



阿苯达唑壳聚糖微球抗小鼠细粒棘球蚴药效实验研究

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Efficacy of Albendazole Chitosan Microspheres against *Echinococcus granulosus* Infection in Mice

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摘要

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摘要 目的 观察阿苯达唑壳聚糖微球 (ABZ-CS-MPs) 治疗感染细粒棘球蚴 (*Echinococcus granulosus*) 小鼠的效果。方法 220只雄性昆明小鼠, 除20只作空白对照组外, 其余小鼠各腹腔接种细粒棘球蚴原头节约5 000个, 于感染12周后将小鼠随机分为感染对照组 (n=20)、ABZ-CS-MPs组、阿苯达唑脂质体 (L-ABZ) 组和阿苯达唑片剂组, 后3组按不同治疗剂量37.5、75.0 和150.0 mg/ (kg·次) 再分为3小组 (每组20只小鼠), 每鼠灌胃相应剂量药物, 每周3次, 每次间隔1 d。感染对照组不作治疗。各组受治鼠于连续治疗12周后处死, 称取各鼠细粒棘球蚴的囊湿重, 计算各组的囊重抑制率。取各组小鼠肝脏进行大体形态观察。HE染色观察细粒棘球蚴组织病理变化。高效液相色谱法测定小鼠血液和肝脏中阿苯达唑主要代谢产物阿苯达唑亚砜 (ABZSX) 的浓度。结果 ABZ-CS-MPs组小鼠棘球蚴囊混浊、实变或钙化程度均较其他治疗组明显。各药物治疗组小鼠棘球蚴囊湿重均显著低于感染对照组 [(3.19±2.94) g] (P<0.05), ABZ-CS-MPs组囊湿重 [低剂量至高剂量组分别为 (0.28±0.28)、(0.24±0.22) 和 (0.20±0.19) g] 显著低于阿苯达唑片剂组 [(0.77±0.74)、(0.55±0.42) 和 (0.76±0.35) g] (P<0.05)。ABZ-CS-MPs组小鼠棘球蚴囊重抑制率均为同剂量药物组中最高, 低剂量组到高剂量组分别为91.1%、92.6%和93.7%。HE染色结果显示, 75.0 mg/ (kg·次) ABZ-CS-MPs组细粒棘球蚴组织 I 和 II 级病理变化的小鼠数量最多 (15/18)。不同剂量ABZ-CS-MPs组和L-ABZ组细粒棘球蚴组织 I 和 II 级病理变化的小鼠数量均高于同剂量阿苯达唑片剂组 (P<0.05)。高效液相色谱法结果显示, 75.0 和150.0 mg/ (kg·次) ABZ-CS-MPs组小鼠血液中的ABZSX浓度 [(0.83±0.39) 和 (0.80±0.50) μg/mL] 显著高于同剂量L-ABZ组 [(0.34±0.03) 和 (0.43±0.15) μg/mL] 和阿苯达唑片剂组 [(0.31±0.02) 和 (0.40±0.10) μg/mL] (P<0.05); ABZ-CS-MPs组小鼠肝脏中的ABZSX浓度 [低剂量至高剂量组分别为 (0.33±0.06)、(0.45±0.31) 和 (0.50±0.30) μg/g] 显著高于阿苯达唑片剂治疗组 [(0.04±0.02)、(0.07±0.04) 和 (0.04±0.03) μg/g] (P<0.05), 37.5mg/ (kg·次) ABZ-CS-MPs组ABZSX浓度高于同剂量L-ABZ组 [(0.14±0.19) μg/g] (P<0.05)。结论 阿苯达唑壳聚糖微球可明显抑制小鼠细粒棘球蚴囊湿重, 并提高阿苯达唑主要代谢产物阿苯达唑亚砜在小鼠血液和肝脏中的浓度。

关键词: 细粒棘球蚴 阿苯达唑 壳聚糖微球 脂质体 昆明小鼠

Abstract: Objective To observe the therapeutic effect of albendazole chitosan microspheres (ABZ-CS-MPs) on cystic echinococcosis in mice. Methods Two hundred male kunming mice were each infected by intraperitoneal inoculation of about 5 000 viable protoscoleces of *Echinococcus granulosus*. Another 20 mice were kept as blank control. After 12 weeks post infection, the mice were randomly divided into four groups named as infection control group (n=20), ABZ-CS-MPs group, albendazole liposome (L-ABZ) group, and albendazole tablet group. The latter three treatment groups were then each divided into three subgroups (n=20) by given the dose of 37.5, 75.0, and 150.0 mg/kg for three times per week, respectively. After 12 weeks of treatment, all mice were sacrificed. The weight of hydatid cysts was measured and the inhibition rate were calculated. Mouse liver was observed. The histopathological changes of *E. granulosus* were observed by microscopy. The concentration of albendazole sulfoxide in plasma and liver tissues was determined by high-performance liquid chromatography. Results Compared with the other treatment groups, the turbidity of contained fluid, the consolidation level and calcification level of hydatid cysts in ABZ-CS-MPs group were higher. The average weight of hydatid cysts in each treatment group was lower than that of infection control group [(3.19±2.94) g] (P<0.05). The cyst weight in 37.5, 75.0, and 150.0 mg/kg ABZ-CS-MPs group [(0.28±0.28), (0.24±0.22), and (0.20±0.19) g, respectively] was lower than that of albendazole tablet groups [(0.77±0.74), (0.55±0.42), (0.76±0.35) g] (P<0.05). Among the same dosage groups, the inhibition rate in ABZ-CS-MPs group (from low to high dosage sub-group: 91.1%, 92.6%, and 93.7%, respectively) was highest. In 75.0 mg/kg ABZ-CS-MPs group, there were 15 mice with class I (degeneration) and II (necrosis) pathological changes of *E. granulosus* hydatid. The number of mice with class I and II pathological changes in each dosage ABZ-CS-MPs sub-group and L-ABZ sub-group was more than that of albendazole tablet group (P<0.05). Plasma concentration of albendazole sulfoxide in 75.0 and 150.0 mg/kg ABZ-CS-MPs sub-groups [(0.83±0.39), (0.80±0.5) μg/ml] were higher than that of L-ABZ sub-groups [(0.34±0.03), (0.43±0.15) μg/ml] and albendazole tablet sub-groups [(0.31±0.02), (0.40±0.10) μg/ml] (P<0.05); ABZ-CS-MPs group mouse liver ABZSX concentration [low dose to high dose group respectively (0.33±0.06), (0.45±0.31) and (0.50±0.30) μg/g] was significantly higher than albendazole tablet treatment group [(0.04±0.02), (0.07±0.04) and (0.04±0.03) μg/g] (P<0.05), 37.5mg/ (kg·次) ABZ-CS-MPs group ABZSX concentration was higher than L-ABZ group [(0.14±0.19) μg/g] (P<0.05). Conclusion Albendazole chitosan microspheres can significantly inhibit the wet weight of mouse hydatid cysts, and increase the concentration of albendazole sulfoxide in mouse blood and liver.

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$\mu\text{g/ml}$] ($P < 0.05$). Compared with 37.5, 75.0, and 150.0 mg/kg albendazole tablet sub-groups [(0.04 ± 0.02) , (0.07 ± 0.04) , (0.04 ± 0.0) $\mu\text{g/g}$], the albendazole sulfoxide concentration in liver tissue was higher in ABZ-CS-MPs sub-groups [(0.33 ± 0.06) , (0.45 ± 0.31) , (0.50 ± 0.30) $\mu\text{g/g}$] ($P < 0.05$). In 37.5 mg/kg dosage sub-group, the albendazole sulfoxide concentration in liver tissue in ABZ-CS-MPs group was higher than that of L-ABZ group [$(0.14 \pm$