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TRYPANOCIDAL ACTION OF *p*-BIGUANIDOACETOPHENONE AMIDINOHYDRAZONE

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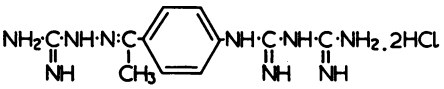
p-Biguanidoacetophenone amidinohydrazone, given in single doses, can cure mice infected with an old laboratory strain of *Trypanosoma rhodesiense*, but it has only slight action on more recently isolated strains. Trypanosomes which are resistant to stilbamidine are resistant to this compound also. Apparently its trypanocidal action is similar to that of the diamidine series of trypanocidal compounds.

This paper describes the trypanocidal action of *p*-biguanidoacetophenone amidinohydrazone dihydrochloride (Ciba 23889 Ba) upon various normal and drug-resistant strains of trypanosomes in mice.



This is a compound which has been investigated by Goble (1962) as a possible cure for trypanosomiasis. The present experiments were made to investigate its probable value for human therapy and its relations to other trypanocidal compounds. According to the report by the manufacturers (Ciba, Basle), the compound is soluble in water to 5% w/v ; doses of 25 mg/kg intraperitoneally or of 250 mg/kg by mouth given on 4 successive days cured mice infected with a laboratory strain of *Trypanosoma rhodesiense* and single doses of these amounts cured mice infected with *T. gambiense* ; the compound is less active against *T. congolense* and inactive against *T. cruzi* ; the LD50 dose for mice is 30 mg/kg intravenously, 125 mg/kg intraperitoneally and 1,500 mg/kg by mouth.

METHODS

In the present experiments all doses were given as single intraperitoneal injections. Mice were treated when the infection was still light (for example, 1 trypanosome per 10 microscopic fields in a coverslip preparation of blood). The results are expressed as the minimum effective dose, that is, the minimum dose required to clear the blood temporarily of trypanosomes in at least 80% of the mice. The maximum tolerated intraperitoneal dose was approximately 50 mg/kg. The results are shown in Table 1.

In other experiments trypanosomes (*T. rhodesiense*, Liverpool and 118 strains) were exposed *in vivo* to doses of 25 to 50 mg/kg and after 5 hr they were subinoculated into fresh mice. The mice became infected at the expected time and there was no evidence that the trypano-

TABLE 1

TRYPANOCIDAL ACTION OF CIBA 23889 Ba IN MICE

Strain	M.E.D. mg/kg	Remarks
T. rhodesiense (Liverpool), old laboratory strain	5	25 mg/kg cured 4/7 mice 50 mg/kg cured 2/2 mice
T. rhodesiense (Liverpool), stilbamidine-fast variety	No action	Trypanosomes specifically resistant
T. rhodesiense EATRO 118, polymorphic strain, 3 years old	25 (Action slow and uncertain)	After 100 mg/kg 2/2 mice relapsed in 10–15 days
T. rhodesiense EATRO 118, tryparsamide-fast variety	25–50	Sensitivity similar to that of normal 118 strain
T. rhodesiense EATRO 133 (freshly isolated melarsoprol-resistant strain from Jovani)	25	The infection develops slowly in mice. Mice were treated when infections were very slight. Even after 50 and 100 mg/kg the trypanosomes soon reappeared. There was no special drug-resistance in this case, but therapeutic effect was only slight
T. congolense (N.I.M.R.), old laboratory strain	50	Action slow and delayed
T. congolense—quinapyramine-fast variety derived from the above	50–100	The action is similar to that on the corresponding normal strain

somes had lost infectivity from exposure to the drug (as happens with quinapyramine, homidium or suramin). Consequently the drug differs from these compounds, and resembles the arsenical and diamidine groups of trypanocides in this respect.

DISCUSSION

From these results it is concluded that Ciba 23889 can cure infections of an old laboratory strain of *T. rhodesiense* but that its action on more recently isolated strains, e.g. 118 and 133, is slight. Accordingly its action in man naturally infected with *T. rhodesiense* would probably be unsatisfactory. The compound had little action on a laboratory strain of *T. congolense* (confirming the manufacturer's report). It acted as well as would be expected on substrains which were resistant to tryparsamide, to melarsoprol, and to quinapyramine respectively, but the stilbamidine-fast strain was fully resistant to it. This resistance is to be expected as Ciba 23889 contains terminal guanidino-groups, a structure resembling that of stilbamidine with its terminal amidino-groups. In fact the compound resembles in structure several of the biguanide compounds described by Jensch (1958) in his account of the chemical studies which led to the production of Berenil. The failure to destroy infectivity of trypanosomes (as described above) is consonant with the compound belonging to the diamidine group of trypanocides.

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