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Antimalarial activity of tripynadine in mice and monkeys

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ABSTRACT The antimalarial activity of tripynadine(M-7204), an analogue of pyronaridine, was evaluated and compared with that of pyronaridine. The ED_{50}s of tripynadine and pyronaridine against *Plasmodium berghei* ANKA strain were 2.63 and 0.85 mg/kg daily × 4 d, respective-

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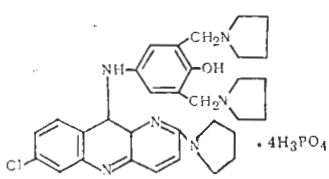
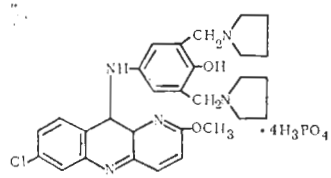
ly. Bothtripynadine and pyronaridine exhibited no cross-resistance to ehloroquine, piperaquine and hydroxypiperaquine. The blood schizontocidal activity of tripynadine against *P cynomolgi* was comparable to that of pyronaridine. The residual activity of killing blood schizcnts lasted 5 d at the doses of 1.5 or $2.0 \times ED_{50}$ value, 20 d at that of $4.0 \times ED_{50}$ value with tripynadine, 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*; *Plasnodium cynomolgi*; pyronaridine; tripynadine(2-pyrrolidino-7-chloro - 10 - [3′, 5′-bis (pyrrolidino - 1-methyl)-4-hydroxyphenyl] amino-benzo (b) 1.5-naphthyridine); chloroquine; pipcraquine; hydroxypiperaquine; drug therapy; microbiol drug resistance.

Pyronaridine phosphate, an antimalarial drug, was proved to be of residual activity and no cross-resistance to piperaquine[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-1-methyl)-4-hydroxyphenyl] amino-benzo (b) 1,5-naphthyridine, named tripynadine and coded M-7204 (Fig 1). The analytical data and spectra of tripynadine were in accordance with the proposed structure[9]. This study is to evaluate its therapeutic effect on *Plasmodium berghei and P cynomolgi*.



M-7204



Pyronaridine

Fig 1. Tripynadine (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 (pyrrolidiyl-1-methyl)-4′-hydroxy-anilino]-benzo (b)-1,5-naphthyridine tetraphosphate.

Physical properties of tripynadine Molecular formula $C_{32}H_{37}ClN_6 \cdot 4\,H_3PO_4$; mol wt 948.5; mp 219-22℃ (decomp); odourless and orange-coloured crystalline powder with bitter taste. Hydroscopic and soluble in water but not in organic solvents; proportion of tripynadine 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 piperaquine-resistant line (MPR line) and hydroxypiperaquine-resistant line (MHPR line) were derived from *P berghei* ANKA strain which were moderately resistant to piperaquine or hydroxypiperaquine. 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 ♂ mice (18.2 ± SD 0.8 g) and *Macaca mulatta* were used as the hosts.

"4-d supressive 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 examed on d 5 after inoculation.

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

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

Strain or line of *P berghei*	Drug	Regression equation*	ED_{50}(95%CL) mg/(kg·d)	Index† of resistance
ANKA	Tripynadine	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	Tripynadine	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	Tripynadine	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	Tripynadine	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. † ED_{50} (resistant line)/ED_{50} (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 tripynadine and pyronaridine exhibited no cross-resistance to chloroquine, piperaquine and hydroxypiperaquine.

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 × ED_{50} value, 20 d at the dose of 4.0 × ED_{50} value with tripynadine; and 5 d at the dose of 2.0 × ED_{50} value and 10 d at 4.0 × ED_{50} value with pyronaridine.

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

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

Drug	mg/kg	Mice (negative/tested) d-5	d-10	d-20	Time of residual activity (d)
tripynadine	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 ED_{50} value, respectively.

Tab 3. Activity of tripynadine (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, piperaquine and hydroxypiperaquine. 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.

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三吡萘啶在动物模型上的抗疟作用

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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]氨基苯骈(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 mg/(kg·d)×4 和 0.85 mg/(kg·d)×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]氨基苯骈 (b)1,5-萘啶, M-7204); 氯喹; 哌喹; 羟基哌喹; 药物疗法; 抗药性