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ARTICLE

Intrahepatic Arterial Delivery of Sorafenib Eluting Beads: A Pharmacokinetics Study

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ABSTRACT

Objective: To determine the slow-release effect of Sorafenib carried beads and its impact on the normal liver of dogs. **Materials and Methods:** (1) To obtain the maximal drug-carrying of beads, different sizes of beads (300-500 μm and 500-700 μm) were tried. Five bottles of different sizes of beads were added into 75% solution of Sorafenid-alcohol with different concentrations: Bottle a,50mg/20ml; Bottle b, 100mg/20ml; Bottle c, 100 mg/40ml; Bottle d, 200mg/40m; Bottle e, 250mg/50ml. (2) In vivo study: 12 dogs were randomly divided into four groups [group A, Sorafenib carried bead (500-700μm); group B, only bead (300-500μm) ; group C, Lipiodol-sorafenib and four dogs in each group. Each group was treated with TAE with emulsion mentioned above. Sorafenib concentration in plasma and liver tissue was determined with HPLC respectively. **Result:** (1) In vitro research: Sorafenib can be dissolved into 75% alcohol and the best concentration for drug-carrying was 100mg/20ml. (2) In vivo study: ① Compared with group D, the Cmax and AUC in plasma in group A and B has a significant statistics difference($p<0.05$)② Sorafenib concentration in liver tissue could be determined in group A in the 3rd day and even after one week while it could not be determined in group D. **Conclusion:** Sorafenib can be carried in DC-Bead in a certain condition. Compared with emulsion with Sorafenib and lipiodol, DC-bead has a definite slow-release function and it is superior to lipiodol.

1. Introduction

Transcatheter arterial chemoembolization (TACE) is the first choice for the treatment of unresectable primary liver cancer and a minimally invasive interventional treatment technology injecting the chemotherapeutic drug-lipiodol emulsion and embolization inactivation tumor tissue into the local tumor supplying artery through the catheter guided by angiography and other imaging devices. However, there are many shortcomings in using lipiodol as carrier [1-2]: uncontrollability and instability. Therefore, a new drug carrier is urgently needed so as to enhance the sustained-release capability of Sorafenib and improve the capability of tumor inhibition and angiogenesis.

The emergence of new DC-bead provides us with new hope. DC-bead is a kind of drug embolism bead with sul-

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fonate (negative charge in solution) synthesized by N-Fil process based on PVA particles[3-4]. Through ion exchange mechanism, the new carried DC-bead can absorb and release chemotherapeutic drugs continuously and at a high concentration, so as to kill tumor tissues and reduce the toxicity to normal tissues.

Based on the above principles, we have carried out an exploratory experimental research of Sorafenib (doxorubicincarried DC-bead) toluene sulfonate. It was found that DC-bead has the mechanism of ion exchange of Sorafenib powder. The structure of toluenesulfonic acid Sorafenib is composed of toluenesulfonic acid and Sorafenib. Toluene sulfonic acid, with acid group, plays the role of material stability; Sorafenib with basic group. In the solution, toluene sulfonic acid and Sorafenib exist in the form of salt, toluene sulfonic acid (SO3 -) has negative charge, Sorafenib (NH +) has positive charge. It has the base of ion exchange with DC — Bead (SO3 -). The purpose of this study is to demonstrate the feasibility of DC — bead carrying Sorafenib powder, investigate its slow-release effect in vivo, evaluate its effect on normal liver tissue and provide experimental parameters for clinical application.

2. Materials and Methods

2.1 Materials

2.1.1 Animals

16 healthy mongrels, 8 males and 8 females, with weighs of 15-19kg and provided by Experimental Animal Center of PLA General Hospital. The animal experiment was approved by the Animal Management Committee of PLA General Hospital.

2.2.2 Drug

Biological target preparation - Sorafenib powder. The tablet is provided by Bayer free of charge and refined by the biochemical room of the Academy of Military Medical Sciences.

3. Methods

3.1 In Vitro Pre Experiment: to Observe Whether DC -Bead Has the Function of Carrying Sorafenib

3.1.1 Dissolving Sorafenib Powder In 75% Ethanol

Add raw Sorafenib powder (100mg) into 2ml solution of 75% ethanol for continuous ultrasonic vibration. Then observe the form of Solafenib powder in ethanol solution at different time points (such as 30min, 1h, 2h), and judge whether it is completely dissolved in ethanol solution. If it has been completely dissolved, we can gradually increase 5 mg per time of Solafenib powder on this basis, and carry out continuous ultrasonic vibration. If it can't be completely dissolved, add 2ml per time of ethanol solution with the same amount of Sorafenib, increase gradually, and continue to carry out ultrasonic vibration.

According to the pre experiment, dissolve 100 mg Sorafenib powder in 75% ethanol, and 20ml ethanol is needed. The solubility is C = 100/20 = 5mg/ml. (Note: This is the maximum dissolved concentration).

3.1.2 Adsorbing Sorafenib with DC-bead (500-700um)

Filter the DC-bead solution through sterile filter paper, filter out the supernatant of DC-bead, put the DC-bead on the filter paper into the prepared sorafenib-75% ethanol solution, and place them in a 4^0C refrigerator for full mixing, homogenization and standing for 24h.

3.1.3 Determining Sorafenib Concentration by HPLC Analysis

HPLC analysis conditions: phenomenex C8 column (5μ, 261mmx4. 6mmx5um); mobile phase: triethylamine phosphate buffer (990ml of ultra-pure water plus 10ml of triethylamine, adjust pH to 5.4 with phosphoric acid): acetonitrile = 50:50; flow rate: 1.0m1/min; detection wavelength: 261nm; column temperature: 25^0C.

3.1.4 Determining the residual Drug Concentration of DC Bead

Firstly, prepare standard solution, and obtain $CX = C_R x A_X /AR$, in which standard CR = 0.22mg/ml, Ar = 51713977, which is the peak area of standard. According to the peak area of the sample and the formula, obtain the concentration of the sample is 0.186mg/ml. Determine the content of Sorafenib in the residual solution as M residue = 18.6mg. After 24 hours of standing, the percentage of DC bear with a diameter of 500-700um will be DC% = (M total –M residue) / M sample total = (100-18.6) / 100 = 81.4%.

3.2 In Vitro Experiment

3.2.1 Purpose

To investigate the characteristics of Sorafenib adsorbed by DC-bead with different particle sizes, obtain the maximum carrying quantity and the best carrying concentration, and improve the experimental parameters for in vivo experiments.

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3.2.2 Experimental Design

Select 5 bottles of DC-bead particles of different sizes (300-500um and 500-700um) and put them into the Solafeni ethanol solution with different concentrations, a: 50mg/20ml, b: 100mg/20ml, c: 100mg/40ml, d: 200mg/40ml, e: 250mg/50ml. Compare the Sorafenib content in different concentrations (e.g. a and b) and the same concentration (a and c), an obtain the maximum carrying quantity of DC-bead of different particle sizes, so as to provide experimental basis for clinical application. In this experiment, the maximum dissolved concentration (100mg/20ml) of 500-700um DC bead is taken as the reference object.

3.2.3 The Carrying Procedures of Different Sizes of DC-Bead and Sorafenib Powder Are Shown in the Vitro Pre-Experiment Steps

3.3 In Vivo Experiment

3.3.1 Experimental Design

Select 12 mongrels with a weight of 15-17kg including 6 females and 6 males, and randomly divide them into three groups according to the random number method with four each group, respectively: group A: DC-bead (500-700um) - Sorafenib group, group B: DC-bead (300-500um) group, and group C: lipiodol Sorafenib group. Conduct transcatheter embolization of the right branch of the hepatic artery, observe the changes of liver function between pre-embolization and post- embolization 3 days, 1 week, 2 weeks and 3 weeks after embolization. Observe the drug concentration in peripheral blood at 10min, 30min, 1h, 4h, 16h, 1day, 2days, 4days, 7days, 10days and 14days after operation. Kill the animals in the three groups at 3 days, 1 week, 2 weeks and 3 weeks after operation respectively, and measure the local Sorafenib concentration of liver tissue after treatment.

3.3.2 Hepatic Artery Intubation Technology (Figure 1, 2, 3, 4)

After intravenous anesthesia, fix an experimental dog in the center of the large animal plate against its back, prepare skin for the right groin, disinfect and cover with a towel, expose the right femoral artery, puncture the femoral artery with a 21g micro puncture needle under the direct vision, introduce a supporting 4f soft sheath (micro puncture system, a product of American COOK), and insert a 4f arterial sheath (24cm, Terumo Corp., Japan). Under fluoroscopy, insert a 4F RH catheter (Terumo Corp. Japan) or a cobra catheter (cordis Corp. USA) into the celiac artery for routine Celiac Arteriography. The contrast medium used for contrast is Euvism (370mgi / ml) with the parameters of 4ml/s, the total volume of 16ml, and the pressure of 300PSI. After angiography (INNOVA 4100, GE, USA) is performed to determine the anatomic details of the hepatic artery, insert a 3F microcatheter (progress, Terumo Corp., Japan) selectively into the right branch of the hepatic artery, and then inject lipiodol Solafenib emulsion (46mg / 5ml lipiodol), DC-bead Solafenib microball and DC-bead beads. Among them, DC-bead Sorafenib is carried with Sorafenib- ethanol (100mg/20ml), which can make the carrying quantity of different size particles basically equal, e.g. 73.0-81.4g, and reduce unnecessary waste of Sorafenib. The end point of interventional embolization will be marked by the presence of contrast retention under fluoroscopy. The actual dosage of experimental animals in group A and group C is A 73.130 ± 6.648, B 71.175 ± 3.650 and D 69 ± 3.464, P = 0.5228 > 0.05.

Remove the catheter and sheath, ligate the right femoral artery and suture the skin after the operation. Keep injecting the gentamicin 20,000 units per Kg of body weight for 3 days

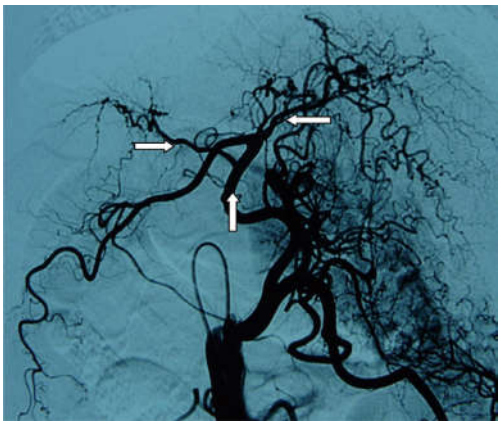

Figure 1. Canine Celiac Arteriography Show: proper hepatic artery (→) and right hepatic artery (↑) and left hepatic artery (←).

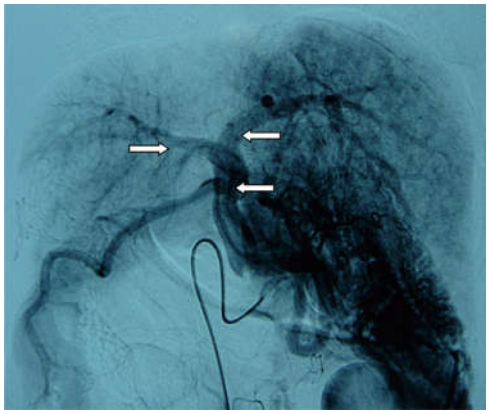

Figure 2. Angiography of the canine celiac artery show: development of the trunk (←) and left branch (←) and right branch (→) in the portal vein phase.

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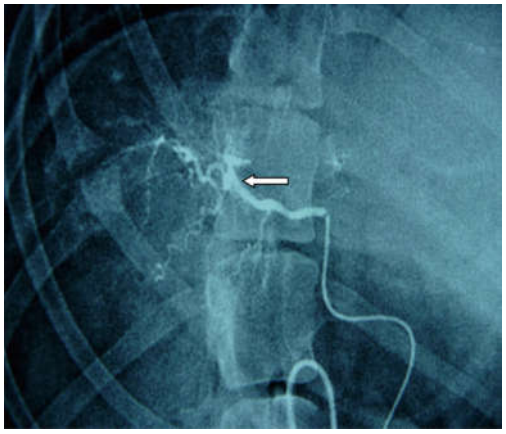

Figure 3. Superselective right hepatic artery embolization with DC-bead-- Sorafenib (←).

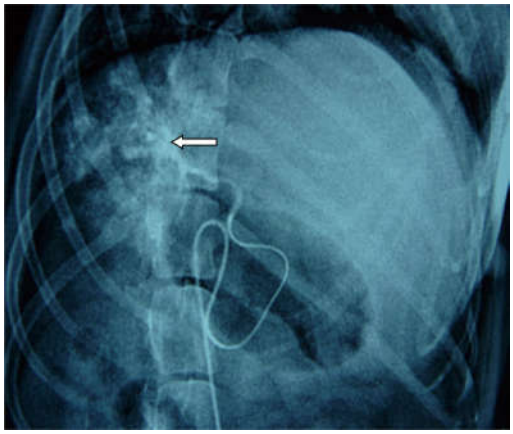

Figure 4. The visible deposition of embolism in the right lobe of the liver (←) after embolization of the right hepatic artery.

3.3.3 Collection of Samples

Observe the peripheral blood drug concentration of experimental animals in different periods of 0 hour (before administration) and 10min, 30min, 1h, 4h, 16h, 1day, 2days, 4days, 7days, 10days, 14 days after operation. Collect blood samples, determine the plasma concentration of Sorafenib by HPLC and investigate the sustained release effect of local administration

3.3.4 Detection of Samples

Determine the concentration of Sorafenib in dog plasma and tissues by HPLC analysis. This part will be completed with the assistance of Pharmacology Research Office of PLA General Hospital.

① HPLC analysis column: chromatographic column: C18 column (10μ, 250 x 4. 0mm); mobile phase: heavydistilled water, water: methanol = 30:70; flow rate: 0. 8m1/min; detection wavelength: 254nm; column temperature: room temperature.

② Preparation of solution:

a. Standard solution: accurately measure 5mg of cisplatin, add normal saline to dilute to 1000ml, and prepare a standard solution with a concentration of 5μ g/ml.

b. NaOH solution: accurately measure 2G of sodium hydroxide, add distilled water to dissolve and dilute to 500ml, and prepare 0.1mol/l NaOH solution.

c. DDTC solution: accurately measure 0.5g of DDTC, clean with 5ml of ether, dry with nitrogen flow, add 10ml of 0.1mol/l sodium hydroxide solution to dissolve, and prepare 5% DDTC solution.

d. Preparation of Na2CO3 solution: accurately measure 1g, add ultra pure water to dissolve and dilute to 100ml, and prepare 0.1mg/ml solution.

e. Preparation of NiCl solution: accurately measure 10mg of NiCl, dissolve it with heavy distilled water and dilute it to 100ml to prepare a solution of 0.1mg/ml.

③ Methods:

a. Processing of plasma sample: 0.6ml of plasma, 0.4ml of 0. 5% sodium carbonate solution, 100 μl of internal standard nickel chloride solution, and 400μl of freshly prepared 5% DDTC solution. Keep vortex oscillation for 15s and 37^0C water for 30min (complexation reaction), and cool down to room temperature. Extract the reaction solution with 2ml of ether, keep vortex oscillation for 5 min, 3000 R / min, and centrifugation for 6 min, and then extract the ether layer. Volatilize in 37^0C water, dissolve the residue in 200μ l chloroform and take 10μ l sample.

b. Tissue sample processing: wash the tissue with normal saline and cut it into pieces. Accurately measure 0.4g (wet weight tissue). Add 100μl of internal standard NiCl solution and 1ml of normal saline, cut them into pieces, homogenize in glass homogenizer for 30min, wash the homogenizer with about 1ml of water, and collect about 2ml of homogenizer. Take 1ml of slurry, keep 4000R / min and centrifugation for 4min, take supernatant, and add 400 μ l of 5% DDTC solution freshly prepared. Keep vortex oscillation for 15s, 37^0C water for 30min (complexation reaction), and cool down to room temperature. Extract the reaction solution with 2 ml of ether, keep vortex oscillation for 5 min, 3000 R / min, and centrifugation for 6 min, and extract the ether layer. Dissolve the residue in 200μl chloroform and take 10μl sample.

④ Linear relationship test:

Take a proper amount of solution under " ② a", add normal saline to dilute it into standard working solution of different concentrations, process it according to the method under " ② b", quantitate it with internal standard method, inject 10μl in turn, conduct regression analysis on corresponding content (X) with peak area (Y), and obtain

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the regression equation: Y = 0.1861X+0.0929 , r = 0.9932 and the regression equation of tissue concentration: Y = 0.1361X — 0.0729 , r = 0.9912, showing the lowest concentration of Sorafenib in plasma and tissue is 0. 1μg/ml. In this experiment, it is determined that the linear relationship of Sorafenib is good in the range of 0. 1-10 μ g / ml.

3.3.5 Observation of Other Indexes after Operation

① Observe liver function changes between pre-embolization and post-embolization at 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks after operation.

② Use deep anesthesia to kill the experimental animals at regular intervals (1, 2, 3, 4 weeks after the operation), take out the liver tissue, soak and fix the normal tissue and necrotic tissue with formalin solution, embed them in paraffin, make 5um sections, and make HE staining.-Observe the pathological changes of liver tissue in different periods, which will be completed with the assistance of the pathology department of PLA General Hospital.

③ Statistical processing: adopt CHISS statistical software, express all measured by x ± s, compare inter-ground data group t inspection or variance analysis (F inspection), and t 'test will be used when the inter-group variance is not uniform or does not conform to normal distribution.

4. Results

4.1 Characteristics of Sorafenib Carried by DC-bead

It is found that sorafenib toluene sulfonate is not (or extremely difficult) directly soluble in aqueous solution, so ion exchange cannot be completed under this condition. However, it has certain solubility in 75% ethanol solution, thus creating conditions for ion exchange

It can be seen from Table 1 that under the same time and the maximum carrying concentration, the carrying of DC-bead with large particles (500-700um) is 63.9 ± 21.7mg/ml, and that of small particles is 57.6 ± 14.8mg/ml, with statistical difference (P = 0.01 < 0.05); under the same time and the same carrying condition, the higher the Sorafenib concentration in 75% ethanol solution, the higher the carrying of DC-bead, however, with the increase of carrying quantity, the carrying rate also gradually decreases. The comparison shows that the maximum carrying of DC-bead with a diameter of 300-500um is 74.4mg; the maximum carrying of DC-bead with a diameter of 500-700um is 82.5mg. With the purpose to prevent excessive loss of residual drugs, the best drug concentration of two different size particles lies in group B (100mg/20ml).

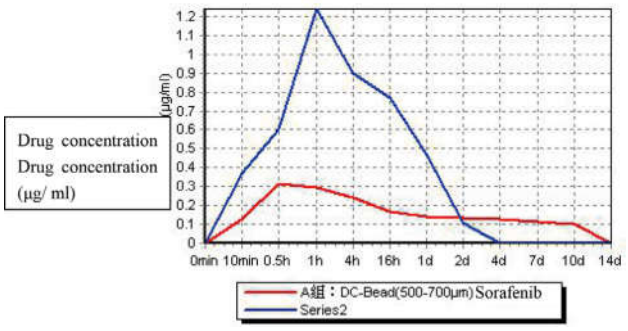
Table 1. Comparison of carrying quantity of different size particles in different concentrations of Sorafenib ethanol solution in 24 hours (mg / ml)

Group / Particle carrying quantity mg / um	a (50mg/20ml)	b (100mg/20ml)	c (100mg/40ml)	d (200mg/40ml)	e (250mg/50ml)
300 — 500	47.1	73.0	68.1	74.4	74.4
500 — 700	48.6	81.4	79.3	82.5	82.5

Ob

4.2 The Change and Comparison of Peripheral Blood Concentration of Sorafenib

Between group A and group C. The results show that there are statistical differences in drug release between the two groups. As shown in Table 2, compared with group A, the drug rise rate of group C (Solafenib lipiodol group) is significantly faster than that of the first two groups, and it is rapidly reduced. There are significant differences in Cmax (0.3 ± 0.06) and AUC (Area Under Curve, 1.82 ± 0.367 μg/mL min) between group A and group C (1. 24 ± 0. 109) and AUC (2. 97 ± 0. 267μg/mL min) (P = 0. 002 < 0. 05). In group C, the drug concentration cannot be measured until the 4th day, indicating the instability and uncontrollability of the release of Sorafenib with lipiodol as carrier.



Group A: Curve of changes of peripheral blood drugs in different carriers with Sorafenib

Table 2. plasma concentration of Sorafenib in group A and C after administration (μ g / ml, X ± s)

Group	10min	30min	1h	4h	16h	1day	2days	4days	7days	10days	14days
A	0.13±0.027	0.13±0.021	0.3±0.055	0.24±0.01	0.17±0.033	0.14±0.020	0.13±0.010	0.13±0.019	0.12±0.007	0.10±0.00	0
C	0.37±0.011	0.6±0.022	1.24±0.109	0.9±0.025	0.77±0.037	0.47±0.021	0.11±0.005	0	0	0	0

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4.3 The Change and Comparison of the Drug Concentration of Sorafenib In Group A and Group C

The results show that the drug concentration in the tissues of group C is very low and cannot be measured at three days after the operation, while the drug concentration in group A is significantly increased, and the Sorafenib concentration in the tissues of group A can still be measured at one week after the operation, showing that DC-bead has better controllability in the release of Sorafenib as a carrier.

Table 3. Plasma concentration of Sorafenib in liver tissue after administration in group A and C (μ g / ml, X ± s)

Group	3days	1week	2weeks
A	4.047±0.03	1.320±0.006	0.455±0.016
C	0.12±0.06	0	0

5. Discussion

5.1 Feasibility and Mechanism Of DC-Bead Carrying Solafenib

The controllable and sustainably releasing drugs with local high concentration can not only act on the target site, but also avoid other non-target sites from being affected and reduce the occurrence of side effects of systemic medication, being one of the directions in the field of medical development. For instance, in the peripheral vascular interventional therapy, the technique of continuous drug infusion through indwelling catheter is often used to treat thrombotic diseases, continuous vasopressin infusion to treat bleeding cases, continuous infusion of chemotherapy drugs to treat malignant tumors, etc. The drug coated stent frequently used in cardiovascular interventional therapy constantly can release drugs through the drugs inside the stent (e.g. paclitaxel, rapamycin) [5] and along with the constant degradation of drug carrier multimers and play the pharmacological role. The anti-tumor drugs with biocompatible and biodegradable polymer materials as carriers can selectively release drugs in the focus, which can greatly improve the bioavailability of drugs and effectively reduce the toxic and side effects and dosage of drugs. With the development of modern technology, new technical means have been provided for the preparation of different carriers that meet the clinical requirements, and more carried DC-bead have been developed, such as gelatin beads, absorbable polymer beads, nano carried DC-bead, sodium alginate beads, polyvinyl alcohol acrylic beads that can carry Pingyangmycin [6-9].

DC-bead is a hydrogel particle prepared by Biocompatibles, which is biocompatible, hydrophilic, non-absorbable and capable of carrying adriamycin. It is a new drug eluted embolization bead prepared by modern biological technology. It can simultaneously embolate tumor vessels and continuously release chemotherapeutic drugs to kill tumor cells [1 - 4].

Drug carrying mechanism of DC-bead: DC-bead is formed by suspension polymerization of acrylic polyvinyl alcohol macromonomer and sulfonate monomer. The formation of covalent bonds transforms the dispersed droplets into insoluble particles. The polymerization starts at the surface of the droplet and forms free radicals. The monomer polymerizes from the outside to the inside, and then forms the cross-linking area on the particle surface. The ion exchange mechanism corresponding to sulfonic acid group is consistent with the charge of particles and drugs. The particles consist of sulfonated hydrogels, which are negatively charged. The carrying mechanism of DC-bead is that the amine matrix of drug (doxorubicin) in the form of hydrochloride is protonated, the whole is positively charged, and the electrostatic interaction between different charges.

According to the principle of ion exchange, foreign scholars have found that in addition to adriamycin, DC-bead can also be carried with other substances with positive charge such as mitoxantrone, irinotecan, topotecan [10-15]. All of the above drugs can achieve the goal of local high concentration and sustained release through in vitro and in vivo ion exchange mechanism, and have achieved good results in experimental and clinical application. Due to the differences of molecular structure and molecular weight, the maximum drug carrying quantity of the above substances is also different, among which adriamycin has the largest drug carrying capacity.

At present, there is no research and report on whether DC-bead can carry Solafenib at home and abroad. By studying the molecular structure of Sorafenib, we found that Sorafenib has the structural basis of exchange with DC-bead. The molecular structure of Sorafenib contains basic sorafenib and acid benzenesulfonic acid. In the solution state, both of them can form salts, i.e. sorafenib with positive charge (NH +) and benzenesulfonic acid (SO3 -) in a dynamic equilibrium state. In this state, benzenesulfonic acid (SO3 -) can exchange with DC-bead (SO3 -) to form ion exchange, and then make the sorafenib with positive charge (NH) + and negative DC-bead(SO3 -) to form salts, and make DC-bead carry Sorafenib successfully. Our in vitro and in vivo experiments further confirm this hypothesis. In vitro experiment, it is confirmed that DC-bead can adsorb Solafenib, while in vivo animal experiment, it is confirmed that Solafenib is controllable and slowly-releasable in the release of Solafenib, which is different from the simple adsorption and release of general

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substances. Therefore, we believe that the ion exchange mechanism may be the main role of DC-bead carrying Solafeni mechanism.

The solubility of drugs is the premise of ion exchange. Sorafenib is a non-water-soluble substance, which is in suspension state in the water for injection, so it is unable to exchange ions with DC-bead. According to the characteristics of its own substances, we found that Sorafenib can be dissolved in methanol and 75% ethanol. The former has higher solubility, but methanol is toxic to human body. Therefore, 75% ethanol with relatively lower solubility is selected to dissolve Sorafenib, so as to prepare conditions for ion exchange.

5.2 Characteristics and Advantages of Carrying Sorafenib with DC-bead as Carrier

Kalayci et al. [15-16] found that there is no statistical difference between Cmax and AUC of chemotherapy drug carried with lipiodol and systemic chemotherapy, so the effect of traditional interventional therapy is limited by systemic toxicity of chemotherapy drug. The sponge embolization combined on the basis of lipiodol chemotherapeutic emulsion embolization can slow down the blood flow speed, but because many chemotherapeutic drugs are soluble in water, a large number of chemotherapeutic drugs have been rapidly released through the blood during the injection of sponge, and we also confirmed the deficiency of lipiodol as the carrier in the experiment. However, we found that the Cmax of sustained-release Sorafenib with lipiodol as the carrier is smaller than that of lipiodol carried chemotherapy drugs reported in literature, and the release time is hours after carrying, rather than minutes or tens of minutes. Our analysis may be related to the physical properties of Sorafenib. Sorafenib is insoluble in both water and lipiodol. Within 20 minutes after mixing, they can still form emulsion with certain stability, and can form stratification with water. With the passage of time and the impact of arterial blood flow, the clearance of lipiodol and the role of lipid soluble substances in the blood increase rapidly.

The release of Sorafenib with DC-bead as the carrier has more obvious advantages. By analyzing the metabolism trend of peripheral blood and histological drugs in group A (DC-bead, 500-700um-sorafenib group), group B (DC-bead, 300-500um, - sorafenib group), and group D (lipiodol sorafenib group), we found that the Cmax and AUC in group A/B are significantly lower than those in group D, with significant statistical difference. The research of histological concentration further found that the Sorafenib concentration in group A/B could still be measured 3 weeks after the intervention, while the Sorafenib concentration in group D could hardly be measured in the tissues from 1 week after the intervention. The results show that the carrier of Sorafenib with DC-bead has better controllability and slow release. DC-bead is capable of carrying and controllable release of Sorafenib. This feature has important clinical significance [17-25]: (1) With DC-bead as the carrier, the release of targeted drugs has the ability to continuously release Sorafenib in local high concentration and slowly, and continuously act on tumor cells and tumor blood vessels. Finally, it can inhibit tumor cells and tumor angiogenesis. (2) When Sorafenib is released by DC-bead as the carrier, combined with traditional TACE treatment, the target is more clear and the effect is stronger in inhibiting tumor blood vessels and tumor growth. Clinical researches have confirmed that TACE combined with molecular targeted drugs (e.g. ENDU) can significantly inhibit tumor growth, improve tumor inactivation level, and prolong the generation time of patients. However, compared with other targeted drugs, Sorafenib has more advantages: (1) it is a multi-target molecular targeted drug, which can inhibit tumor growth and angiogenesis. (2) it has a good synergistic antitumor effect with TACE common chemotherapy drugs (e.g. epirubicin, gemcitabine, cisplatin). (3) compared with oral Sorafenib, the advantage of local medication is more obvious. Clinical research found that TACE combined with sorafenib can control tumor progression and prolong the survival time of patients. However, the high cost of long-term oral medication, the low bioavailability of drugs, the large side effects, and the low objective effective rate have brought serious physiological and psychological burden to patients, making only a few patients can afford it. Local continuous drug use not only has a sustainable effect on the target, but also can improve the drug concentration and enhance the anti-tumor effect within a certain range without causing major side effects. In addition, local medication is expected to greatly reduce the clinical cost of systemic medication. Finally, because of the small toxicity of local drugs, it is possible to improve the efficacy of multiple interventional therapy.

However, the release of Sorafenib from different sizes of DC-bead is different, and is affected by the concentration of Sorafenib ethanol solution. We found that the amount, release rate and duration of Sorafenib carried by beads with small particles are shorter than those with large particles, while Cmax is higher than those with large particles. This phenomenon is not only related to the lower dosage of Sorafenib, but also related to the larger surface area, more negative charges and strong adsorption capacity of the beads. It is suggested that different doses of Sorafenib shall be selected for different sizes of DC-bead beads, and the effect of drug concentration in ethanol

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solution on drug carrying shall be considered. In addition, different drug carrying methods also have an impact on the drug's look-around performance. The research shows that compared with the traditional iodized oil drug, the new drug carried particles have longer sustained-release time in peripheral blood and tissue, and have better sustained-release performance.

5.3 Deficiencies of the Research

There are certain deficiencies in this research: 1. In this research, ethanol is used as the solvent to dissolve Solafenib, and the maximum drug carrying quantity is only 82.5 mg, while the solvent used is 40ml, which is not conducive to full contact with the drug carrying. To increase the dissolution of Solafenib in ethanol is one of the directions of future research. 2. This research is based on the normal liver tissue instead of blood rich liver tumor model, so how to inhibit the liver tumor still needs to be further researched. We will improve the detection of VEGF, MVD and image in the tumor model of tumor bearing rabbits in the next step, so as to further evaluate the effect of DC-bead drug Sorafenib on malignant tumors (e.g. VX2 tumors).

6. Conclusion

The new Sorafenibcarried DC-bead is feasible in preparation technology, exact in the sustained-release effect, and superior to the carrying effect of lipiodol.

The safety and effectiveness need further research.

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