Pharmacokinetics and tissue distribution of SU2162, a novel anticancer drug, after intravenous administration in rats

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Abstract

**Background:** SU2162, a novel anticancer agent, was investigated in the rat, and pharmacokinetics and tissue distribution were observed. These data will be used to design a SU2162 dosage form for clinical use.

**Methods:** After IV administration of SU2162, HPLC with UV detection was used to analyze rat samples. A two compartment model was used to evaluate the pharmacokinetics of SU2162.

**Results:** SU2162 pharmacokinetics in the rat depicts a two-compartment model, and the weighting coefficient was 1/c². The distribution half life (T1/2α) was 0.1066 h; the elimination half life (T1/2kel) was 0.3910 h. SU2162 was distributed widely in tissues studied. The AUC in the spleen was the highest of all the tissues assayed (6.7685 mg/l*h). The LZ in the liver was the greatest (1.5729 1/h) but liver MRT was the smallest (0.6760 h).

**Conclusion:** SU2162 is eliminated quickly in the rat and distributes to tissues extensively, and warrants further development as an anticancer candidate.

**Keywords:** SU2162, pharmacokinetics, tissue distribution, compartment model, HPLC

Background

Cancer is a threat to human health and its incidence is increasing worldwide. According to the American Cancer Society (ACS), in 2008, 12.66 million new cancer cases were documented and by 2030, new cancer cases are estimated to increase by 75%. Not only does cancer causes illness, multiple organ failure and death, it also contributes to social economic losses, and cancer is reported to cause the greatest economic loss than any other disease ($895.2 billion per year), followed by cardiovascular and cerebrovascular diseases, HIV/AIDS, lower respiratory infections (including pneumonia), hepatitis, and malaria [1].

(3aRS, 4SR, 7RS, 7aSR)-2-[(tricyclo-[3.3.1.1^3,7]decan-1-yl)-4,5,6,7-tetrahydro-4,7-epoxyisoindoline-1,3-dione(SU2162) is a novel anticancer agent (Figure 1: structure). Pharmacodynamic studies of SU2162 suggest that it has remarkable, dose-response inhibitory effects on glioma growth (IC50 =0.721 mmol/l) [2]. The chemical synthesis of SU2162 from norcantharidin and amantadine has been established [2] and its crystal structure is known [3,4]. Also, a methodological study of SU2162 pharmacokinetics has been established [5].

Understanding pharmacokinetics and tissue distribution of SU2162 in the rat will guide future designs of SU2162 dosage forms and direct its clinical use [6]. Here, we report the pharmacokinetics and tissue distribution of SU2162 after administration (iv) in the rat.

Methods

**Reagents and chemicals**

SU2162 was supplied by the School of Pharmacy, Guangdong Pharmaceutical University. Acetonitrile (HPLC grade) was purchased from Tianjin Kermel Chemical Reagent Co, Ltd (Tianjin).

**Animals**

Sprague–Dawley rats, weighing 290±30 g (pharmacokinetics studies) and 200±30 g (tissue distribution studies), were obtained from the Experimental Animal Center of Guangzhou University of Chinese Medicine. They were housed separately in metal cages with access to tap water and standard rat chow ad libitum. Studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH Publication No.85-23, revised 1985). The ethic report number was SD-R-201108005, issued by GDPU Experimental animal center, year 2011.

**Administration of SU2162**

Each rat was administered a single dose of SU2162 (5.5 mg/kg, iv) that had been prepared (2 mg/ml) in ethanol, propylene glycol and water (1:4:5). The formulation was administered...
An HPLC system with UV detection was used, consisting of a Shimadzu LC-10ATvp pump, a SPD-10Avp detector, and a manual injector with a 20 µl fixed loop. A Phenominex prodigy analytical guard column (12.5 mm×4.6 mm) was used in tandem with a reversed-phase C18 column (Luna C18 column; 250 mm×4.6 mm; 5 µm particle size; purchased from Phenomenex Co. Ltd, Guangzhou, China), and maintained at ambient temperature. Analytes were eluted at 1 ml/min under isocratic conditions using acetonitrile: water (40:60) for 80 min and detected at 211 nm. The injection volume was 25 µl [7].

Our HPLC plasma method has been previously validated [5]. The SU2162 retention time was 70.133 min. The calibration curve for SU2162 in rat plasma was linear over 0.200–16.00 µg/ml and the detection limit was 0.204 µg/ml. The quantitation limit was 0.816 µg/ml with a coefficient of variation (CV) of 14.5% and an accuracy of 92.2%. The precision for each concentration was evaluated by CV%. The CV% of the intra-day precision at 0.408, 4.08, 12.24 µg/ml was 12.36, 4.95, 8.61%, respectively and the CV% of the inter-day precision at 0.408, 4.08, 12.24 µg/ml was 6.31, 8.63, 7.24%, respectively. The CV% of the relative recovery at 0.408, 4.08, 12.24 µg/ml was 113.26, 114.24, 96.45%, respectively. The CV% of the absolute recovery at 0.408, 4.08, 12.24 µg/ml was 10.21, 4.85, 8.54%, respectively. SU2162 for plasma pharmacokinetic studies after freezing at -20°C for 4 days were stable as well. Extracted plasma samples in reconstituted solutions were stable after five freeze-thaw cycles. The average concentrations of all samples were 95–105% of the initial concentration (See Tables 1 and 2).

The extracted samples were comprised of blank plasma plus 0.400, 4, or 12 µg/ml of the standard solution and solution samples contained an equivalent concentration of the standard solution without the blank plasma. Absolute recovery of SU2162 was calculated by comparing the respective peak areas of the chromatograms between extracted samples and solution samples (Table 3).

### Results

SU2162 pharmacokinetics was measured in the rat after 5.5 mg/kg SU2162 was administered (iv). Statistics were performed

#### Table 1. Stability of SU2162 in residue after storage at -20°C for 4 days.

| Concentration (mg/ml) | Mean initial concentration (mean±SD; mg/ml) | Mean measured concentration (mean±SD; mg/ml) | (Mean measured Concentration/ Mean initial Concentration, %) |
|-----------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------------|
| 0.4080                | 0.3857±0.0579                                | 0.3789±0.01830                              | 98.25%                                           |
| 12.24                 | 13.28±1.2860                                 | 13.90±1.2730                                | 104.7%                                           |

#### Table 2. Stability of exacted plasma samples in reconstituted solutions after five freeze-thaw cycles.

| Concentration (mg/ml) | Mean initial concentration (mean±SD; mg/ml) | Mean measured concentration (mean±SD; mg/ml) | (Mean measured Concentration/ Mean initial Concentration, %) |
|-----------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------------|
| 0.4080                | 0.3857±0.0579                                | 0.4042±0.06940                              | 101.8%                                           |
| 12.24                 | 13.28±1.2860                                 | 13.48±1.797                                | 101.5%                                           |
with Kinetic Software version 5.0 (Therm, Innaphase Corp, Philadelphia, PA, USA). Plasma pharmacokinetics of SU2162 in the rat indicated a two-compartment model (weighting coefficient=1/c²). Pharmacokinetic data of SU2162 are summarized in Table 4. The mean plasma concentration-time curve for SU2162 after administration (iv) is shown in Figure 2. The T_{1/2a} and the T_{1/2b} for SU2162 were 0.1066 and 1.1407 h, respectively, and the AUC was 5.2810 (mg/L)*h.

### Tissue distribution study
Tissue distribution was measured in heart, liver, spleen, lung, kidney, brain samples at 0.03, 0.1, 0.42, 0.83, 1.33 h after SU2162 (5.5 mg/kg, iv). SU2162 concentrations in tissues at each time point are shown in Figure 3. Mean concentration versus time profiles of SU2162 in tissues are shown in Figure 4. Pharmacokinetics of SU2162 in tissues was calculated using Kinetic Software version 5.0 (Therm) and this is summarized in Table 5. At 0.03 h post-administration, SU2162 was greatest in all tissues except for the liver, which had a peak concentration at 0.1 h.

### Discussion
We investigated the pharmacokinetics and tissue distribution of SU2162 in the rat after administration (iv) using a reliable HPLC method. SU2162 depicted a two-compartment model in the rat (weighting coefficient=1/c²). Table 4 shows these data. K_{a1} and K_{e1} data suggest the SU2162 in the rat is distributed quickly after administration, and that a distribution equilibrium between the peripheral and central compartment is attained in a short time.
Figure 4. Tissue distribution curves of SU2162 after intravenous administration. (A) Heart (B) Liver (C) Spleen (D) Lung (E) Kidney (F) Brain.

SU2162 was distributed widely in rat tissue with the highest AUC in the spleen, followed by the liver and kidney. The smallest disposition rate constant (LZ) of SU2162 in liver was the maximum. The LZ value in the spleen was the minimum, followed by the kidney. The liver $T_{1/2}$ was the shortest, and the spleen $T_{1/2}$ was the longest. The mean residence time (MRT)
SU2162 accumulated more in the spleen and the elimination rate there was the slowest. Hepatic SU2162 accumulation was significant, too, and clearance of SU2162 was fast, suggesting that the liver may be a therapeutic target for cancer treatment. In Asia, especially in China’s coastal areas, liver cancer is a serious concern. From 1998 to 2007, in China the incidence of liver cancer accounted for 25.84% of cancer cases. And the incidence of liver cancer had increased between 2008 and 2015 [8].

In fact, drugs which can be used to treat liver cancer are very few. This lack of an effective liver targeting drug may seem being a problem. The design and developing the targeted therapy medicine for liver cancer has the significant meaning. Especially for disease survival rate and cure rate.

Parent- compound of the SU2162 is an original extract from an insect Mylabris cichorii L.de. Our ancestor had used this kind of insect as traditional Chinese medicine for the liver disease and already had outstanding result. Cantharidin is the active ingredient in this Chinese medicine. Yet although the Cantharidin has the strong power to cure the cancer cell, the side effect is still a major concern. In clinical, the urinary toxicity had been observed [9]. Therefore there come to the norcantharidin, which is the derivative from the Cantharidin and with much less toxicity and has the incredible effectiveness on the liver cancer [10]. The Patent compound SU2162 is the derivative from the norcantharidin and we optimized the chemical structure to lower the urinary toxicity. Here our study was focus on the Pharmacokinetics and tissue distribution. It’s essential to get those basic pharmacokinetics data for a whole new compound. As we know, successful development of a new drug ultimately depends on the absorption characteristics, and overall capacity of the drug to modulate the magnitude and duration of an anticipated pharmacological response. A series of in vivo performances evaluations and pharmacokinetic data from animal studies can provide useful preliminary information about drug absorption rates. Animal data can also offer early insights into potential mechanisms of drug distribution, metabolism, and elimination. The data shows the SU2162 has the high hepatic accumulation which indicated that maybe SU2162 has liver affinity (liver was the second widely distributed organ and the residence time in liver was the greatest). And the SU2162 might have the potential as the fine drug for the target treatment of liver cancer.

Renal accumulation of SU2162 approximated that of the liver, and the renal clearance was slow. We also noted that rats had occasional hematuria, suggesting renal or urinary adverse effects that may require monitoring.

Conclusion
As the development phase of an investigational drug product progresses, in vivo animal studies are typically conducted before any human studies are initially performed. Animal models can effectively be used to obtain early pharmacokinetic knowledge of a new drug’s absorption characteristics. Fundamental animal data can also be used to document preliminary mechanisms of a novel drug absorption, distribution, metabolism, and elimination. Consequently, animal data from in vivo pharmacokinetic evaluation are often used to support selection of a novel drug or an optimal formulation, and to guide the overall design of the final product’s dosage form. In the study, our pharmacokinetic data from animal in vivo show that SU2162 is eliminated quickly in the rat and extensively distributes to tissues, and it has characteristic liver targeting, specifically, and warrants further development as anticancer candidate.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions | ZT | HY | RL | XL | QY | WG | XZ | YH | CT | WC |
|------------------------|----|----|----|----|----|----|----|----|----|----|
| Research concept and design | ✓ | ✓ | ✓ | -- | -- | ✓ | -- | -- | -- | -- |
| Collection and/or assembly of data | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Data analysis and interpretation | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Writing the article | ✓ | ✓ | ✓ | -- | -- | ✓ | -- | -- | -- | -- |
| Critical revision of the article | ✓ | ✓ | ✓ | -- | -- | ✓ | -- | -- | -- | -- |
| Final approval of article | ✓ | ✓ | ✓ | -- | -- | ✓ | -- | -- | -- | -- |
| Statistical analysis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

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