Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

# A multiple-dose pharmacokinetics of polyethylene glycol recombinant human interleukin-6 (PEG-rhIL-6) in rats*

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Received Mar. 10, 2010; Revision accepted Aug. 29, 2010; Crosschecked Dec. 12, 2010

**Abstract:** Radiation therapy has been widely applied in cancer treatment. However, it often causes thrombocytopenia (deficiency of white blood cells) as an adverse effect. Recombinant human interleukin-6 (rhIL-6) has been found to be a very effective way against this thrombocytopenia, but IL-6 has low stability in blood, which reduces its efficacy. To increases the stability and half-life of rhIL-6, it was modified by polyethylene glycol (PEG). The pharmacokinetics and the tissue distribution of PEG-rhIL-6 labeled with $^{125}$I were examined after subcutaneous injection in rats. The pharmacokinetic pattern of PEG-rhIL-6 was defined with linear-kinetics, and we fitted a one-compartment model with half-lives of 10.44–11.37 h (absorption, $t_{1/2K_a}$) and 19.77–21.53 h (elimination, $t_{1/2K_e}$), and peak concentrations at 20.51–21.96 h ($t_{peak}$) in rats. Half-lives and $t_{peak}$ of PEG-rhIL-6 were longer than those of rhIL-6 previously reported. In the present study, for deposition of PEG-rhIL-6 in rats, the tissue distribution examination showed that blood was the major organ involved, rather than liver. However, as to the elimination of PEG-rhIL-6, the major organ was the kidney. The excretion fraction of the injection dose recovered from urine was 23.32% at 192 h after subcutaneous administration. Less than 6% of PEG-rhIL-6 was eliminated via the feces at 192 h. These results indicate that PEG-rhIL-6 is a good candidate drug formulation for patients with cancer.

**Key words:** Polyethylene glycol, Recombinant human interleukin-6, Pharmacokinetics, Rat
**doi:**10.1631/jzus.B1000085 **Document code:** A **CLC number:** R969.1

## 1 Introduction

Recombinant human interleukin-6 (rhIL-6) is a novel cytokine produced by monocytes, fibroblasts, and other cell lines, and exhibits a pleiotropic action (Nakanishi *et al*., 2004). Some studies have shown that rhIL-6 is a candidate drug that can prevent thrombocytopenia caused by chemotherapy and irradiation therapy (Drayer *et al*., 2000; Yin *et al*., 2005). The targets of rhIL-6 are the megakaryocytes which are used to promote the formation of platelets: there are high-affinity rhIL-6 receptors in megakaryocytes (rhIL-6 receptor-gp130 complex) (Bracho *et al*., 2001; Kashiwakura *et al*., 2005; Kishimoto, 2005). However, the stability of rhIL-6 in vivo is limited because of proteolysis. Also, the half-life of rhIL-6 is short due to rapid renal excretion and broad systemic distribution (Banks *et al*., 2000; Tsunoda *et al*., 2001). Therefore, it is necessary to achieve a sufficient increase in peripheral platelet numbers, and very high dosages and frequent administration of rhIL-6 are required. However, the high dosages and frequent administration give rise to adverse effects. One of the

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* Project (Nos. 10802054 and 30700149) supported by the National Natural Science Foundation of China

most important adverse effects is that rhIL-6 will induce various acute-phase proteins including C-reactive protein (CRP), β2-fibrinogen, amyloid protein, haptoglobin, hemopexin, and so on. In addition, pyrexia and anorexia are also the common adverse effects of rhIL-6 (Kishimoto, 2010).

As we know, rhIL-6 is a long-term maintenance therapy, and adverse effects are partly caused by the rhIL-6 accumulation in and transfer to the liver and spleen (Shibata *et al*., 2005). Therefore, modified rhIL-6 was used in this study to improve rhIL-6 retention in blood. Some studies indicated that the properties of biologically active compounds can be improved by covalent attachment to polymers. Polyethylene glycol (PEG) is one of the most widely used polymeric materials for this purpose (Dosio *et al.*, 2001; Parveen and Sahoo, 2006; Rawat *et al*., 2010), and has been used to modify various enzymes, proteins, and drug delivery systems, including interferon-R (Bailon *et al.*, 2001; Wang *et al.*, 2002), asparaginase (Kodera *et al.*, 1992), granulocyte colony-stimulating factor (G-CSF) (Cindric *et al*., 2007), lactoferrin (Nojima *et al*., 2008), adenosine deaminase (Levy *et al.*, 1988), and growth hormone receptor antagonist (Pradhananga *et al.*, 2002). Obtaining long half-lives of these proteins depends on the high molecular weight ($M_W$) of PEG. Attachment of PEG to small proteins leads to a larger PEG-protein conjugate with a reduced rate of renal clearance. In addition, the attachment leads to the formation of a 'shell' around the protein, which reduces or eliminates the immunogenicity and sensitivity of the PEG-protein proteolysis (Mehvar, 2000; Kozlowski *et al.*, 2001). Chemical modification of rhIL-6 with PEG effectively prolongs its half-life by increasing its molecular size, improving its resistance to proteases, decreasing its renal excretion rate, and reducing the production of antibodies. This could enhance the desirable thrombopoietic effect of rhIL-6 and reduce undesirable effects in vivo. The purpose of this study was to investigate the pharmacokinetics, distribution, and excretion of rhIL-6 chemically modified with PEG (PEG-rhIL-6) in rats using a radiotracer technique.

## 2 Materials and methods

### 2.1 Chemicals

PEG-rhIL-6 was provided by Chengdu Rongsheng Pharmaceuticals Co., Ltd., China. The $M_W$ of PEG is about 20 kDa. The mixture ratio of rhIL-6 and PEG for modification is 1:3. The number of mono-PEG-rhIL-6 in all PEG-rhIL-6 was greater than 85%; less than 15% of PEG-rhIL-6 was di-PEG-rhIL-6. The $M_W$ of PEG-rhIL-6 was about 46 kDa. All PEG-rhIL-6 was stored at −20 °C. Carrier-free protein iodination $Na^{125}I$ (>500 MBq/pg) was purchased from the Radiochemical Centre, Amersham, and iodogen (1,3,4,6-tetrachloro-3α,6α-diphenylglycoluril) from Rockford, IL, USA. The other reagents and solvents used in this study were of analytical grade.

### 2.2 Iodination of PEG-rhIL-6

PEG-rhIL-6 (5 μg) was iodinated according to previous studies (Markwell, 1982; Castell *et al*., 1990). Briefly, iodobeads were used as an oxidant, and the reaction was stopped after 20 min by removing the catalyst. A final concentration of 5 g/L bovine serum albumin was added, and then the mixture was gel-filtered by a Sephadex G-25 column, which was equilibrated with 10 g/L bovine serum albumin. The specific activity of the iodinated PEG-rhIL-6 was similar to that reported by Markwell (approximately 150 kBq/pg). $^{125}$I-PEG-rhIL-6 was found to contain only about 3% [$^{125}$I]iodide by paper chromatography analyzing. Only a single band with an apparent molecular mass of 20 kDa was found by sodium dodecyl sulfate/polyacrylamide gel electrophoresis (SDS-PAGE) and autoradiography. There were no significant differences in biological activities between $^{125}$I-PEG-rhIL-6 and PEG-rhIL-6.

### 2.3 Determination of PEG-rhIL-6 activity

The capability of PEG-rhIL-6 for inducing rat hepatoma cell line Fao *p*-fibrinogen mRNA was used to assess its activity. The protocol for the cytoblot and the mRNA hybridization has been described in previous reports (Kishimoto, 2003; 2005).

### 2.4 Animals and treatment

Male and female healthy Wistar rats, with weight ranging from 200 to 220 g, were purchased from the Laboratory Animal Center of Sichuan University, China. The animals were acclimated for one week in the Laboratory Animal Center of Sichuan University before any experimental procedures. Then, all rats were housed in a room with

controlled temperature of (24±1) °C, a relative humidity of (55±5)%, and a 12-h light/dark cycle (7:00 am to 7:00 pm). All animals had free access to water and a standard rat diet. The animal experimental protocols were approved by the Ethics Committee of Sichuan University and in accordance with the Principles of Laboratory Animal Care of the National Institutes of Health, China.

### 2.5 Validation for radioactivity determination in plasma, tissues, and excreta by trichloroacetic acid (TCA) precipitation assay

Validation for all samples' radioactivity was determined according to the method previously reported by Hu *et al.* (2006). Briefly, the determination of validation for the PEG-rhIL-6 concentrations was conducted using the precipitation of the iodinated protein by ice-cold TCA (100 g/L). To examine the reliability of TCA precipitation assay in the determination of radioactivity in rats, all blank rat samples (including plasma, tissue homogenate, and excreta) were used in the preliminary experiments. The ratios of radioactivity recovered from TCA precipitable pellet (in vitro) and from supernatant of the excreta (in vivo) were greater than 98% of the added radioactivity. At the same time, the ratios of radioactivity recovered from TCA precipitable to total radioactivities in the rats' plasma, tissue, and excreta samples decreased in a time-dependent manner after intravenous (i.v.) administration. Moreover, there was only intact protein present in the TCA precipitation using SDS-PAGE assay for plasma, tissue, and excreta samples. To calculate the concentration of $^{125}$I-PEG-rhIL-6 in plasma and tissue homogenate samples of rats, TCA precipitable radioactivity was used instead of total radioactivity. In the excretion studies, however, total radioactivity, rather than TCA precipitable radioactivity, recovered from the excreta, was used to obtain the mass balance information. The plasma, tissue, and excreta homogenate samples of examined blank rats were used to prepare a series of calibration standards by adding seven concentrations (0–50 ng/ml) of radiolabeled PEG-rhIL-6. The relationship between the added concentrations and counted radioactivity of the standards showed a strong correlation ($R^2$>0.98) and recovery (>95%) for the entire matrix. To determine the background counts for each matrix, all the plasma, tissue, and excreta homogenate samples of blank rats were counted.

### 2.6 Pharmacokinetics study

The rats were grouped randomly (three groups, $n$=5 per group) based on their genders and body weights (BWs). The three groups of Wistar rats were injected with $^{125}$I-PEG-rhIL-6 at a single dose of 3, 20, or 40 μg/kg BW by subcutaneous (s.c.) administration. After the injection, serial blood samples (approximately 100 μl each) were obtained from the tail vein of the rats and stored in heparinized Eppendorf tubes. All blood samples were centrifuged at 2000×$g$ for 10 min before 10 μl of plasma was pipetted into plastic tubes, and then stored at −20 °C until assay. Plasma samples were detected in a γ-counter (FT-2008γ, Xi'an, China). Plasma samples were diluted by adding 190 μl 9 g/L saline, and then equal amounts of cold TCA solution (200 g/L) were added to mix. The centrifugation was used to obtain the precipitation. The γ-counter was used to detect the radioactivities of all samples. The concentration of PEG-rhIL-6 at each time point was used to determine its blood clearance rates (Zhang *et al*., 2007).

### 2.7 Tissue distribution study

Wistar rats were injected with $^{125}$I-PEG-rhIL-6 at a single dose of 2 μg/kg BW s.c. ($n$=15). Five rats for each duration, 8, 24, and 48 h post-dose, were sacrificed by decapitation after administration of $^{125}$I-PEG-rhIL-6, respectively. The whole brain, womb, testis, heart, spleen, stomach, kidney, intestine, liver, lung, bladder, muscle (at injection site and skeletal), and plasma were harvested, and all tissues and organs were weighed on an analytical balance (FA1004, Shanghai, China). A γ-counter was used to detect the radioactivities of all weighed tissues. Some of these samples were homogenized in 9 g/L saline. Centrifugation (2000×$g$, 10 min) was used to clarify the suspensions. A total of 10 μl supernatants were pipetted into plastic tubes, and then mixed with equal amounts of human plasma. A total of 180 μl 9 g/L saline and 200 μl 200 g/L TCA solution were added and centrifuged (Zhang *et al*., 2007). The radioactivities of the pre-precipitation and post-precipitation were counted.

### 2.8 Excretion study

Wistar rats were each administered $^{125}$I-PEG-rhIL-6 at a single dose of 2 μg/kg BW s.c. ($n$=5). The urine and feces of these rats were collected and weighted in pre-designed intervals. A total of 10 μl urine was pipetted into each plastic tube, and the radioactivity was analyzed by the TCA precipitation method. The radioactive counts of pre-precipitation and post-precipitation were detected. The radioactivity of aliquot feces was detected by the TCA precipitation method.

### 2.9 Data analysis

Pharmacokinetic analysis was performed using 3P97 computer software (Chinese Pharmacological Society). Results were expressed as the mean± standard derivation (SD). Data were subjected to a one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) post-hoc test, and differences were considered statistically significant at $P$<0.05. Statistical analyses were performed with the SPSS software package (SPSS Inc., Chicago, IL, USA).

## 3 Results

### 3.1 Pharmacokinetics study

Blood samples of rats were collected at the expected duration after s.c. administration of $^{125}$I-PEG-rhIL-6. The plasma disappearance curves of three groups are displayed in Fig. 1. PEG-rhIL-6 showed a one-compartment model in rats after single s.c. injection (3, 20, and 40 μg/kg BW, respectively), with half-lives of 10.44–11.37 h (absorption, $t_{1/2K_a}$) and 19.77–21.53 h (elimination, $t_{1/2K_e}$), time of peak concentration ($t_{peak}$) 20.51–21.97 h, clearance (CL/F) 20.44–25.59 ml/(kg·h), area under curve up to 72 h ($AUC_{0–72}$) 120.49–1651.94 ng·h/ml, maximum concentration ($c_{max}$) 2.05–27.40 ng/ml, and mean residence time (MRT) 43.28–46.66 h. The main pharmacokinetics parameters in rats are displayed in Table 1. Except for $AUC_{0–72}$ and $c_{max}$, no significant differences ($P$>0.05) were observed in the pharmacokinetic parameters among the three different doses.

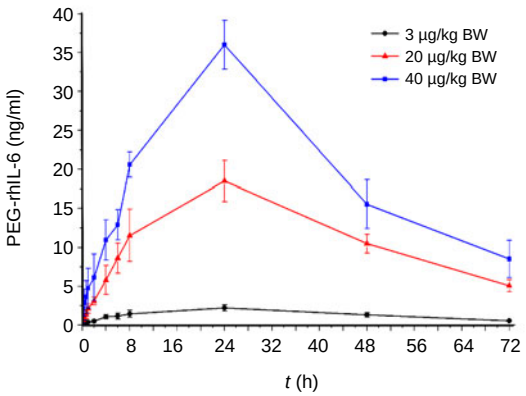


**Fig. 1 Mean plasma PEG-rhIL-6 concentration-time curves in rats after single subcutaneous administration of $^{125}$I-PEG-rhIL-6 at 3, 20, and 40 μg/kg BW**
Data are expressed as mean±SD ($n$=5)

**Table 1 Pharmacokinetic parameters of $^{125}$I-PEG-rhIL-6 after single subcutaneous administration to rats**

| Dose (μg/kg BW) | $c_{ave}$ (ng/ml) | $K_e$ ($h^{-1}$) | $K_a$ ($h^{-1}$) | $t_{1/2K_a}$ (h) | $t_{1/2K_e}$ (h) |
|---|---|---|---|---|---|
| 3 | 9.12±3.57 | 0.0340±0.0020 | 0.0690±0.0160 | 10.44±2.29 | 20.47±1.33 |
| 20 | 69.15±14.66 | 0.0320±0.0010 | 0.0620±0.0980 | 11.25±1.65 | 21.53±1.20 |
| 40 | 143.39±31.73 | 0.0354±0.0037 | 0.0610±0.0036 | 11.37±0.66 | 19.77±2.05 |
| Dose (μg/kg BW) | $t_{peak}$ (h) | $AUC_{0–72}$ (ng·h/ml) | $c_{max}$ (ng/ml) | CL/F (ml/(kg·h)) | MRT (h) |
| 3 | 20.51±2.34 | 120.49±23.50 | 2.05±0.46 | 25.59±4.46 | 43.28±1.80 |
| 20 | 21.30±1.61 | 988.22±113.26* | 15.72±2.39* | 20.44±2.19 | 46.66±2.55 |
| 40 | 21.97±0.83 | 1651.94±166.33* | 27.40±2.27* | 24.41±2.41 | 43.58±6.70 |

$c_{ave}$: average concentration; $K_e$: elimination rate constant; $K_a$: absorption rate constant; $t_{1/2K_a}$: half-life of absorption; $t_{1/2K_e}$: half-life of elimination; $t_{peak}$: time of peak concentration; $AUC_{0–72}$: area under the curve up to 72 h; $c_{max}$: maximum concentration; CL/F: clearance; MRT: mean residence time. Data are expressed as mean±SD. * $P$<0.05 among the three different doses of 3, 20, and 40 μg/kg

### 3.2 Tissue distribution study

The tissue distribution of $^{125}$I-PEG-rhIL-6 was investigated in Wistar rats. The radioactivities for $^{125}$I-PEG-rhIL-6 in brain, womb, testis, heart, spleen, stomach, kidney, intestine, liver, lung, bladder, muscle (at injection site and skeletal), and plasma of Wistar rats were determined by a γ-counter. Fig. 2 illustrates the main tissue distribution of $^{125}$I-PEG-rhIL-6 in rats. Except the plasma and muscle at the injection site, the highest deposition was found in the bladder, followed by the stomach and kidney. Less deposition of $^{125}$I-PEG-rhIL-6 was found in the brain. These results show that the major organs for deposition of PEG-rhIL-6 were the plasma and bladder (Zhang *et al*., 2007).

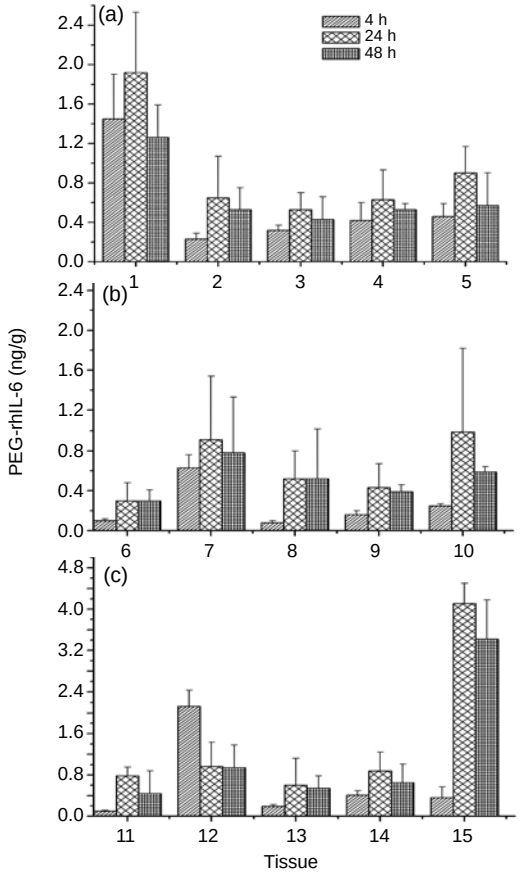


**Fig. 2 Tissue distribution of PEG-rhIL-6 following single injection of $^{125}$I-PEG-rhIL-6 to rats at 4, 24, and 48 h**

Tissue: (a) 1, blood; 2, heart; 3, liver; 4, spleen; 5, lung; (b) 6, brain; 7, stomach; 8, large intestine; 9, small intestine; 10, uterus; (c) 11, didymus; 12, muscle at the injection site; 13, skeletal muscle; 14, kidney; 15, bladder. Data are expressed as mean±SD ($n$=5)

### 3.3 Excretion study

The urine and feces of Wistar rats were collected, weighed, and counted at the expected duration. The cumulated excretion fractions of rats are illustrated in Fig. 3. The major organ of PEG-rhIL-6 elimination was the kidney. The integral excretion fractions of the injection dose from urine were 9.95% within 24 h, 20.74% within 96 h, and 23.32% within 192 h after injection, respectively. Only about 6% of PEG-rhIL-6 was eliminated via feces during 192 h.

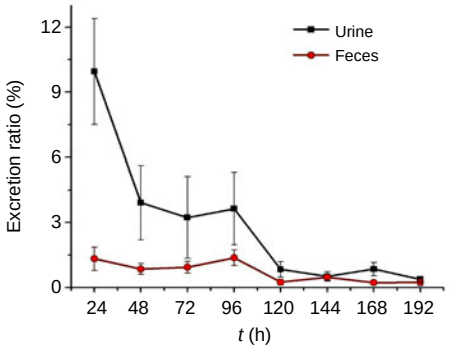


**Fig. 3 Daily excretion ratios of PEG-rhIL-6 in urine and feces after subcutaneous administration**

Data are expressed as mean±SD ($n$=5)

## 4 Discussion

To our knowledge, this is the first report to evaluate the pharmacokinetics, tissue distribution, and excretion of PEG-rhIL-6 in rats. Dose linearity of the pharmacokinetics over the s.c. dosage range examination (3–40 μg/kg BW) was demonstrated. The $c_{max}$ and $AUC_{0-72}$ values of the three doses showed a similar dose proportionality. There was an approximately 14-fold increase in $c_{max}$ (2.05 vs. 27.40 ng/ml) and $AUC_{0-72}$ (120.49 vs. 1651.94 ng·h/ml) caused by the 14-fold increase in dosage (Table 1). Although $t_{peak}$ and $t_{1/2K_a}$ seemed to vary in a dosage-dependent manner ($P$>0.05), there were no significant differences of other parameters including CL/F and $t_{1/2K_e}$ among the three dosages analyzed by ANOVA ($P$>0.05). Therefore, our results show that PEG-rhIL-6 across the investigated dosage range in rats (3–40 μg/kg BW) displayed a linear plasma pharmacokinetics and fitted a one-compartment model (Castell *et al*., 1988).

In some previous studies (Ryffel *et al*., 1994; Zha *et al*., 1995; Banks *et al*., 2000), pharmacokinetic studies showed different results in humans and rats. They have reported that rhIL-6 displayed a very short plasma half-life. In this study, we investigated the plasma half-life of PEG-rhIL-6 in the rat in detail. We found that the half-life of PEG-rhIL-6 in the rat appeared to be 200 times and 20 times, respectively, longer than that in the rat ($t_{1/2K_a}$ =3 min, $t_{1/2K_e}$ =55 min) (Castell *et al*., 1988), and 2 to 10 times longer than that in humans ($t_{1/2}$=5 h) (Banks *et al*., 2000). The plasma half-life of PEG-rhIL-6 in this study is also longer than that of rhIL-6 in non-human primates (Ryffel *et al*., 1994). The time to reach the maximum concentration of PEG-rhIL-6 appeared to be longer than results reported in some previous studies after s.c. administration (Zha *et al*., 1995; Banks *et al*., 2000). For example, the mean $t_{peak}$ of 4.1 h at doses of 2.5–5.0 μg/(kg·d) was seen in the patients with cancer (Banks *et al*., 2000) and $t_{peak}$ of 0.73 h at the dose of 10 μg/kg BW has been found in mice (Zha *et al*., 1995), in contrast with 20.51, 21.30, and 21.97 h in this study for the rats receiving 3, 20, and 40 μg/kg BW, respectively.

These differences may be due to the different administration routes and assay methods utilized. The modification of rhIL-6 with PEG may also contribute to our findings. PEG had been used to modify various enzymes and proteins to improve their properties and increase the size of proteins and enzymes, excluding them from immediate uptake by organs and prolonging blood circulation (Parveen and Sahoo, 2006; Rawat *et al*., 2010). In the previous studies, it was reported that the $t_{1/2}$ of interferon-alpha-2a (IFNα-2a) was only 2.3 h; however, its $t_{1/2}$ reached to 50 h after PEG modification (Zeuzem *et al*., 2003). PEG can obviously prolong the $t_{peak}$ (Hinds and Kim, 2002). As a consequence, the mean residence time was increased.

In order to ensure the effectiveness and safety of the dosages used in the present study, the results of our pharmacodynamic and toxicological studies in dogs and rats on the tested PEG-rhIL-6 were referenced (Yin *et al*., 2005). PEG-rhIL-6 was found to impede thrombocytopenia caused by cyclophosphamide at the dosages of 1–3 μg/kg BW by once-daily s.c. injection in dogs for one week, and at the dosages of 66 and 40 μg/kg BW by once-daily s.c. injection in rats for 5 d. These results are illustrated in Fig. 4 (Yin *et al*., 2005), indicating that PEG-rhIL-6 can alleviate thrombocytopenia significantly and recover the platelet level more rapidly. On the other hand, the toxicological studies on PEG-rhIL-6 demonstrated the increasing risk for pharmacodynamics in dogs at the dosages of 6.0, 12.0, and 30 μg/kg BW by once-daily s.c. injection for 30 d (data not shown). Therefore, it was reasonable for us to choose the 3, 20, and 40 μg/kg BW in our experiments. At the same time, the dosages that were used in the present study keep the results consistent and comparable.

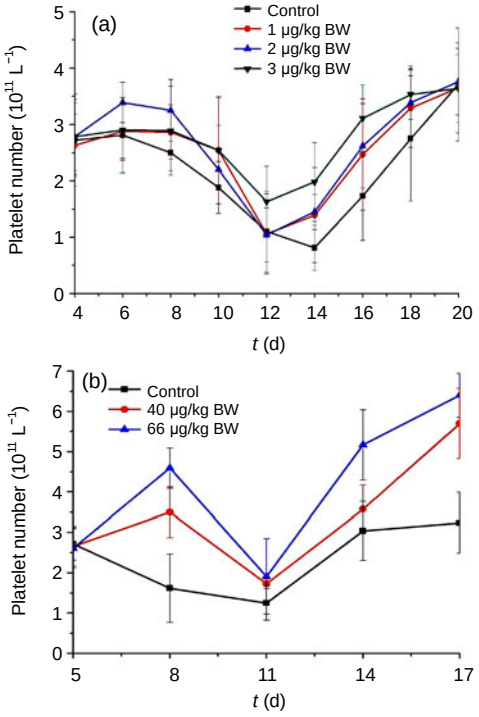


**Fig. 4 Changes in the number of platelets following injection of PEG-rhIL-6**

(a) Injection of PEG-rhIL-6 (1, 2, and 3 μg/kg BW) to dogs; (b) Injection of PEG-rhIL-6 (40 and 66 μg/kg BW) to rats. Data are from Yin *et al*. (2005)

Tissue distribution of $^{125}$I-PEG-rhIL-6 was investigated following a single s.c. administration to rats at 2 μg/kg BW dosage. The total radioactivity was determined in various tissues at 4, 24, and 48 h after s.c. injection. The results show that there was a slow and wide distribution in the tissues (or organs) throughout the whole body for the TCA-precipitable PEG-rhIL-6 within the time course examined. The amount of radioactivity in the plasma, muscle at the

injection site, and bladder was found to be extremely high. The amount of TCA-precipitable radioactivity sharply increased at 24 h in the bladder. However, there was no marked increase of radioactivity in the liver with time. Considerable TCA-precipitable radioactivity was also found in reproductive tissues. The amount of TCA-precipitable radioactivity in the brain was extremely low, only 0.3 ng/g of brain at 24 and 48 h post-dosing, respectively. Considerable amount of the radioactivity was found in the kidney at 48 h post-dosing. There was an extremely high amount (2.130±1.3 ng/g) of radioactivity in the muscle at the injection site at 48 h post-dosing, indicating that PEG-rhIL-6 was being slowly absorbed.

It has been previously reported that, after 20 min i.v. injection, about 80% of the rhIL-6 disappeared from the circulation in the liver. RhIL-6 was exclusively localized on the surface of parenchymal cells, suggesting the existence of an IL-6 receptor on the hepatocytes (Castell *et al*., 1988). However, the radioactivity was relatively low in the liver, but relatively high in the blood at various time points after s.c. administration of PEG-rhIL-6 in this study. These may be accounted for by the modification of rhIL-6 with PEG **(**Caliceti and Veronese, 2003). These findings were thought to be consistent with the literature of a relatively high radioactivity in plasma of human serum albumin-paclitaxel (Dosio *et al*., 2001). There was a relatively low radioactivity of PEG-rhIL-6 in the brain, which means that PEG-rhIL-6 may not pass through the blood-brain barrier (BBB). These findings imply that $^{125}$I-PEG-rhIL-6 is unlikely to accumulate in the tissues (or organs) examined following a single s.c. administration. The data of the excretion after a single s.c. administration of 2 μg/kg BW $^{125}$I-PEG-rhIL-6 are illustrated in Fig. 3. The results suggest that the dominant route of elimination for $^{125}$I-PEG-rhIL-6 is urinary excretion following s.c. administration, as 23% administered radioactivity was recovered in urine, and recovery in the feces was only 6% over 192 h. The elimination for most of PEG-rhIL-6 was through the urine after metabolism. Therefore, it is not surprising that there was a relatively high radioactivity in the bladder. The kidney plays a more important role in the elimination for TCA-precipitable protein than the liver does. Therefore, one should monitor renal function and adjust the dose when PEG-rhIL-6 is used in patients with renal impairment.

## 5 Conclusions

The findings in this study indicate a linear disposition of PEG-rhIL-6 at the used s.c. dosage range, and the $c_{max}$ and AUC showed an similar dose proportionality in rats. The PEG-rhIL-6 has favourable biokinetics. Because of its longer half-life, PEG-rhIL-6 is able to accumulate in blood and effectively increase peripheral platelet numbers. It appears to be a good candidate drug for patients with cancer.

## Acknowledgements

PEG-rhIL-6 was kindly provided by Rongsheng Co., Chengdu, China. We wish to thank Prof. Xian-yin ZEN (Sichuan Agricultural University, China) for expert technical assistance. We also would like to thank Ms. Xian-kun XU and Ms. Shu-fang WANG (Sichuan Agricultural University, China) for their valuable assistance in this research.

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