胃道中的吸收. 因此当 SD 与它们合用时，也能提高它们的抗生育作用. 目前 RU-486在临床上应用，常与前列腺素合用. 本文结果将为临床医生在使用抗早孕药物时，提供更多的选择余地.

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精脒对氯喹进入伯氏疟原虫的影响[1]

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Effect of spermidine on uptake of chloroquine by *Plasmodium berghei*

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ABSTRACT To probe into the effect of spermidine on chloroquine (Chl) uptake by *P berghei* and its role of Chl-resistance, mice infected with Chl sensitive strain (CS) of *P berghei* were given Chl 20 mg·kg^{-1} ig combined with spermidine (Spe) 42 mg·kg^{-1} ip. It was found that 3 and 16 h after combined administration, Chl quantity uptaken by the parasites was reduced respectively by 59.6% and 53.8% in comparison with that in the Chl group. However, there was no difference in parasitaemia between Chl group (2.3±1.0) and Chl-Spe group (1.7±1.0), whereas the untreated control group remained a parasitaemia of 36±9. The authors deemed that Chl resistance is not merely attributed to the insufficient quantity of Chl in the Chl resistant parasites, the change in the sensitivity to Chl of Chl resistant parasites and the role of Spe in Chl resistance production should also be taken into consideration.

KEY WORDS chloroquine; spermidine; *Plasmodium berghei*; combination drug therapy

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A

摘要 伯氏疟原虫氯喹敏感株(CS)感染小鼠ig 氯喹20 mg·kg^{-1}及合并精脒42 mg·kg^{-1}后3 h 与16 h，测定疟

原虫中的氯喹量，均较单独 ig 氯喹组减少59.6%与53.8%，认为精脒影响氯喹进入疟原虫、但比较其减虫率，两组无明显差异．认为抗氯喹机制不仅是由于CR疟原虫中的氯喹量不足，应考虑抗氯喹疟原虫对氯喹敏感性的变化与重视精脒在产生抗性中的作用．

关键词　氯喹；精脒；伯氏疟原虫；联合药物疗法

不少学者认为疟原虫的抗氯喹机制是由于抗氯喹感染红细胞或疟原虫中的氯喹量不足[1,2]，作者亦证明伯氏疟原虫抗氯喹株(CR)中的氯喹量仅为敏感株(CS)的35%[3]，其原因Verdier 等[2]认为是高铁原卟啉区与氯喹结合的亲和力低，Martin 等[4]主张与 P-糖蛋白的药泵有关．我们从 CR 感染红细胞中精脒高于 CS 4—5倍[5]，增高的精脒80%在疟原虫，与精脒、氯喹又都具有双胺结构特点，认为有必要观察精脒对氯喹进入疟原虫的影响与考虑疟原虫中的氯喹量与氯喹抗性的关系．本文以 CS 感染鼠为材料，ig 氯喹同时给予精脒，然后测定 CS 中的氯喹量，以期反证 CR 中氯喹量的减少与精脒的关系，进而探讨抗氯喹机制．

MATERIALS AND METHODS

伯氏疟原虫(*Plasmodium berghei*)印度株由本所病原生物研究室提供．磷酸氯喹(上海中西制药厂)，磺化乙基纤维素(Serva)、葡聚糖凝胶 G-25 (Pharmacia)，精脒·3 HCl (Sigma)．

疟原虫样品的制备与测定　CS 5%感染血0.2 ml (约含10^7感染红细胞) ip NIH 小鼠，于感染后3 d (平均感染率达(20—25%)，感染鼠分为两组、一组 ig 氯喹(20 mg·kg^{-1})，另一组在 ig 氯喹20 mg·kg^{-1}同时 ip 精脒42 mg·kg^{-1}，分别于3 h 与16 h 后，摘除眼球取血，经磺化乙基纤维素—葡聚糖凝胶 G-25柱，除去白细胞[5]，—20℃放置，次日或一周内冻融后，皂溶法(0.0015%)破红细胞、获得游离疟原虫、然后按 Rombo 等荧光分光光度法测定氯喹量[6]，按 Bradford 方法测定蛋白质[7]．

精脒合并氯喹的抗疟效果观察　同上方法感染小鼠，3 d 后选择感染率在18%左右的感染鼠分成三组，第一组为不给药对照，第二组 ig 氯喹20 mg·kg^{-1}·d^{-1}×3 d，第三组 ig 氯喹20 mg·kg^{-1}，并 ip 精脒42 mg·kg^{-1}·d^{-1}×3 d、每次给药后24 h，自尾 iv 取血镜检感染率(感染 rbc/500 rbc)．

RESULTS

精脒对氯喹进入疟原虫的影响　ig 氯喹合并精脒组，进入的氯喹量仅为单独 ig 氯喹组的40.4%，16 h 后，还是维持在同样水平(Tab 1)．单独给氯喹与合并精脒组中的氯喹量，具有非常显著性的差异($P<0.01$)．

Tab 1.　Effect of spermidine on uptake of ig chloroquine 20 mg·kg^{-1} by *Plasmodium berghei*.　Number of samples in parentheses; each sample contained 3 mice.　$\bar{x}\pm s$.　$^cP<0.01$ *vs* control.

Spe ip (mg·kg^{-1})	Chloroquine, μmol·g^{-1} After 3 h	After 16 h
—	0.94±0.25 (12)^c	1.34±0.36 (9)^c
42	0.38±0.14 (16)^c	0.62±0.28 (10)^c

CS 感染鼠接受氯喹与合并精脒治疗后抗疟效果的比较　仅 ig 氯喹20 mg·kg^{-1}一次，24 h 后镜检，大部分的疟原虫均已萎缩，感染率下降19.3%；给药二次后，疟原虫全部萎缩，感染率下降71.9%，给药三次，疟原虫几乎全部消灭，而合并精脒组，疟原虫的萎缩及感染率的下降与单独 ig 氯喹组接近(Tab 2)．

Tab 2.　Parasitemia before and 24 h after ig chloroquine (Chl) 20 mg·kg^{-1}·d^{-1}×3 d with or without ip spermidine (Spe) 42 mg·kg^{-1}·d^{-1}×3 d *vs* control in 1 mouse.　Number of samples in parentheses.

Time	Parasitemia/% (Infected rbc/100 rbc) Control	Chl	Chl+Spe
Before	15.5±5.6 (11)	18.7±5.9 (19)	17.9±4.3 (14)
First	22.3±6.8 (11)	15.1±2.1 (19)	10.9±4.4 (14)
Second	29.4±10.6 (11)	4.7±1.7 (17)	4.2±1.2 (13)
Third	35.9±9.4 (11)	2.3±1.0 (16)	1.7±1.0 (11)

DISCUSSION

作者曾经给 CS 感染鼠 ip 精脒前体^{3}H-丁

二胺(0.74 GBq/鼠)，30 min 后标记物即在疟原虫中测得(待发表资料)，给 CR 感染鼠 ig MGBG，精脒生物合成途经中 S-腺苷甲硫氨酸脱羧酶的有力抑制剂，能够抑制 CR 疟原虫生长，但是 ip 等克分子量的精脒完全拮抗 MGBG 的作用[3]，显示外界提供的精脒能为疟原虫吸收和利用.

本文给 CS 感染鼠 ig 氯喹合并精脒，3 h 后疟原虫中的氯喹量较单独给氯喹组减少 59.6%，16 h 后仍维持在此低水平，说明提高疟原虫中的精脒，是可以影响氯喹进入疟原虫.

但是尽管合并精脒后，CS 疟原虫中的氯喹量已减少到与 CR 中的相接近，但是两组原虫血症的影响并无差异，氯喹组(2.3±1.0)，合并精脒组(1.7±1.0)，而不给药的对照组为(35.9±9.4). 另方面异博定能够提高抗氯喹疟原虫感染红细胞中的氯喹量[7]，即使抗氯喹原虫中的氯喹浓度上升达敏感株同样水平，而氯喹对虫的作用仍低于敏感的[8]. 从上述二方面显示疟原虫的抗氯喹机制，并非仅仅由于 CR 疟原虫的氯喹量低所致，自抑制两株疟原虫50%精脒需要的氯喹量，CR 要高于 CS 20 倍，分别为400 $mg \cdot kg^{-1}$与20 $mg \cdot kg^{-1}$[3]，认为抗氯喹机制的研究应该重视 CR 对氯喹敏感性的变化.

此外，既然精脒可以影响氯喹进入疟原虫，则 CR 中增高的精脒可能以其双胺结构替代或干扰了氯喹与疟原虫重要组分的结合，继而影响氯喹的疗效. 氯喹与疟原虫 DNA 结合时，其侧链上双胺间的长短可以影响抗疟效果[9]. 因此对 CR 中增多的精脒在氯喹抗性中的作用值得研究.

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