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EFFECT OF OXAMNIQUINE ON LIVER, SPLEEN, KIDNEY AND BLADDER B-GLUCURONIDASE IN NORMAL AND *SCHISTOSOMA MANSONI* INFECTED MICE

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Abstract—Oxamniquine therapy was accompanied by an elevation in B-glucuronidase enzyme activity in liver, spleen, kidney and bladder tissue homogenates of both controls and *S. mansoni* infected mice. This increase in enzyme activity is characterized by the observations that: (a) in control animals the effect on liver and bladder was more prolonged than that on spleen and kidney; (b) the effect of oxamniquine on liver B-glucuronidase was more prolonged than infection itself while the effect of infection was more evident; and (c) the effect of oxamniquine is much more pronounced in infected mice than in either treated or infected controls.

Oxamniquine (6-hydroxymethyl-2-isopropylamino-methyl-7-nitro1,2,3,4-tetrahydroquinoline) is a promising single-dose agent for the treatment of *Schistosoma mansoni* infection in man [1]. It is more effective than hycanthone, lucanthone and niridazole [2]. It is well tolerated and the only side-effect recorded was dizziness which was reduced by giving the drug after meals or before sleep [3].

The effect of oxamniquine on B-glucuronidase activity is important because indications have been obtained to suggest a link between an increased urinary excretion of the enzyme B-glucuronidase and the development of cancer of the bladder [4,5]. An increased B-glucuronidase activity has been reported in the urine of bilharzial patients [6–9], as well as in the whole tissue homogenate of liver and spleen of *S. mansoni* infected mice [10]. The origin of the increased enzyme activity in urine of bilharzial patients has not been definitely clarified. The blood and albumin usually present in the urine of the bilharzial bladder were blamed for the potentiation of the activity of the enzyme [11]. The increase in the amount of the enzyme was also attributed to its release from the excessive destruction of leucocytes usually increased in the urine of these patients [11]. Fripp [12] proposed the hypothesis that the increase of enzymatic activity in urine was due to cellular disintegration of the bladder mucosa. He found that the mucosal cells contained large amounts of B-glucuronidase enzyme. It was also speculated that rupture of the mucosal cells which have been damaged by the passage of the ova and shed in the urine was the cause of the increased enzyme activity [12]. The schistosomicidal drugs are one of the important factors which could not be ignored as affecting B-glucuronidase activity. It was found that B-glucuronidase enzyme increased in the urine of bilharzial patients following treatment with tartar emetic [13].

MATERIALS AND METHODS

Swiss albino mice, age 2 months, weight 15 g, were divided into four groups: Group 1, in which animals were neither treated nor infected, served as controls; Group II served to study the effect of the schistosomicidal drug on uninfected animals; Group III served to study the effect of *S. mansoni* infection on B-glucuronidase and Group IV served to study the effect of the drug on B-glucuronidase in *S. mansoni* infected animals. Mice in Groups III and IV were infected by the paddling technique [14] with 100 cercariae. Fifty days from infection, oxamniquine was given in a single oral dose (50 mg/kg) to animals of Groups II and IV. Mice were then killed at 10, 40 and 70 days from treatment, i.e. 60, 90 and 120 days from infection, respectively. Autopsies were performed on between 7 and 13 mice from each group on each occasion, and liver, spleen, kidney and bladder were quickly removed for B-glucuronidase determination. Preparation of homogenates and determination of enzyme activity were carried out as previously reported [10].

Activity on B-glucuronidase was expressed in Fishman units. One unit liberates 1 μg phenolphthalien per hr at 37° [15]. Statistical analyses were made to compare the values obtained from each group with the corresponding values of controls, using the standard t-test [16]. A difference with probability value of less than 0.05 was considered significant.

RESULTS

The effect of oxamniquine on liver, spleen, kidney and bladder B-glucuronidase in both controls and *S. mansoni* infected animals was illustrated in Table 1. In control mice, B-glucuronidase significantly increased in all organs after oxamniquine adminis-

Table 1. Effect of oxamniquine on B-glucuronidase activity in whole tissue homogenates of liver, spleen, kidney and bladder of the different groups of mice by duration of infection and treatment

Group	No. of Mice	Mean values (± S.E.) of B-glucuronidase activity in Fishman units in Liver	Spleen	Kidney	Bladder
Controls					
60 days from infection	(7)	1429 (101)	3028 (171)	833 (87)	871 (97)
90 days from infection	(9)	2448 (43)	3837 (335)	1406 (170)	1140 (121)
120 days from infection	(8)	2969 (106)	4216 (264)	1305 (90)	990 (91)
Controls treated					
10 days from treatment	(7)	2835* (198)	4561* (167)	1510* (116)	1168* (120)
40 days from treatment	(9)	3600* (290)	5041* (314)	1738 (143)	1464 (174)
70 days from treatment	(11)	3546* (194)	4773 (409)	1297 (67)	1567* (113)
Infected mice					
60 days from infection	(10)	4260* (356)	5583* (506)	1383* (99)	2238* (208)
90 days from infection	(13)	3797* (167)	4836* (242)	1442 (190)	1246 (92)
120 days from infection	(7)	2917 (316)	4709 (179)	1462 (146)	1529* (178)
Infected treated mice					
10 days from treatment	(10)	4906* (544)	6719* (749)	1635* (120)	2667* (418)
40 days from treatment	(9)	3420* (287)	4643 (468)	1291 (52)	1250 (132)
70 days from treatment	(9)	4473* (376)	5382* (274)	1713* (158)	1597* (83)

* Difference from the corresponding control value statistically significant.

tration. This increase reached its maximum after 40 days from treatment (Table 1, Group II), then it decreased to normal levels in spleen and kidney after 70 days from oxamniquine administration, while significantly increased values for enzyme activities were observed in liver and bladder (3546 and 1567 units, compared with 2969 and 990 units for controls).

Schistosoma mansoni infection was accompanied by a significant increase in B-glucuronidase activity which decreased gradually until normal enzyme activity levels were obtained in liver, spleen and kidney after 120 days from infection.

A pronounced effect of oxamniquine in infected animals was also obtained. A maximum significant increase in B-glucuronidase activities was observed in all organs and from the 10th day of treatment. After 40 days the enzyme activities decreased to normal levels in all organs except in the liver (3420 units compared with 2448 units in controls). After 70 days from treatment, a significant rise in enzyme activity was again observed in all organs.

DISCUSSION

The effect of oxamniquine on liver and bladder B-glucuronidase activity was more prolonged than that on spleen and kidney (Group II). This was indicated by the enzyme activity levels achieved in the two latter organs 70 days after treatment (4773 and 1297) and which were statistically identical to the control values (4216 and 1305). Moreover, results of this study indicate that the effect of oxamniquine on liver B-glucuronidase is more prolonged than the infection itself, while the effect of infection is more evident than the effect of drug. In other words, although high enzyme activity levels (mean value of 4260 units) of liver B-glucuronidase had been observed in infected animals 10 days from treatment, it decreased to control levels at the end of this study (Group III), while the increase in liver enzyme activity observed in controls treated with oxamniquine (mean value of 2835 units) did not decrease to the control levels after that (Group II).

The effect of oxamniquine is much more pronounced in infected animals. The increase in the enzyme activity is higher than that observed in treated controls of *S. mansoni* infected animals. This increase in enzyme activity was observed in all organs and even after 70 days from treatment. This may be due to the combined effect of both infection and drug chemotherapy in increasing this enzyme activity.

The increase in the enzyme activity either by infection or treatment may be attributed to the biochemical and metabolic disturbances of the parenchymal cells [17]. Moreover, electron microscopic studies in murine hepatosplenic bilharziasis have shown an increase in the number of lysosomes in the parenchymal cells [18], which in turn increases the lysosomal enzyme B-glucuronidase [19,20]. The increased B-glucuronidase activity in the liver may as well be due to the intense cellular infiltration taking place with granuloma formation 6 weeks after infection [21].

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