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Experimental Study

Assessment of localized therapeutic effect for prolonged release biodegradable implants loaded with 5-Fluorouracil on rats with induced liver cancer

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المخلص

أهداف البحث: يهدف هذا البحث إلى تقييم قدرة الحقن المنغرس القابل للتحلل المحمل بالدواء 5 فلورويوراسيل من تحقيق أقصى قدر من التعرض الموضعي من الدواء مع الحد من سميته الجهازية في الفئران المصابة بسرطان الكبد المستحث.

طرق البحث: بعد إحداث سرطان الكبد في فئران ويستار الذكور بنجاح باستخدام بروتوكول مختار تلى ذلك غرس غرسة محملة بـ 5- فلورويوراسيل القابل للتحلل. ثم تم ذبح الفئران على فترات زمنية متفرقة وتم تجميع الدم واستخدامه لأداء مختلف التجارب، كما تم استرجاع الغرسات وتحليلها لحساب كمية الدواء المتبقي فيها باستخدام جهاز قياس لون السوائل عالي الضغط. وأجريت أيضا دراسة للكبد ومستوى أنزيمات كبد الفئران، وحساب نسبة وزن الكبد إلى وزن الجسم، وتحليل صورة الدم كاملة. كما فحصت أنسجة الكبد لتقييم علامات نخر الكبد.

النتائج: لوحظ وجود مناطق نخر في عينات أنسجة كبد الفئران بعد 5 أيام في محيط من 0,3 - 0,6 سم حول غرسات الجهاز مما يدل على تأثير علاجي

موضعي لـ 5- فلورويوراسيل. وكذلك تم الكشف عن استمرار تأثير الدواء في الفئران لمدة شهرين تقريبا، كما تم حساب الكميات التي تصل إلى الدم من الجهاز المحمل بـ 5- فلورويوراسيل لتمثل أقل من 13%.

الاستنتاجات: الحقن المنغرس القابلة للتحلل البيولوجي المغلفة والمصنعة والمحملة بـ 5 – فلورويوراسيل يمكن أن تكون شكل علاجي واعد لعلاج سرطان الكبد.

الكلمات المفتاحية: حمض عديد اللينيك; في الجسم الحي; المضادة للسرطان; فئران ويستار

Abstract

Objectives: The objective of this research was to assess ability of biodegradable implantable 5-Fluorouracil dosage forms, to maximize the regional exposure of the drug while limiting its systemic toxicity in rats with induced liver cancer.

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Methods: Liver cancer was successfully induced in male Wistar rats using a selected protocol followed by surgical implantation of prepared 5-FU biodegradable implant. Rats were sacrificed at time intervals and the pooled blood used to perform the different tests and the implant was retrieved, and analyzed to calculate the amount of drug left in implant. The amount of 5-FU in blood was quantified using high pressure liquid chromatography (HPLC). Gross examination of rat liver, calculation of liver to body weight percentage, and complete blood picture analysis were also performed. Liver biopsies were examined to assess signs of liver necrosis.

Results: Localized necrotic areas were noted in rat liver biopsies after 5 days with a perimeter of 0.3 to 0.6 cm around the implants indicating the localized 5-FU therapeutic effect. Sustained drug release was detected in rats for about 2 months and the amount of 5-FU released from implant into the systemic circulation was found to represent less than 13%.

Conclusion: PLA coated injection molded implants loaded with 5-FU could present a promising dosage form for liver cancer treatment.

Keywords: Anticancer; In vivo; Poly-L-lactic acid (PLA); Wistar rats

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Introduction

Liver cancer is one of the major lethal malignancies worldwide. The main histological subtype is hepatocellular carcinoma (HCC), which is derived from hepatocytes, the predominant epithelial cell type in the liver.^{1,2} Surgery is the only curative modality for HCC, if the cancer is localized. Standard chemotherapy approaches and external beam radiation for treatment of HCC have little utility. The liver and its surrounding viscera are very sensitive to radiation. Thus, the dose required to achieve a decrease in tumor size will kill the host due to liver failure. Similarly, chemotherapy as a primary or adjuvant approach has had no benefit. A good reason for not using standard chemotherapy is that liver cancer patients often have marked decrease in their ability to metabolize drugs and thus often experience significant systemic toxicity.²

The poor efficiency of conventional anticancer drugs can be explained by the special solid tumor structure like liver and brain tumors.³ This would prevent anticancer drugs from reaching the tumor area in required concentration, and the doses of anticancer drug have to be increased consequently. However, toxicity is a very limiting factor for most of the chemotherapeutic agents. Therefore, there is a need for a therapy, that would be able to concentrate drugs close to the tumor site, and avoid their too large distribution.³

Local administration of biodegradable polymeric drug delivery systems can present a promising method that gives clinicians the opportunity to deliver large dose of chemotherapeutic drugs close to the tumor site for a prolonged period of

time. This would help to augment the therapeutic effect of chemotherapy together with minimizing the possible toxic side effect.⁴ 5-Fluorouracil (5-FU) was selected as a model chemotherapeutic drug as it is one of the widely used anticancer drugs for liver cancer treatment.⁵

This research work aimed to assess ability of implantable dosage forms in liver cancer region, manufactured using biodegradable polymers like Polylactic acid (PLA) and loaded with 5-Fluorouracil, to concentrate 5-FU in liver cancer region, and decrease the systemic exposure and side effects in rats with induced liver cancer.⁶

Materials and Methods

Materials

PLA was prepared as previously described.⁶ Methyl nitroso Urea (MNU), Diethyl nitrosamine (N-Nitrosodiethylamine) (DEN) No: 7566 and N-(2-fluorenyl)acetamide (AAF) A7015 were bought from SIGMA, USA. Carbon Tetrachloride (CCl₄) was bought from ADWIC Co. (Elnasr Pharmaceutical Chemical Company), Egypt. Ethanol 95%, Formalin 10%, Dimethyl Sulfoxide (DMSO) (high purity grade), corn oil, sterile sodium chloride solution 0.9%, heparin (5000 IU) ampoules (Nile Co.), Nylon sutures, Catalar anesthesia, Betadine surgical solution, Ciprofloxacin Hydrochloride powder (Cipla Co.), Cataflam drops, 5-Fluorouracil powder (Beckmann Chemikalien KG), trichloroacetic acid (TCA) (Analar grade), ethyl acetate (Analar grade), sodium hydroxide (high purity grade), Potassium dihydrogen phosphate (Analar grade).

Preparation of 5-FU biodegradable implants

PLA injection molded implant formulation containing an equivalent amount of 12 mg 5-FU per 120 mg implant and coated with 200 mg PLA and which produced in vitro prolonged release for approximately 45 days as has been previously described.⁶ PLA implants were sterilized using gamma radiation at 25 kGy under air prior to implantation.⁷

Induction of liver cancer in Wistar rats

Two different protocols were used to induce liver cancer in Wistar rats weighing 100 g each. The first protocol included injecting rats with 60 mg/kg MNU dissolved in sodium citrate 0.01 M pH 6 intraperitoneally (ip injection), on day 26 the injected rats received CCl₄ 2 mL/kg dissolved in corn oil by gavage.⁸ While, the second protocol included injecting rats with 200 mg/kg DEN (Diethyl nitrosamine) dissolved in 0.9% sodium chloride intraperitoneally (ip injection), on days 18,19,20, and 22 a daily gavage dosage 20 mg/kg of 2-AAF dissolved in DMSO and corn oil, (1:29 V/V) was given to Wistar rats. On day 21, 2 mL/kg of CCl₄ in corn oil was given to Wistar rats by gavage.⁹ On days 42 and 72, 6 rats were examined from control and treated group using the tests discussed below to decide if successful induction of liver cancer occurred. Rats were examined physically for any rat skin color change and for presence of rat fur sheds. Rats were then

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