Quantification of Doxorubicin Concentration in Rat Tissues using Polymeric Micelles in Ultrasonic-Drug Delivery

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Pitt, William G.; Roeder, Beverly; and Staples, Bryant J., "Quantification of Doxorubicin Concentration in Rat Tissues using Polymeric Micelles in Ultrasonic-Drug Delivery" (2006). Faculty Publications. 61.  
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Introduction

The triblock copolymer, Pluronic P105, has been found to be an ideal ultrasonically activated drug delivery vehicle because it forms micelles with hydrophobic poly(propylene oxide) cores that sequester hydrophobic drugs (Fig. 1). These micelles release their contents upon the application of low frequency ultrasound [1] such that drugs can be released specifically at the ultrasonicated region (Fig. 2). Such ultrasound delivery has been effective against cancer cells in vitro [2] and in vivo [3].

The purpose of this research is to assess the use of novel polymeric micelles in ultrasonically activated Doxorubicin® (DOX) delivery to tumors. This cancer therapy involves the exposure of the animal to localized ultrasound. Currently, one of the most effective therapies for cancer treatment involves the use of chemotherapeutic agents such as DOX. One of the major drawbacks of this therapy is that the drug attacks all rapidly dividing cells, causing healthy tissues to die. These localized treatment using micelles and ultrasound may alleviate the side effects of the drug on healthy tissues.

Methods

The drug carrying micelles were formed from Pluronic™ P105, a tri-block copolymer consisting of a central block of poly(propylene oxide) flanked by blocks of poly(ethylene oxide). These micelles were stabilized by polymerizing an interpenetrating network of a thermally responsive N,N-diethylacrylamide within the core of the micelle [4]. DHD/K12 (murine interperitoneal) colon cancer cells were subcutaneously injected and grown in each lower leg of the BIDX rat model. All rats received an injection of micelle-encapsulated DOX at 2.67 mg/kg. Ultrasound exposure followed to a period of 12 minutes to only one leg of the animal. Ultrasound was applied by a 20 kHz probe (1.0 W/cm²) in ultrasound-conducting gel on the skin over the tumor (Fig. 3). Each rat was euthanized at 0.5, 1, 6, 12, 24, 48, 96, or 168 hours after ultrasound application. Some rats were given the drug/ultrasound treatment for four consecutive weeks before being euthanized 24 hours after the last treatment in order to test for accumulation effects. After euthanization, DOX was immediately extracted from heart, muscle, liver, and tumor tissue (both ultrasonically treated and untreated) and quantified using high performance liquid chromatography and a fluorescence detector (Figure 4).

Results

Figure 3. Rat with subcutaneous tumors grown on each leg. Ultrasound (20 kHz, 1 W/cm²) was applied to one of the tumors and the other was the control.

Figure 4. High Performance Liquid Chromatography Setup used to separate and quantify the amount of doxorubicin in a sample.

Figure 5. Comparing average doxorubicin concentration in solid tumors over a period of one week. Tumors which received ultrasound following the carrier injections showed almost twice as much drug as non-ultrasoundized tumors within the first thirty minutes.

Figure 6. Mass of doxorubicin per mass of tissue over a period of one week for liver and muscle tissues. The liver and muscle tissues showed high initial concentrations and rapid removal while the drug slightly entered the muscle tissues and slowly cleared.

Conclusions

The drug is initially at higher concentrations in the blood-perfused organs such as the liver and heart. However, the drug is quickly removed from these organs. Though the drug in the tumors is very slowly cleared (less than one week) while the drug in the high vascular organs, the drug is slowly cleared, leaving a measurable amount even after one week. While longer retention of drug in the tumor cells is effective in chemotherapy, it is detrimental in the heart. The micelles appear to protect the heart from long-term drug exposure.

The results from comparing doxorubicin concentration in ultrasound-treated tumors to that in non-treated tumors show that ultrasound increases the amount of drug delivered to the tumor soon after its application. It is hypothesized that this is due to ultrasonically increased membrane permeability.