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硝喹（Nitroquine）对小鼠疟原虫叶酸代谢的影响

朱清平 胡友梅 刘富安

（药理教研室）

提 要

为确定硝喹作用于叶酸代谢哪一环节，分别给感染伯氏疟或约氏疟原虫的小鼠灌服不同剂量的硝喹，另一部分感染同种疟原虫的动物在服用同样剂量硝喹的基础上，分别加服对氨苯甲酸、肌注甲酰四氢叶酸钙和肌注叶酸，结果对氨苯甲酸使硝喹的量效曲线右移，CD_{50} 明显加大，表明对氨苯甲酸对硝喹的抗疟作用有明显的拮抗作用，甲酰四氢叶酸钙和叶酸对硝喹基本上无拮抗作用。

鉴于对氨苯甲酸能拮抗硝喹的抗疟作用，认为其作用环节可能是与对氨苯甲酸竞争二氢碟酸合成酶。对叶酸代谢过程中的其它环节，本文也进行了讨论。

醋酸硝喹（简称硝喹，原名 CI—679）对人、鼠、猴、家禽等各型疟疾都有效[1]，且能抑制鸡疟原虫孢子增殖期中卵囊的DNA复制[2]。硝喹是抗叶酸代谢类药物[3]，其作用是否与疟原虫的叶酸代谢有关？这方面的报导不多。本文旨在探讨硝喹的抗疟作用与疟原虫的叶酸代谢的关系。

材料与方法

动物及疟原虫 动物系我校动物所繁殖的昆明株小白鼠，体重18—22克。本实验共用小鼠2000只，分13批进行，每批实验用100—130只，均雌雄各半。疟原虫采用伯氏疟原虫和约氏疟原虫两种。伯氏疟原虫系1970年引自上海寄生虫研究所，对磺胺类药物敏感而对乙胺嘧啶耐药；约氏疟原虫系1982年引自北京军事医学科学院。

药物 硝喹醋酸盐为上海医药工业研究院合成（批号8005010）。甲酰四氢叶酸钙为上海第十二制药厂生产（批号75—05—30）。叶酸为常州制药厂生产、上海化学试剂厂分装。对氨苯甲酸（PABA）为北京化工厂生产（批号610608）。药品均系粉剂，于临用前配制。药品剂量按每天每公斤体重计算，醋酸硝喹的最大剂量为0.3mg，按等比级数稀释。对氨苯甲酸和叶酸均为20mg。此三药均加入吐温80配成乳剂。甲酰四氢叶酸钙（即亚叶酸）为6mg，用蒸馏水配制。

方法 以伯氏疟原虫进行的实验有7批，其中3批用口服对氨苯甲酸作拮抗药，2批用肌注叶酸作拮抗药，2批用肌注甲酰四氢叶酸钙作拮抗药。以约氏疟原虫进行的实验有6批，其中3批用肌注叶酸作拮抗药，另3批用肌注甲酰四氢叶酸钙作拮抗药。所有13批均给口服硝喹作治疗药。

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每批实验用感染伯氏疟原虫或约氏疟原虫小白鼠的血液定量接种，每只鼠接种500万感染的红细胞，接种后第三天，将小鼠随机分成10—13个组，每组10只。其中4—6个组单用硝喹治疗，4—6个组硝喹合用拮抗药治疗，另设1—2组不给药的作对照。硝喹的剂量，最大的一组为每公斤体重0.3mg，其余的组按70%等比级数稀释；拮抗药的剂量，PABA和叶酸均为每公斤体重20mg，甲酰四氢叶酸钙为每公斤体重6mg。均每天给药一次，连续给三天。第七天从鼠尾采血涂片检查，每张血片用油镜查200个视野，如无原虫发现则定为转阴治愈，计算原虫的阴转率，用加权直线回归法求硝喹半数治愈量（CD_{50}）。

结　果

一、PABA对硝喹抗伯氏疟作用的影响

单用硝喹时CD_{50}为0.117±SE0.011mg/kg/日（99%可信限为0.087—0.159mg/kg/日）。合用PABA后CD_{50}提高至0.231±SE0.011mg/kg/日（99%可信限为0.174—0.306mg/kg/日）。两者比较，合用PABA后的CD_{50}超出单用硝喹时CD_{50}的99%可信限，剂量为单用时的一倍。

二、叶酸对硝喹抗伯氏疟及约氏疟作用的影响

单用硝喹治疗伯氏疟，其CD_{50}为0.167±SE0.012mg/kg/日（99%可信限为0.030—0.250mg/kg/日）。而合用叶酸时则为0.185±SE0.010mg/kg/日（99%可信限为0.173—0.197mg/kg/日）。对约氏疟的治疗，硝喹单用与合用叶酸，其CD_{50}分别为0.128±SE0.011mg/kg/日（99%可信限为0.105—0.157mg/kg/日）和0.127±SE0.011mg/kg/日（99%可信限为0.097—0.167mg/kg/日）。

三、甲酰四氢叶酸钙对硝喹抗伯氏疟及约氏疟作用的影响

单用硝喹与合用甲酰四氢叶酸钙治疗伯氏疟，其CD_{50}分别为0.106±SE0.011mg/kg/日（99%可信限为0.074—0.149mg/kg/日）和0.100±SE0.012mg/kg/日（99%可信限为0.063—0.161mg/kg/日）。对约氏疟的治疗，单用硝喹的CD_{50}为0.094±SE0.011mg/kg/日（99%可信限为0.074—0.121mg/kg/日），当合用甲酰四氢叶酸钙时，其CD_{50}为0.113±SE0.011mg/kg/日（99%可信限为0.092—0.139mg/kg/日）。对约氏疟，合用甲酰四氢叶酸钙时，其CD_{50}虽比单用硝喹有所升高，但仍在单用硝喹的CD_{50}的99%可信限之内。

小结与讨论

从以上实验结果得出，当硝喹与PABA合用，其量效曲线比单用硝喹时，有明显的右移现象；合用与单用硝喹时的CD_{50}之比为2:1，并且二者的99%可信限并无重叠之处，因此说明PABA对硝喹有明显的拮抗作用。当硝喹与叶酸或甲酰四氢叶酸钙合用，无论用伯氏疟或约氏疟实验，合用后的量效曲线未见有明显的右移，且单用与合用后的CD_{50}亦较接近，说明叶酸和甲酰四氢叶酸钙对硝喹无拮抗作用。

硝喹的抗疟作用可被PABA拮抗，提示硝喹的作用机理可能与磺胺类药物的作用类似，二者均可与PABA竞争二氢蝶酸合成酶，因而干扰了原虫的叶酸代谢，影响DNA的合成，从而发挥其抗疟效果。

叶酸或甲酰四氢叶酸钙对硝喹的抗疟作

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用无拮抗效应，可能与疟原虫不能利用外源性叶酸有关[4]。硝喹除对疟原虫二氢蝶酸合成酶有作用外，对疟原虫叶酸代谢的其它环节，如二氢叶酸还原酶亦可能有作用，因硝喹的抗疟作用可被氨苯砜（DDS）明显地加强[5]。对乙胺嘧啶耐药的伯氏疟原虫（乙胺嘧啶CD_{50}为101.13±10.45mg/kg）或对乙胺嘧啶敏感的约氏疟原虫（乙胺嘧啶CD_{50}为0.59±0.03mg/kg）对它都敏感，说明硝喹的抗叶酸代谢，不单作用于一个环节，而可能作用在多个环节上。

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Effect of Nitroquine on Folate Metabolism of Mice Plasmodia

Zhu Qingping, Hu Youmei, Liu Fuan,

(Department of Pharmacology, Third Military Medical College)

In order to locate the level of nitroquine action on the folate metabolism, nitroquine was given to the mice infected with P. berghei or P. yoelii. To the first group of mice, different doses of nitroquine were given to its five subgroups. The second group of mice received the same doses of nitroquine as the first group but calcium leucovorin (folinic acid) 6 mg/kg/day intramuscularly, folic acid 20 mg/kg/day intramuscularly, or PABA 20 mg/kg/day orally were given to different subgroups respectively at the same time.

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It was found that the dose-effective curve of nitroquine was shifted to the right when PABA was administered simultaneously and the CD_{50} of nitroquine at that time was larger than that of nitroquine used singly. Both calcium leucovorin and folic acid essentially showed no antigonistic effects.

From the antigonistic action of PABA against nitroquine, it is suggested that nitroquine is likely to achieve its antimalarial effect through its competition for dihydropteric acid synthetase with PABA. Other chains on the folic acid metabolism were also discussed.

(上接 178 页)

a hugely enlarged heart shadow with a spherical configuration due to the marked dilatation of the right atrium. The infundibulum of the right ventricle was prominent and the pulmonary artery segment was depressed. There was diminished pulmonary vascularity with narrow vascular pedicle. On fluoroscopy and kymograph, except for the upper left border where vigorous pulsations existed, all parts of both cardiac borders showed much weakened pulsations. The angiographic findings of this group of patients were similar to those described in the textbooks or other references.

A discussion was made on the differentiation of this anomaly from the tetralogy and trilogy of Fallot on plain films. The differentiation of Ebstein's anomaly from tetralogy was considered to be easy since the cardiac configurations of the two diseases are quite different. Three points were listed to be the differentiating criteria between Ebstein's anomaly and trilogy.

In case the diagnosis of Ebstein's anomaly on plain films is not conclusive, or specific anatomical or hemodynamical abnormalities are required to be demonstrated, right cardiac catheterization and angiographic study should be performed.

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