Phase Ⅰ clinical pharmacokinetics of glycididazolum natrium

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Abstract: **AIM** To study the pharmacokinetics of a new radiosensitizing agent glycididazolum natrium (CMNa) in lung cancer patients after single- and multiple-dose administration. **METHODS** Twenty-four cancer patients were for single-dose study; and 5 patients were for multiple-dose study. The CMNa and metronidazole concentrations in blood and urine were determined by HPLC with UV detector. The blood CMNa concentration-time curves were simulated by 3P97 software and the pharmacokinetic parameters were calculated. **RESULTS** The blood CMNa concentration-time curves in single-dose groups were fitted to two-compartment open model, $t_{1/2\beta}$ were 0.76-2.62 h, c_{max} were 13.31-43.90 mg·L^{-1}, AUC were 8.68-29.94 mg·h·L^{-1} in 400, 500, 600, 700, 800 and 900 mg·m^{-2} dose groups, respectively and their c_{max} and AUC were direct proportional to doses. The blood concentration-time curves, pharmacokinetics parameters, and excretion ratios between single-dose and multiple-dose were similar, and there was no significant difference. **CONCLUSION** CMNa distributed and eliminated rapidly, so CMNa will not accumulate in patients' bodies if it is administered at an appropriate interval.

Key words: glycididazolum natrium; pharmacokinetics; chromatography, high pressure liquid; radiotherapy

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It is well known that radiation therapy is one way of treating cancers. However, radiation would kill not only tumor cells but also normal tissues because of its low selectivity. It is very important to increase the selectivity of radiation to tumor cells.

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Radiosensitizers are one kind of drugs making tumor cells sensitive to radiation. Since 1950s, radiosensitizer misonidazole has been extensively studied[1], however it has been abolished recently because of its serious side-effects in nervous system[1].

Glycididazolum natrium (CMNa) is a new kind of radiosensitizer. Animal experiments showed that it has better radiosensitive effect to S180 tumor[2,3], Lewis lung cancer, B_{16} melanoma and EMT breast cancer[4-7]; CMNa is the new nitroimidazole compounds possessed overt radio-enhancement effect which was designed, screened and studied by the Second Military Medical University. According to the Guardline of National as to first type new drugs, the systematic study of preclinical pharmacology, pharmacy, toxicology and drug metabolism, etc have been completed. And now it is in phase Ⅲ clinical study.

In this work, we studied the pharmacokinetics of CMNa in 6 single dose groups as a part of phase Ⅰ clinical study to provide an appropriate dose for its phase Ⅱ and Ⅲ clinical study.

1 MATERIALS AND METHODS

1.1 Chemicals

CMNa and its metabolite metronidazole were provided by Guangzhou S and H Pharmaceutical Factory. Internal standard furazolidone was a generous gift from Tianjin Pharmaceutical Institute. Methanol and acetonitrile were of analytical grade, and doubly distilled water was used for HPLC with UV detector.

1.2 High pressure liquid chromatography

The chromatography consisted of PE 200 series, a Waters reversed-phase ODS C_{18} column (150 mm×4.6 mm, 5 μm particle size) and

PE235C ultraviolet detector. The UV detector was set at 320 nm. The mobile phase was a mixture of methanol and ammonium oxalate solution 0.02 mol·L^{-1}(63:37)[8]. The flow ratio was 1.0 mL·min^{-1}.

1.3 Subjects

Lung cancer patients (n = 24), age (43 – 63) years, weight (55 – 73)kg, were divided into 6 single dose groups at random. The study was approved by the Ethic Committee and informed consents have been signed by all the subjects. No prior chemotherapy was given 1 month before enrollment.

1.4 Dosage escalation for single dose studies

Cancer patients (n = 24) were administered CMNa 400 mg·m^{-2}(n = 3), 500 mg·m^{-2}(n = 3), 600 mg·m^{-2}(n = 4), 700 mg·m^{-2}(n = 6), 800 mg·m^{-2}(n = 5), 900 mg·m^{-2}(n = 3) by iv infusion at the rate of 5 mL·min^{-1} for 30 min, respectively. Heparinized venous blood samples (0.3 mL) were drawn from each patient before the start of infusion and 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 h after the completion of the infusion and the blood samples were immediately extracted and measured out of light (because CMNa is sensitive to light, it can be transformed 91.8% in 90 min in blood). And urine samples were collected in 0 – 4 h, 4 – 8 h, 8 – 12 h and 12 – 48 h, respectively.

1.5 Multiple dosage studies

Cancer patients (n = 5) were given an iv dose of 700 mg·m^{-2} CMNa every other day for 9 consecutive infusions, and blood concentration of CMNa and its metabolite after the 1 st and 9 th infusion were measured in the same manner as in the single dosage studies.

1.6 Sample pretreatment and assay

Internal standard solution in methanol (15 μL of 200 μg·L^{-1}) was added to 0.2 mL whole blood sample. The mixture was extracted by 0.2 mL acetonitrile and 50 μL upper layer was injected into HPLC[3-6] (using a Perkin-Elmer instrument) by which the blood concentration of CMNa and its metabolite metronidazole were determined. All the processes were rapid and out of light.

1.7 Data analysis

The pharmacokinetic parameters were calculated by 3p97 software developed by the Chinese Pharmacological Society. And the correlation among AUC, c_{max} and doses were determined by linear regression.

2 RESULTS

2.1 Validation study

The chromatograph was shown in Fig 1. No endogenous components interfered in the analysis. The calibration curve of CMNa was obtained with concentrations in range of 0.625 – 50 mg·L^{-1} with a regression equation Y = 0.01294 + 0.06268X (r = 0.9994, n = 5), and of its metabolite metronidazole in range of 0.25 – 100 mg·L^{-1} with a regression equation Y = 0.0900 + 0.1139X (r = 0.9998, n = 5). The limit of detection was 0.5 mg·L^{-1} for CMNa and 0.25 mg·L^{-1} for metronidazole. The inter-day variation coefficients of CMNa were < 6.14%, and the mean recoveries were 76.9%, 88.4%, 89.0% for three checked concentrations of CMNa at the same condition as assay.

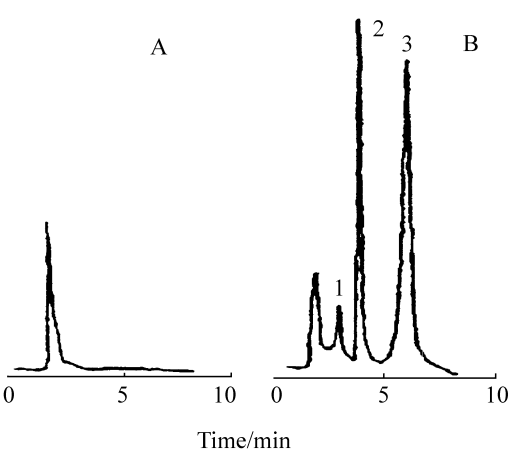

Fig 1. The chromatography of glycididazolum natrium (CMNa), metronidazole and internal standard. A: blank blood; B: blood sample in 0.25 h in a subject. peak 1: metronidazole, peak 2: internal standard, peak 3: CMNa.

2. 2 Pharmacokinetic characteristics of CMNa for single-dosage escalation studies

After iv administration, CMNa was rapidly eliminated from the central compartment and was extensively distributed into the peripheral compartment, and the maxinum CMNa concentraion in blood (c_{max}) was attained immediately after 30 min of infusion completion and the CMNa concentrations began to decline immediately after cessation of the infusion, and blood drug disappearance was biphasic. CMNa can seldom be detected after 4 h, it was metabolized to its metabolite metronidazole, and concentration of metronidazole was lower than detection limit in 48 h. The CMNa and metronidazole concentration-time curves were shown in Fig 2 and Fig 3, respectively.

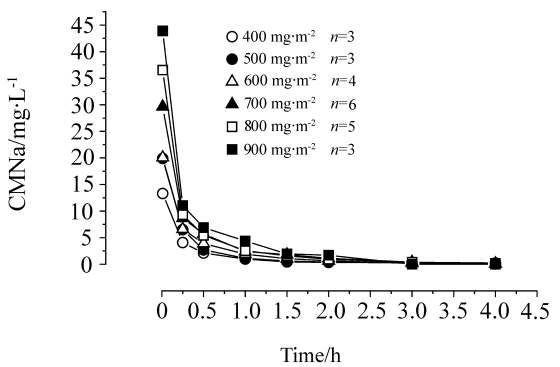

Fig 2. The CMNa concentration-time curves after intravenous infusion of 400 – 900 mg·m^{-2} CMNa.

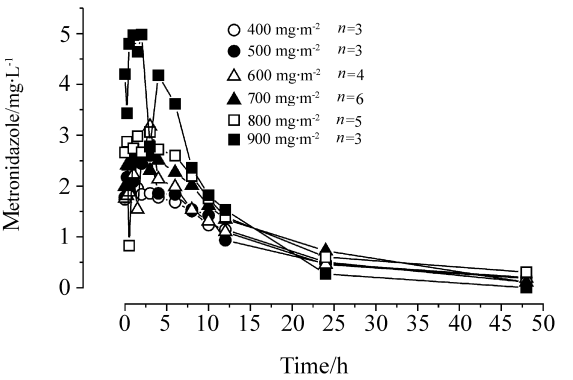

Fig 3. The metronidazole concentration-time curves after intravenous infusion of 400 – 900 mg · m^{-2} CMNa.

The CMNa blood concentration-time data were simulated by 3p97 software, and they were fitted to linear open two-compartment model, mean pharmacokinetic parameters of 6 single dose subgroups were calculated, and listed in Tab 1. Their c_{max} and AUC were directly proportional to doses, and their regression equation were $Y = -12.2222 + 0.0607X$ ($r = 0.9816$) and $Y = -8.9982 + 0.04253X$ ($r = 0.9923$), respectively. This suggests that single dose pharmacokinetics of CMNa appear to be linear over the range from 400 to 900 mg·m^{-2}.

Tab 1. Main pharmacokinetic parameters of glycididazolum natrium(CMNa) after different doses in tumor patients

Parameter	CMNa/mg·m^{-2}					
	400	500	600	700	800	900
c_{max}/mg·L^{-1}	13 ± 3	20 ± 3	20 ± 6	30 ± 17	37 ± 11	44 ± 21
$t_{1/2\alpha}$/h	0.18 ± 0.06	0.17 ± 0.02	0.13 ± 0.10	0.14 ± 0.07	0.14 ± 0.06	0.08 ± 0.02
$t_{1/2\beta}$/h	2.0 ± 0.8	2.6 ± 1.6	2.6 ± 3.8	1.1 ± 0.3	1.0 ± 0.5	0.8 ± 0.2
k_{21}/h^{-1}	0.5 ± 0.3	0.4 ± 0.2	1.5 ± 1.3	1.4 ± 1.4	1.2 ± 0.6	1.6 ± 0.5
k_{10}/h^{-1}	3.2 ± 1.0	3.3 ± 0.6	5.8 ± 4.0	4.0 ± 2.0	4.1 ± 1.0	5.9 ± 2.0
k_{12}/h^{-1}	0.89 ± 0.30	0.85 ± 0.10	3.4 ± 4.0	1.1 ± 0.6	1.2 ± 0.7	3.2 ± 1.0
Vc/L·m^{-2}	16 ± 7	12 ± 3	11 ± 8	14 ± 9	9 ± 3	6 ± 3
AUC/mg·L^{-1}·h^{-1}	8.7 ± 0.6	13 ± 3	15 ± 5	20 ± 8	25 ± 7	30 ± 11
Cl/L·h^{-1}·m^{-2}	42 ± 3	40 ± 8	44 ± 14	38 ± 11	34 ± 11	33 ± 9

$\bar{x} \pm s$, $n = 3 - 6$.

After administration, CMNa was mainly eliminated from kidney in the forms of CMNa itself and its metabolite metronidazole. Elimination ratios of CMNa and metronidazole were shown in Tab 2. CMNa elimination ratios in different time interval urine samples in 5 dose-groups were shown in Tab 3, and for all single dose groups, CMNa elimination quantity in the first 4 h was more than 95% of that in 48 h urine samples.

Tab 2. The elimination ratio of CMNa and metronidazole in 48 h

CMNa /mg·m^{-2}	Elimination ratio/%		
	CMNa	Metronidazole	Total
500	74 ± 8	4.6 ± 7.5	79 ± 5.6
600	65 ± 7	3.9 ± 6.6	69 ± 9.6
700	54 ± 10	5.1 ± 2.4	59 ± 9.6
800	58 ± 2	5.2 ± 2.2	63 ± 0.9
900	55 ± 4	3.7 ± 2.8	59 ± 5.9

$\bar{x} \pm s$, $n = 3-6$.

Tab 3. CMNa elimination rate of different time interval in 5 dose-groups

Time /h	CMNa/mg·m^{-2}				
	500	600	700	800	900
0 – 4	74 ± 5.4	63 ± 7	52 ± 10	55 ± 2	54 ± 4
4 – 8	0.3 ± 1.0	2.0 ± 1.3	0.8 ± 2.1	0.6 ± 3.1	0.5 ± 1.2
8 – 12	-	0.5 ± 1.0	0.1 ± 0.9	0.2 ± 0.8	0.2 ± 0.7
12 – 24	-	0.4 ± 0.5	0.4 ± 0.8	0.8 ± 1.5	0.1 ± 1.0
24 – 48	-	0.1 ± 0.9	0.8 ± 1.4	1.1 ± 2.8	0.2 ± 0.2

$\bar{x} \pm s$, $n = 6$.

2.3 Pharmacokinetic characteristics of CMNa for multiple-dose studies

Doses of 700 mg·m^{-2} have been given to 5 lung cancer patients for 9 consecutive administrations every other day with evaluation occurring after the 1st and 9th infusion. CMNa and metronidazole concentration-time curve and pharmacokinetic parameters of CMNa between the 1 st and 9 th administration are shown in Fig 4, Fig 5, and Tab 4.

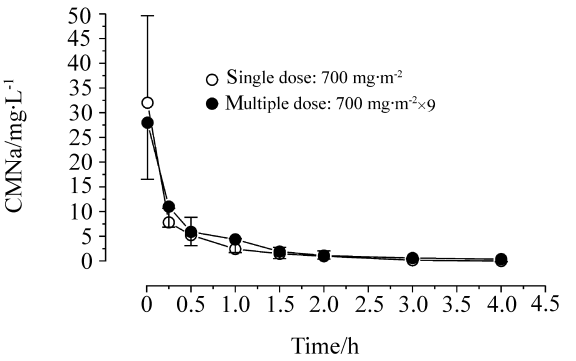

Fig 4. Profile of mean concentration-time for CMNa after single and multiple intravenous infusion dose of 700 mg·m^{-2} CMNa in 5 tumor patients.

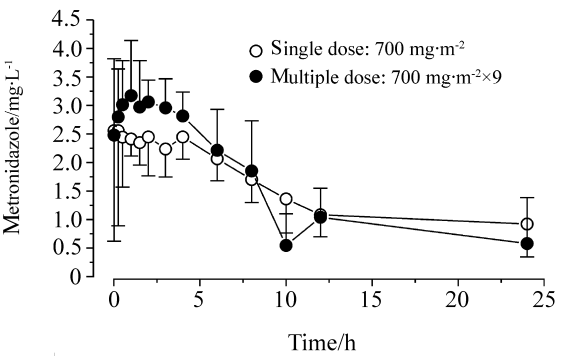

Fig 5. Profile of mean concentration-time for metronidazole after single and multiple intravenous infusion dose of 700 mg·m^{-2} CMNa in 5 tumor patients.

Tab 4. Main pharmacokinetic parameters of CMNa after single and multiple intravenous infusion dose of 700 mg·m^{-2} CMNa in 5 tumor patients

Parameter	Single-dose	The last dose
c_{max}/mg·L^{-1}	32 ± 17	27 ± 11
$t_{1/2\alpha}$/h	0.09 ± 0.03	0.21 ± 0.09
$t_{1/2\beta}$/h	0.8 ± 0.4	2.5 ± 2.7
k_{21}/h^{-1}	2.4 ± 2.1	0.6 ± 0.3
k_{10}/h^{-1}	5.5 ± 2.5	2.7 ± 1.3
k_{12}/h^{-1}	1.9 ± 1.3	0.9 ± 0.3
Vc/L·m^{-2}	10 ± 9	17 ± 12
AUC/mg·L^{-1}·h^{-1}	19.0 ± 7.9	20.0 ± 6.9
Cl/L·m^{-2}·h^{-1}	38 ± 12	36 ± 13

$\bar{x} \pm s$, $n = 5$.

Five patients was administered 700 mg·m^{-2} CMNa via infusion every other day for 9 consecutive infusions. After the 1 st and 9 th infusion, CMNa and its metabolite metronidazole concentrations in urine were measured by HPLC, and elimination ratios of CMNa and its metabolite metronidazole in 5 patients were 69%, 63%; 64%, 87%; 53%, 49%; 45%, 43% and 44%, 37%, respectively.

Concentration-time curves and pharmacokinetic parameters between single and multiple-dose administration were similar, neither c_{max} or AUC provided any evidence of accumulation at the doses gived, and they showed no significant difference. The whole elimination-ratios of CMNa and metronidazole after single- and multiple-dose administration were 54.94, 55.90, and no significant difference existed between them.

3 DISCUSSION

It is well known that radiosensitizer was usually administered before radiotherapy, and lasted for several weeks. Therefore it is important to know whether it would accumulate in patients' bodies or not. In our study, CMNa distributed and eliminated rapidly whatever in single- or in multiple-dose. The CMNa concentration-time curves of single- and multiple-dose were almost overlapped, the pharmacokinetic parameters of single- and multiple-dose were similar, all showed no significant difference. So the conclusion can be made that CMNa would not be accumulated in patients' bodies if the interval not less than 48 h.

In multiple dose studies, the CMNa concentration-time curve and pharmacokinetic parameters and elimination ratio of in No.1, 3, 4, 5 patient showed no difference between after the first and after the 9 th administration, and there were not significant individual difference among these 4 patients. However, in No.2 patient, c_{max} of CMNa was significant higher than those of the other patients after the first administration; from Tab 4, total elimination ratio of CMNa and metronidazole in No.2 patient for the first administration was 64.24% which is lower than 87.31% for the 9 th consecutive administration. All these showed that metabolism of CMNa in No.2 patient was different from that in other patients. No.2 patient was not only a lung cancer patient, but also a diabetic. It implies that diabetes may be one of factors which effect on metabolism of CMNa, and more studies would be needed about the influence of diabetes in metabolism of CMNa.

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甘氨双唑钠的Ⅰ期临床药代动力学

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摘要: 目的　对一类新药肿瘤放射增敏剂甘氨双唑钠(CMNa)进行单剂量和多剂量Ⅰ期临床药代动力学研究,对其吸收、分布、代谢、排泄及 CMNa 在体内的蓄积性作一评价。**方法**　6 个单剂量组有 24 名肿瘤病人, 5 名肿瘤病人受试者参与多剂量研究;采用高效液相-二极管阵列色谱法测定肿瘤放疗增敏剂 CMNa 及其代谢产物甲硝唑的血药浓度和尿药浓度,用 3P97 软件对各单剂量组和多剂量组的血药浓度-时间曲线拟合,并计算药代动力学参数。**结果**　6 个单剂量组和多剂量组的 CMNa 血药浓度-时间曲线经拟合均符合开放型二室模型,400, 500, 600, 700, 800 和 900 $mg\cdot m^{-2}$组的主要药代动力学参数 $t_{1/2\beta}$为 0.76 ~ 2.62 h, c_{max}为 13.31 ~ 43.90 $mg\cdot L^{-1}$, AUC 为 8.68 ~ 29.94 $mg\cdot h\cdot L^{-1}$,且单剂量组的 c_{max}及 AUC 与剂量成正比。700 $mg\cdot m^{-2}$单次给药和连续 9 次给药的多剂量组的肿瘤病人血药浓度-时间曲线几乎相吻合,各药代动力学参数值和排泄率没有统计学差异。**结论**　CMNa 在肿瘤病人体内分布和消除均很快,一定间隔服用不会在病人体内蓄积,是一个较安全的放射增敏药物。

关键词: 甘氨双唑钠; 药代动力学; 色谱法, 高压液相; 放射疗法

(本文编辑　石　涛)

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