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LABORATORY INVESTIGATION

Controlled Release and Antitumor Effect of Pluronic F127 Mixed with Cisplatin in a Rabbit Model

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Abstract The purpose of this study was to evaluate pluronic F127 for the controlled release of cisplatin in a rabbit model. Pluronic F127 becomes liquid at temperatures <25°C and converts to a gelatinous state at temperatures between 25 and 60°C. Six Japanese white rabbits were injected with pluronic + cisplatin ($n = 3$, renal group A) or saline + cisplatin ($n = 3$, renal group B) to measure the platinum concentration in kidneys. Another 25 rabbits with VX2 liver tumors were divided into five equal groups. They were injected with saline, saline + cisplatin, iodized oil + cisplatin, pluronic alone, or pluronic + cisplatin and labeled as liver groups A, B, C, D, and E, respectively. The antitumor effect of pluronic was then assessed. In the presence of pluronic, the platinum concentration in the kidneys of rabbits remained relatively high. In animals with liver tumors, the delivery of pluronic + cisplatin produced higher tumor reduction rates ($P < 0.05$) than in the other groups, without apparent damage to normal liver tissue. We conclude that pluronic is useful for the controlled release of cisplatin in a rabbit model.

Keywords Cisplatin · Pluronic F127 · Controlled release · Antitumor effect · A rabbit model

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Introduction

Transcatheter arterial chemoembolization (TACE), using materials such as embospheres, gelatin sponges, and polyvinyl alcohol [1–6], is used to treat malignant liver tumors. In patients with multiple or diffuse hepatocellular carcinoma (HCC) in whom TACE cannot be performed and in whom drug distribution to normal liver tissue cannot be avoided, transient hepatic hypofunction induced by embolizing agents may worsen the prognosis. In such cases, treatment options include transarterial infusion of short-term embolizing agents, placement of an in-dwelling reservoir, or no delivery of embolizing agents [7–9].

Although degradable starch microspheres (DSM) have been used as short-term embolic agents, [1, 9, 10] they are fluoroscopically undetectable, and we encountered problems determining the quantity of DSM that is appropriate while avoiding back-flow into other arteries. Therefore, we considered pluronic F127 (pluronic) as a short-term embolizing agent for TACE in HCC. Pluronic consists of nonionic triblock copolymer surfactants composed of polyoxyethylene–polyoxypropylene–polyoxyethylene [11], and it has been widely used in medical, pharmaceutical, and cosmetic settings [12–18]. It is not metabolized and is excreted renally; its half-life is approximately 25 h [19]. Short-term embolizing agents have been used in studies on swine and rabbit arteries [15, 19].

Pluronic, known as LeGoo (Pluromed, Woburn, MA), is available for clinical use in Europe. Ohta et al. reported that pluronic (20% w/v) is liquid at temperatures <25°C, that it converts to a gelatinous state at temperatures between 25 and 60°C, and that a solution containing 20% w/v pluronic and iodine contrast medium can easily be detected by fluoroscopy after conversion into a gelatinous state in the body [15]. In rabbits, these investigators

demonstrated the feasibility of using pluronic as a short-term embolic agent. After renal artery embolization, recanalization occurred within several hours without prominent infarction in the renal parenchyma. Bouchot et al. [19] detected no endothelial dysfunction after injecting pluronic into coronary arteries of swine undergoing bypass surgery, thus indicating its low toxicity when delivered intra-arterially. Moreover, its unique properties and temperature sensitivity suggest it as a possible delivery system for antitumor drugs [20–22].

We hypothesized that antitumor drugs in pluronic emulsion become embedded in its gelatinous form in the blood vessels and that gradual dissolution releases the antitumor drugs slowly into the blood while retaining relatively strong local antitumor effects. Therefore, we tested the possibility of releasing cisplatin slowly from pluronic after injection into the renal arteries of rabbits. We also assessed the locoregional antitumor effects and the induction of damage to normal liver tissue in rabbits with liver tumors using magnetic resonance imaging (MRI) scans and pathologic analysis.

Materials and Methods

Animals

The study protocol was approved by the Animal Experimentation Committee. All experiments were performed according to the Animal Care Guidelines of our institution. One rabbit with a transplanted VX2 liver tumor and 31 healthy adult Japanese white rabbits (2.5–3.5 kg.) were purchased from SHIMIZU Laboratory Supplies Co., Ltd (Tokyo, Japan).

Chemicals and Devices

The following were purchased: pluronic F127 (molar weight 12,500) from Sigma-Aldrich (St. Louis, MO), iopamidol 370 (Iopamiron 370) from Nihon Schering (Osaka, Japan), 4F cobra-shaped catheters, 2.3F microcatheters (Sniper 2 selective type), and 4F sheaths from Clinical Supply (Gifu, Japan), cis-diamminedichloroplatinum (cisplatin; IAcall) from Nippon Kayaku (Tokyo, Japan), medetomidine hydrochloride (Domitor) from Meiji Seika (Tokyo, Japan), ketamine hydrochloride (Ketalar 50) from Sankyo Yell Yakuhin (Tokyo, Japan), pentobarbital (Nembutal) from Dainippon Sumitomo Pharma Co. (Tokyo, Japan), and 2.5% enrofloxacin (Baytril) from Bayer Healthcare (Tokyo, Japan).

The pluronic concentration (20% w/v) was based on the work of Ohta et al. [15] Briefly, we prepared a solution of saline and iopamidol 370 (1:1 v/v, 5°C), and pluronic powder was added to obtain a 20% w/v solution of pluronic F127.

Measurements of Blood Platinum Concentration and Histopathologic Analysis of Rabbit Kidney

Six adult Japanese white rabbits were randomly divided into two equal groups. One group (three rabbits; renal group A) was injected with pluronic (1 ml) + cisplatin powder (1.67 mg/kg). The other three rabbits (renal group B) received saline (1 ml) + cisplatin powder (1.67 mg/kg). The cisplatin dose was based on studies reported by Sonoda et al. [23]. Mixing of the cisplatin powder with liquid was followed by ultrasonic agitation at 5°C (Fig. 1). All rabbits were placed under general anesthesia with an intramuscular (IM) injection of medetomidine hydrochloride (0.1 mg/kg) and ketamine hydrochloride (25 mg/kg). The right femoral artery was surgically exposed, and a 4F sheath was inserted under fluoroscopy by way of the cut-down method. A 4F cobra-type catheter was introduced into a trunk of the left renal artery; iopamidol (2 l) was injected manually; and renal arteriographs were obtained.

In renal group A, pluronic (1 ml) + cisplatin powder (1.67 mg/kg) was infused under fluoroscopy into the renal artery, thus avoiding back-flow into the aorta. As soon as back-flow was observed, the infusion was stopped. In renal group B, 2 l iopamidol were injected manually during 30 s and arteriography was performed. After confirming that there was no back-flow into the aorta, saline (1 ml) + cisplatin powder (1.67 mg/kg) were infused during 30 s into the left renal artery. In all rabbits, serum platinum concentrations were measured at 5, 15, 30, 60 min, and 1 day using the atomic absorption method (AA-6800 atomic absorption spectrometer, Shimadzu, Kyoto, Japan). Blood was collected from the auricular vein. All rabbits were killed on day 7 after the procedure by injecting the heart with an overdose of pentobarbital. Both kidneys were surgically removed, fixed in 10% formaldehyde solution, processed, and embedded in paraffin. Coronal histological sections were stained with hematoxylin and eosin (HE) for microscopic study of pathologic changes in the renal parenchyma. Histopathologic analysis was made by consensus of two radiologists (A.S. and N.N.) in consultation with a pathologist.

Antitumor Effects in Rabbits with VX2 Liver Tumors and Histopathologic Analysis

To obtain tumor tissue to induce tumors in 25 Japanese white rabbits, a rabbit bearing a VX2 intrahepatic tumor was placed under general anesthesia. The tumor was isolated and cut with scissors into 3-mm pieces, which were then stored in liquid nitrogen.

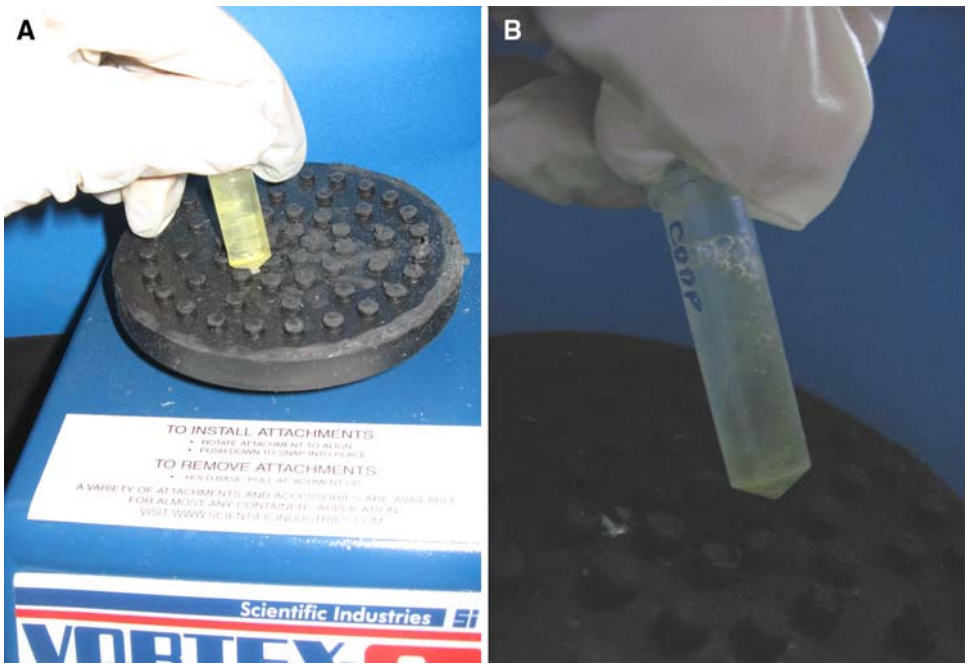

Fig. 1 Mixing of pluronic and cisplatin. To a solution of saline and iopamidol 370 (1:1 v/v, 5°C) pluronic powder was added to obtain a 20% w/v solution of pluronic F127. (**A**) Mixing of cisplatin powder with liquid pluronic was followed by ultrasonic agitation at 5°C. (**B**) Pluronic combined with cisplatin becomes a straw-colored emulsion

The abdominal cavity of 25 rabbits was opened at the subxiphoid process, and VX2 tumor tissues measuring approximately 3 mm were implanted into the right medial lobe of the liver by two radiologists (A.S. and S.O.). Then 2.5% enrofloxacin was administered (1 ml/d IM for 3 days). The 25 rabbits were randomly divided into five equal groups. The volume of the induced liver tumor was measured using ultra-high field MRI (7-Tesla coil; Jastec). Imaging sequences were obtained using the spin-echo method and respiratory gating. The repetition time (TR) was 2000 ms; echo time (TE) 30 ms, average 1; field of view 150 mm; matrix size 256 × 128; slice thickness 4 mm; and interslice gap 0 mm. Images were interpolated on a 256 × 256 matrix on a console (Varian), saved as JPEG files, and transferred to a computer workstation. The tumor volumes were estimated using Photoshop 7.0.1 (Adobe, CA). Briefly, tumors shown on the MRI scans were manually outlined by consensus of two radiologists (S.O and A.S), and the values were assessed using the total number of pixels within the drawn outline; these were considered directly proportional to the subjective tumor volumes.

A 4F cobra-type catheter was introduced into the trunk of the celiac artery as previously described, and celiac arteriography was performed by manually injecting 2 ml iopamidol. Then a 2.3F microcatheter was placed in the proper hepatic artery, and arteriographs were acquired after manually injecting 2 ml iopamidol during the course of 1 min to confirm that the contrast medium did not back-flow from the proper hepatic into the gastroduodenal artery. Liver group A received 0.5 ml saline only; group B received saline (0.5 ml) + cisplatin powder (1.67 mg/kg); group C received iodized oil (0.5 ml) + cisplatin powder (1.67 mg/kg); group D received pluronic (0.5 ml) only; and group E received pluronic (0.5 ml) + cisplatin powder (1.67 mg/kg).

In liver groups C through E, the injections were carried out slowly and under fluoroscopy to prevent back-flow. The injection was stopped when the blood flow stagnated (Fig 2). In groups A and B, the injections were delivered slowly during the course of 1 min. In group B, arteriographs were obtained by manually injecting 1 ml iopamidol during 1 min before the delivery of saline + cisplatin. We confirmed that there was no back-flow into the aorta.

After 7 days the size of the induced liver tumor was measured on MRI scans as previously described. The antitumor effect of cisplatin was determined by the methods of Pauser et al. and Yoshikawa et al. [24, 25]. After the acquisition of MRI scans, performed as previously described, the rabbits were killed and normal peritumoral liver tissues removed, processed, stained with HE, and examined under a microscope. The histopathologic analysis was made by consensus of two radiologists (A.S. and N.N.) in consultation with a pathologist.

Tumor Growth Rate

Tumor growth rate was calculated as follows: (total number of pixels in the tumor area after administration—total number of pixels in the tumor area before administration)/ total number of pixels in the tumor area before administration)× 100.

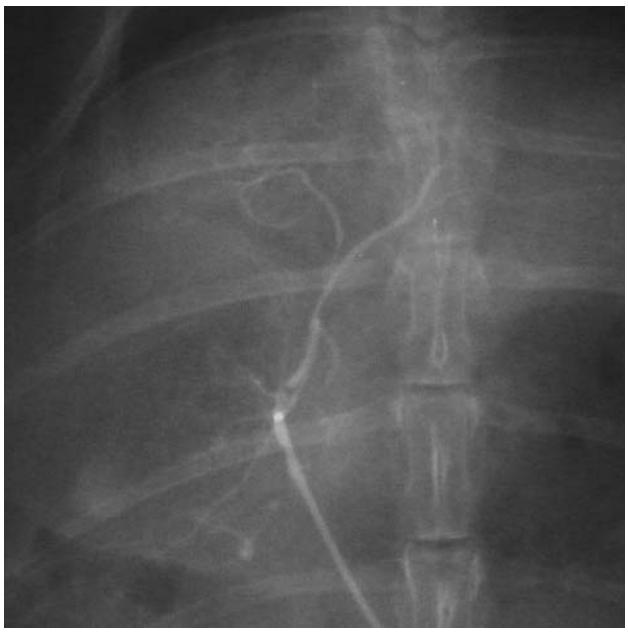

Fig. 2 Radiographic image at infusion of pluronic + cisplatin. The proper hepatic artery was occluded with injection. Pluronic and iodine contrast medium can easily be detected by fluoroscopy

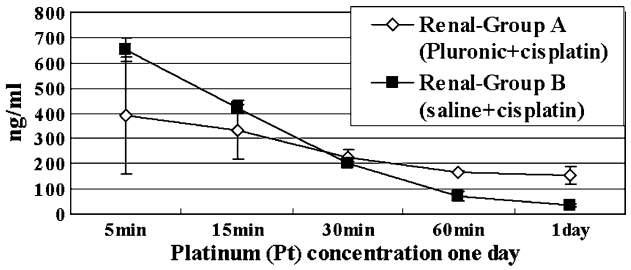

Fig. 3 Blood platinum (Pt) concentration after injection into the renal artery. In renal group A (pluronic F127 [1 ml] + cisplatin powder [1.67 mg/kg]), a slow decrease in Pt concentration was observed. In renal group B (saline [1 ml] + cisplatin powder [1.67 mg/kg]), the Pt concentration rapidly decreased 1 h after injection and was undetectable after 1 day

Statistical Analysis

Dr. SPSS II for Windows (SPSS Japan, Tokyo, Japan) was used for statistical analysis. Significant differences in blood platinum concentrations were evaluated using Student *t* test. Tumor growth rates were assessed with Tukey's Honestly Significant Differences (HSD) test. A P value < 0.05 was considered significant.

Results

Renal Groups (A, B): Blood Platinum Concentration

In renal group B, the platinum concentration decreased rapidly within 1 h after administration of saline + cisplatin (Fig. 3). In group A, it decreased gradually up to one day after the administration of pluronic + cisplatin. At 15 and 60 min and at 1 day after administration, the differences between groups A and B were significant ($P < 0.05$), whereas at 5 and 30 min there was no significant difference.

Renal Groups (A, B): Pathologic Features of the Kidney

Slight infiltration by inflammatory cells was noted in two of three animals from each renal group. However, the intergroup differences were not significant (Fig. 4).

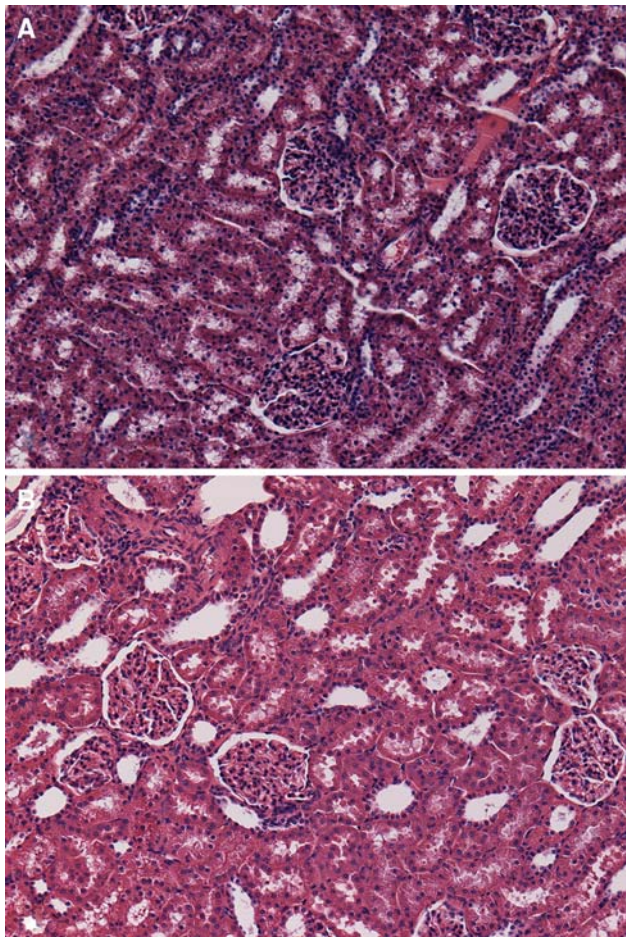

Fig. 4 Pathologic features of the kidney. (**A**) In renal group A (pluronic F127 [1 ml] + cisplatin powder [1.67 mg/kg]), infiltration by inflammatory cells was observed. (**B**) In renal group B (saline [1 ml] + cisplatin powder [1.67 mg/kg]), infiltration by inflammatory cells was also observed (HE stain; original magnification× 100)

Liver Groups (A–E): Pathologic Features of the Liver Parenchyma

In liver groups C through E, because blood flow stagnated before the whole dose could be delivered, the total injected was approximately 0.1 to 0.2 ml. MRI detected no anomalies indicative of significant tissue damage in the surrounding liver parenchyma of rabbits in groups D (pluronic only) and E (pluronic + cisplatin). There were no apparent pathologic changes in surrounding hepatocytes (Fig. 5).

Groups A (saline), B (saline + cisplatin), D (pluronic), and E (pluronic + cisplatin) showed no necrosis, although all specimens exhibited infiltration by inflammatory cells. However, in group C (iodized oil + cisplatin) periportal infiltration by inflammatory cells and necrotic foci were observed in liver (data not shown).

Liver Groups (A–E): Antitumor Effects

In group E, tumor size was smaller after administration of pluronic + cisplatin. In contrast, in groups A (saline) and B (saline + cisplatin), tumor growth rates were >100%, and tumor size more than doubled after 1 week. In group C (iodized oil + cisplatin), the tumor growth rate was between 50 and 100%, which was significantly less than that in groups A and B. In addition, tumor growth rates for groups A through C were significantly different from that in group E ($P < 0.05$**). In group D, the tumor growth rate was significantly lower than those in groups A and B ($P < 0.05$*). There were no differences between groups C and D or between groups D and E (Fig. 6).

Discussion

We found that intra-arterial injection in rabbits of combined pluronic + cisplatin resulted in a slow release of cisplatin by way of gradual dissolution, thus producing antitumor effects. Although pluronic has been suggested as a delivery system for antitumor drugs, [20, 22] we are not aware of any previous studies reporting the intra-arterial injection of pluronic for drug delivery with consequent antitumor effects. We first investigated whether pluronic F127 + cisplatin could be used for the controlled release of cisplatin into the renal artery of rabbits. The renal artery was used to assay the blood concentrations of the delivered cisplatin doses. Because the antitumor effects were assessed in rabbits with liver tumors, it can be contended that the hepatic artery was more appropriate for measuring the concentration of cisplatin in the blood. However, because the hepatic arteries in rabbits are narrow and became even narrower on catheter insertion, it was difficult to inject a sufficient dose of cisplatin with pluronic. In a preliminary experiment, only 20% of the cisplatin + pluronic solution could be injected into the hepatic artery of a rabbit, and the cisplatin concentration was undetectable in blood from an

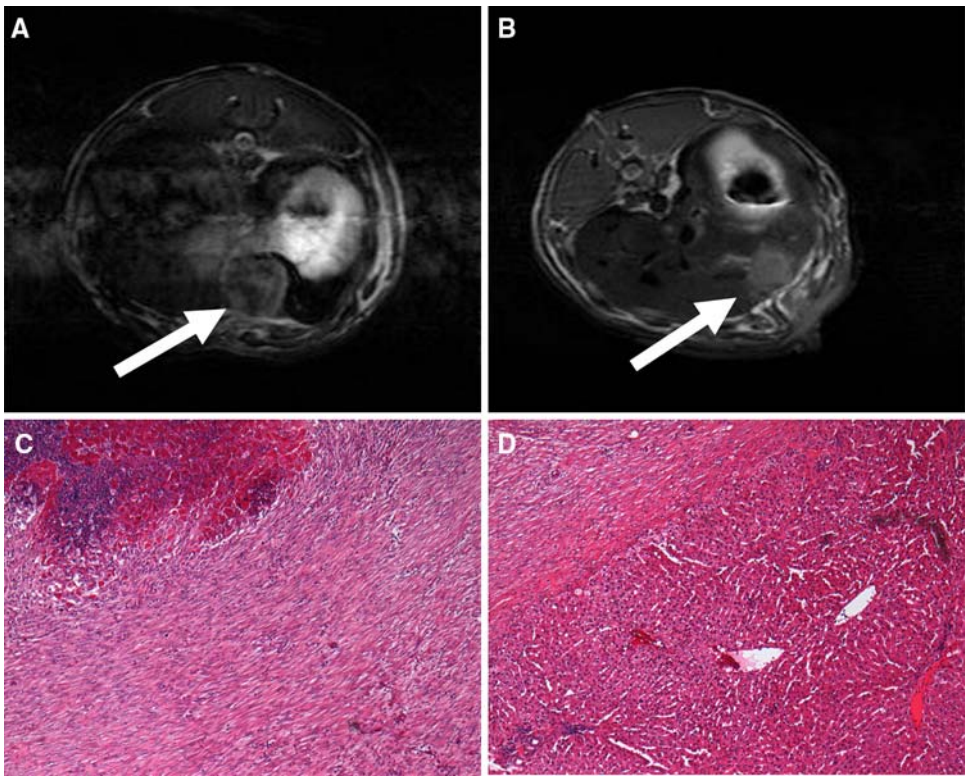

Fig. 5 Preoperative and postoperative MRI findings (*arrow*) and pathology in liver group E (pluronic + cisplatin). MRI images (TR: 2000, TE: 30) before (**A**) and 7 days after (**B**) the injection of pluronic + cisplatin. Note the change in the tumor size. No abnormal signals indicating prominent tissue injury were detected in the surrounding hepatic parenchyma. (**C**) Pathologic specimens showed a necrotic focus in the center of the VX2 tumor, and in the peritumoral areas of normal liver tissue (**D**) there was periportal infiltration by inflammatory cells but no distal necrosis (HE stain; original magnification× 100)

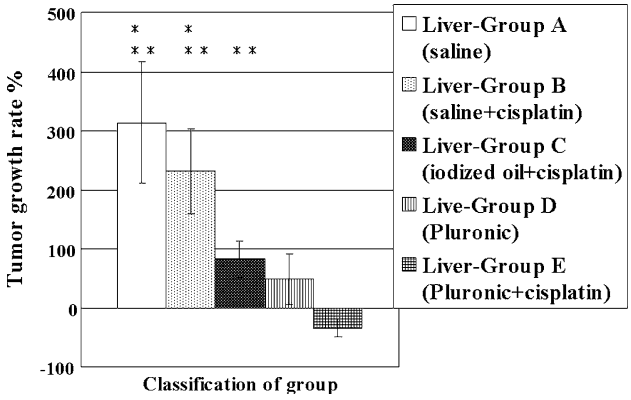

Fig. 6 Tumor growth rate (±SEM) in the liver groups. Group A: saline (0.5 ml); group B: saline (0.5 ml) + cisplatin powder (1.67 mg/kg); group C: iodized oil (0.5 ml) + cisplatin powder (1.67 mg/kg); group D: pluronic F127 (0.5 ml); and group E: pluronic F127 (0.5 ml) + cisplatin powder (1.67 mg/kg). N = 5 in each group. * In group D, the tumor growth rate was significantly slower than in groups A and B ($P < 0.05$). ** In group E, the tumor growth rate was significantly slower than in groups A through C ($P < 0.05$). There were no differences between groups D and E and between groups C and D

auricular vein (data not shown). Therefore, we considered it impossible to assess the release of cisplatin, as well as assay for platinum in the peripheral blood, when delivery was by way of the hepatic artery. For periodic measurements of the platinum concentration in peripheral blood, it would have been necessary to inject higher doses of cisplatin. Because of the narrowness of the hepatic arteries in rabbits, we could not rule out back-flow and entry of the administered drug into the systemic circulation. This would have complicated the precise measurement of changes in cisplatin blood concentration. Based on these considerations, as well as the fact that the renal artery is a relatively large-end vessel into which the catheter could be inserted1 and that even in the event of arterial embolization the risk of death was not immediate, the choice was made for the renal artery.

A significant difference was noted in the blood platinum concentration between renal groups B (saline + cisplatin) and A (pluronic + cisplatin) at 15 min after renal infusion. Moreover, the gradient of renal group A showed a gentler sloping trend than for renal group B at 60 min. Our findings suggest that with the concomitant administration of pluronic, a high blood concentration of cisplatin can be maintained for 60 min. We submit that this is due to the controlled release of cisplatin delivered with pluronic. At 5 min after renal infusion, the difference between the two groups was not significant. This may be due to embolization of the renal artery, which resulted in blood-flow stagnation lasting at least 30 min [15] and resulted in back-flow of the drug into the aorta at the time of intra-arterial infusion. Alternatively, the distribution of intravascular pluronic may have been uneven because the agent changed from a liquid to a gelatinous state [15, 19]. Consequently, partial recanalization could have occurred in areas with low pluronic concentrations.

In contrast, complete recanalization of the renal artery after 120 min, which has been reported elsewhere [15], is not consistent with the results of our present study in which renal groups A (pluronic + cisplatin) and B (saline + cisplatin) showed a significant difference in cisplatin concentration even after 1 day. It is conceivable that the persistent release of cisplatin and/or infusion of pluronic impaired renal function.

Both renal groups (A and B) manifested slight inflammatory changes and similar pathologic findings. These observations are consistent with the results of our previous study [15]. Inflammatory changes were attributed to catheter manipulation rather than to pluronic because similar findings were obtained in both renal groups.

In control studies, rabbits in the liver groups were injected with saline alone, with cisplatin + saline, and with cisplatin + iodized oil. Although some do not consider iodized oil to be a short-term embolizing agent, [1] its administration produces transient arterial blood flow stasis. Furthermore, iodized oil is widely used in transarterial oily chemoembolization (TACE) for the delivery of antitumor drugs in patients with poor liver function [3, 26–28]. Although DSM are accepted as a short-term embolization agent, [1, 9, 10] they are fluoroscopically undetectable, and thus it was difficult to determine the appropriate quantity of DSM needed to obtain embolization of the proper hepatic artery without back-flow into the gastroduodenal artery or aorta.

Pluronic reportedly increased the cytotoxicity of antitumor drugs in cell lines [20, 29]. Tumor growth suppression was greatest in liver group E (pluronic + cisplatin). By Tukey's HSD test, the difference between group E and groups B (saline + cisplatin) and C (iodized oil + cisplatin) was significant ($P < 0.05$). In addition, it was discovered that pluronic, when delivered alone, exerted antitumor effects (liver group D). Khattak et al. [14] reported that at a concentration of 10% w/v, liquid pluronic decreased the viability of cells grown in culture. In gel form, it induced cell death and hampered cell proliferation in three different cell lines. Khattak et al. [14] speculated that these effects were caused by cell-membrane injury by pluronic. The concentration of pluronic was 20% w/v in our experiments, and the possibility exists that a similar injury affected the proliferation of VX2 tumor cells. In contrast, Krupka et al. [21] delivered pluronic intratumorally to rats with colorectal cancer and found no antitumor effects. Studies are underway in our laboratory to determine whether the antitumor effect of intra-arterially injected pluronic observed in rabbits can be achieved only

when its direct effects on cellular membranes and embolizing effects are combined. Pathologic study showed that damage to normal hepatic tissue in liver groups D and E (pluronic alone and pluronic + cisplatin, respectively) consisted solely of invasion by inflammatory cells. There was no difference between liver groups A (saline only) and B (saline + cisplatin). These observations suggest that pluronic could be a promising agent for transient embolization that causes only slight damage to the liver. In contrast, in liver group C (iodized oil + cisplatin) we observed not only periportal inflammatory cell infiltration but also focal hepatic necrosis.

To our knowledge, this is the first study that combined pluronic and cisplatin to treat VX2 tumors by intra-arterial injection. We recognize that our experimentally induced VX2 liver tumors and our treatments are not identical to the physiologic characteristics and treatments of spontaneously occurring liver tumors. However, rabbits constitute the only animal model that allows the same catheter procedures that are employed in humans. Moreover, rabbit models of VX2 liver tumors represent an accepted HCC model [30–32]. Although our study sample was small, the clarity of our results led us to use as few rabbits as possible because our experiments exposed the animals to significant distress. Pluronic concentration was not assayed over time after injection because these levels can be estimated from changes in the platinum concentration in peripheral blood after renal artery embolization [15]. The safety of intra-arterial delivery of pluronic in humans remains to be established. However, pluronic F127, known as LeGoo, has been used clinically in Europe, and we believe that it is safe with respect to toxicity when delivered intra-arterially. There were no differences between liver groups D (pluronic only) and E (pluronic + cisplatin), or between groups D and C (iodized oil + cisplatin), with respect to tumor growth. Further studies addressing this issue are underway. Although both lipiodol and pluronic are defined as transient embolization materials, the two agents were not compared. Because our study sought to determine whether pluronic could be used as a controlled-release agent in patients requiring the administration of anticancer drugs, a comparison of the obstruction grade of the two agents was not deemed necessary at this time.

Serum platinum concentrations were compared during the first 24 h after administration of cisplatin + pluronic or cisplatin + saline. Our pharmacokinetic comparisons did not include other drug-delivery systems, such as DSM or iodized oil. We restricted our study to the possibility of using pluronic as a drug-release agent rather than examining its superiority or inferiority to other drug-delivery systems. Further studies are planned to investigate this issue.

In conclusion, we showed that pluronic is useful for a controlled release of cisplatin in a rabbit model, which is detectable by fluoroscopy, and inflicts only minor damage to normal liver parenchyma. An incidental finding was that the intra-arterial injection of pluronic per se appeared to block the in-vivo proliferation of VX2 tumor cells in rabbits.

Practical Applications

The sustained release of cisplatin, delivered with pluronic F127, may help to achieve and maintain a therapeutically effective antitumor drug concentration. Transient embolization with pluronic F127 causes little damage to normal liver parenchyma. Finally, because relatively slow controlled drug release can be achieved even in patients ineligible for drug-reservoir implantation or liver resection, the combined intra-arterial delivery of pluronic F127 and antitumor agents opens new treatment options for such patients.

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