

Antimalarial activity of tripynadine in mice and monkeys

LI Cong-Jun, DAI Zu-Rui, CHEN Lin

(*Lab for Antimalarial Drug Research, Second Military Medical College, Shanghai 200433*)

CHEN Chang, ZHENG Xian-Yu

(*Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine, Shanghai 200025*)

ABSTRACT The antimalarial activity of tripynadine(M-7204), an analogue of pyronaridine,

was evaluated and compared with that of pyronaridine. The ED₅₀s of tripynadine and pyronaridine against *Plasmodium berghei* ANKA strain were 2.63 and 0.85 mg/kg daily × 4 d, respective-

Received 1985 Jul 22 Revised 1986 Jun 18

ly. Both tripyridine and pyronaridine exhibited no cross-resistance to chloroquine, piperazine and hydroxypiperazine. The blood schizontocidal activity of tripyridine against *P. cynomolgi* was comparable to that of pyronaridine. The residual activity of killing blood schizonts lasted 5 d at the doses of 1.5 or $2.0 \times ED_{50}$ value, 20 d at that of $4.0 \times ED_{50}$ value with tripyridine, and 5 d at the dose of $2.0 \times ED_{50}$ value and 10 d at $4.0 \times ED_{50}$ value with pyronaridine.

KEY WORDS *Plasmodium berghei*; *Plasmodium cynomolgi*; pyronaridine; tripyridine(2-pyrrolidino-7-chloro-10-[3',5'-bis(pyrrolidino-1-methyl)-4-hydroxyphenyl] amino-benzo (b) 1,5-naphthyridine); chloroquine; piperazine; hydroxypiperazine; drug therapy; microbial drug resistance.

Pyronaridine phosphate, an antimalarial drug, was proved to be of residual activity and no cross-resistance to piperazine⁽¹⁻⁸⁾. On the basis of structure-activity relationship of some antimalarials, the authors synthesized an analogue, 2-pyrrolidino-7-chloro-10-[3',5'-bis-(pyrrolidino-

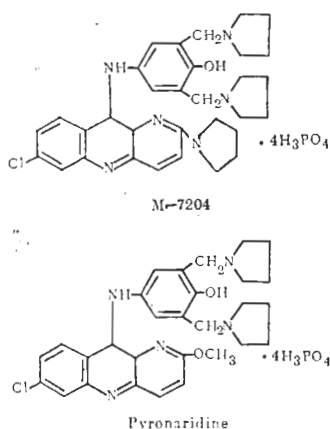


Fig 1. Tripyridine (M-7204): 2-pyrrolidino-7-chloro-10-[3',5'-bis-(pyrrolidino-1-methyl)-4'-hydroxyphenyl] amino-benzo (b) 1,5-naphthyridine;

Pyronaridine: 2-methoxy-7-chloro-10-[3',5'-bis(pyrrolidyl-1-methyl)-4'-hydroxy-anilino]-benzo (b)-1,5-naphthyridine tetraphosphate.

1-methyl)-4-hydroxyphenyl] amino-benzo (b) 1,5-naphthyridine, named tripyridine and coded M-7204 (Fig 1). The analytical data and spectra of tripyridine were in accordance with the proposed structure⁽⁹⁾. This study is to evaluate its therapeutic effect on *Plasmodium berghei* and *P. cynomolgi*.

Physical properties of tripyridine
Molecular formula $C_{32}H_{37}ClN_8 \cdot 4H_3PO_4$; mol wt 948.5; mp $219-22^\circ C$ (decomp); odourless and orange-coloured crystalline powder with bitter taste. Hydroscopic and soluble in water but not in organic solvents; proportion of tripyridine base 58.7%. Its aqueous solution shows a pH 3.2.

Malaria parasites *Plasmodium berghei* ANKA strain was cyclically transmissible, drug sensitive. *P. berghei* NS strain, cyclically transmissible but moderately resistant to chloroquine. Blood passages were carried out under drug pressure. Both the piperazine-resistant line (MPR line) and hydroxypiperazine-resistant line (MHPR line) were derived from *P. berghei* ANKA strain which were moderately resistant to piperazine or hydroxypiperazine. Blood passages were carried out under drug pressure also. *P. cynomolgi* was cyclically transmitted in author's laboratory through *Anopheles stephensi* Hor strain.

Animals Kunming σ mice ($18.2 \pm SD 0.8$ g) and *Macaca mulatta* were used as the hosts.

"4-d suppressive test" was used for evaluation of blood schizontocidal action.

Residual activity test The mice were administered orally on d -5, -10, and -20 before ip inoculating (d 0) *P. berghei* ANKA strain-infected erythrocytes. The blood smears were examined on d 5 after inoculation.

Blood schizontocidal activity The monkeys were inoculated iv with $1-5 \times 10^7$ *P. cynomolgi*-infected erythrocytes. When the parasitaemia density rose to over 1%,

Tab 1. Antimalarial activity of tripyridine and pyronaridine against the parent strains of *P berghei* and its drug-resistant lines

Strain or line of <i>P berghei</i>	Drug	Regression equation*	ED ₅₀ (95%CL) mg/(kg·d)	Index† of resistance
ANKA	Tripyridine	Y = 7.648 X - 3.215	2.63(2.31-3.00)	
	Pyronaridine	Y = 4.667 X - 5.340	0.85(0.68-1.10)	
NS	Tripyridine	Y = 13.448 X - 0.420	2.53(2.08-3.07)	0.96
	Pyronaridine	Y = 22.640 X - 6.120	0.89(0.64-1.25)	1.05
MPR from ANKA	Tripyridine	Y = 13.337 X - 0.503	2.59(2.04-3.28)	0.98
	Pyronaridine	Y = 6.990 X - 4.579	1.15(0.95-1.40)	1.35
MHPR from ANKA	Tripyridine	Y = 11.118 X - 0.326	2.63(2.40-2.88)	1.00
	Pyronaridine	Y = 10.644 X + 5.688	0.86(0.77-0.96)	1.00

*X = log dose of drug, Y = probit of effective rate. † ED₅₀ (resistant line)/ED₅₀ (sensitive line)

the drugs were administered ig daily for 7 d. Thin and thick blood films were made daily from d 1 to d 60.

Throughout the experiments, dosages were in terms of bases. Drugs were suspended in saline with Tween 80 and administered by intragastric gavage, pyronaridine was used as control.

RESULTS

Activity against *P berghei* The results were summarized Tab 1. Both tripyridine and pyronaridine exhibited no

cross-resistance to chloroquine, piperazine and hydroxypiperazine.

Residual activity against the blood schizonts of *P berghei* ANKA strain.

The results (Tab 2) showed that the residual activity of killing blood schizonts lasted 5 d at the doses of 1.5 or 2.0 × ED₅₀ value, 20 d at the dose of 4.0 × ED₅₀ value with tripyridine; and 5 d at the dose of 2.0 × ED₅₀ value and 10 d at 4.0 × ED₅₀ value with pyronaridine.

Blood schizontocidal activity against *P cynomolgi* in rhesus monkeys See Tab 3.

Tab 2. Residual blood schizontocidal activity with a single dose of tripyridine and pyronaridine against *P berghei* ANKA strain

Drug	mg/kg	Mice (negative/tested)			Time of residual activity (d)
		d-5	d-10	d-20	
tripyridine	15.8*	10/10	1/10	—	5
	20.1†	10/10	5/10	—	5
	42.0‡	—	10/10	10/10	20
pyronaridine	5.1*	2/8	0/9	—	—
	6.8†	10/10	0/9	—	5
	13.6‡	—	8/9	0/10	10

*, †, ‡ 1.5, 2.0 and 4.0 times of ED₅₀ value, respectively.

Tab 3. Activity of tripyridine (T) and pyronaridine (P) against *P cynomolgi* in ♂ monkeys

Body wt (kg)	Parasitaemia density(%) 1 d before medication	Drug	Daily dose (mg/kg) × 7 d	Parasite cleared on	Recrudesced on
2.9	1.0	T	3.5	d 4	d 19
2.2	8.5	P	5.0	d 5	d 21
3.1	3.5	T	5.0	d 3	d 22
2.6	6.3	P	10.0	d 4	d 31
2.1	5.8	T	10.0	d 4	d 19

The results (Tab 3) showed that the blood schizontocidal activity of tripynadine against *P cynomolgi* was comparable to that of pyronaridine.

DISCUSSION

This paper showed that tripynadine had a significant blood schizontocidal activity against *P berghei* or *P cynomolgi* and no cross-resistance to chloroquine, piperazine and hydroxypiperazine. On the other hand, a certain degree of residual blood schizontocidal activity on *P berghei* ANKA strain were obviously noticed. The results suggest that the antimalarial activity of tripynadine be comparable to that of pyronaridine. It is worthy to develop tripynadine as an antimalarial drug.

ACKNOWLEDGMENT *Plasmodium berghei* ANKA strain and *P berghei* NS strain were kindly provided by Prof W Peters, London school of Hygiene and Tropical Medicine.

REFERENCES

- 1 中国医学科学院寄生虫病研究所疟疾研究室新药组. 抗疟新药 7351 的疗效和毒性的实验研究. 药学报 1980; 15: 630
- 2 邵葆若、叶秀玉、郑浩. 伯氏疟原虫对咯萘啶抗药性的研究. 同上 1982; 17: 566
- 3 邵葆若、叶秀玉、郑浩. 咯萘啶对鼠疟原虫红内期裂殖体的特效作用. 寄生虫学与寄生虫病杂志 1984; 2: 232
- 4 倪奕昌、徐月琴、邵葆若. 抗疟药咯萘啶在鼠伤寒沙门氏菌/微粒体系统中的诱变性. 中国药理学报 1982; 3: 51
- 5 陈克涌、林宝英、张家坝、邵葆若. 七种抗疟药对小鼠感染抗咯萘啶伯氏疟原虫的实验治疗. 同上 1983; 4: 269
- 6 邵葆若、湛崇清、哈淑华. 磷酸咯萘啶对大鼠三代生殖的影响. 同上 1985; 6: 131
- 7 邵葆若、叶秀玉、郑浩. 抗咯萘啶伯氏疟原虫抗药性的稳定性. 同上 1985; 6: 183
- 8 吴莉菊. 咯萘啶对伯氏鼠疟原虫红内期超微结构的影响. 同上 1985; 6: 280
- 9 郑贤育、陈昌、高芳华、朱佩萼、郭惠珠. 抗疟新药咯萘啶及其类似物的合成. 药学报 1982; 17: 118

中国药理学报 1987年1月, 8(1): 68-71

三吡萘啶在动物模型上的抗疟作用

李从军、戴祖瑞、陈林 (第二军医大学抗疟药研究室, 上海 200433)
陈昌 郑贤育 (中国预防医学科学院寄生虫病研究所, 上海 200025)

提要 三吡萘啶系陈昌等合成的一种新化合物, 化学名 2-四氢吡咯-7-氯-10[3', 5'-双(四氢吡咯-1-甲基)-4-羟基苯基]氨基苯并(b)1,5-萘啶, 是抗疟新药咯萘啶的类似物。本文报道了其在鼠疟和猴疟模型上的抗疟作用。三吡萘啶和咯萘啶治疗伯氏疟原虫 ANKA 株的 ED_{50} 分别为 $2.63 \text{ mg}/(\text{kg}\cdot\text{d}) \times 4$ 和 $0.85 \text{ mg}/(\text{kg}\cdot\text{d}) \times 4$ 。三吡萘啶和咯萘啶与氯喹、哌喹和羟基哌喹均无交叉抗性。治疗食蟹猴疟原虫时三吡萘啶与咯萘啶的效果基本相当。三吡萘啶与咯萘啶对鼠疟均显示了一定程度的滞效作用。三吡萘啶以 1.5,

2.0 倍 ED_{50} 的剂量给药其滞效作用在 5 d 以上, 以 4.0 倍 ED_{50} 的剂量给药其滞效作用达 20 d; 咯萘啶以 2.0 倍 ED_{50} 剂量其滞效作用为 5 d 以上, 以 4.0 倍 ED_{50} 剂量其滞效作用在 10 d 以上。

关键词 伯氏疟原虫; 食蟹猴疟原虫; 抗疟药; 咯萘啶; 三吡萘啶(2-四氢吡咯-7-氯-10[3', 5'-双(四氢吡咯-1-甲基)-4-羟基苯基]氨基苯并(b)1,5-萘啶, M-7204); 氯喹; 哌喹; 羟基哌喹; 药物疗法; 抗药性