# Treatment of *Wuchereria kalimantani* Infection in *Presbytis cristata* with a Single Dose of CGI 18041

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**Abstrak**

*Obat baru untuk parasit filaria, CGI 18041, telah dievaluasi pada lutung Presbytis cristata yang diinfeksi parasit filaria Wuchereria kalimantani untuk mengetahui khasiat mikrofilarisidal dan makrofilarisidal. Sebanyak 22 ekor lutung yang menderita mikrofilaremia telah dikelompokkan secara acak ke dalam kelompok perlakuan dan kontrol menurut berat badan dan jumlah mikrofilaria. Pada kelompok perlakuan, lutung-lutung diberi pengobatan CGI 18041 dengan dosis tunggal 100 mg/kg, 50 mg/kg, 25 mg/kg, 12,5mg/kg dan 6,25 mg/kg. Hasil penelitian menunjukkan bahwa pengobatan dosis tunggal CGI 18041 100 mg/kg dan 50 mg/kg memberikan khasiat mikrofilarisidal dan makrofilarisidal. Pada pengobatan dosis tunggal CGI 18041, angka rata-rata geometrik jumlah mikrofilaria menurun sampai 0% pada hari ke-42, tetapi ditemukan cacing dewasa yang hidup pada saat lutung tersebut diautopsi. Sedangkan pada pengobatan dosis tunggal 12,5 mg/kg dan 6,25 mg/kg diketahui bahwa obat tersebut hanya berkhasiat mikrofilarisidal dan banyak ditemukan cacing dewasa yang hidup pada saat lutung diautopsi.*

**Abstract**

*A new drug for filarial parasite, CGI 18041, was evaluated for the microfilaricidal and macrofilaricidal effects in Presbytis cristata infected with Wuchereria kalimantani. Twenty two microfilaremic leaf monkeys were randomly assigned to the various treatment groups according to their body weight and microfilarial density. They were treated with a single oral dose of 100 mg/kg, 50 mg/kg, 25 mg/kg, 12.5 mg/kg and 6.25 mg/kg CGI 18041. The results showed that CGI 18041 at a single oral dose of 100 mg/kg and 50 mg/kg had complete microfilaricidal and macrofilaricidal effects against W. kalimantani in P. cristata. At a single oral dose of 25 mg/kg CGI 18041, the geometric mean of microfilarial counts (GMMC) were decreased to 0% by day 42 but live adult worms were recovered at autopsy. At a single oral dose of 12.5 mg/kg and 6.25 mg/kg, the drug was found to be effective as a microfilaricidal only; because at autopsy many live adult worms were found.*

**Keywords:** *Wuchereria kalimantani, Presbytis cristata, CGI 18041, Mikrofilaricidal, Makrofilaricidal*

## INTRODUCTION

Diethylcarbamazine Citrate (DEC) has been used world wide for lymphatic filariasis control programme but the drug is inconvenient to use as it has to be given in multiple doses over days or weeks. Furthermore, side reactions of DEC in heavy microfilaremic persons can be severe and more than one course of treatment may be needed to clear the parasite.[1]

Recently, several studies on Ivermectin have been reported. The drug was reported only potent as a microfilaricide.[2,3] Therefore, a newer antifilarial drugs which are more effective, have less side reactions and can be used in more convenient dosage will be needed.

CGI 18041, benzothiazol isothiocyanate N-methyl piperazine (Ciba Geigy, Switzerland) is a new antifilarial compound. The drug needs to be tested in animal model in order to evaluate the efficacy of drug against microfilariae and adult worms (microfilaricidal and macrofilaricidal effects).

Indonesia took part in a World Health Organization multicentered effort to test new antifilarial compounds. For the tertiary screening a non-human primate model was used, that is the *Wuchereria kalimantani - Presbytis cristata* model which has been establised in the Department of Parasitology, Faculty of Medicine, University of Indonesia since 1987.[4]

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*W. kalimantani* has been found naturally in wild leaf monkeys in South Kalimantan. *W. kalimantani* is a new species which is morphologically and taxonomicallly related to the human species *Wuchereria bancrofti.* [5]

This paper will present the results on drug trials of single doses of CGI 18041 (100, 50, 25, 12.5 and 6.25 mg per kg body weight) in *P.cristata* infected with *W.kalimantani.*

## MATERIALS AND METHODS

Wild leaf monkeys (*P. cristata*) were captured in Sumatera. The leaf monkeys were then screened for filarial infection using nucleopore filtration. The animals which were negative for filarial infection, were quarrantined for three months and then subcutaneously infected with 50 *W. kalimantani* infective larvae every week for six weeks with a total of 300 infective larvae. After seven months post infection, they were examined for the presence of microfilarial parasites in the blood.

Twenty two microfilaremic leaf monkeys were randomly assigned to five various treatment groups according to their body weight and microfilarial density. The number of monkeys in each group and the doses are as follows:

1. Four monkeys received a single oral dose of 100 mg/kg body weight
2. Three monkeys received a single oral dose of 50 mg/kg body weight
3. Four monkeys received a single oral dose of 25 mg/kg body weight
4. Four monkeys received a single oral dose of 12.5 mg/kg body weight
5. Four monkeys received a single oral dose of 6,25 mg/kg body weight
6. Three monkeys served as controls

The compound CGI 18041 was suspended in 0.1% natrium chloride-tween 80, sonicated and administered orally through a disposable stomach tube. Control animals were given an equivalent of 0.1% natrium chloride-tween 80.

Microfilarial counts were monitored the night before treatment and one, three, seven, fourteen, twenty one, twenty eight and fourty two days after treatment. Clinical adverse reactions (food intake, daily activities, stool) were observed daily for 12 days. Body temperature was monitored before treatment and one, three, and seven days after treatment. Laboratory examinations for SGOT, SGPT, alkali phosphatase, Gamma GT, Total bilirubin, BUN, Creatinine and eosinophil count were done before treatment and one, three, seven, fourteen and twenty one days after treatment. At the end of the study, the treated and control monkeys were sacrified to evaluate the macrofilaricidal effect of CGI 18041.

## RESULTS

In monkeys treated with an oral dose of 100 mg per kg body weight given for one day, the percentage geometric mean of microfilariae counts (GMMC) started to decrease from day 1 and reached zero level by day 3 and remained so until day 42 when the animals were sacrified. There were also rapid microfilaricidal effects at a single oral dose of 50 mg per kg body weight in which the GMMC reached zero level by day 7 and at a single oral dose of 25 mg per kg body weight, the GMMC was 0% by day 14. The incomplete microfilaricidal effect was observed at a single dose of 12.5 mg/kg. The GMMC decreased to below 5% by day 7 and sligthly increased to 9% before the animals were sacrified. The drug was found to be ineffective as a microfilaricidal with a single oral dose of 6.25 mg per kg body weight (Figure 1).

At autopsy, no live adult worms were recovered from a single oral doses of 100 mg and 50 mg CGI 18041. Live adult worms were recovered at autopsy of the treated monkeys with a single oral doses of 25 mg, 12.5 mg and 6.25 mg CGI 18041. While live adult worms were recovered from all the control animals (Table 1).

Table 1. The macrofilaricidal effect of a single oral dose of CGI 18041

| Dose/ kg BW | No. of monkeys | Male adult worm | | Female adult worm | |
|---|---|---|---|---|---|
| | | Live | Dead | Live | Dead |
| 100 mg | 4 | 0 | 5 | 0 | 10 |
| 50 mg | 3 | 0 | 3 | 0 | 2 |
| 25 mg | 4 | 0 | 0 | 3 | 2 |
| 12.5 mg | 4 | 17 | 0 | 29 | 0 |
| 6.25 mg | 4 | 18 | 0 | 9 | 1 |
| control | 3 | 7 | 0 | 8 | 0 |

None of the treated monkeys were adversely affected by the drug. They were all healthy and constantly active after treatment and their daily food consumption was not decreased. The eyes were constantly alert and shiny, a good indication of their normal health. The results of laboratory examinations were stable during

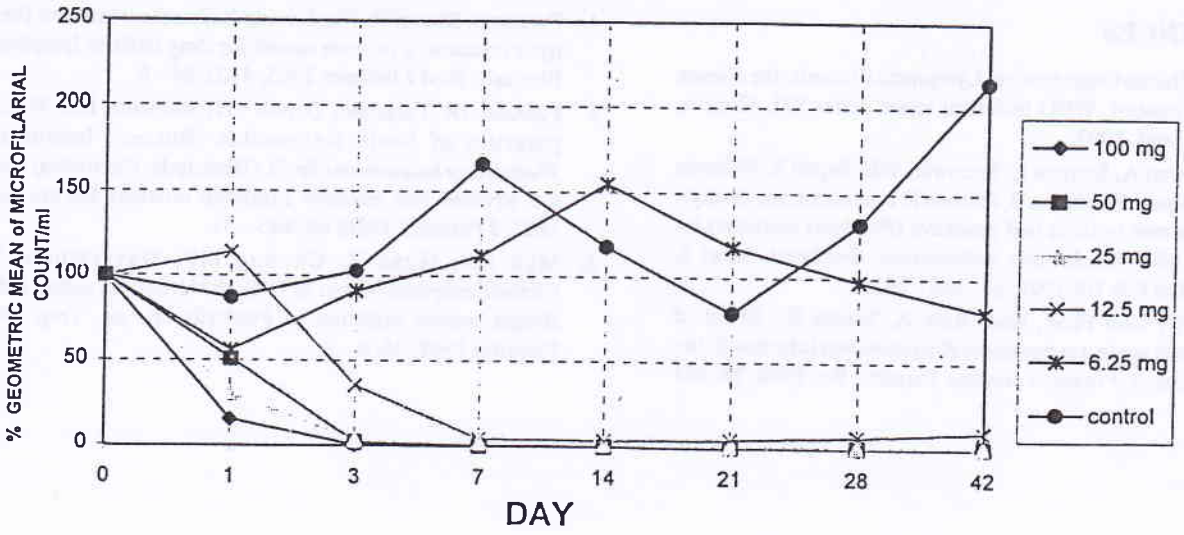


*Figure 1. The microfilaricidal effect of a single oral dose of CGI 18041*

before and after treatment period and the values were comparable between the treated and the control groups.

## DISCUSSION AND CONCLUSION

CGI 18041 has been tested for *B. malayi* infected leaf monkeys. The drug has microfilaricidal and macrofilaricidal effects in monkeys treated with 25 mg per kg body weight for 5 consecutive days or 50 mg per kg body weight for one day orally.[6]

In *W. kalimantani* infected leaf monkeys treated with an oral doses of 100 mg CGI 18041 and 50 mg CGI 18041 per kg body weight given for one day, the drug had complete microfilaricidal and macrofilaricidal effects. The GMMC reached 0% by day 3 at 100 mg and day 7 at 50 mg. No live adult worms were recovered at the two dosage schedules mentioned previously. A single oral dose of 25 mg CGI 18041 had incomplete antifilarial effect. The drug decreased the GMMC to 0% on day 14 and remained 0% on day 42 before the animals were killed but there were live adult worms recovered at autopsy.

In contrast, there was no microfilarial clearance in the treated monkeys given a single oral dose of 12.5 mg CGI 18041 or 6.25 mg CGI 18041 per kg body weight. Lively adult worms were recovered at autopsy.

There were no clinical and laboratory adverse reactions observed in this study.

The available drug, ivermectin has only microfilaricidal effect whereas DEC has microfilaricidal and macrofilaricidal effects. However, DEC has to be given in multiple doses. As CGI 18041 has both microfilaricidal and macrofilaricidal effects and as it can be given in a single dose the drug is a promising antifilarial drug.

In conclusion, we may state that at a single oral dose of 100 mg/kg and 50 mg/kg CGI 18041 had both complete microfilaricidal and marofilaricidal effects against *W. kalimantani* in *P. cristata*. It was also very effective at a single dose of 25 mg/kg, while at a single dose of 12.5 mg/kg and 6.25 mg/kg the drug showed only microfilaricidal effect. So it is possible to develop drugs which are effective in a proper single oral dose against both the /macrofilaria and microfilaria of lymphatic filarial parasites. If this drug is available, then it will contribute significantly to the treatment of individual patients as well for the control of filariasis in the endemic areas.

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## REFERENCES


1. World Health Organization. Lymphatic filariasis: the disease and its control. WHO technical report series 821. Geneva, Switzerland. 1992.
2. Kurniawan A, Sartono E, Setiowati WE, Supali T, Wibowo H, Purnomo, Rukmono B, Partono F. Ivermectin and diethylcarbamazine trials in leaf monkeys *(Presbytis cristatus)* infected with *Wuchereria kalimantani.* Southeast Asian J. Trop Med Pub Hlt 1992; 23: 288 - 292.
3. Mak JW, Lam PLW, Noor Rain A, Suresh K. Effect of Ivemectin against subperiodic *Brugia malayi* infection in the leaf monkey, *Presbytis cristata.* Parasitol Res 1988; 74: 383 - 385.
4. Purnomo, Bintari R. *Wuchereria kalimantani* infected Presbytis cristatus: a primate model for drug trials in lymphatic filariasis. Med J Indones 1995; 4 (2): 84 - 6.
5. Palmieri JR, Purnomo, Dennis DT, Marwoto HA. Filarid parasites of South Kalimantan (Borneo) Indonesia, *Wuchereria kalimantani* Sp. N. (Nematoda: filarioidea) from the silvered leaf monkey Presbytis cristatus Eschscholtz 1821. J Parasitol 1980; 66: 645 - 51.
6. Mak JW, Ngah Z, Choong MF, Navaratnam V. Chemotherapeutic effect of CGI 18041 against subperiodic Brugia malayi infection in Presbytis cristata. Trop Med Parasitol 1995; 46: 6 - 8.