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Assessment of 35972 RP (Oltipraz) a new antischistosomal drug against *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma intercalatum*

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In this paper we report the first therapeutic results we obtained with 35972 RP in the studies supervised by the Parasitology and Tropical Medicine Department of the “Hôpital Pitié-Salpêtrière”.

The studies included 321 cases with a positive parasitological stool or urine examination or a positive rectal mucosa biopsy. All the patients were followed-up to one month or more after the day of drug intake. They were divided as follows:

Mali (rural area)

116 *Schistosoma haematobium* cases were studied in 4 different villages in the Dogon region: Koyo (28 cases), Yuna (19 cases), Tupéré (22 cases) and Nakara (47 cases). Two dosages were prescribed: 15 and 25 mg/kg/day for 2 days, respectively.

The tolerance supervision was based upon the patient's report during the treatment period. A urine parasitological examination was performed as an efficiency check-up between day 65 and day 74 post treatment. (The sediment was examined after two centrifugations.)

Gaboon

72 *Schistosoma intercalatum* cases were studied in two different places (28 cases in Donguila and 44 cases in Libreville). The doses were related to the patient's age and weight:

- in the adult: 4.50 g divided in 1.50 g/day for 3 days three times a day,
- in the adolescent (15–18 years old): 4.50 g or 3 g according to the patient's weight,

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- in the child: half the adult dose below 12 years old and a quarter of the same dose below 8 years old. The tolerance supervision was based upon the patient's reports during the treatment period. A parasitological stool examination was done as an efficiency check up (it included: a direct examination and a MIF [merthiolade, iodine, formol] coloration and concentration method which were systematically realized for each patient).

The controls have been performed as follows:

- between D.30 and D.40: 20 cases
- between D.45 and D.60: 39 cases
- between D.60 and D.90: 12 cases
- beyond D.120: 1 case

Paris

133 cases were studied (47 patients were suffering from a *Schistosoma mansoni* schistosomiasis and 86 had a *Schistosoma haematobium* schistosomiasis). Five different dosages were used:

- group a: 5 g over 5 days once a day (19 cases)
- group b: 7.50 g over 5 days twice a day (26 cases)
- group c: 4.50 g over 3 days three times a day (54 cases)
- group d: 3 g over 2 days twice a day (25 cases)
- group e: 2 g in a single day twice a day (9 cases)

The tolerance supervision was based upon the patient's reports during the treatment period. The efficiency check ups were realized as follows:

D.0: (before treatment) hemogram, SMAC¹, parasitological urine examination (PUE), parasitological stool examination (PSE), rectal mucosa biopsy (RMB)², serology

D.1, 2 or 3: hemogram, SMAC, schistosomal serology

D.30: hemogram, PUE or PSE, serology

D.60: hemogram, PUE or PSE, serology

D.90: hemogram, PUE or PSE, RMB, serology

The PSE included: a direct examination and a MIF coloration and a Ritchie and a Baerman concentration methods and a Kato technique. The serology included three techniques: indirect immunofluorescence and hemagglutination and counter immunoelectrophoresis.

Results

Clinical tolerance

The most frequent side-effects were always minimal and transient (nauseas, vomiting, abdominal pain, headaches, extremity paresthesias). They

¹ SMAC: triglycerides, calcium, phosphorus, iron, uric acid, total and direct bilirubin, alkaline phosphatase, SGPT, SGOT, proteins, albumin, creatinine, urea, blood sugar, CO₂ content, sodium, potassium, chloride.

² The rectal mucosa biopsy was not systematically performed.

were related to the total and individual dose absorbed by the patient. In Paris nausea and vomiting were observed in about 25% cases. These side-effects did not keep any relationship neither with age, sex, parasitism intensity nor with the presence of an anemia or hepatosplenomegaly. It was noticed that the extremity paresthesias were increased after sunlight exposure.

Biological tolerance

It was studied in Paris in 125 cases and it showed:

a) *Hemogram. Red blood cells*: no significant modification was noticed; *white blood cells*: the variations were related to the eosinophilia: Hypereosinophilia was observed in 94% patients. The eosinophil count peak was noted before treatment in 20% cases and between D.1 and D.30 in 65% cases. Eosinophilia returned to normal limits during the follow-up period of time in 65% cases (many patients had multiple parasites).

b) *Liver function tests. Transaminases*: a slight elevation was noticed in 3 cases with a rapid subsequent return to normal levels. Two patients received a treatment while having an active HB_sAg⁺ hepatitis and no significant elevation of the hepatic parameters was reported. *Alcaline phosphatases*: a slight elevation was noticed in 7 cases with a subsequent return to normal levels within a few days. – These modifications of the liver function tests were minimal and transient and cannot be attributed to the treatment. Moreover in a certain number of patients transaminases and phosphatases levels were slightly above normal range before treatment and returned to normal limits on different check-ups performed after the 35972 RP treatment.

c) *Renal function tests*. No significant alteration of uremia or creatininemia levels was noticed.

d) *Serology evolution*. 3 techniques were realized simultaneously: 1. quantitative immunofluorescence, 2. passive hemagglutination, 3. counter immunoelectrophoresis. – The serology could be followed-up with the 3 techniques in 95 patients. They were divided as follows: 36 cases were followed-up to day 120 post treatment and beyond, 59 cases had a follow-up to day 100 post treatment or shorter.

I. *Three-month follow-up*: 17 patients didn't show any modification of their serological parameters, and these remained negative (using the 3 techniques) for 6 of them; 78 patients (82%) revealed an increase in their schistosomal antibodies (in one or more techniques). An increase in antibody titers occurred sooner and more frequently with the hemagglutination-test. 73 patients had an increase in their hemagglutination antibodies which was significant (i.e. at least 2 dilutions variations) for 62 of them (65% of the overall patients).

II. *Long-term follow-up*: Hemagglutination became negative or showed a significant decrease between the 3rd and 8th month in 8 cases only.

Efficiency

Treatment success was established upon complete egg clearing from stool or urine.

a) *S. haematobium schistosomiasis*: 86% cure with 15 mg/kg/24 h (over 2 days in 63 patients in Mali); 94% cure with 25 mg/kg/24 h (over 2 days in 53 patients in Mali); 92% cure in 86 patients who received total doses ranging from 2 to 7.50 g (over 1 to 5 days) in Paris. There appeared to be no significant decrease of efficiency at the lowest dosages but the small number of patients treated with 2 g and 3 g as well as the follow-up which was shorter than for other groups does not allow us to draw an ultimate conclusion.

b) *S. intercalatum schistosomiasis*: 87% cure for 72 patients who received a total dose ranging from 1.25 to 4.50 g over 3 days.

c) *S. mansoni schistosomiasis*: 100% cure in 47 patients who received a total dose ranging from 3 to 5 g over 2 to 5 days.

Consequently it appeared that 35972 RP was clinically and biologically well tolerated and very efficient at the lowest tested doses. We are presently studying and evaluating the lowest efficient dose in order to improve the digestive tolerance of the drug as well as to minimize the overall cost of treatment.