研究简报

口服双氢青蒿素在兔和狗体内的药代动力学研究

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青蒿素是一带有双氧桥结构的倍半萜内酯类抗疟药，已获我国卫生部新药审批委员会批准正式生产，用于临床。青蒿素用硼氢化钠还原得双氢青蒿素，其抗疟作用为青蒿素的 4～8 倍[1]。我们曾报告[2]给狗 po 青蒿素 50 mg/kg 后，用放射免疫法在血中未测到青蒿素。本文用同样方法研究了双氢青蒿素给兔和狗口服后的药代动力学，

双氢青蒿素片剂及青蒿素片剂均由中国中医研究院中药所提供。选用 1.5～2.0 kg 家兔 15 只均分为 3 组，每组雄兔 4 只，雌兔 1 只，分别 po 双氢青蒿素片剂 10，20 和 30 mg/kg；另选体重 13～21 kg 雄狗 5 只，分别 po 双氢青素素片剂 20 mg/kg（2 只）和青蒿素片剂 70 mg/kg（3 只）。给药后不同时间由静脉取血，分离血清，置于－30°C 下保存备测。青蒿素和双氢青蒿素浓度均用放射免疫法测定[3]。

图 1 为兔 po 双氢青蒿素片剂后的血药时程，由图可见兔 po 双氢青蒿素后吸收较好，给药后 1～2 h 血药浓度达高峰。在 10，20 和 30 mg/kg 剂量时，峰浓度分别为 0.03，0.05 和 0.13 μg/ml；药物的消除半衰期分别为 1.19，1.00，和 1.10 h；药物在兔体内的平均驻留时间（MRT）分别为 1.73，1.36 和 1.53 h，三个剂量组间无明显差异。其它有关药代动力学参数列于表 1。

Tab 1. Pharmacokinetic parameters of dihydroqinghaosu tahlets given orally to rabbits and dogs

Animal	Rabbit			Dog
Dose (mg/kg)	10	20	30	20
Peak time (h)	0.77±0.27	0.57±0.32	1.50±0.50	20
Peak level(μg/ml)	0.03±0.01	0.05±0.02	0.13±0.11	0.13
AUC (μgih/ml)	0.06±0.04	0.09±0.04	0.20±0.16	0.26
MRT (h)	1.73±0.56	1.36±0.17	1.53±0.21	3.04
$T_{1/2}$ (h)	1.19±0.37	1.00±0.13	1.10±0.26	2.10

狗 po 双氢青蒿素片剂 20 mg/kg 后 2 h 血药浓度达高峰如图 2 所示，峰浓度为 0.13 μg/ml，MRT 和 $T_{1/2}$ 分别为 3.04 h 和 2.10 h，其它药代动力学参数亦见表 1。但狗

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口服青蒿素片剂 70 mg/kg 后，在血清中竟未测到药物。

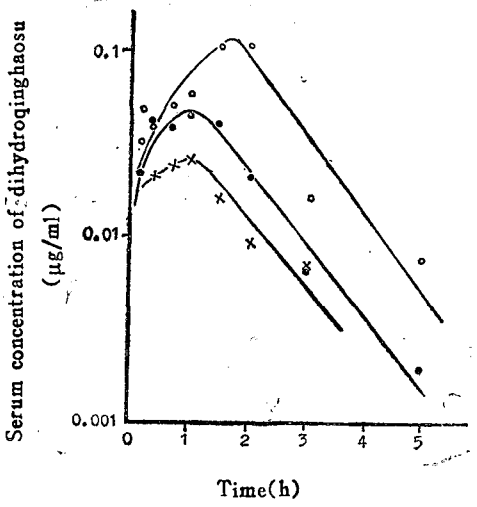

Fig 1. Serum concentration-time course of dihydroqinghaosu given orally to rabbits. Each point representes the mean of 5 rabbits. (x—x 10 mg/kg, •—• 20 mg/kg and ∘—∘ 30 mg/kg).

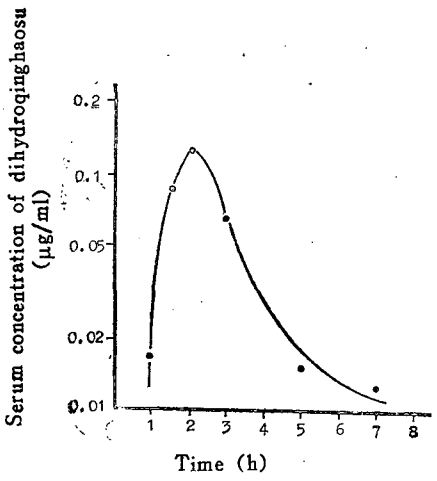

Fig 2. Serum concentration-time course of dihydroqinghaosu given orally to dogs at the dose of 20 mg/kg. Each point is the average of 2 dogs.

姚乾元等 (4) 曾报道给兔灌胃双氢青蒿素乳剂 800 mg/kg 后，吸收慢且吸收量很低，同时发现雄兔血浆中双氢青蒿素含量极少。但应指出他们所用的测定方法虽有一定特异性，但灵敏度极差，双氢青蒿素剂量虽高达 800 mg/kg，仍未测到血浆中的药物。我们用放射免疫法测定，给家兔的双氢青蒿素片剂 po 剂量虽仅 10～30 mg/kg，但发现药物吸收很快，峰浓度可达 0.03～0.13 μg/ml，狗 po 双氢青蒿素片 20 mg/kg 后，吸收亦好，峰浓度可达 0.13 μg/ml，狗 po 青蒿素片虽剂量高达 70 mg/kg，但未在血清中测到药物，虽所用动物数较少，结果与我们以前的报告 (2) 相同，我们曾给 2 只狗灌胃青蒿素淀粉悬液 50 mg/kg，但在血清中未测到药物。可见，给狗 po 后，双氢青蒿素的生物利用度远较青蒿素者高。应该指出，本研究所用放射免疫法对具双氧桥结构的青蒿素、双氢青蒿素及其活性衍生物有完全交叉反应，而对无此结构的其它类似物交叉反应很小，所以用此法测定的青蒿素或双氢青蒿素的血药浓度包括原形药及其活性代谢产物。

致谢 本项研究得到联合国开发计划署/世界银行/国际卫生组织热带病研究培训特别规划，疟疾化疗科学工作组及中国中医研究院中药研究所部分资助。

关键词 青蒿素；双氢青蒿素；药代动力学；放射免疫测定法

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THE PHARMACOKINETICS OF DIHYDROQINGHASU GIVEN ORALLY TO RABBITS AND DOGS*

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ABSTRACT Qinghaosu (QHS), also known as artemisinine and arteannuin, is isolated from the Chinese herb *Artemisia annua* L. It is highly active against both chloroquine-sensitive and chloroquine-resistant strains of *P. berghei* and has been approved by the Ministry of Health for the treatment of malaria. When QHS is treated with sodium borohydride, dihydroqinghaosu (DHQHS) is resulted with the antimalarial activity enhanced several fold. This paper reports the pharmacokinetics of DHQHS studied with the radioimmunoassay method.

When the drug was given orally in tablet form to rabbits at doses of 10,20 and 30 mg/kg, peak serum levels of 0.03, 0.05 and 0.13μg/ml, respectively, were obtained in 1 to 2 h. The corresponding $T_{1/2}$ of the drug were found to be 1.19, 1.00 and 1.10 h and the MRTs were 1.73, 1.36 and 1.53 h. No significant difference between dosages used was observed. When dogs were given DHQHS tablets at the dose of 20 mg/kg, a peak serum concentration of 0.13 μg/ml wes reached in about 2 h with a $T_{1/2}$ of 2.10 h and an MRT of 3.04 h. However, when dogs were given QHS tablets at the dose of 70 mg/kg, no drug was detected in the serum. It would appear that the bioavailability of DHQHS tablets is much higher than that of QHS when given orally to the dog.

Key words Qinghaosu; Artemisinine; Arteannuin; Dihydroqinghaosu; Pharmacokinetics

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