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7种抗疟药抑制疟色素形成及其体外、体内抗日本血吸虫作用的比较观察

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Comparative Observation on Inhibition of Hemozoin Formation and Their in vitro and in vivo Antischistosome Activity Displayed by Antimalarial Drugs

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摘要 目的 比较、观察7种抗疟药抑制疟色素（hemozoin）的形成，与其体外和体内抗血吸虫的作用。 方法 抑制疟色素形成是通过观察25 μmol/L磷酸氯喹、盐酸奎宁、奎尼丁、盐酸甲氟喹、磷酸咯萘啶和苯芴醇，以及100 μmol/L蒿甲醚在pH 4.0～5.0的乙酸钠-高铁血红素（hematin）溶液中对β-hematin形成的抑制作用。用含10%小牛血清的RPMI 1640培养基培养日本血吸虫成虫，测定上述7种抗疟药的半数和95%致死浓度（LC50和LC95）。观察奎宁、氯喹和咯萘啶伍用氯化血红素对体外培养血吸虫的致死作用，以及7种抗疟药口服或腹腔注射对感染日本血吸虫成虫小鼠的疗效。 结果 25 μmol/L咯萘啶对pH 4.4～5.0的乙酸钠溶液中的hematin具有明显抑制β-hematin形成的作用，抑制率为81.3%～97.0%。在pH为4.6的乙酸钠-hematin溶液中，25 μmol/L甲氟喹、氯喹或奎宁对β-hematin形成的抑制率分别为79.7%、72.8%和65.8%；在pH为4.8～5.0的乙酸钠-hematin溶液中，上述3种药物明显抑制β-hematin的形成，抑制率分别为83.1%～90.6%、41.9%～49.0%和53.2%～62.0%。25 μmol/L本芴醇在pH为4.6、4.8和5.0的乙酸钠-hematin溶液中分别有74.3%和40.4%～40.5%的β-hematin形成抑制率。在相同浓度下，奎尼丁在pH为4.8和5.0的乙酸钠-hematin溶液中对β-hematin形成的抑制率分别为53.4%和50.9%，而100 μmol/L蒿甲醚对pH 4.4～4.8的乙酸钠-hematin溶液中的β-hematin形成仅有轻度抑制作用，抑制率为16.6%～25.0%。甲氟喹、咯萘啶、奎宁和奎尼丁对体外培养血吸虫的LC50和LC95分别为4.93和6.123 μg/ml，37.278和75.703 μg/ml，93.688和134.578 μg/ml，101.534和129.957 μg/ml；而血吸虫在含100或120 μg/ml氯喹、本芴醇和蒿甲醚的培养液中培养3 d，无或仅少数虫体死亡。用对血吸虫无效的奎宁50 μmol/L（20 μg/ml）和氯喹50 μmol/L（26 μg/ml）与氯化血红素153.4 μmol/L（100 μg/ml）伍用培养血吸虫，前者在培养的1～3 d内全部虫体死亡，而氯喹与氯化血红素伍用组仅18.8%（3/16）的虫体死亡。相反，对血吸虫具有杀灭作用的咯萘啶50 μmol/L （46 μg/ml） 与氯化血红素153.4 μmol/L （100 μg/ml）伍用示拮抗作用，无虫体死亡。感染血吸虫成虫的小鼠每天口服氯喹、咯萘啶和本芴醇400 mg/kg，连服3 d，或前两者每天腹腔注射100 mg/kg，连续2～3 d，均无效。顿服蒿甲醚、奎宁和奎尼丁400 mg/kg或甲氟喹200 mg/kg均有明显疗效，减虫率为61.1%～98.1%。 结论 7种抗疟药抑制疟色素形成的作用与体外和体内抗血吸虫作用无明确的相关性。奎宁与氯化血红素伍用可明显增强其体外抗血吸虫的作用，而咯萘啶与氯化血红素伍用则示拮抗作用。

关键词： 日本血吸虫 抗血吸虫作用 抗疟药 疟色素 氯化血红素 体外试验 体内试验

Abstract： Objective To observe and compare the inhibition of hemozoin formation and the in vitro as well as in vivo antischistosomal activity induced by seven antimalarial drugs. Methods Inhibition of hemozoin formation displayed by chloroquine phosphate， quinine hydrochloride， quinidine， mefloquine hydrochloride， pyronaridine phosphate and lumefantrine at 25 μmol/L， and artemether at 100 μmol/L was performed by assay of inhibition of β-hematin formation in 1 mol/L sodium acetate buffers containing hematin with various pH of 4.0， 4.2， 4.4， 4.6， 4.8， and 5.0. In in vitro antischistosomal study， the medium of RPMI 1640 supplemented by 10% calf serum was used to maintain the adult Schistosoma japonicum， and the 50% and 95% lethal concentratrions（LC50 and LC95） to kill the adult worms of each drug were then determined. Meanwhile， the interaction of quinine， pyronaridine and chloroquine combined with hemin against adult schistosomes was also undertaken. As to in vivo test， the efficacy of seven antimalarial drugs administered orally or intraperitoneally to mice infected with adult schistosomes was observed. Results In the acidic acetate-hematin solution， 25 μmol/L pyronaridine showed significant inhibition of β-hematin formation at pH 4.4-5.0 with inhibition rates of 81.3%-97.0%. At pH 4.6， the inhibition rates of β-hematin formation in acetate-hematin solution induced by mefloquine， chloroquine or quinine at concentration of 25 μmol/L were 79.7%， 72.8% or 65.8%， respectively， and the β-hematin formation was continually inhibited by these 3 antimalarial drugs at pH 4.8 and 5.0 with inhibition rates of 83.1%-90.6%， 41.9%-49.0% or 53.2-62.0%. The inhibition rates of β-hematin formation at pH 4.6 and 4.8-5.0 induced by lumefantrine 25 μmol/L were 74.3% and 40.4%-40.5%， respectively. While under the same concentration of quinidine， 53.4% and 50.9% inhibition rates of β-hematin formation were observed at pH 4.8 and 5.0. As to artemether， higher concentration of 100 μmol/L only showed light inhibition of β-hematin

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formation at pH 4.4-4.8 with inhibition rates of 16.6%-25.0%. As regard to in vitro test, the LC50 and LC95 of mefloquine, pyronaridine, quinine and quinidine were 4.93 and 6.123 μg/ml, 37.278 and 75.703 μg/ml, 93.688 and 134.578 μg/ml, as well as 101.534 and 129.957 μg/ml, respectively. When adult schistosomes were exposed to the medium containing chloroquine, lumefantrine or artemether at higher concentrations of 100 or 120 μg/ml for 72 h, no or only individual worms died. Hence the LC50 and LC95 of these 3 drugs could not be determined. In other in vitro test, adult schistosomes exposed to quinine 50 μmol/L (20 μg/ml) in combination with 153.4 μmol/L (100 μg/ml) hemin, all worms died within 72 h post incubation. While the worms exposed to 50 μmol/L (26 μg/ml) chloroquine combined with the same concentration of hemin, only 18.8% (3/16) of worm died at 72 h post exposure. Unexpectedly, in schistosomes exposed to pyronaridine at a toxic concentrations of 50 μmol/L (46 μg/ml) in combination with 153.4 mol/L (100 μg/ml) hemin for 72 h, all of the worms were protected from the toxic action induced by pyronaridine, which revealed in normal motor activity and appearance of morphology in majority of the worms. In in vivo test, mice infected with adult schistosomes were treated orally with chloroquine, pyronaridine or lumefantrine at a daily dose of 400 mg/kg for 3 days, or intraperitoneally with chloroquine or pyronaridine at a daily dose of 100 mg/kg for 2 or 3 days, no apparent efficacy was seen. When mefloquine, quinine, quinidine or artemether were administered orally to infected mice at a single dose of 400 mg/kg or 200 mg/kg (mefloquine), all groups of mice treated showed moderate or higher efficacy with worm burden reductions of 61.1%-98.1%. Conclusion