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Mode of Action of CIBA 32644-Ba in Experimental Schistosomiasis

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1. Introduction

There are many problems involved in evaluating the efficacy of anti-schistosomal drugs. Immunological reactions, to give just one example, differ considerably from one animal species to the other. Consequently, what is true of animal experiments does not necessarily hold good for the clinical application of the drug. This study was therefore undertaken in order to investigate the alterations that take place in the worm under the influence of the new compound, CIBA 32644-Ba (LAMBERT et al.).

2. Method

We fixed the schistosomes in Carnoy's solution, using the method described by VOGEL (1941); paired worms were separated. Schistosomes must be fixed very soon after collection, because morphological alteration may occur if they are kept for too long in physiological solutions, such as Thyrode's or Hank's. The livers of all the infected and treated animals were perfused at relatively high pressure in accordance with YOLLES' method and then fixed in Carnoy's solution, embedded in paraffin using the butanol method and sectioned at 7 μ. The fixed worms were stained with alum-carmine or Giemsa's stain and mounted whole in Eukitt[1]. The length of the worms was measured by projecting them through the microscope with a drawing mirror on to white paper. It was then an easy matter to run along the centre-line of the screened worm with an opisiometer, calibrated against a stage-micrometer

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[1] Eukitt is a neutral resin for microscopic slides which does not alter Giemsa's stain and hardens quickly.

having exactly the same optical combination. The ovaries of all female worms were drawn on paper of the same thickness. The shape of the ovaries was then cut out, and the piece of paper weighed. In this way we were able to determine the size of the ovary.

For the purpose of statistical analysis, the average lengths of both male and female worms, the average size of the ovary in the females, and the statistical error were calculated. To compare the mean values of the different measurements STUDENT's t-Test was used. The 5% probability level was taken as the limit of significance. Results with t-values below this level are referred to in this paper as non-significant, and those above it as significant.

3. Morphological and histological changes in the worm

Following doses of 10 mg/kg daily for 10 consecutive days, the first alterations in the female genital organs can be seen. Signs of destruction appear in the distal portion of the vitellogenic gland, which normally extends from the ovary to the end of the worm. Here the vitelline cells are destroyed. Histological sections of this portion reveal vitelline cells completely depleted of egg-shell substance. A dosage of 10 × 20 mg/kg causes complete arrest of shell formation in the ootype. At this dosage level, no normal eggs can be seen in *S. mansoni* females. After a dosage of 10 × 50 mg/kg, no eggs at all can be found, even in the uterus of *S. japonicum,* which normally contains 100-200 eggs. These findings are quite different from VOGEL's and MINNING's observations with trivalent antimony compounds in experimental *S. japonicum* infections where the uterus always contains a few eggs, even at dose-levels that are almost 100% active. In most female worms, doses of 10 × 50 mg/kg cause complete destruction of the vitellogenic gland and the worms are "emptied". The motility of these females seems to be quite normal after they have been expelled from the liver by perfusion.

The destruction of the vitellogenic gland in the female coincides with a reduction in body-length in both male and female worms and in the size of the ovary in the female. Comparison with the control worms shows that this reduction is already significant following doses of 10 × 10 mg/kg. At low dosage-levels, i.e. 10 × 10, 10 × 20 and 10 × 50 mg, hepatic shift is not observed in all worms. We therefore distinguished between "peripheral" worms, which were still found in the mesenteric vessels one day after the last treatment, and "liver" worms. Upon comparison of the average measurements of

the "peripheral" groups with those of the controls, significant differences were found between worms exposed to the drug and the worms in the control animals. This fact shows that a drug may be active against schistosomes without inducing a hepatic shift. Hence, we believe that screening methods based solely on the hepatic shift one day after the last treatment, are not always reliable tests as regards the evaluation of potential new drugs for schistosomiasis.

Male worms seem to be less sensitive to CIBA 32644-Ba. Alterations first became evident following doses of 10 × 50 mg/kg. In the testes, spermatogenesis is stopped; the spermatocytes are vacuolated, and the nucleus increases in size. After doses of 10 × 100 mg, the cell structure in the testes is completely destroyed and the contents form a granulated basophilic mass.

4. Tissue reactions in the host

In the experimental host, such as the mouse or the hamster, tissue reactions to damaged worms vary considerably according to the sex of the schistosomes. The living worms are first blocked in the liver by an embolus of leucocytes, which surrounds the anterior part of the live worms. This embolus formation is responsible for the focal necrosis seen in the liver of infected and treated laboratory animals. Later on, the female is penetrated by the leucocytes and undergoes disintegration before the male. Histological sections of the liver show more or less normal, live, male worms, which still copulate with completely necrotic females. The following table illustrates the higher sensitivity of females to CIBA 32644-Ba. Experimental treatment in mice infected with *S. mansoni* and in those infected with *S. japonicum* was started at the same time. The mice were divided at random into different groups and treated for

Infected with	S. mansoni				S. japonicum			
Dose (level) mg/kg day	Total worm count	%	♀♀	%	Total worm count	%	♀♀	%
Control	20.5	100	10.25	100	50.5	100	26.0	100
10 × 50 mg/kg	19.5	95	9.5	92.5	21.0	42	8.0	30.8
10 × 100 mg/kg	3.0	14.5	1.0	9.8	4.0	8	0.4	1.5
Beginning of treatment	46 days after infection				55 days after infection			

Mean values of worm count in treated mice one day after the last treatment

10 consecutive days. At each dosage-level 12 mice were used in studies on *S. mansoni* and 10 in studies on *S. japonicum*.

Contrary to the female, the male worm provokes no inflammatory reaction, but is fixed by connective tissue which penetrates its body. The reaction of the surrounding host tissue to the male schistosome strongly resembles the tissue reaction to a foreign body with no immunogenic properties. At a later stage of disintegration only a few leucocytes can be found in the body of the male, which becomes autolysed after a time and can still be found in liver-sections taken from mice 42 days after the completely effective treatment.

Summary

In experimental schistosomiasis treated with CIBA 32644-Ba, the following observations were made:

1. Doses of as little as 10 mg/kg daily for 10 days caused a significant reduction in the length of worms of both sexes.
2. The size of the ovary also diminishes in response to treatment.
3. The reduction in the worm-length and in the size of the ovary shows a clear-cut dose-effect relationship.
4. The organ of the parasite most affected by treatment is the vitellogenic gland.
5. Female worms are more sensitive to treatment than males.
6. The changes seen in the worms are not necessarily related to their hepatic shift.
7. The damaged females are destroyed in the liver by leucocyte infiltration.
8. The damaged males are immobilised in the liver by a connective-tissue reaction.
9. In the mouse, CIBA 32644-Ba is equally effective against *S. mansoni* and *S. japonicum*.

Résumé

Sous l'action du CIBA 32644-Ba dans la schistosomiase expérimentale, les altérations suivantes ont été observées chez le parasite :

1. Des doses de 10 mg/kg/jour pendant 10 jours ont déjà montré un raccourcissement des vers des 2 sexes.
2. La grandeur de l'ovaire est également diminuée sous l'influence du traitement.
3. La relation dose/activité peut être démontrée par la diminution de grandeur des parasites et de l'ovaire.
4. L'organe le plus sensible au traitement est la glande vitellogène du parasite.
5. Les femelles sont plus sensibles au traitement que les mâles.
6. Les altérations observées chez le parasite ne sont pas nécessairement en relation avec leur migration hépatique.

7. Les femelles altérées succombent, dans le foie, à une infiltration leucocytaire.
8. Les mâles altérés sont immobilisés dans le foie par une réaction du tissu conjonctif.
9. Chez la souris, l'activité du CIBA 32644-Ba est égale pour *S. mansoni* et *S. japonicum*.

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