

Ali, (1984) observed that,negligable fluctuations in serum LDH levels were obtained in the three groups from before to after praziquantel therapy .

Sidhom, 1985, recorded that , serum LDH level did not show any significant change following medication with praziquantel

3- **SERUM CHOLINESTERASE**

Our deta revealed that the serum cholinesterase activity in the control group(untreated) were,1.42 ±0.011, 1.39 ± 0.012 and 1.41 ±0.017units/l at 24 hours, 2 weeks and 4 weeks, (Table,4). And the results obtained post the Oxamniquine treatment were found to be 1.38± 0.013,1.40± 0.025 and 1.42±0.013 units/l at 24 hours, 2 weeks and 4 weeks.

While, the results after the treatment with the praziauantel werel.39 ±0.018 ,1.40±0.001 and 1.42 ± 0.001 units/l at 24 hours, 2 weeks and 4 weeks(Table,4).

Kalow, et al .,(1958) and Shakir,et al., (1964), they reported that plasma (CH.E) is synthesized in liver, it is considered as a sensitive parameter giving an idea about the synthetic function of the liver. On this bases, changes of (CH.E) may be partly releated to the toxic effect of the these drugs on the liver cells .

Foster,(1973) found that oxamniquine has a bad effect on liver .

In this work, a non significant decrease in the level

of CH.E activity was detected at 24 hours post Oxaminquine treatment and non significant increase was detected at 2 weeks and 4 weeks (Fig. 4), and our present result is in aggreement with the observations of Ongom et al.,(1975).

Gamil, et al.,(1984) they reported that, the oral antischistosomal drugs(oxamniqune & praziquantel) were invesigated experimentally on albino rats with paracetamol induced hepatorenal toxicity .

A biochemical and histopathological studies were done on such animals and were compared with normal and paracetamol treated ones, it is found that oxamniquine(Vansil) is less toxic than praziquantel(Biltricid), because praziquantel in the presence of hepatic affection is far from safety while oxamniquine is more safe in patients with hepatic lesions .

In this study, non significant decrease in the level of CH.E activity was detected at 24hours post praziquantel treatment and non signifcant increase was occured at 2 and 4 weeks (Fig.,4) And our results is in aggreement with results of wegner,(1979) where recorded that cholinesterase values revealed no clinical relevant deviation following praziquanteladministration .

Serum enzymatic Comparative study of present work following oxamniquine and praziquantel administration indicated that these drugs especially praziquantel is safe and have no any side effect on liver function. while oxamniquine have mild hepato side effect and is transient and short lived with a relatively rapid correction to word normal level .

4- **CERULOPLASMIN.**

Our results concerned the level of ceruloplasmin activity in the control group were, 41.67 ±4.17, 43.18±5.38 and 44.79 ±5.21 i.u/l at 24 hours, 2 weeks and 4 weeks. While the results obtained post Oxamniquine administration were 49.48 ± 6.17, 46.88 ± 4.77 and 45.83 ± 5.02 u/l at 24 hours, 2 weeks and 4 weeks resctively .

The results post praziquantel treatment were 46.88±6.60 43.75 ± 3.61 and 46.35 ±3.82 u/l at 24 hours, 2 weeks and 4 weeks (Table,5).

There is a releationship, between plasma ceruloplasmin and liver, williams etal., (1974 a) explained the function of ceruloplasmin in iron mobilization that Fe II released from ferritin binds to specific sites on the reticulo-endothelial cells membranes and ceruloplasmin interacts with the iron binding sites to form a fe II-ceruloplasmin complex. Then finally Fe II was oxidized and transferred to apotransferrin by a specific ligand- exchange reaction. And this confirmation gives an idea for the increased level of ceruloplasmin post antibilharizal drugs administration .

In the present work, there is a non significant increase in the ceruloplasmin level post Oxamniquine administration at 24 hours, 2 weeks and 4 weeks (Fig,5). Our results are aggreed with the results observed by Fripp,(1973) which reported that Oxamniquine had little effect on the level of biochemical components of the blood and produced no pathology in the liver .

Hence there was no evidence of hepato- toxicity or liver damage resulting from the administration of this drug.

In concerning to the ceruloplasmin level post praziquantel administration , the result revealed that, there is non significant increase in the ceruloplasmin level following praziquantel administration at 24 hours, 2 weeks and 4 weeks (Fig,5). Ceruloplasmin has a relationship to liver and their function and it's level is increased in blood in liver disease (Thompson, and wooton , 1970).

There are several results indicated that praziquantel has no any toxic side effect on liver and their function. And our results are aggreed with the result obtained by Sidhom,(1985) who concluded that praziquantel given in therapeutic doses has neither early nor late toxic effect on liver

structure and functions as evidenced from the different physiological, biochemical and histopathological techniques, and it is very safe and there are several similar results obtained by other workers

This means that both Oxamniquine and praziquantel have no toxic side effect on liver function and did not showing a significant elevation in the level of ceruloplasmin in our study .

It has no found any studies concerning the action of our choice drugs as iron depleting factors .

On the other hand Ibrahim (1984) found a significant increase in ceruloplasmin level after treated with Ambilhar. He attributed such increase due to the action of Ambilhar as iron depleting drug.

5- **SERUM PROTEINS:**

In the present study, our results revealed that, the total Serum protein level in the control group after 24 hours, 2 weeks and 4 weeks were 6.18 ± 0.12, 6.02±0.16 and 5.97±0.21 9/dl.

The results after oral administration with Oxamniquine were 5.95 ± 0.09, 6.17 ±0.17 and 6.12±0.17 9/dl at 24 hours, 2 weeks and 4 weeks respectively .

While praziquantel administration at 24 hours, 2 weeks and 4 weeks showed a level of 5.83 ± 0.08, 6.17±0.14 and 6.15 ± 0.18 9/dl (Table,6.)

Mean while the albumin level in the control group at 24 hours, 2 weeks and 4 weeks were 3.48 ± 0.17, 3.52 ±0.13 and 3.57 ±0.07 9/ dl .

In the Oxamniquine treated group, the results were 3.2 ±0.10,3.6 ± 0.10, 3.6±0.10 and 3.7±0.05 G/dl at 24 hours, 2 weeks and 4 weeks. Moreover the results after praziquantel administration at 24 hours,2 week and 4 weeks were 3.25±0.13, 3.67 ± 0.12 and 3.75± 0.12 g/dl(Table, 7).

On the other hand globulin level in control group were 2.7 ± 0.19 , 2.5 ±0.12 and 2.4 ±0.18 g/dl at 24 hours,2 weeks and 4 weeks .

The results related to Oxamniquine treated group at 24 hours, 2 weeks and 4 weeks were 2.75 ± 0.18, 2.53±0.16 and 2.42 ± 0.18 g/dl.

While praziquantel administration at 24 hours, 2 week and 4 weeks showed a level of 2.58 ± 0.17 , 2.50 ±0.20 and 2.40 ±0.18 g/dl (Table 8)

The results of albumin/globulin ratio in control group at 24 hours, 2 weeks and 4 weeks were 1.35 ± 0.16, 1.43±0.09 and 1.53 ± 0.13 g/dl .

In relation to Oxamniquine, the results were 1.21±0.12, 1.47 ±0.11 and 1.59 ± 0.15 at 24 hours, 2 weeks and 4 weeks.

The results after praziquantel oral administration at 24 hours, 2 weeks and 4 weeks were 1.3 ±0.12, 1.53 ±0.17 and 1.63 ±0.18 g/dl .

In this study a non significant decrease in total protein, albumin and albumin/globulin ratio and non significant increase in globulin level was detected after 24 hours in oxamniquine treated group(Fig, 6,7,8 and 9).

This is consistent with the results obtained by Fripp, (1973) who recorded that, Oxamniquine produced no pathology in the liver . Hence there was no evidence of hepatotoxicity or liver damage resulting from the administration of this drug .

Also Siongok et al.,(1975),they reported that Oxamniquine has no toxic side effect on biochemical examination including liver functions .

Also El- Masry et al., (1986) reported that oxamniquine produced no side effects and it has no effect on serum protein and their fractions .

There is non significant alteration at 2 weeks and 4 weeks in protein and their fractions.

While in praziquantel treated group there is also non

significant decrease in total protein, albumin and albumin globulin ratio and non significant increase in globulin level was detected, at 24 hours but at 2 week and 4 weeks, there is non significant changes in serum protein and their fractions.

Our results aggreed with the results obtained by Ali, (1984) who observed that a non significant transitory decrease was found in serum total protein, albumin, A/G ratio and non significant change in globulin one day post treatment with praziquantel.

After one week there was a non significant increase in serum total protein and albumin with a corresponding decrease in globulin level.

The A/G ratio showed a rise to the pre-treatment value. Also our study is consistent with the observation of Ambroise-Thomas & Goullier (1981), they found no change in serum protein or in the A/G ratio after praziquantel therapy.

On the other hand Coutinho et al.,(1983) recerded a significant increase in serum albumin with a corrosponding decreae in gamma- globulin after praziauantel therapy, and both results returned to normal level during 6-12 months.

Post praziqunatel administration the transient decreasing in protein and their fraction especially albumin one day post- drug administration may be a little direct toxic effect of the drug on the synthetic function of the liver which was of no clinical significance to produce prolonged reduction and normalized after one week and such results could be attributed to the decreased liver function and this indicated that liver play an important role in production of plasma protein(Ali, 1984).

Bauer, (1982 b) reported that liver plays an important role in the production of plasma proteins, and in the progressive stages of liver disease, albumin is decreased and the globulins are increased mean while in the early stages of acute hepatitis, the serum protein level to be normal.

Frohberg and Schenking, (1981), they stated that liver is the main site which tolerate various drugs given to vital body .

Katz, et al. (1979); Santos, et al., (1979);El -Alamy, et al., (1981), they stated that after 24 hours from drug administration, the results of total protein and globulin

had a non significantly increase, but the albumin level was non significant.

Shank, et al.,(1968) reported that, the decrease in the albumin level may be due to insufficient protein intake or low amount formed by the liver. i.e the reduction in the liver effeciency concerning plasma protein synthesis especially albumin may be due to the effect of these drugs on liver .

6- SERUM BILIRUBIN :

In our present work, our results concerning serum bilirubin level showed that the mean values in control group were 0.43 ± 0.05, 0.43 ± 0.04 and 0.46 ± 0.04 mg/dl at 24 hours , 2 weeks and 4 weeks .

Meanwhile results after oral administration with oxamniquine at 24 hours , 2 weeks and 4 weeks were 0.67 ± 0.07, 0.62 ± 0.09 and 0.57 ± 0.07 mg/dl.

The data obtained ofter the praziquantel administration were 0.53±0.05,0.50±0.05, and 0.51 ± 0.03 mg/dl at 24 hours 2 weeks and 4 weeks (Table , 10).

In this study a significant increase in serum bilirubin level was observed after Oxaminiquine administration and detected only after 24 hours and 2 weeks then corrected to the normal level. (Fig, 10), this is consistent with the results obtained by Katz, et al., (1973) who reported that serum bilirubin level was elevated after oxaminiquine treatment but was normalized within two months this may be due to that their patients present under the effect of schistosomiasis infection, but in our investigation, there was no

infection and the laboratory animals present only under drug administration. So serum bilirubin was normalized after 2 weeks. Da silva, et al., (1975); pitchford, et al., (1978); pedro,et al., (1980) and Katz, (1980), they reported that Oxaminiquine is an efficacious agent with minimal toxicity.

On the other hand Madwar et al., (1980) recorded that Oxamniquine has no toxic side effect on liver functions tests.

Popper et al., (1976) stated that drugs might exert a direct toxic effect on biliary secretory apparatus normely canaliculi, canalicular membrane, Golgi appartus and mitochondria with the end result of cholestasis (obstructive jaundice).

In our present study, there was a significant elevation in serum bilirubin level at 24 hours and 2 weeks only after Oxaminiquine oral administration and this may be due that this drug interfer with bilirubin metabolism during any stage

Sherlock (1981), stated that drugs can affect bilirubin metabolism at any stage, in its production from heam., in it's transport in the blood, in it's uptake into the liver cells, in it's conjugation and in it's canalicular excretion.

While in the praziquantel treated group there was a non significant rise in serum bilirubin was detected at the different interval at 24 hours, 2 weeks and 4 weeks .

Our present results is inconsistent with the results obtained by katz et al., (1979) and Diallo et al., (1981), they found non significant increase in the total serum bilirubin one day post - treatment

Also Ali, (1984) and El-Shinnawy, (1985) in agreement with our results. Ambroise - Thomas & Goullier (1981); Nash et al., (1982) and Sidhom, (1985), they reported that no change in its serum levels following praziquanted administration .

On the other hand Davis et al., (1981) reported no significant decrease in serum bilirubin post - treatment with praziquantel .

But Katz et al., (1979) and Santos et al., (1979) reported an increase in serum bilirubin in some treated patients i.e Praziquantel did not affect at any of the different stages of the bilirubin metabolism.

Omer (1981) and Oyediran et al., (1981), They reported that, the absence of significant changes in Al. T & As.T and serum bilirubin suggested that the drug has no hepato toxic effect.

It's clear from this study that Oxamniquine have a direct effect on the bilirubin level, but praziquantel did not revealed any significant effect .

B- Effects of Oxaminiquine (Vansil) and Praziquantel (Biltricid) on kidney function tests :

1- SERUM UREA :

In the present work, our results showed that the urea level in the control group after 24 hours, 2 weeks and 4 weeks were, 26.53 ± 1.67, 29.52 ± 0.94 and 24.69±2.18mg/dl.

The results after oral administration with Oxamniquine were 28.77 ± 2.12, 28.30 ± 1.6 and 25.58 ± 2.22 mg/dl.at 24 hours, 2 weeks and 4 weeks.

While Praziquantel administration, at 24 hours, 2 weeks and 4 weeks showed a level of 27.96 ± 1.91, 30.07 ± 2.85 and 25.17 ± 1.8 mg /dl (Table, 11).

In this investigation a non significant increase in urea level was detected at 24 hours and 4 weeks, but there was a non significant decrease was detected only at 2 weeks.

This means that Oxamniquine administration did not cause a significant alteration from pre and post treatment in the level of serum urea (Fig, 11).

Our results are inconsistents with the finding obtained by Shafei, (1979) he reported that Oxamniquine has no effect on serum urea.

Also Sigmund, et al., (1983), reported that Oxamniquine has no effect on blood urea.

While, the results of serum urea which related to the Praziquantel treated group showed a non significant increase in urea level at the different time intervals 24 hours 2 week and 4 weeks.

From our results concerning blood urea, we concluded that praziquantel administration did not cause any significant alteration from pre- and post treatment in serum urea (Fig, 11).

This results is inagreement with Observation of Leopold et al., (1978), Ambrosise - Thomas & Goullier (1981) and Ali, (1984), they postulatedthat No significant changes in the level of serum urea.

2- SERUM GREATININE :

In the present study, our results related to serum creatinine level in the control group at 24 hours, 2 weeks and 4 weeks were, 0.71 ± 0.06, 0.76 ± 0.08 and 0.71 ± 0.07 mg/dl.

The results following Oxamniquine administration were 0.81 ± 0.09, 0.71 ± 0.07 and 0.81 ± 0.15 mg/dl at 24 hours 2 weeks and 4 weeks.while, the level in praziquantel treated group were 0.82 ± 0.05, 0.75 ± 0.06 and 0.75 ± 0.09 mg/dl at 24 hours, 2 weeks and 4 weeks (Table, 12).

Our results concerning the serum creatinine level showed a non significant increase were detected at 24 hours and 4 weeks.

But there was a non significant decrease was detected only at 2 weeks.

This indicated, that oxamniquine administration did not cause significant change from pre-and post treatment in the level of serum creatinine (Fig, 12).

Our results are inagreement with the finding obtained by Shafei, (1979) he recorded that Oxamniquine has no effect on serum creatinine.

Also Madwar, et al., (1980), they postulated that Oxamniquine has no toxic side effect on kidney function tests.

While the results of serum creatinine which related to the praziquantel treated group showed a non significant increase in creatinine level at 24 hours and 4 weeks, but showed a non significance decrease at 2 weeks (Fig, 12).

Our results are inconsistent with the finding of katz et al., (1979); Coutinho et al., (1983) and Sidhom, (1985), They stated that, No significant changes in serum creatinine level following praziquantel administration.

Also , El-Shinnawy, (1985) reported that, after Praziquantel administration, no significant change in serum creatinine.

SUMMARY

This study is carried out to investigated the biochemical changes in blood serum of rats orally administered with antibilharzial drugs represented by both Oxamniquine and praziquantel

Fivty four (54) albino rats were taken, divided into three main groups (each of 18 rats).

The first group was given saline only and kept as control.

The second group (Oxaminquine treated group) was orally administered with 42 mg / 200 gm b.w and this doses was divided into three successive days.

The third group (Praziquantel treated group was given orally a single dose of 42 mg/200 gm body weigh of rats.

The doses for rats were corresponded to the adult human dose extrapolated to rats by the method of pagets and Barnes (1964) for interspecies conversion scheme of the doses .

Blood sample from the experimental rats were collected after 24 hours, 2 weeks and 4 weeks (Six rats from each group were taken at the corresponding time intervals .)

The separated sera were analyzed for the measurment of liver and kindey effeciency tests.

The results obtained were statistically analysed and summarized in 12 tables and 12 graph revealing the following :-

1- Transaminases :

As a result of oxamniquine oral administration, glutamic oxal acetic transaminase and glutamic pyruvic transaminase showed a significant increase after 24 hours only .

The transaminases were normalized at 2 weeks and 4 weeks from the drug administration. But praziquantel had no revealed any significant alteration throughout 24 hours, 2 weeks or even 4 weeks.

2- Lactate dehydrogenase.

The average of lactate dehydrogenase activity in normal rats at 24 hours was (503.78 ± 24.49) i.u/l

Serum level of lactate dehydrogenase activity did not showed any significant change following oral antibilharzial drugs (Oxamniquine and Praziquantel medication.

3- Cholinesterase .

Serum cholinesterase activity in the control group at 24 hours was (1.42 ±0.011), but its level at the same time in both Oxammiquine and praziquantel treated groups were , (1.38±0.013) and (1.39 ±0.018) u/l.

Our data revealed that oral antibilharzial drugs represented by both Oxammiquine and praziquantel had no effect on cholinesterase activity at the different times intervals.

4- Ceruloplasmin .

the average level of ceruloplasmin activity in normal rats at 24 hours was (41.67 ± 4.17), while in both oxamniquine treated group and praziquantel treated group were (49.48 ± 6.17) and (46.88 ± 6.60) at 24 hours. There was no significant difference in ceruloplasmin level following Oxamniquine and Praziquantel administration through 24 hours, 2 weeks and 4 weeks.

5- Protein and their fractions

The results concerned the protein and their fractions in the normal rats(untreated ones) and post oral antibilharzial

drugs represented by Oxamniquine and Praziquantel administration to the second and third group, at the different time intervals, demonsterated that there was no any significant alteration in the protein contents , albumin, globulin following both drugs administration after 24 hours, 2 weeks or even 4 weeks .

6- Bilirubin

The average of bilirubin level in normal rats was (0.43 ± 0.05) at 24 hours .

A sharp rise in serum bilirubin concentration was observed reaching to (0.67 ± 0.07) after 24 hours from oxamniquine administration and this level showed a highly significant increase. followed by gradual decrease till 2 weeks and its level was 0.62 ± 0.09 and this level also showed significant rise.

Then gradual decrease in its concentration was observed at the end of experiment (4 week) and its normalized. But this work showed that praziquantel did not cause any significant change in the serum levels of bilirubin indicating

that it does affect bilirubin metabolism at different times intervals.

7- Serum urea .

The average of urea level in the normal rats was (26.53 ± 1.67) at 24 hours. while its level following oral antibilharzial drugs administration represented by oxamniquine and praziquantel were (28.77 ± 2.12) and (27.96 ± 1.91) at 24 hours also.

The urea level was witin the normal range before and after Oxamniquine and Praziquantel administration at the different time of experiment .

8- Serum Creatinine .

The means of serum creatinine level in normal control group at 24 hours was (0.71 ± 0.06), but its level at the same time (24 hours) following both Oxamniquine and Praziquantel administration to the second and third group were (0.81±0.09) and (0.82 ± 0.05). The serum creatinine level showed a non significant change post oral antibilharzial drugs administration, during the time of experiment, and this denoting that the absence of any injurious effect on the kidney.

" CONCLUSION "

From the obtained results we can realized that oxamniquine showed a significant increase in transaminases activities after 24 hours only from the drug administration and then normalized again.

At the same time, the drug have a significant rise in serum bilirubin level till 2 weeks, followed by gradual decrease and normalization at the end of experiment (4 weeks), and this means that this abnormalities had a transient elevation and short lived with relatively rapid correction toward normalization.

So we can recomended that this drug have a mild hepato side effect on liver functions, but this drug has no any side effect on kindney functions.

At the same times, our results suggested that praziquantel has no any side effect on liver functions, and also showed that, the drug did not affect on serum urea and creatinine indicating unaffection of both glomerular and tubular functions of the kindney and this means that praziquantel being easily applicable, safe and not affect the liver and kidney functions during using it's therapeutic dose

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ARABIC SUMMARY

" بسم الله الرحمن الرحيم "

ملخص الدراسة والاستنتاجات

========

" دراسة كيمائية حيوية عن تأثير أدوية البلهارسيا "
التى تعطى عن طريق الفم على وظائف الكبد والكلى
فى الفئران

تُعد البلهارسيا من أحد المشاكل التى يعانى منها الجنس البشرى • وفى مصر تعتبر البلهارسيا من أحد أهم المشكلات القومية ومن أكثر الامراض انتشارا ، وأهم المشاكل الصحية التى تسبب تدهور تدريجى للصحة وتقليل كفاءة قطاع كبير من المواطنين •

وبالرغم من التقدم الكبير الذى أحرز فى الفترة الأخيرة وذلك بالتوصل الى اكتشاف مركبات فعالة مضادة للبلهارسيا ، الا أنه قد تلاحظ فى كثير من الأحيان بأن بعض هذه الأدوية له من الآثار الجانبية مايترك المريض فى حالة اعياء شديد يفوق المرض نفسه ومن أهم الأدوية المتداولة لعلاج البلهارسيا فى السنوات الأخيرة نظرا لفاعليتها ولسهولة تعاطيها عن طريق الفم هما عقار الأوكسامينيكوين عقار البرازيكوانتيل •

ولقد أستهدف هذا البحث دراسة التغيرات الكيمائية الحيوية التى تحدث فى مصل الفئران الطبيعية نتيجة تجريعها عن طريق الفم بعقار الأوكسامينيكوين والبرازيكوانتيل وذلك بعد مرور أربعة وعشرون ساعة ، وأسبوعين وأربعة أسابيع من التجريح •

وقد أستخدم فى هذه الدراسة عدد أربعة وخمسون فأرا • وقسمت الى ثلاث مجموعات أساسية ومتساوية كل منها ثمانية عشرة فأرا •

١ ــ المجموعة الأولى :ــ حقنت بمحلول ملحى واستخدمت كمجموعة ضابطة •
٢ ــ المجموعة الثانية :ــ تم تجريعها بعقار الأوكسامينيكوين بجرعة قدرها ٤٢ ملليجرام /٢٠٠ جرام وزن حى ومقسمة هذه الجرعة على ثلاث أيام متتالية بواقع ١٤ جرام يوميا •

٣ ــ المجموعة الثالثـــة : ــ فقد جرعت بعقار البرازيكوانتيل بجرعة قدرها ٤٢ ملليجرام / ٢٠٠ جرام وزن حسى وذلك كدفعة واحـــدة ٠

أخذت عينات من الدم بعد مرور ٢٤ ساعة وأسبوعين وأربعة أسابيع من التجريـــح٠ وقد أخذت عدد ستة فئران من كل مجموعة خلال الثلاث فترات المختلفة للتحليل ٠

وقد تم تحليل مكونات مصل هذه العينات حيث التحليلات الأحصائية للنتائج مايلى :ــ

١ ــ خمائـــر الترانساميينز

حدث زيادة معنوية فى خمائر الترانساميينز والتى تشمل كل من خميرة الاوكسالاسيتيـك ترانساميينز ، والبيروفيك ترانساميينز وذلك بعد ٢٤ ساعة من اعطاء عقار الأوكساميتيكوين فقط وعادت الى مستواها الطبيعى بعد ذلك وحتى نهاية التجربة ٠ بينما لم يحـــدث أى تغيرات معنوية لنشاط هذه الخمائر نتيجة التجريح بعقار البرازيكوانتيل خلال فـــترات التجربة المختلفـــة ٠

٢ ــ خميرة لاكتيـك ديهيدروجنيز :ــ

كان المتوسط الحسابى لهذه الخميرة فى الفئران الطبيعية بعـد ٢٤ ساعة هـــو (٥٠٣ر٧٨ ± ٢٤ر٤٩) ٠

لم يلاحظ هناك أى تغيرات معنوية لهذه الخميرة نتيجة التجريح بالأدوية المضـــادة للبلهارسيا والتى تعطى عن طريق الفم والممثلة بالاوكساميتيكوين والبرازيكوانتيل وذلـــك خلال الفترات المختلفـــة ٠

٣ ــ خميرة الكولين أستيريـــز :

كان المتوسط الحسابى لهذه الخميرة فى الفئران الطبيعية هو (١ر٤٢ ± ٠ر١١) بينما كان المتوسط فى المجموعة المجرعة بعقار الأوكساميتيكوين هـــو (١ر٣٨ ± ٠ر١٣) وكان فى المجموعة المجرعة بعقار البرازيكوانتيل هـــو (١ر٣٩ ± ٠ر١٨) وذلك بعد مرور ٢٤ ساعة من التجريـــح٠

وقد أوضحت هذه النتائج بأن التجريع بالادوية المضادة للبلهارسيا والتي تعطى عن طريق الفم والممثلة بهذين العقارين ليس لها تأثير معنوى ملحوظ على نشاط هذه الخميره خلال فترات التجربة المختلفة .

٤ـ أنزيم السيرو بلازمين :

كان متوسط هذا الانزيم فى فئران المجموعة الضابطة هو (٤١ر٦٧ ± ٤ر١٧) ، بينما كانت نسبته فى كل من المجموعة المجرعة بعقار الاوكسا مينيكوين هو (٤٩ر٤٨ ± ٦ر١٧) وفى المجموعة المجرعة بعقار البرازيكوانتيل هو (٤٦ر٨٨ ± ٦ر٦٠) وذلك بعد مرور ٢٤ ساعة من التجريع .

ولم يتلاحظ لنا بأن هناك ذيادة معنوية فى نسبة هذا الانزيم عقب اعطاء هذين العقارين وذلك خلال الأوقات المختلفة للتجربة .

٥ـ البروتين الكلى وجزئياته المختلفة فى المصل :

أوضحت النتائج المتعلقة بنسبة البروتين الكلى وجزئياته المختلفة فى مصل الفئران الطبيعية وكذلك فئران المجموعتين الآخرتين والذى تم تجريعهما بعقار الأوكساميتيكوين والبرازيكوانتيل بأنه نتيجة التجريع بهذين العقارين لم يحدث أى تغيير معنوى فى نسبة البروتين ،الالبومين، ، والجلوبيولين وذلك خلال فترات التجربة المختلفة .

٦ـ البيللوروبين (صبغة الصفراء) :ـ

كان متوسط صبغة الصفراء فى الفئران الطبيعية هو (٤٣ر٠ ± ٠٥ر٠) وذلك عند ٢٤ ساعة .

حدث ارتفاع حاد ومعنوى فى تركيز هذه الصبغة بعد التجريع بعقار الأوكساميتيكوين بفترة ٢٤ ساعة حيث وصل متوسط معدل تركيز هذه الصبغة الى (٠٫٦٧ ± ٠٫٠٧) وبدأ معدل هذه الصبغة فى الانخفاض التدريجى حتى أسبوعين وكان معدله هو (٠٫٦٢ ± ٠٫٠٩) ومازال يشير بأن هناك زيادة معنوية ملحوظة ولكنها أقل من المعدل الملاحظ عند ٢٤ ساعة . بعد ذلك حدث انخفاض تدريجى فى تركيز الصفراء حتى وصلت الى مستواها الطبيعى عند نهاية التجربة (عند ٤ أسابيع) ولكن أوضحت هذه الدراسة بأن عقار البرازيكوانتيل لم يحدث أى تغيير معنوى ملحوظ فى معدل تركيز هذه الصبغة خلال فترات التجربة المختلفة .

٧ ــ نسبة البولينا فى المصل :

كان المتوسط الحسابى لنسبة البولينا فى مصل الفئران الطبيعية هو (٢٦٫٥٣±١٫٦٧) بينما كان المتوسط بعد مرور ٢٤ ساعة من التجريع بعقار الاوكساميتيكوين وكذلك البرازيكوانتيل على التوالى هو (٢٨٫٧٧ ± ٢٫١٢) و (٢٧٫٩٦ ± ١٫٩١) . وقد أوضحت النتائج بأن معدل البولينا كان فى مستواه الطبيعى قبل وبعد التجريع بالعقارين المختلفين ولم يتلاحظ هناك أى تغيير معنوى خلال فترات التجربة المختلفة .

٨ــ نسبة الكرياتينيين فى المصل :

كان متوسط الكرياتينيين فى فئران المجموعة الضابطة هو (٠٫٧١ ± ٠٫٠٦) بينما كان معدله بعد التجريع بعقار الاوكساميتيكوين والبرازيكوانيل وذلك بعد مرور ٢٤ ساعة من اعطاء الأدوية هو (٠٫٨١ ± ٠٫٠٩)، (٠٫٨٢ ± ٠٫٠٥) . لم يحدث أى تغيير معنوى فى معدل الكرياتينيين وذلك بعد التجريع بهذين العقارين خلال فترات التجربة . مما يشير بأنه ليس هناك أى آثار جانبية ضارة لهذه الادوية على وظائف الكليـــة .

*** الخلاصـــــــــــــــة ***

مما سبق يتضح لنا أن عقار الأوكساميتيكويـن أحدث زيـادة معنوية فى نشـاط خمائـر الترانساميتيز وذلـك بعد مرور ٢٤ ساعة فقط من اعطاؤه ، ثم انتظم معدل هذه الخمائـر بعد ذلك وعادت لمستواها الطبيعـــى .

فى نفس الوقت أحدث الدواء زيادة معنوية ملحوظة فى تركيز صبغة الصفـــراء (البيللـوروبـــين) وذلـك لمدة أسبوعـين فقط من تجريع الدواء متبوعا بنقـص تدريجـى حتى أنتظم معدله فى نهايـة التجربـة .

هذا يعنى أن الارتفاع فى نسبة تركـيز البيللوروبين نتيجة استعمال هذا الـدواء ما هو الا ارتفاع وقتى وقصير المـدى وسرعـان ما ينتظـم ويعود لمستواه الطبيعـى خلال فترة زمنيـة محـدودة وقبل نهاية التجربة التى أستمرت أربعـة أسابيـع .

من هنا يتضح لنا أن هـذا العقـار له آثار جانبيـة بسيطـة ووقتيـة علـى بعـض وظائف الكبد وفى نفس الوقت تلاحظ لنا أنه ليس له آثار جانبية ضـارة على وظائـف الكلـــى .

أما بخصـوص عقـار البرازيكـوانتيـل فقد اوضحـت نتائج هذه الدراسة بـأن هذا العقار ليس له أى آثار جانبيـة ضارة سواء على وظائف الكبـــد أو وظائـف الكلـى وذلـك اذا أستعمـل بالجرعـات الدوائيـــة المطبيـة .

* * * * *

دراسة كيميائية حيوية عن تأثير ادوية البلهارسيا التى تعطى عن طريق الفم على وظائف الكبد والكلى فى الفئران

رسالة مقدمة من

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جامعة القاهرة (١٩٨١)

للحصول على

درجة الماجستير فى العلوم الطبيه البيطرية
" تخصص كيمياء حيوية **واكلينيكية**

مقدمة الى

كلية الطب البيطرى
جامعة الاسكندرية

١٩٩٠

تحت اشراف

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