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Difference of effective antitrypanosomal dosages of benznidazole in mice and man. Chemotherapeutic and pharmacokinetic results

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In cultures of KB cells infected with either cultures or mouse blood containing large numbers of infective trypomastigotes of *Trypanosoma cruzi* (strain Y), numerous intracellular amastigotes and metacyclic trypomastigotes developed within 4–5 days. Concentrations of 0.4–0.8 μg/ml of benznidazole inhibited the growth of the parasite, whereas 3–6 μg/ml were needed for killing both intracellular amastigotes and extracellular trypomastigotes within 4 days.

In patients suffering from parasitologically proven acute or chronic Chagas' disease, high parasitological cure rates (~80%) were achieved in Argentina (Barclay et al., 1976) and Brazil (Coura et al., 1978), with daily doses of 5–7 mg/kg of benznidazole given for one month. Parasitological cure was established by repeated negative xenodiagnosis and, especially in acute cases, by a drop of the titres in 3 representative serological tests (haemagglutination, immunofluorescence and complement fixation tests) (Cerisola, 1977).

Pharmacokinetic evaluation of plasma obtained from 8 patients treated with daily doses of 7 mg/kg of benznidazole was carried out using differential pulse polarography (Raaflaub and Ziegler, 1979) on days 10, 15, 20 and 25 of the four-week treatment (the respective results are compiled in Table 1). Average elimination half-life of benznidazole was 13.75 h. The highest individual steady-state level of benznidazole measured was 16.4 μg/ml, and the lowest 5.4 μg/ml. Thus, the plasma benznidazole level of these patients was permanently above the minimal trypanosomicidal concentration of 3–6 μg/ml as found in tissue cultures.

In contrast, in experimental acute Chagas' disease in mice, daily doses of 10 mg/kg of benznidazole had no favourable effect on the lethal course of the infection. However, as can be seen from Table 2, by increasing the daily dose of benznidazole to 100 mg/kg, parasitological cure was achieved in 20 to 25% of

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Table 1. Steady-state maxima and minima of benznidazole in the blood plasma of 8 patients measured during a four-week treatment course with Radanil® (μg/ml)*

Patient	*Jos. Sil.*	*Lea. Cor.*	*Jos. San.*	*Luc. Her.*	*Joa. Oli.*	*Exp. Mor.*	*Joa. Mol.*	*Mar. Mor.*
Sex, age (y), body weight (kg)	♂, 32, 58	♀, 40, 39	♂, 44, 43	♀, 52, 55	♀, 60, 50	♂, 32, 63	♂, 35, 57	♀, 32, 60
Dose (mg/kg)	3.45	3.85	3.50	3.64	3.47	3.18	3.48	3.34
Dose interval (h)	12	12	12	12	12	12	12	12
Steady-state maxima $C^{s.s.}_{t\text{-}3h.}$								
10th day	15.1	9.9	9.1	12.8	11.0	12.3	16.4	14.2
15th day	14.3	10.6	9.8	12.3	12.4	10.7	14.6	(7.6)
20th day	14.2	11.7	9.6	13.2	12.4	11.2	13.6	13.8
25th day	13.1	11.6	8.1	14.0	12.2	9.0	11.7	15.8
average	14.18	10.95	9.15	13.08	12.00	10.80	14.08	14.60
Steady-state minima $C^{s.s.}_{t\text{-}0h.}$								
10th day	11.2	5.9	5.4	8.8	7.4	7.8	11.3	9.2
15th day	–	7.2	6.2	8.9	–	–	–	–
20th day	10.7	7.1	6.2	9.1	7.0	7.4	9.2	–
25th day	10.6	7.2	5.5	9.0	6.9	6.2	7.9	10.8
30th day	10.3	7.8	6.3	8.2	7.7	7.2	9.1	11.3
average	10.70	7.04	5.92	8.80	7.25	7.15	9.38	10.43

* J. Raaflaub, unpublished results

Table 2. Comparison of cure rate in mice infected with *Trypanosoma cruzi** after treatment with benznidazole (Ro 7-1051)

Daily dose mg/kg p.o. (on 5 days per week)	Period of treatment (weeks)	Number of animals per group	Animals surviving 1, 3 or 6 weeks after end of treatment (as a rule microscopically free of trypanosomes)	Animals parasitologically cured (blood cultures 1, 3 or 6 weeks after end of treatment negative)
30	6	24	19	0
50	8	10	9	2
100	4	35	20	5
100	6	24	23	21
100	8	35	30	20
200	2	20	19	2
200	4	35	32	29
200	8	20	20	20
Controls (untreated)	–	32	0	0

* Strains Y and CL were used in these trials.
Intraperitoneal infection with approximately 10^5 trypomastigotes contained in 0.2 ml of citrated mouse blood.

Table 3. Blood level (μg/ml) of benznidazole (Ro 7-1051) in plasma of mice after one single oral dose

Dose 1 × mg/kg p.o.	Hours after treatment									
	½	1	2	3	4	6	8	9	12	24
10*	2.2	1.8	0.68	0.4	0.165	–	–	–	–	–
100*	9.5	8.2	7.8	4.5	3.8	3.4	1.55	–	0.32	–
100**	10.5	9.7	7.6	6.1	4.7	3.3	1.5	–	–	–

Pools of citrated plasma of 6 mice were used for each determination.

* measured in conventional mice

** measured in specifically pathogen-free mice

– not measurable or not done

the mice after 4 weeks of treatment. By extending the period of treatment to 6–8 weeks with 100 mg/kg/day of benznidazole, about the same high rate of parasitological cure (70–100%) was achieved as that experienced in human Chagas' disease with daily doses of 5–7 mg/kg administered for one month.

Pharmacokinetic evaluation of plasma of mice treated with daily doses of 10 mg and 100 mg/kg of benznidazole explained the higher dosage needed for parasitological cure in mice. From the results compiled in Table 3 it can be seen that the highest benznidazole concentration measured in plasma of mice treated with a single oral dose of 10 mg/kg was only 2.2 μg/ml, which is below the 3–6 μg/ml needed for a trypanosomicidal effect. On the other hand, after a single oral dose of 100 mg/kg, maximum benznidazole plasma levels of 9.5–10.5 μg/ml were measured. This concentration was within the range of the benznidazole plasma levels found in humans during successful treatment with 7 mg/kg daily doses. Furthermore, it was found that the benznidazole plasma levels of mice receiving 100 mg/kg fell below trypanosomicidal values within a few hours as the elimination half-life was only 0.9 hour.

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