Pharmacokinetics and tissue distribution of iv injection of polyphase liposome-encapsulated cisplatin (KM-1) in rats[1]

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KEY WORDS pharmacokinetics; liposomes; cisplatin; induced coupled plasma atomic emission spectrometry

ABSTRACT

AIM: The pharmacokinetics and biodistribution of cisplatin encapsulated in polyphase liposome (KM-1) were compared with those of free drug in rats. **METHODS**: The platinum levels in serum and normal organs, after a single dose of iv injection of free or encapsulated cisplatin to rats, were determined by induced coupled plasma atomic emission spectrometry. **RESULTS**: Serum platinum concentration-time curve after a single iv dose of KM-1 4.5 mg/kg in rats was fitted with an open three-compartment model. The pharmacokinetic parameters were as follows: V_c=0.10 L/kg, $T_{1/2\pi}$=0.3 h, $T_{1/2\alpha}$=3.5 h, $T_{1/2\beta}$=2.7 h, AUC=265 mg· h· L^{-1}, and CL(s) =0.02 g· L^{-1}· h^{-1}. KM-1 was cleared from the circulation much more slowly than free cisplatin. Liver and spleen had the highest concentration of platinum after KM-1 treatment. **CONCLUSION:** KM-1 remained in the bloodstream longer than its free drug, and was taken mainly by the reticuloendothelial system.

INTRODUCTION

Cisplatin (*cis*-dichlorodiamine platinum II) is an anti-neoplastic platinum agent commonly used alone or in combination with other agents in a variety of chemotherapeutic regimens[1-3]. However, expansion of the clinical utility of cisplatin has been limited by its toxicity, as well as the emergence of intrinsic and acquired resistence in many common tumor types. These make the improvements of the drug necessary[4-6].

Liposomal encapsulation reduces the toxicity associated with many antitumor agents by altering their pharmacokinetics and distribution[7-11]. But the development of liposome containing cisplatin has been hampered by poor water solubility and low lipophilicity of free drug, which results in unstable liposome formulations that have a low drug encapsulation rate and tend to leak their content rapidly during storage. With the help of water-solubility enhancement reagents, we have developed a new formulation of cisplatin, polyphase liposome KM-1, which has a high total drug encapsulation rate (85 %) and is stable at 4 °C for at least 30 months. Preliminary studies have shown that, compared with cisplatin, KM-1 showed a lower cisplatin-associated toxicity and was superior in the treatment of mouse tumor in liver. In this report, the pharmacokinetics and biodistribution of KM-1 and free cisplatin in rats at a dose of 4.5 mg/kg were comparatively studied.

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Platinum determination The total platinum levels in all samples were determined using a sensitive and specific ICP-AES based method. The assay does not differentiate liposomal and nonliposomal platinum or free and protein-bound platinum. The sensitivity of the assay is 12.8 mg/L . The calibration curve for Pt was linear over the range of 0-100 mg/L. Linear equation: C=0.2268I-123.73 (r=0.998). The within and between day variabilities were within 5 % and 10 %, respectively. The recoveries of Pt from tissues were above 70 %. All concentrations are expressed as mg cisplatin equivalent/L or μg cisplatin equivalent/g.

Data analysis The platinum concentration-time curves were analyzed with 3P87 program to determine the pharmacokinetic parameters.

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Pharmacokinetics KM-1 was cleared from the circulation much more slowly than cisplatin (Fig 1). The serum platinum concentration with cisplatin treatment was 12 mg/L at 15 min, while that with KM-1 treatment was 51 mg/L at the same time point, showing a 4-fold increase of platinum in serum. At 8 h, the serum platinum concentration with KM-1 treatment was still 10 mg/L, while only 1 mg/L of platinum was left in that with cisplatin treatment. The serum platinum concentration-time data in KM-1-treated group were well characterized by an open three-compartment model. Some of the parameters were listed in Tab 1. Due to cisplatin fast elimination from the circulation in free cisplatin-treated group, serum platinum concentration dropped quickly with time. There were not enough concentration-time data available in free cisplatin group for the calculation of pharmacokinetics parameters in this study.

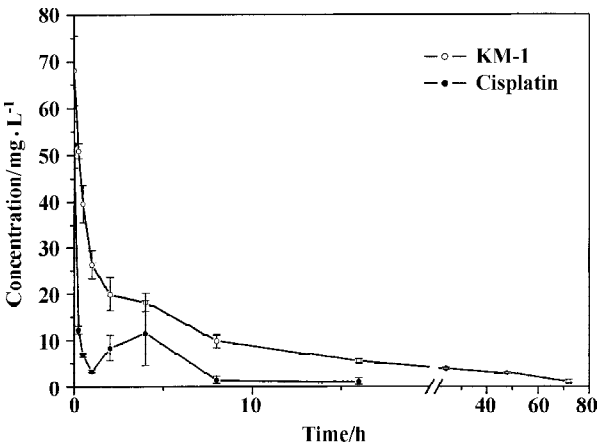

Fig 1. Serum concentrations of cisplatin following KM-1 or cisplatin administration (4.5 mg/kg of body weight each). n=5. Mean±SD.

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AUC/mg·h·L^{-1}	265
CL(s)/g·L^{-1}·h^{-1}	0.02

Tissue distribution After a single iv dose of KM-1, both the liver and spleen showed the highest platinum concentration at 24 h (Fig 2), 4-, and 3-fold higher, respectively, than those after free cisplatin treatment ($P<0.01$). In the kidney, the primary target organ of cisplatin toxicity, both KM-1 and cisplatin treatment had similar platinum levels ($P>0.05$). Concentration of KM-1 in kidney reached its highest level at 16 h and then began to decline with time, while in cisplatin-treated group, the platinum concentration in kidney fluctuated with time during the whole observation period. The platinum levels in heart, lung, and testicle were slightly higher following treatment with KM-1 than with cisplatin.

DISCUSSION

It has been demonstrated that, due to the altering of pharmacokinetics and disposition of the drugs, liposomal encapsulation of many antitumor agents attenuates their toxicity or changes their target organs of chemotherapy. And this is also the case in cisplatin. Gondal *et al* has reported a fomulation of cisplatin encapsulated in multilamellar liposomes[11]. They found that the liposome had a lower platinum level in the kidney and maintained reduced nephrotoxicity compared with free cisplatin. Newman *et al* had cisplatin encapsulated in long-circulating, pegylated liposomes (SPI-077). They observed an increasing tumor Pt disposition and improved antitumor effect in murine colon and lung cancer models[10]. Our present study showed that the platinum levels in the spleen and liver following KM-1 treatment were several times higher than those achieved with cisplatin, which was caused by the greater uptake of liposomal fomulation by the reticuloendothelial system. This offers a greater potential for the treat-

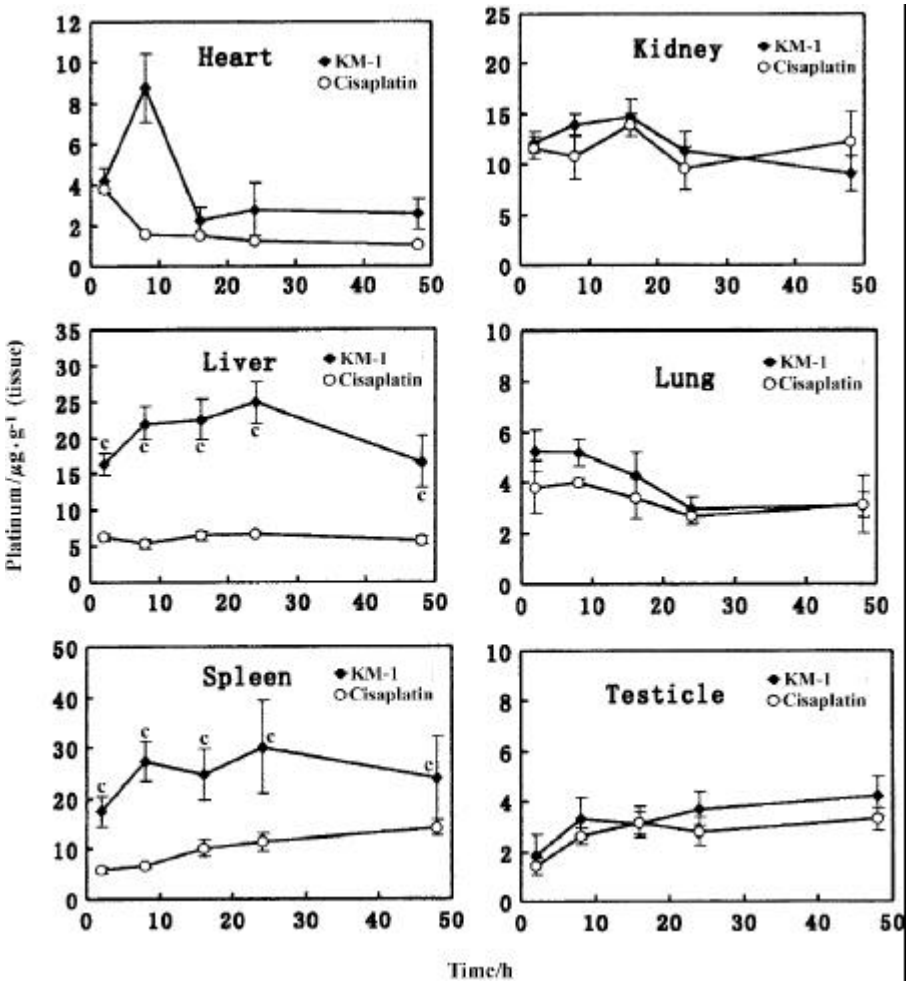

Fig 2. Concentration-time profiles of platinum in tissues following a single iv dose of KM-1or cisplatin 4.5mg/kg. *n*=5. Mean±SD. $^cP<0.01$ *vs* cisaplatin group.

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We did not discern lower platinum concentrations in the kidney with KM-1 than with free cisplatin. To outward seeming, this is not consistent with our preliminary study showing that nephrotoxicity in KM-1-treated mice was less than that in cisplatin-treated ones. The explanation may lie in the different reactive mechanism between free drug with tissues and liposomal-entrapped drug with tissues. Since most of the drug is retained in liposome, the total amount of platinum messured in KM-1-treated group is not equivalent to that of platinum that can react with biological substances and has a pharmacological or toxicological efficacy. Cisplatin encapsulated in liposome was released gradually with time and tissues were continuously exposed to a low-dose drug environment. This could avoid a high peak free cisplatin level that would produce a severe toxicological effect. Similar situation occurred in liver with KM-1 treatment, which had high platinum levels and showed no hepatotoxicity. The result agrees with the studies of Gondal *et al*[11].

No significant eliminations of platinum in tissues were observed during the first 48 h after dosing. This is due to the characteristics of cisplatin which would bind to protein or other tissue compositions firmly through covalent bonds. Excretion studies had also shown that only 25 % of total KM-1 taken by rats was excreted during (0-48) h period of time.

REFERENCES

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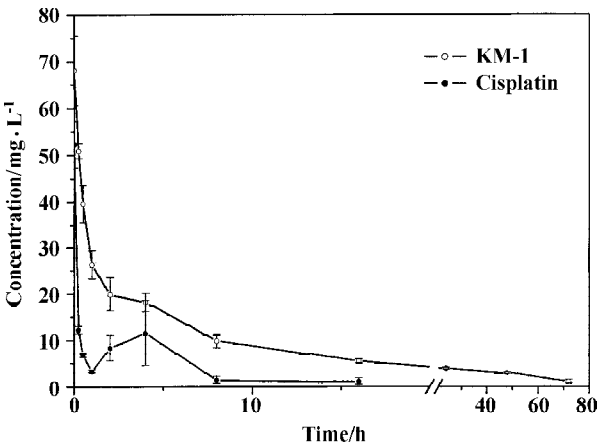

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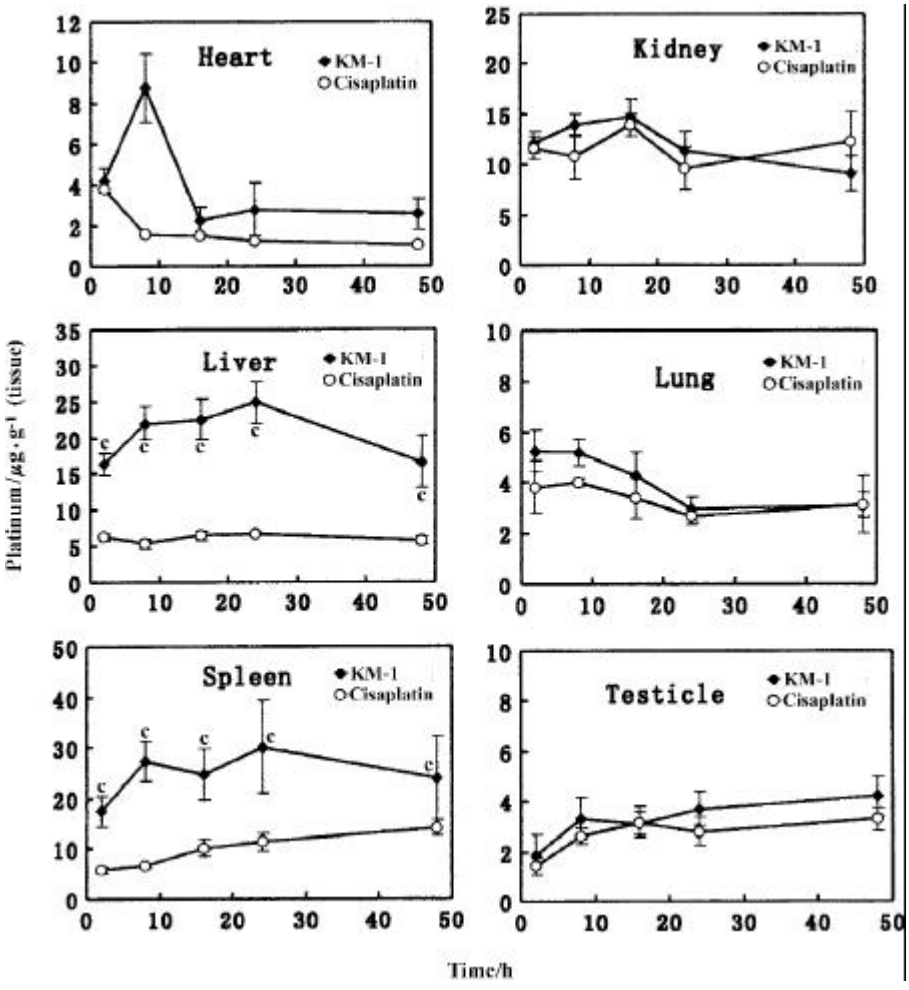

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