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Development and pharmacokinetics of nimodipine-loaded liposomes

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Abstract

In order to improve the water solubility of nimodipine and prolong the time of the drug in the circulation, nimodipine-loaded liposomes with a small size and high entrapment efficiency were prepared by a method that was easy to scale up (the modified ethanol injection method). The nimodipine liposome dispersions were characterized with respect to particle size distribution, zeta potential and entrapment efficiency. Liposomal nimodipine and nimodipine solution were intravenously administered to mice as a single dose of 4 mg kg^{-1}. The pharmacokinetic parameters of nimodipine changed significantly when encapsulated in liposomes. The clearance of nimodipine encapsulated in liposomes was reduced and the elimination half-life was prolonged. The ratios of the area under the curve values of nimodipine liposomes to nimodipine solution were 1.78 and 1.90 in plasma and cerebral tissue, respectively. The drug concentration in cerebral tissue and in plasma showed a good linear correlation, which showed that liposomes could efficiently deliver nimodipine into brain tissue. These findings suggest that intravenous administration of liposomal nimodipine produces higher and more stable plasma and cerebral drug concentrations compared with nimodipine solution. In conclusion, liposomal nimodipine is a promising alternative to the solution preparation.

Introduction

Nimodipine is a dihydropyridine calcium antagonist with a preferential effect on cerebral blood vessels. It is an important treatment for cerebrovascular spasm, stroke and migraine (Langley & Sorkin 1989). It has also been shown to be effective in treating Alzheimer's disease (Ban et al 1990). The oral use of nimodipine is, however, restricted because of its very limited aqueous solubility (2.30 μg mL^{-1}) and first-pass metabolism. The bioavailability of orally administered nimodipine is very low (Blardi et al 2002). Intravenous nimodipine administration is an alternative to oral administration and offers greater bioavailability than oral dosing. The maintenance of stable, therapeutic plasma concentrations during the course of long-term therapy is essential, but nimodipine pharmacokinetics show that nimodipine is eliminated rapidly from the blood. In addition, due to its poor solubility in aqueous solutions, nimodipine is formulated for clinical use in a solution that contains 25% ethanol and 17% polyethylene glycol 400 for solubilization of the drug and sometimes nimodipine precipitates when the injection is diluted with saline or glucose solution for infusion (Zhang 1998). Moreover, ethanol causes serious irritation to blood vessels. Given the drawbacks of the commercial product, it is apparent that there is a need for the development of safer and more effective dosage forms.

In this study, liposomes were used as drug delivery vehicles for nimodipine in order to overcome the water insolubility of nimodipine, prolong the residence time of the drug in the circulation, maintain therapeutic drug levels in the blood for a longer time and deliver more nimodipine into brain tissue.

Liposomes are phospholipid bilayer membrane vesicles that can encapsulate a wide variety of hydrophobic and hydrophilic drugs either within their lipid membranes or in their central aqueous cores. Liposomes have attracted great interest and found a great many applications in the field of therapeutics because they have obvious advantages such as increasing

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solubility, prolonging biological activity and reducing toxic effects (Charrois & Allen 2003; Mourao et al 2005). Different methods can be used for the preparation of liposomes. Xia et al (2002) have prepared liposomal nimodipine by the film dispersion method, but this method requires the use of pharmaceutically unacceptable solvents such as chloroform and methanol. Yang et al (2006) prepared nimodipine liposomes by the lipid-dripping method and the size of the liposomes prepared was reduced using a high-pressure homogenizer. Then they lyophilized the liposomes and a stable nimodipine proliposome preparation was obtained. This method has the disadvantage of being a multi-step preparation procedure. The ethanol injection method can be carried out on an industrial scale and is technically simple to perform. In this study, nimodipine liposomes were prepared by the modified ethanol injection method and the liposomes were characterized. The pharmacokinetic behaviour of nimodipine liposomes in plasma and cerebral tissue following intravenous administration to mice was compared with nimodipine solution.

Materials and Methods

Materials

Nimodipine was purchased from Shandong Xinhua Pharmaceutical Factory (Zibo, China); nitrendipine, used as an internal standard, was obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China); soybean phosphatidylcholine (Epikuron 200) was a generous gift from Degussa (Freising, Germany); cholesterol was obtained from Sigma Chemical Corporation (St Louis, MO, USA); methanol and acetonitrile were of high-performance liquid chromatography (HPLC) grade and purchased from Concord Technology Company (Tianjin, China); double-distilled deionized water was used throughout the study; other chemicals were of analytical grade.

HPLC analysis of nimodipine

The content of nimodipine in the samples was determined by HPLC (Chinese Pharmacopoeia 2005). The HPLC system consisted of a Waters model 510 pump (Waters Corporation, USA), an SPD-10A UV-vis detector (Shimadzu, Japan), and an N2000 chromatography data system (Zhejiang University, China) was used for data acquisition and integration. Chromatographic separation was achieved at room temperature on a Chromasil ODS column (4.6 mm × 250 mm, 5 μm) (Elete, Dalian, China) with UV detection at 237 nm. The mobile phase consisted of methanol/acetonitrile/water (38:35:27 v/v/v) at a flow rate of 1.0 mL min^{-1} and the injection volume was 20 μL. These conditions resulted in a typical elution time for nimodipine of 8.5 min.

Preparation of nimodipine liposomes

Nimodipine liposomes were prepared by the modified ethanol injection method. In brief, nimodipine (10 mg) and the hydrophobic excipient, such as soybean phosphatidylcholine (300 mg), cholesterol (75 mg), were dissolved in 2 mL dehydrated alcohol, and the solution was rapidly injected into a 10-mL magnetically stirred 0.9% NaCl solution thermostated at 55 ± 2°C. Ethanol was removed under reduced pressure. The final volume was adjusted to 10 mL by addition of distilled water, to yield a liposome suspension with a nimodipine concentration of 1 mg mL^{-1}. The liposomal dispersion was then extruded under nitrogen sequentially through a 0.45-μm and 0.22-μm polycarbonate membrane using a high-pressure extruder (Northern Lipids Inc., Vancouver, Canada) at room temperature.

The encapsulation efficiency of nimodipine liposomes was determined by dialysis. For this, 1.0 mL drug-loaded vesicles was placed in a pre-treated dialysis membrane bag (MW cut-off 12–14 kDa), which was then transferred to 500 mL 0.9% NaCl. The receiver medium was stirred with a magnetic stirrer. The dialysis was carried out at room temperature for 8 h and the dialysis medium was replaced with fresh medium every 2 h. The encapsulation efficiency was calculated as the ratio of the amount of nimodipine retained in the liposomes at the end of dialysis to total nimodipine in the initial 1.0 mL liposome suspension. The drug content of the liposomes was determined by HPLC analysis after the pellet was dissolved in methanol and diluted with mobile phase.

Physicochemical properties of nimodipine liposomes

The mean particle size and size distribution of the liposomal dispersions were studied using a LS230 laser diffraction particle size analyzer (Beckman, USA). For size measurement, the suspension sample was diluted to the appropriate concentration with distilled water.

The zeta potential of liposomes was measured by a Delsa 440SX zeta potential analyzer (Beckman, USA). All analyses were performed on samples diluted with 0.9% NaCl in order to maintain a constant ionic strength.

The osmotic pressure of nimodipine liposomes was measured with a vapour pressure osmometer 5520 (Wescor, USA). To measure the osmotic pressure, a sample (10 μL) was injected into the osmometer after the apparatus was calibrated with standard solutions (290 mmol kg^{-1}, 1000 mmol kg^{-1} and 100 mmol kg^{-1}). The osmotic pressure was digitally displayed once the sample had reached equilibrium.

In-vitro release

In-vitro drug release from liposomal nimodipine dispersions was determined using the dialysis method. A portion (1.0 mL) of the liposomal suspension was transferred to the pretreated dialysis bags with a molecular cut-off of 12–14 kDa, which was tied to the paddle of the dissolution apparatus. The dialysis medium was 0.9% NaCl thermostated at 37.0 ± 0.5°C; the paddle rotation speed was kept at 50 ± 2 rev min^{-1}. Aliquots were withdrawn at scheduled intervals and the same volume of fresh medium was added immediately. The drug concentration in the samples was analysed by HPLC. All experiments were carried out in triplicate and the average values were calculated. The cumulative amount of drug released at each time point was plotted.

Animal experiments

Pharmacokinetic study of nimodipine liposomes and nimodipine solution

The study protocol was developed following the Ethical Guidelines for Investigations in Laboratory Animals and was approved by the Animal Ethical Committee of Shenyang Pharmaceutical University. Male mice, 22 ± 2 g, were supplied by the Lab Animal Center of Shenyang Pharmaceutical University and were deprived of food for 12 h before intravenous administration, but were allowed water ad libitum. The mice were divided randomly into two groups and injected with either nimodipine liposomes or solution via the tail vein as a single dose of 4.0 mg per 1.0 kg bodyweight. Blood samples were taken from the retro-orbital plexus at 2, 5, 10, 15, 30, 45, 60, 120 and 240 min following the injection. The heparinized blood samples were immediately centrifuged and plasma samples were stored at −20°C until analysis. The animals were decapitated immediately after blood was collected. Then the skull was cut open and the brain tissue was quickly rinsed with saline and blotted with filter paper to remove any blood and macroscopic blood vessels as far as possible.

Sample pre-treatment

The total brain tissue sample was homogenized with 1.0 mL saline. Nimodipine in plasma and homogenized brain tissue was extracted using the following method. First, 50 μL nitrendipine (2 μg mL^{-1} internal standard) and 100 μL 1 M NaOH were added to 200 μL plasma or 0.8 mL brain tissue homogenate in a screw-top glass test tube. This mixture was extracted with 2.0 mL organic solvent (*n*-hexane: diethyl ether 1:1) by vortexing for 3 min and sonicated for 5 min. The organic phase was separated by centrifugation at 4000 *g* for 10 min. The supernatant was transferred to a screw-top glass test tube and the extraction repeated with another 2.0 mL extraction solvent. The organic phases were then combined and evaporated to dryness at 37°C under a gentle stream of nitrogen. The residue was reconstituted with 100 μL of the HPLC mobile phase, mixed by vortexing for 30 s, and centrifuged at 4000 *g* for 10 min. Then, 50-μL aliquots of supernatant were injected into the HPLC system.

Analysis of nimodipine in plasma and cerebral tissue

The HPLC system was the same as that described above. Chromatograhic separation was achieved on a Chromasil ODS column (4.6 mm × 250 mm, 5 μm) fitted with a guard column (4.6 mm × 10 mm, 5 μm), with UV detection at 358 nm at room temperature. The mobile phase consisted of acetonitrile/ammonium acetate (0.05 M) (60:40, v/v) and this was filtered through a 0.45-μm millipore membrane and degassed ultrasonically before use. The flow rate was 1.0 mL min^{-1} and the injection volume was 50 μL. The retention time of nimodipine and internal standard was 12.0 and 10.5 min, respectively, and these values were consistent during the analytical run. The nimodipine and internal standard peaks were well separated and the peak shape was satisfactory.

Data analysis

The plasma and brain concentration–time data of nimodipine liposomes and solution were fitted using a 3p87 pharmacokinetics program (Pharmacological Committee, Chinese Pharmacological Society, China), and the pharmacokinetic parameters were calculated. The area under the concentration–time curve (AUC) was determined by the trapezoidal rule.

Statistical analysis

All results are expressed as the mean ± s.d. Statistical differences in the formulation and time for in-vitro release were determined using Friedman's test followed by a post-hoc test. The effect of the formulation and time on the plasma and cerebral drug concentrations was analysed using a repeated measures analysis of variance, and a post-hoc test was used to examine differences in the individual formulation type and time. The difference between the liposome and solution formulations with respect to the various pharmacokinetic properties was statistically examined using an unpaired *t*-test.

Results and Discussion

Factors affecting the encapsulation efficiency of nimodipine liposomes

Formulation development was conducted to identify a liposome-based formulation that possessed the greatest drug entrapment efficiency per mole of lipid. Nimodipine is a hydrophobic drug and it distributes in the phospholipid bilayer of liposomes. When the drug-to-lipid molar ratio added during preparation of liposomes was high, the formulation was not stable and the drug precipitated during liposome sizing or upon storage. A study revealed that the liposome formulation was stable and the encapsulation efficiency was 97.1 ± 1.43% when the drug-to-lipid molar ratio was 1:15.

The surface charge of liposomes had an effect on the encapsulation efficiency of nimodipine liposomes. Adding a positively charged material such as stearylamine would reduce the encapsulation efficiency, whereas negatively charged phospholipid materials such as phosphatidylserine or phophatidylglycerol would increase the encapsulation efficiency. This is because nimodipine has a dihydropyridine chemical structure, and it would be protonated and positively charged in neutral aqueous solution. The change in encapsulation efficiency produced by the surface charge was owing to an electrostatic interaction. Given that a surface charge would influence the clearance of liposomes from the blood and, when liposomes carry no net surface charge, the rate of clearance from the blood is generally low and a long half-life would be obtained, we did not use any negative phospholipid material during the nimodipine liposome preparation.

Cholesterol is a rigid steroid molecule that can stabilize the liposomal bilayer and make liposomes more rigid. The presence of cholesterol could enhance the retention of entrapped solutes and improve the stability of liposomes in the blood. To increase the liposome stability both in-vitro and in-vivo, cholesterol was included in the formulation. A high cholesterol molar ratio would reduce the entrapment efficiency of nimodipine and so, because both cholesterol and drug distribute in the phopholipid bilayer, they will compete for the hydrophobic space in the lipid bilayer. In addition, the cholesterol

in liposomes also restricts the flexibility of the hydrocarbon chains of the lipids, and hinders nimodipine penetration into the lipid bilayer. The formulation was optimized by single-factor experiments and the optimum molar ratio of phospholipid to cholesterol was 2:1.

Size distribution, zeta potential, entrapment efficiency and osmotic properties of nimodipine liposomes

The vesicles prepared exhibited a Gaussian distribution with a mean diameter of 57 ± 9 nm. A typical number weighted particle size distribution showed a single narrow peak and the polydisperse index was 0.123 ± 0.011. Xia et al (2002) prepared nimodipine liposomes with a mean vesicle size of 160–180 nm. Studies have demonstrated that the longest half-life is obtained when liposomes are small (<100 nm). The small-sized liposomes obtained in this study helped the liposomes to remain in the circulation for extended periods of time.

Nimodipine liposomes had a negative zeta potential with a mean value of -21.53 ± 1.02 mV, which could be due to the presence of impurities in Epikuron 200 such as phosphatidylserine and phosphatidylglycerol. These negatively charged phospholipids caused a modification of the net charge of the system and gave it a degree of steric stabilization that finally led to a reduction in the mean particle size.

The entrapment efficiency of nimodipine liposomes was $97.20 \pm 1.32\%$. The high encapsulation efficiency obtained was owing to the hydrophobic interaction between drug and phospholipids. Yang et al (2006) prepared proliposomal nimodipine with an entrapment efficiency of 89.9%, which was lower than in the present study. Perhaps the surfactant poloxamer 188 and sodium deoxycholate they added during the preparation of liposomes increased the fluidity of the liposome membrane and reduced the partition of nimodipine in the phospholipid bilayer.

Liposomes can exhibit a change in particle size or release their contents when exposed to media of different osmotic strengths. The osmotic pressure of the nimodipine liposomes was 283 ± 6 mmol kg^{-1} and was similar to that of human plasma (291 mmol kg^{-1}).

In-vitro release of nimodipine liposomes

Figure 1 shows the release profiles of nimodipine from liposomes and solution. The results show that nimodipine is released slowly from liposomes, and less than 20% of the drug was released at the end of the test. This indicates that most of the drug was entrapped in the liposomes and there was very little surface located. The drug was released very rapidly from nimodipine solution and the accumulated percentage release was above 90% within 2 h. For each formulation, the amount of drug released increased with time up to 2 h ($P < 0.05$). At each time point, the amount of drug released from the solution was markedly higher compared with that from the nimodipine liposomes ($P < 0.001$).

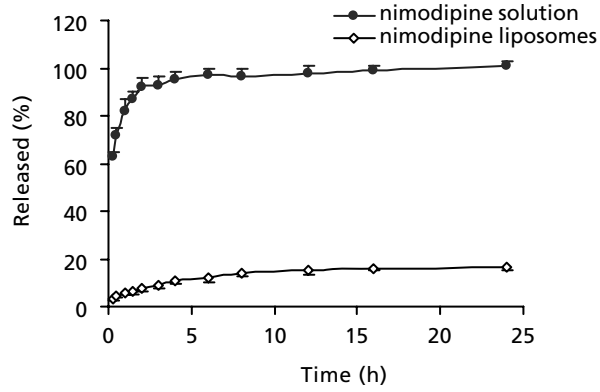

Figure 1 In-vitro release profiles of nimodipine liposomes and nimodipine solution in 0.9% NaCl (n = 3).

Assay validation

The calibration curve, generated by plotting the peak area ratios of analyte to internal standard versus the concentration using a least squares fit, showed good linearity for nimodipine in both plasma and brain tissue. The calibration curves were: plasma ($y = 0.0014x + 0.0061$, $r = 0.9997$, 10–2000 μg L^{-1}) and brain tissue ($y = 0.0015x + 0.0218$, $r = 0.9995$, 50–8000 ng g^{-1}).

The accuracy and precision of the method were determined at three levels for nimodipine in plasma and brain tissue. The accuracy was expressed as the relative error and the precision as the relative standard deviation. The extraction recovery of nimodipine at three concentrations was determined by comparing peak area ratios of the analyte to internal standard in samples to which the analyte had been added prior to extraction with samples to which the analyte had been added post extraction. The precision, accuracy and extraction recovery of nimodipine in plasma and brain tissue are reported in Table 1.

The intra-day and inter-day assay precision was below 7% for both plasma and brain tissue. The extraction yield assays showed that the mean recovery was greater than 90% for nimodipine at three concentrations in both plasma and brain tissue.

Blood pharmacokinetics

The plasma concentration versus time profiles of liposomal nimodipine and solution are shown in Figure 2. The pharmacokinetic parameters of nimodipine are shown in Table 2. In the case of intravenous administration of nimodipine solution, a high concentration of 1967.79 ± 424.12 μg L^{-1} was obtained and the drug disappeared from the circulation very rapidly owing to its short half-life. In contrast, the initial plasma concentration of nimodipine after intravenous administration of nimodipine liposomes was lower than that in the nimodipine solution group, and 15 min after intravenous administration, the nimodipine concentration in plasma was always higher than that in the nimodipine solution group ($P < 0.001$). The initial low drug concentration in the liposome group could be owing to the uptake of liposomes by the mononuclear phagocyte system. The elimination rate constant

Table 1 Analytical precision and accuracy of the liquid chromatographic determination of nimodipine in plasma and brain tissue

Concentration added	Mean concentration recovered	Precision (% RSD)	Accuracy (% RE)
Plasma (μg L^{-1})			
Intra-day (n = 3)			
10	9.58	3.89	–4.20
200	195.54	2.24	–2.23
2000	1929.03	1.43	–3.55
Inter-day (n = 3)			
10	9.17	5.98	–8.32
200	193.60	2.36	–3.20
2000	1960.38	3.82	–2.01
Brain tissue (ng g^{-1})			
Intra-day (n = 3)			
50	46.41	4.78	–7.18
1000	947.52	2.31	–5.25
8000	7554.39	3.37	–5.56
Inter-day (n = 3)			
50	45.63	6.75	–8.74
1000	956.03	6.38	–4.10
8000	7459.15	5.32	–6.76

RSD, relative standard error; RE, relative error.

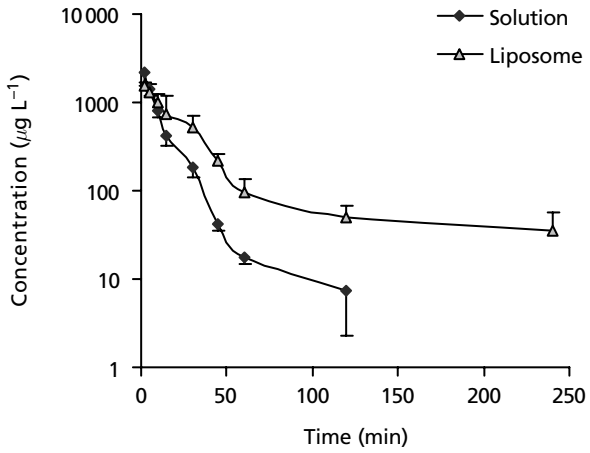

Figure 2 Mean plasma concentration–time profiles of nimodipine after intravenous administration of nimodipine liposomes and solution to mice (n = 6).

obtained for liposomal nimodipine was 55.56% that obtained for the nimodipine solution ($P < 0.01$). The encapsulated nimodipine had an AUC that was significantly higher than that of unencapsulated nimodipine ($P < 0.05$), which was associated with the delivery of high levels of drug to cerebral tissue. The high AUC of encapsulated nimodipine could be attributed to the low clearance rate of nimodipine liposomes in the blood. The mean residence time of nimodipine in the circulation for the solution group was only 12.29 min, suggesting that it is necessary to develop a sustained delivery formulation of nimodipine. The mean residence time of liposomal nimodipine was 22.93 min and this was significantly longer

Table 2 Plasma pharmacokinetic parameters of nimodipine following intravenous administration of nimodipine liposomes and solution at a dose of 4 mg kg^{-1} to mice (n = 6)

Parameters	Nimodipine liposomes	Nimodipine solution
C_0 (μg L^{-1})	1651.85 ± 644.61	1967.79 ± 424.1
K_e (min^{-1})	0.045 ± 0.011**	0.081 ± 0.001
$V_{(c)}$ (mL)	69.31 ± 33.93	52.38 ± 10.96
t½ (min)	15.89 ± 3.86*	8.52 ± 0.10
AUC_{0-t} (μg min mL^{-1})	42.72 ± 9.54*	24.03 ± 5.10
$AUC_{0-\infty}$ (μg min mL^{-1})	43.66 ± 9.67*	24.12 ± 5.14
$CL_{(s)}$ (mL min^{-1})	2.93 ± 0.74	4.26 ± 0.84
MRT (min)	22.93 ± 5.57*	12.29 ± 0.14

Values are expressed as mean ± s.d., n = 6. *$P < 0.05$, **$P < 0.01$, compared with nimodipine solution.

than that of the nimodipine solution group ($P < 0.05$). The pharmacokinetic behaviour of nimodipine in plasma revealed that it remained for an extended period, and the clearance of nimodipine was retarded, following intravenous administration of nimodipine liposomes. The increased circulation time could also be attributed to the small size of the liposomes prepared.

Cerebral pharmacokinetics

It was important to study the pharmacokinetic behaviour of nimodipine in brain tissue because this is the target organ of nimodipine. Figure 3 shows the mean brain concentration–time profiles of nimodipine after intravenous administration of nimodipine liposomes and nimodipine solution to mice. The pharmacokinetic parameters are presented in Table 3. Following intravenous administration of nimodipine solution, the nimodipine concentration in brain tissue reached a peak at

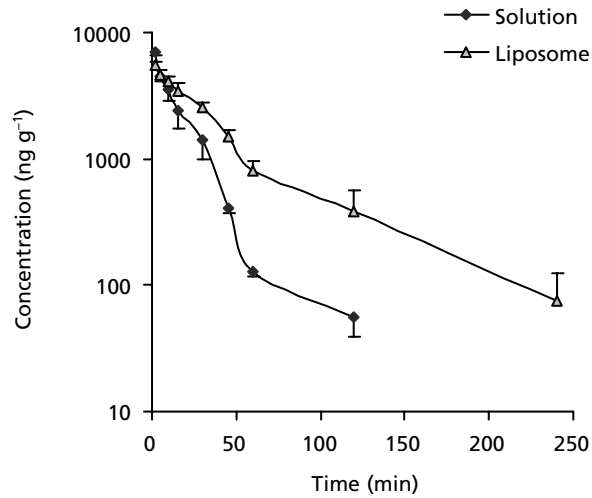

Figure 3 Mean cerebral concentration–time profiles of nimodipine after intravenous administration of nimodipine liposomes and solution to mice (n = 6).

Table 3 Cerebral pharmacokinetic parameters of nimodipine following intravenous administration of nimodipine liposomes and solution at a dose of 4 mg kg^{-1} to mice (n = 6)

Parameters	Nimodipine liposomes	Nimodipine solution
C_0 (ng g^{-1})	5716.26 ± 506.07	7171.72 ± 1224.80
K_e (min^{-1})	0.031 ± 0.002***	0.065 ± 0.0017
$V_{(c)}$ (g)	17.59 ± 1.58	14.23 ± 2.55
t½ (min)	22.22 ± 1.07***	10.07 ± 0.29
AUC_{0-t} (μg min g^{-1})	217.32 ± 35.73*	114.59 ± 20.29
$AUC_{0-\infty}$ (μg min g^{-1})	219.60 ± 35.95*	115.45 ± 20.13
$CL_{(s)}$ (mg min^{-1})	549.81 ± 59.29*	917.20 ± 139.83
MRT (min)	32.06 ± 1.55***	15.48 ± 0.42

Values are expressed as mean ± s.d., n = 6. *$P < 0.05$, ***$P < 0.001$, compared with nimodipine solution.

2 min and then declined rapidly, with an elimination half-life of 10.07 ± 0.29 min. As far as the nimodipine liposomes were concerned, the brain concentration decreased more slowly than in the case of the solution. The AUC after intravenous administration of liposomal nimodipine was approximately 1.90-fold (217.32 ± 35.73 μg min g^{-1} vs 114.59 ± 20.29 μg min g^{-1}) that obtained after intravenous injection of nimodipine solution ($P < 0.05$). The elimination half-life of liposomal nimodipine was approximately 2.21-times longer than that of nimodipine solution ($P < 0.001$). The elimination constant of liposomal nimodipine in brain tissue was only 48.0% that of nimodipine solution ($P < 0.001$). The pharmacokinetic behaviour of liposomal nimodipine in brain showed a prolonged mean residence time and an improved bioavailability compared with nimodipine solution. Liposomal nimodipine with a favourable pharmacokinetic profile may have potential advantages over a commercial injection and may be more efficacious for the treatment of cerebrovascular disease.

Correlation between cerebral tissue and plasma nimodipine concentrations

To evaluate whether liposomes can deliver nimodipine to cerebral tissue efficiently, a correlation between the brain and plasma drug concentrations was made. The correlation equation between the cerebral and plasma drug concentrations of nimodipine solution was $y = 3.0798x + 492.31$, $r = 0.9819$, n = 6, whereas the correlation equation for nimodipine liposomes was $y = 3.4737x + 448$, $r = 0.9853$, n = 6. There was a clear linear correlation between the cerebral and plasma drug concentrations. The slope of the correlation equation for the nimodipine liposome group was steeper than that of the solution group (3.4737 vs 3.0798), suggesting that nimodipine liposomes in plasma could efficiently deliver the drug to the brain via the blood–brain barrier and there was no lag-time. In conclusion, the liposome formulation was an excellent carrier of nimodipine.

Conclusions

Using the modified ethanol injection method, small-sized nimodipine liposomes with a high entrapment efficiency were obtained. The encapsulation of nimodipine into liposomes significantly improved the pharmacokinetic profile of the drug in plasma and cerebral tissue. The concentration–time profiles showed a sustained presence of nimodipine in plasma and cerebral tissue following intravenous administration of nimodipine liposomes compared with solution. Liposomal nimodipine had a significantly higher AUC compared with solution both in plasma and cerebral tissue, indicating that liposomal nimodipine had an improved bioavailability. In conclusion, the liposome system is a promising approach for the intravenous administration of nimodipine.

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