

# Difference of effective antitrypanosomal dosages of benznidazole in mice and man : chemotherapeutic and pharmacokinetic results

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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  $\mu\text{g/ml}$  of benznidazole inhibited the growth of the parasite, whereas 3–6  $\mu\text{g/ml}$  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 ( $\sim 80\%$ ) 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  $\mu\text{g/ml}$ , and the lowest 5.4  $\mu\text{g/ml}$ . Thus, the plasma benznidazole level of these patients was permanently above the minimal trypanosomicidal concentration of 3–6  $\mu\text{g/ml}$  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® ( $\mu\text{g/ml}$ )\*

| 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        |
| <i>Steady-state maxima</i> $C_{t-3h}^{S.S.}$ |           |           |           |           |           |           |           |           |
| 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     |
| <i>Steady-state minima</i> $C_{t-0h}^{S.S.}$ |           |           |           |           |           |           |           |           |
| 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<br>mg/kg p.o.<br>(on 5 days per week) | Period of<br>treatment<br>(weeks) | Number of<br>animals<br>per group | Animals surviving<br>1, 3 or 6 weeks<br>after end of treatment<br>(as a rule microscop-<br>ically free of<br>trypanosomes) | Animals parasitologically<br>cured (blood cultures<br>1, 3 or 6 weeks after<br>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 ( $\mu\text{g/ml}$ ) of benznidazole (Ro 7-1051) in plasma of mice after one single oral dose

| Dose<br>$1 \times \text{mg/kg p.o.}$ | Hours after treatment |      |     |      |     |       |      |   |      |    |
|--------------------------------------|-----------------------|------|-----|------|-----|-------|------|---|------|----|
|                                      | $\frac{1}{2}$         | 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   | 1.55 | — | 0.32 | —  |
| 100**                                | .....                 | 10.5 | 9.7 | 7.6  | 6.1 | 4.7   | 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.

Barclay C. A., Cerisola J. A., Lugones H., Ledesma O., López Silva J., Mouzo G., Sierra J. P.: Resultados de la actividad anti-*T. cruzi* del benznidazol en el hombre. VI. Congreso Latinoamericano de Farmacología, Buenos Aires, 2.–9. 12. 1976.

Coura J. R., Brindeiro P. J., Ferreira I.: Benznidazole in the treatment of Chagas' disease. In: Siegenthaler W., Luethy R. (eds.): Current chemotherapy. Proceedings of the 10th Int. Congr. of Chemotherapy, Zurich, Switzerland, 18–23 September 1977, Vol. 1, p. 161–162. Amer. Soc. Microbiol., Washington, D.C. 1978.

Cerisola J. A.: Chemotherapy of Chagas' infection in man. PAHO 347, 35–47 (1977).

Raaflaub J., Ziegler W.: Single-dose pharmacokinetics of the trypanosomicide benznidazole in man. Arzneimittel-Forsch. (Drug Res.) 29, 1611–1614 (1979)