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Research Article

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Preclinical pharmacokinetics and toxic kinetics study of 2, 4-dinitrophenol (DNP)

Abstract

Purpose: To research the pharmacokinetics and tissue distribution of 2,4-dinitrophenol (DNP) in tumor-bearing mice and the pharmacokinetics and toxicokinetics in beagle dogs.

Methods:

a. Pharmacokinetics in tumor-bearing mice: DNP was administrated intra tumorally to the mice with three different dosages, the drug concentration and tissue distribution were determined by the HPLC at different time, then analyze the pharmacokinetic parameters.

b. Pharmacokinetics in beagle dogs: DNP was intravenously administrated in forelimb with three different dosages and drug concentrations were determined in dog's plasma before and after each injection to calculate pharmacokinetic parameters.

c. Toxicokinetics: the beagle dogs received intramuscular injection for two weeks and the plasma on the first day and the 13th day after the treatment were collected for the toxicity evaluation.

Results:

i. DNP showed the characteristics of linear dynamic when administrated intra temporally in mice from the dosage of 8mg/kg to 32mg/kg. DNP was widely distributed with the relative targets including liver, kidney and lung.

ii. Pharmacokinetics in beagle dogs: both of the elimination half time ($T_{1/2}$) and the area under curve (AUC) of DNP increased with the increasing dose of DNP, showed the characteristics of non-linear dynamics. The systemic toxicity increased with the increasing dose of DNP, showed the characteristics of linear dynamics after multiple injections. No drug accumulation or sex differences happened in beagle dogs.

Conclusion: DNP is a relatively safe agent, showing the characteristics of linear dynamics after intratumor and intramuscular injection. Thus, the study provides reference for the clinical application.

Keywords: 2,4-dinitrophenol (DNP), intratumor injection, pharmacokinetics, tissue distribution, tumor cell, molecule

Volume 4 Issue 6 - 2016

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Received: December 01, 2015 | **Published:** November 18, 2016

Introduction

2,4-dinitrophenol (DNP) was showing up in easily available weight-loss medicines in the 1930's and toxic at high concentration.[1] It was widely used as the common happen in the 1990's, which was a small molecule that can induce an immune response once coupled to a larger molecule. Several clinical trials have revealed locally administration of a vaccine consisting of antilogous tumor cells modified with the DNP induced T cell infiltration- the development of inflammation in metastatic masses.[2,3] The mechanism of enhancing the immunity was mostly attributed to greatly increase the binding sites of antigen and T cells to result in the T cell receptor rearrangement, further to expanse the T cells clones via altering the MHC antigenic determinant of in the preface of the dendritic cell.[4] Therefore, DNP played a role in antigen modify and immune activation. In this study, we research the pre-clinical including pharmacokinetic and Toxicokinetics of DNP in the mice and beagle dogs for clinical application.

Materials

Tumor-bearing model

Mice: Babl/c mice both sexes weighing between 18-22g were provided by the Experimental Animal Center of Shandong province (Jinan, China). They were maintained under controlled conditions with a standard palled diet and water. Sarcoma (180) cells were injected into the subcutaneous tissue of the right axillary fossa with the dosage of 2×106/ml. The animal experiments conducted were approved by the Animal Ethics Committee of Shandong University (Jinan, China).

Beagle dogs: 24 beagle dogs were used in the study of pharmacokinetics (6 dogs) and toxicokinetics (18 dogs), purchased from the Experimental Animal Center of Weiguang (Fuyang, China).

Reagents and instruments

Chemicals and reagents: 2,4-dinitrophenol (standard), methanol

(chromatographically pure, lot no. 610811, Tedia, USA), acetonitrile (chromatographically pure, lot no. 403040, Tedia, USA), ultrapure water, potassium dihydrogen phosphate (analytically pure, XK13-001-0802-113 II, Shanghai, China), acetic acid (analytically pure, lot no. 060110, Ji'nan China).

Instruments: SHIMADZU high performance liquid chromatography (HPLC), SPD-10A detector, CTO-10A temperature control system, LC-10AD pump, DGU-4A gas separation device, N-2000 double channel chromatography workstation, HITACHI high performance liquid chromatography, L2400 detector, L2200 auto-sampler, L2130 pump, XH-C vortex mixer (Lot no. 006030702, Jiangsu, China), low speed centrifuge (TGL-16G), BP211D electronic balance (Sartorius, Germany).

Method

Pharmacokinetics of DNP in the tumor-bearing mice

Dosage regimen: 126 tumor-bearing mice were divided into three groups (high-dose group (32mg/kg), middle-dose group (16mg/kg) and low-dose group (8mg/kg), with DNP concentration respectively 1mg/ml, 2mg/ml and 4mg/ml.

The disposal of the sample: Blood sample were withdrawn from the eyeballs of 6 mice at 10min, 30min, 1, 2, 4, 6, 8hours after administration, samples were immediately centrifuged at 5000rpm for 15min and the separated plasma was frozen at -20 ℃ for further analysis of pharmacokinetics. Chromatographic conditions adopted the Lichrospher C_{18} (150mm×4.6mm, 3.0μm) with mobile phase of acetonitrile (1% acetate) – water (0.05mol/L KH_2PO_4) (32.5:67.5) the wave length for detection was 254nm and the internal standard was p-nitrophenol.[5]

Data processing: By using the excel software to compute the individual density, the average ($\bar{x}$), the standard deviation (SD), relative standard deviation (RSD) and analyze the pharmacokinetic parameters of DNP injection with the DAS 2.1 program statistical moment.

Tissue distribution of DNP in tumor-bearing mice

Dosage regimen: 30 tumor-bearing mice, half male and female, were divided into five groups according to the time after the injection of DNP (15min, 30min, 2h, 5h, 8h) with 6 mice in each group. The mice were administrated DNP (4mg/ml) intra tumorally at the dosage of 0.08ml/10g.

The disposal of the sample: The blood sample were also with drawled from the eyeballs at 15min, 30min, 2h, 5h, 8h after administration and plasma was dissociated and frozen at -20 ℃ until assay, then killed all the mice and excised the tumor and tissues. To prepare the tissue homogenate, the methanol was added into each tissue as follow, heart:1ml, liver:2 ml, spleen:1ml, lung:1 ml, kidney (unilateral):1ml, bowel:1ml, brain:1ml, muscle:1ml, stomach:1ml, testis (double side):1ml, fat:1ml, ovary (double side):0.5ml, tumor:1ml/0.5g. The separated supernatant of tissue homogenate (0.3ml) after centrifuged at 12000 rpm was mixed with the p-nitrophenol (10μl) as the internal standard and then 20μl of mixture was used in the determination.[6,7] The chromatographic condition was the same as the above.

Data processing: By using the excel software to determining the content and average of the DNP injection in each tissue, the concentration of each tissue and tumor was calculated by the tissue homogenate calibration curve.

The pharmacokinetic study of the beagle dogs

Dosage regimen: The beagle dogs were divided into three groups including high-dose group (4mg/kg), middle-does group (2mg/kg) and low-dose group (1mg/kg) according to cross-over design. After one--week washout period, the dogs received the single DNP injection of right for elegore intravenous at a dosage of 1.0ml/kg.

The processing and determination of the sample: Blood sample (2ml) were collected from the right foreleg vein of each dog before and at the 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24hours after administration. The separated plasma (0.2ml) was mixed with the p-nitrophenol (100μg/ml)-methanol (20μl) and following protein precipitation with methanol solution (0.4ml), immediately centrifuged at 12000rpm for 10min after well-mixing, then 20μl of mixture was used in the determination.[8]

Chromatographic conditions were as follow: chromatographic column: Di C_{18} chromatographic column (250mm×4.6mm, 5.0μm) with the temperature 30℃ acetonitrile (1% acetic acid)-water (0.05mol/L KH_2PO_4) (45:55) mobile phase with the flow rate of 1.0ml/min the wave length for detection was 254 nm and the internal standard was p-nitrophenol.

Data processing: The method was the same as the 2.1.3.

Toxic kinetics study of beagle dogs

Dosage regimen: The beagle dogs were divided into three groups including high-dose group (2mg/kg), middle-dose group (1mg/kg) and low-dose group (0.5mg/kg) with 6 dogs in each group. DNP (4mg/ml) was administrated intramuscular for two weeks and blood sample was collected on the 1st day and the 13th day after DNP injection.

The processing and determination of the sample: Blood sample (2ml) were collected from the right for elegore vein of each dog before and at the 0.25, 0.5, 1, 2, 2.5, 3, 3.5, 4.5, 5.5, 6.5, 8, 10,12hours after administration. The separated plasma (0.2ml) was mixed with the p-nitrophenol (100μg/ml)-methanol (20μl) and following protein precipitation with methanol solution (0.4ml), immediately centrifuged at 12000rpm for 10 min after well-mixing, then 20μl of mixture was used in the determination. Chromatographic conditions were the same as the 2.1.3.

Data processing: The method was the same as the 2.1.3.

Results

The pharmacokinetic results of tumor-bearing mice

The mean plasma concentration-time profiles of DNP and its metabolite at 8, 16, and 32mg/kg (n=6) are illustrated in Figure 1 and pharmacokinetic parameters are listed in Table 1, respectively. Following intravenous administration, DNP was detected in plasma up to 24h. The maximum concentration(C_{max}) for DNP was 38.402, 24.776, and 11.670μg/mL for 32, 16 and 8mg/kg, respectively, showing the linear correlation between AUC and the dosage of DNP injection with the linear correlation coefficient of 0.996.The elimination half-life ($T_{1/2}$) of DNP varied from1.459 to 1.330hours.

Tissue distribution in tumor-bearing mice

DNP injection had a rapid tissue distribution with the short re-

Citation: Lu Y, Han Y, Fu Q, et al. Preclinical pharmacokinetics and toxic kinetics study of 2, 4-dinitrophenol (DNP). *Pharm Pharmacol Int J.* 2016;4(6):460–465. DOI: 10.15406/ppij.2016.04.00096

maining time, low concentration and uneven distribution. It was mainly distributed in the spleen, lung and kidney, but not detected in the ovarian. It still had a high concentration of DNP 8 hours after administration in the tumor and lung but none in heart, liver, stomach, bowel, testicles, skeletal muscle or fat 2hours after administration. We just detected the high concentration of the DNP at the 15min-30min after dosing in the fat and brain.

The pharmacokinetic of DNP injection intravenous injection beagle dog

The high-dose group was detected until 24hours after the intravenous injection by HPLC and 12hours in the middle-dose group and low-dose group. ND represented the DNP concentration less than 0.25μg/ml in the plasma on the 24hours after injection. The Table 2 provided a summary of pharmacokinetic data of DNP. The results reflected the dosage of DNP had obviously dose-dependence with the AUC in the process of the increasing DNP injection intravenous. The increase of C_{max} and AUC was inconsistent with the dosage, especially in high-dose group and middle-dose group. DNP of the 2mg/kg and 4mg/kg intravenous in the beagle was slow metabolism. The intravascular clearance ($T_{1/2}$) was prolonged (3.333h to 4.030h) and the total clearance (CL_t) was decreased with the increase of the dosage (0.038L/h/kg to 0.024L/h/kg). The concentration-time curve was depicted in figure 2.

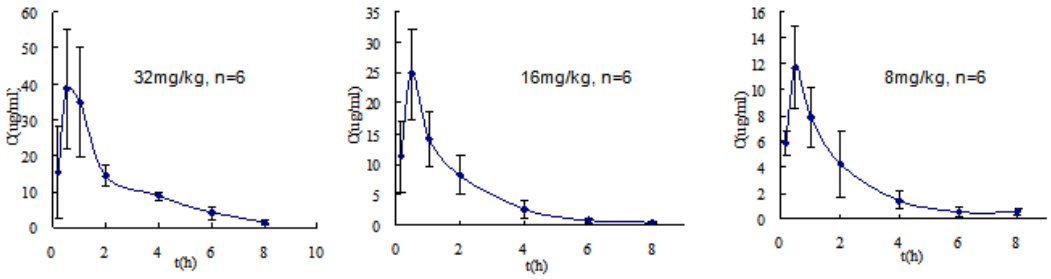

Figure 1 The drug concentration-time curve of the mice received DNP intratumoral injection.

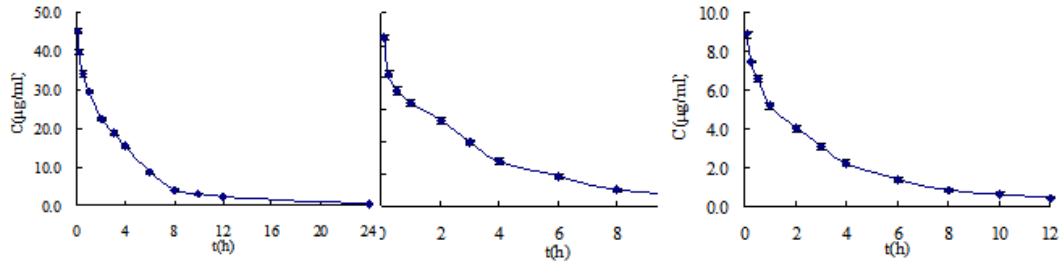

Figure 2 The concentration-time curve of the beagle dogs treated by the DNP intravenous injection (n=6).

Table 1 Plasma concentration of different dosage of DNP (μg/ml) in mice

Time(h)	32mg/kg	16mg/kg	8mg/kg
0.17	15.480±12.693	11.256±5.819	5.875±0.954
0.5	38.402±16.544	24.766±7.502	11.670±3.197
1	34.708±15.267	14.090±4.587	7.817±2.311
2	14.467±2.784	8.163±3.131	4.233±2.592
4	8.783±1.215	2.670±1.387	1.488±0.694
6	4.017±1.840	0.707±0.395	0.560±0.346
8	1.255±0.665	0.404±0.120	0.516±0.229

Data are mean±SD, n=6

Table 2 The correlation analysis between the AUC and dosage of DNP injection

Parameter	32mg/kg	16mg/kg	8mg/kg
$AUC_{(0-t)}$ mg/L·h	94.457	43.129	23.076
AUC/D (mg/L·h) /(mg/kg)	2.95	2.7	2.88

The toxicokinetics of the DNP injection intramuscular in the beagle dogs

The plasma-concentration of beagle dogs: The high-dose and middle-dose group were detected until 10hours after administration by HPLC and 8hours in the low-dose group (ND represented that the DNP concentration in the plasma was less than 0.25μg/ml).The average of the plasma-concentration and the average of the Toxicokinetics parameter of the DNP of the 1st day and 13th day after injection were showed in the Table 3.

The analysis of the TK parameters of DNP injection: Compare the TK parameters at different time in a group utilizing the C_{max} and AUC 0-t by DAS2.1.1 software (Table 4) and further to statistics the difference between the male and female (t-test) after dosage adjustment (Table 5).The results showed that there was no difference between the

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Cmax and AUC0-t on the 1st day and 13th day after intramuscular injection of different dosage of DNP (P value>0.05). The dosage of the DNP (0.5mg/kg, 1mg/kg, 2mg/kg) in beagle showed the linear dynamics after intramuscular injection. The Cmax and AUC0-t of different doses of DNP had no obvious increase, indicated that no accumulation was in beagle dog and also no sex difference on the 1st and 13th day. Moreover, it was toxicity as the AUC was greater than 11.9mg/L•h and safe as less than 5.5mg/L•h.

Table 3 Concentration of DNP in tissue of tumor-bearing mice

The time after the administration	Plasma	Tumor	Heart	Liver	Spleen	Lung	Fat	Stomach	Musculi skeleti	Supremary	Kidney	Brain	Bowel
15min	9.058± 5.281	124.847± 23.897	18.159± 25.813	3.255± 0.960	6.066± 1.967	24.682± 8.635	7.235± 2.674	5.644± 1.747	8.232± 2.851	2.187	6.072± 2.625	1.307± 0.558	4.563± 1.411
30min	17.517± 6.066	47.509± 22.167	2.143± 0.404	6.720± 2.524	5.478± 2.080	17.743± 3.143	23.846± 17.989	2.899± 0.647	8.802± 3.349	2.432	4.418± 1.042	1.899± 0.924	3.189± 0.692
2h	8.304± 1.216	27.526± 16.572	ND	ND	3.182± 1.057	7.454± 1.034	ND	ND	ND	ND	2.037± 0.376	ND	ND
5h	4.913± 2.662	14.473± 4.667	ND	ND	1.991± 0.255	8.578± 2.057	ND	ND	ND	ND	ND	ND	ND
8h	0.569± 0.215	3.878± 1.692	ND	ND	ND	6.518± 2.863	ND	ND	ND	ND	ND	ND	ND

$\overline{X}$ ±S, *μg/g (wet tissue); ND: no detected

Table 4 Plasma concentration (μg/ml) of DNP in beagle dogs by intravenous route

Time (h)	4 mg/kg±	2 mg/kg	1mg/kg
0.083	45.009±5.640	26.137±7.220	8.901±1.331
0.25	39.576±4.558	20.557±2.192	7.470±1.122
0.5	34.125±2.852	18.310±2.220	6.573±0.980
1	29.458±2.026	15.984±1.460	5.182±0.887
2	22.350±2.019	13.336±1.617	4.020±0.931
3	18.798±1.676	9.934±1.181	3.061±0.712
4	15.358±0.870	6.987±0.355	2.217±0.583
6	8.674±0.788	4.696±0.473	1.338±0.442
8	4.045±0.392	2.449±0.379	0.810±0.261
10	2.864±0.456	1.813±0.353	0.622±0.230
12	2.297±0.463	1.385±0.376	0.439±0.217
24	0.271±0.029	ND	ND

$\overline{X}$ ±S, n=6

Table 5 Pharmacokinetic of beagle dogs treated by DNP intravenous route

Parameter	unit	4mg/kg	2mg/kg	1mg/kg
AUC(0-t)	mg/L*h	163.782±10.632	80.573±7.589	25.789±5.293
AUC(0-∞)	mg/L*h	165.360±10.767	87.320±10.111	27.717±6.519
AUMC(0-t)		682.249±66.217	263.578±27.406	82.838±23.549
AUMC(0-∞)		729.279±69.876	380.577±106.167	115.879±46.946
MRT(0-t)	h	4.162±0.217	3.274±0.187	3.171±0.280

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Table Continued..

Parameter	unit	4mg/kg	2mg/kg	1mg/kg
MRT(0-∞)	h	4.406±0.217	4.314±0.771	4.059±0.677
VRT(0-t)	h^2	16.893±1.224	8.348±0.639	8.500±0.735
VRT(0-∞)	h^2	23.266±1.186	23.003±10.664	20.860±7.896
$t_{1/2z}$	h	4.030±0.170	3.333±0.729	3.201±0.673
T_{max}	h	0.08±0.000	0.083±0.000	0.083±0.000
CL_z	L/h/kg	0.024±0.002	0.023±0.003	0.038±0.008
V_z	L/kg	0.141±0.011	0.110±0.015	0.170±0.035
Zeta		0.172±0.007	0.215±0.038	0.225±0.046
C_z		0.272±0.030	1.322±0.448	0.388±0.198
C_{max}		45.009±5.640	26.137±7.220	8.901±1.331

Discussion

DNP had historically been caused a marked increase in fat metabolism,[9,10] but it was banned for two death caused by orally DNP and the concentration of 2,4-DNP in the admission blood samples of the two deaths were 36.1 and 28mg/L, respectively.[1] Most side affects concerns about the hyperthermia, tachycardia, diaphoresis and tachypnoea for high concentration.[11–13] However, it was reported that the low-dose of the DNP protected neurons against the toxicity of the amyloid-beta peptide[14] and promoted neuritogenesis and neuronal differentiation.[15] So, this study investigates the pharmacokinetics and toxicokinetics of DNP with the mice and beagle dogs to further analyze the toxicity of different dose.

The pharmacokinetics parameters including CL, $T_{1/2z}$, T_{max}, MRT, V_z had no significant change in the low-dose, middle-dose and high-dose groups after intratumor injection of DNP and demonstrated the linear correlation between AUC and the dosage with the linear correlation coefficient of 0.996, showing the linear dynamic in the DNP metabolism in the tumor-bearing mice. Meanwhile, tissue distribution indicated that the DNP was more easily entering into the fat-soluble organs and passing through the blood brain barrier with the relative target distribution to the spleen, lung and kidney. Encouraged, it was still detected the high concentration of DNP in the tumor 8hours after administration.

The DNP high performance liquid chromatographic method suggested that the blank plasma did not interfere with the determination of the sample. The average recovery of DNP in plasma was above 80% with the coefficient of variation less than 15% and the minimum quantitative limit of 0.25μg/ml. The correlation index of plasma concentration of the correlation coefficient was higher than 0.99. Days and daytime precision were both less than 15%.When DNP in plasma were placed at room temperature for 6h and plasma cryopreserved for 4days, plasma were repeated freezing and thawing three times the RSD was less than 15%. Keep the standard solution (500.0μg/ml) and internal standard solution (100.0μg/ml) under the condition of 4°C for 7days, the RSD was less than 15%.

Cmax and AUC were obvious dose-dependent manner as the dosage of the intravenous DNP increased. The increase of Cmax and AUC was inconsistent with the dosage, especially in high-dose group and middle-dose group. DNP of the 2mg/kg and 4mg/kg intravenous in the beagle was slow metabolism. Both of the intravascular clearance ($T_{1/2}$) and the total clearance (CL_t) were decreased with the increase of the dosage, which demonstrated the nonlinear dynamics of DNP in the beagle dogs within the dose range from 1mg/kg to 4mg/kg.

The $T_{1/2}$ on the 13th day of three groups were nearly unchanged compared to the $t_{1/2Z}$ on the 1st day and the linear dynamics presented between the AUC0-t and dosage on the 1st and 13th day after injection ($r>0.99$) with no significant increase of the AUC0-t and Cmax ($P>0.05$). The results suggested that DNP was no accumulation in the beagle and showed linear dynamics characteristic by repeated injections. In addition, after dose correction, C_{max} and AUC0 - t showed no gender differences after muscle injection of different doses of DNP on 1st and 13th days. According to intoxication degree of the beagle, the dosage of 2mg/kg and 1mg/kg could induce the severe toxicity two weeks after administration, it meant it was toxicity as the AUC was greater than 11.9mg/L•h and 5.5mg/L•h was a maximum safe dose. The above results indicated that the DNP metabolism in tumor-bearing mice presented the characteristics of linear pharmacokinetic. Additionally, DNP was widely distributed in the tissues of the body and relative targeting. However, the DNP in beagle dogs showed the characteristics of non-linear dynamics after single intravenous. No accumulation was in the beagle after repeat intramuscular injection with linear dynamic characteristics. Therefore, the research provided a reference role for further research.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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Citation: Lu Y, Han Y, Fu Q, et al. Preclinical pharmacokinetics and toxic kinetics study of 2, 4-dinitrophenol (DNP). *Pharm Pharmacol Int J.* 2016;4(6):460–465. DOI: 10.15406/ppij.2016.04.00096