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论文

N-(2-羟丙基)甲基丙烯酰胺聚合物-5-氟尿嘧啶接合物的体外释药规律、体内分布及抗肿瘤活性研究

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摘要:

考察本实验室合成的*N*-(2-羟丙基)甲基丙烯酰胺［*N*-(2-hydroxypropyl) methacrylamide，HPMA］聚合物-5-氟尿嘧啶(5-flurouracil，5-FU)接合物(P-FU)的体外释药、体内分布及抗肿瘤活性。以小鼠血浆为介质，考察P-FU中5-FU的释放规律；以小鼠H22肝癌实体瘤模型(皮下型)为肿瘤模型，考察接合物在荷瘤小鼠体内的分布情况、药代动力学规律及抑瘤活性。结果表明，37 ℃时P-FU在小鼠血浆中具有一定的稳定性，半衰期($t_{1/2}$)为32.4 h。与5-FU相比，P-FU在荷瘤小鼠体内的循环时间明显延长(血浆中$t_{1/2}$为原药的166倍)，在肿瘤中的沉积量(AUC为5-FU的3.3倍)及滞留时间($t_{1/2}$为5-FU的2.3倍)均有明显增加。体内药效学研究表明，P-FU组对荷瘤小鼠的肿瘤生长抑制率(69.09%)显著高于5-FU组(56.49%，$P<0.05$)，瘤块组织病理学观察结果也显示P-FU组小鼠肿瘤组织中细胞凋亡程度大于5-FU组。HPMA聚合物可被用于为5-FU构建一种新型实体瘤高分子给药系统。

关键词： *N*-(2-羟丙基)甲基丙烯酰胺聚合物 5-氟尿嘧啶 抗肿瘤药物

In vitro release study, *in vivo* evaluation of biodistribution and antitumor activity of HPMA copolymer-5-fluorouracil conjugates

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Abstract:

The *in vitro* release behavior, *in vivo* biodistribution and antitumor activity of *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-5-fluorouracil conjugates (P-FU) were studied. The *in vitro* release behavior was evaluated by determining the amount of 5-fluorouracil (5-FU) released from P-FU in mice plasma at 37 ℃. The *in vivo* biodistribution and therapeutic evaluation were investigated with Kunming mice bearing hepatoma 22 (H22). The *in vitro* half-life ($t_{1/2}$) of P-FU in mice plasma was 32.4 h. It appeared that the circulation life time of the conjugates were 166 times longer than that of 5-FU. The AUC and $t_{1/2}$ of P-FU in tumor were 3.3 times and 2.3 times more than those of 5-FU, respectively. Therapeutic evaluation also demonstrated that the treatment with P-FU displayed stronger inhibition of the tumor growth when compared with that of 5-FU ($P<0.05$). HPMA copolymer is a potential carrier for 5-FU for effective treatment of cancer.

Keywords: 5-fluorouracil antitumor drug *N*-(2-hydroxypropyl) methacrylamide copolymer

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