# Toxicokinetics and toxicological studies of sodium 9-[2-(phosphonomethoxy) ethyl] adenine in beagle dogs

WANG Wen-Yan[1], SHEN Zi-Long[1], YAO Quan-Sheng[2*], YAO Jun[2], BAI Wen-Xia[2], PAN Yu-Ying[2]
(1. *Center of Biotechnology, China Pharmaceutical University, Nanjing* 210009, *China*; 2. *Jiangsu Province Center for Drug Safety Evaluation, Nanjing* 210009, *China*)

**Abstract**: **AIM** To provide toxicokinetics data for toxicity studies of repeated doses of sodium 9-[2-(phosphonomethoxy) ethyl] adenine (PMEA-Na). **METHODS** The concentrations of PMEA-Na in plasma and urine were determined by HPLC/MS/MS method after single and multiple iv administrations in dogs. Data were executed by the statistical moment method to acquire the toxicokinetics parameters. Serum biochemical tests and histopathological examination were performed. **RESULTS** The system exposure of PMEA-Na in dogs was dose-dependent over the dose range of 1.0－6.0 mg·kg$^{-1}$. The areas under the plasma concentration-time curve of PMEA-Na after single and multiple iv administrations at 1.0, 3.0 and 6.0 mg·kg$^{-1}$ dosage were (2.3±0.5), (8.4±1.6), (17.5±3.7) and (5.0±0.4), (15.9±3.2), (30.3±4.7) mg·L$^{-1}$·h, respectively. The urinary excretion of PMEA-Na in 72 h after iv administration was (87.0±4.8)% at the dose of 3.0 mg·kg$^{-1}$. In 6.0 mg·kg$^{-1}$ dose group, liver enzyme activity of glutamic-pyruvic transaminase and serum levels of total bilirubin, blood urea nitrogen, creatinine and triglycerides were all significantly elevated; glucose level significantly decreased comparing with the control group. Histopathological observation showed distinct pathological changes in liver and kidney tissues of 6.0 mg·kg$^{-1}$ dose group. **CONCLUSION** There was evidence of toxicity after repeated-dose (14 d) of PMEA-Na in dogs and the major toxicity target organs were the kidney and liver.

**Key words**: sodium 9-[2-(phosphonomethoxy) ethyl] adenine; toxicokinetics; pathology

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**Biography**: WANG Wen-Yan (1976－), female, native of Chengfeng, Inner Mongolia Autonomous Region, candidate PhD, main research field is toxicokinetics.
[*] Corresponding author. Tel and Fax: (025) 83274013 E-mail: quansheng_yao@163.com

9-[2-(Phosphonomethoxy) ethyl] adenine (PMEA, Fig 1) is a nucleotide analogue of adenosine with potent activity against retrovirus replication that has not 3′-hydroxylic root so as to compete DNA polymerases and reverse transcriptases and inhibit DNA synthesis[1]. In view of the low oral bioavailability of PMEA because of the limitation in intestinal permeation of phosphonate, iv injection is used as a way of administering the drug. The pharmacokinetics of PMEA by iv administration has been examined in mice, rats, cynomolgus monkeys and human[2-5], which have demonstrated that the

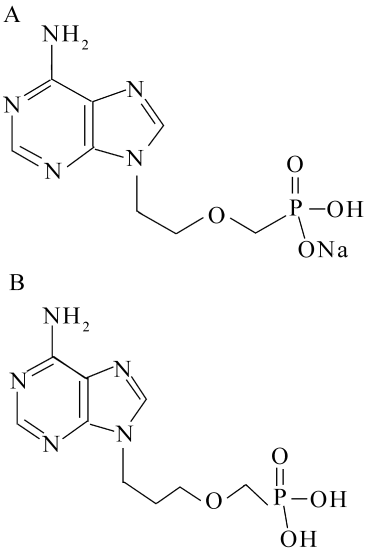


**Fig 1. Chemical structure of sodium 9-[2-(phosphonomethoxy) ethyl] adenine (PMEA-Na, A) and 9-[2-(phosphonomethoxy) propyl] adenine (B).**

concentrations of PMEA in plasma generally declined in a biexponential manner and PMEA was cleared by the kidney and excreted mainly as unchanged PMEA in the urine.

The toxicokinetics data can assist to explain toxicological results and play an important role in preclinical evaluation [6,7]. At present, State Food and Drug Administration of China requests that toxicokinetics studies should be performed for innovated drugs. In the paper, during the period of chronic toxicity study of PMEA-Na in beagle dogs, we carried out its accompanied toxicokinetics studies of single and multiple dosages.

## 1 MATERIALS AND METHODS

### 1.1 Chemicals

PMEA-Na (99.4%, Fig 1A) was obtained from Jiangsu Wuzhong Suyao Medicine Development Co. Ltd.. 9-[2-(Phosphonomethoxy) propyl] adenine (99.1%, Fig 1B) as internal standard was presented by Prof. ZHONG Da-Fang of Shenyang Pharmaceutical University. All other chemicals and solvents were analytical reagent.

### 1.2 Instruments

Alliance 2695-Quattro micromass API (HPLC/MS/MS, Waters) including solvent delivery system, auto-injector, column oven, triple quadrupole tandem mass spectrometry detector equipped with an ESI source, Masslynx 4.0 workstation and quanlynx software. Automated serum biochemistry analytical instrument (Dimension Xpand AMSA-18).

### 1.3 Animals

Thirteen male and 13 female beagle dogs (4.7 – 7.1 kg) were used for the study, which were purchased from Nanjing Xinxueren Technology Development Inc.. The certificate number was 2002-0028(SCXK). The dogs were divided randomly into 4 groups: one control group and three test groups. The dogs were conscious and acclimated throughout the blood collection procedure. On d 1 and d 14 of administration, the dogs were fasted 12 h prior to dosing and until 6 h post-dosing but could drink water freely. The uptaken food quantity and body weight of dogs were measured every week, and the behavior of the dogs was observed every day.

### 1.4 Drug administration

PMEA-Na solution in 0.9% NaCl was injected iv in forelimb vein for 14 d. The daily doses were 1.0, 3.0 and 6.0 $mg \cdot kg^{-1}$, respectively. At the same time, the dogs of the control group were injected with physiological saline.

### 1.5 Sample collection

On d 1 and d 14 of administration, blood samples (0.6 mL) were collected from another leg and placed into heparinized tubes at 0 (predose), 1, 5, 15, 30, 45 min and 1, 2, 4, 6, 8, 12 and 24 h post dosing. Blood was chilled and immediately processed by centrifugation at 2000 × *g* for 10 min to obtain the plasma. Plasma samples were frozen and maintained at ≤ −20℃.

### 1.6 Determination of PMEA-Na concentration in plasma

The concentration of PMEA-Na in plasma was determined by using HPLC/MS/MS analysis method. 9-[2-(Phosphonomethoxy) propyl] adenine was used as the internal standard for analysis. A linear relationship was good over the concentration range of 0.02 – 20 $mg \cdot L^{-1}$. The lower limit of quantitation (LOQ) was 20 $\mu g \cdot L^{-1}$. The within-day and between-day precisions were less than 6.5% and 10.8%, respectively. The accuracy (recovery) of PMEA-Na was 97.1% – 107.3%.

### 1.7 Urine excretion after single iv administration of PMEA-Na

Five beagle dogs (3 males and 2 females, weighted 6.9 – 7.3 kg), housed in stainless-steel cages, were used for the study. PMEA-Na 3.0 $mg \cdot kg^{-1}$ was administered iv. Urine samples were collected at intervals of 0 – 4, 4 – 8, 8 – 12, 12 – 24, 24 – 36, 36 – 48 and 48 – 72 h post dosing. Samples of urine were centrifuged at 4000 × *g* for 10 min, the supernatants were filtered through 0.4 μm filters. The filtrate was frozen and maintained at ≤ −20℃,

and analyzed with HPLC/MS/MS method.

### 1.8 Serum biochemical tests

Prior to the last dose of PMEA-Na, blood samples (1 mL) were collected from behind-limb vein of dogs. After coagulation, blood samples were centrifuged at 2000 × *g* for 10 min to obtain the serum. Glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBI), blood urea nitrogen (BUN), creatinine (CRE), glucose (GLU), triglycerides (TG), cholesterol (CHO) and creatine kinase (CK) in serum were analyzed by corresponding reagent kits and automated analytical instrument.

### 1.9 Pathological morphology observation

At the end of experiment, necropsy was conducted in 4 dogs of 6.0 mg·kg$^{-1}$ group and two dogs of the control group after bleeding from jugular vein. The heart, liver, spleen, lung, kidney, thymus, adrenals, lymph node, thyroid, brain, marrow, testis, epididymis, ovary and uterus were fixed in 12% formaldehyde solution. Tissue samples were embedded into paraffin, sliced, dyed with HE and examined microscopically[8].

### 1.10 Calculation of toxicokinetic parameters and statistical analysis

Data were analyzed by statistical moment method to obtain the toxicokinetics parameters[9]. The data were presented $\bar{x} \pm s$. Statistical analysis was performed by Student-Newman-Keuls test.

## 2 RESULTS

### 2.1 Animal behavior appearance

During 14 d dosing period of PMEA-Na, at 6.0 mg·kg$^{-1}$ group, animals showed signs of poor health such as inappetence, vomit, weight loss or inactivity, and 1 male and 1 female dog died on d 12 and d 13, respectively. Animals of 3.0 mg·kg$^{-1}$ group also showed inappetence, whereas the animals of 1.0 mg·kg$^{-1}$ and control groups were normal. The body weight and the uptaken food quantity of 6.0 mg·kg$^{-1}$ group had significant difference compared with the control group ($P$ values were 0.023 and 0.031, respectively, data were not published).

### 2.2 Evaluation of toxicokinetics parameters

The concentration-time course for PMEA-Na in plasma and the mean toxicokinetics parameters of PMEA-Na in dogs after single and multiple iv administrations were shown in Tab 1 and Fig 2. The results suggested that the AUC be dose-dependent over the dose range of 1.0 – 6.0 mg·kg$^{-1}$ in single and multiple doses studies,

**Tab 1. Toxicokinetics parameters of PMEA-Na after single and multiple iv administrations of PMEA-Na to dogs**

| PMEA-Na / mg·kg$^{-1}$ | $AUC_{0-24}$ / mg·L$^{-1}$·h | $AUC_{0-\infty}$ / mg·L$^{-1}$·h | $c_{max}$ / mg·L$^{-1}$ | CL / L·h$^{-1}$·kg$^{-1}$ | R / $AUC_{14th}$: $AUC_{1st}$ |
|---|---|---|---|---|---|
| | | | Initial dose studies | | |
| 1 | 2.3 ± 0.5[a] | 2.4 ± 0.5 | 3.4 ± 0.8 | 0.448 ± 0.097 | |
| 3 | 8.4 ± 1.6 | 9.1 ± 1.9 | 9.3 ± 2.5 | 0.365 ± 0.055 | |
| 6 | 17.5 ± 3.7 | 18.2 ± 3.7 | 19.5 ± 6.5 | 0.360 ± 0.104 | |
| | | | Multiple dose studies | | |
| 1 | 5.0 ± 0.4 | 5.2 ± 0.5 | 5.6 ± 0.6 | 0.200 ± 0.019 | 2.17 |
| 3 | 15.9 ± 3.2 | 17.2 ± 3.4 | 12.4 ± 2.1 | 0.194 ± 0.038 | 1.89 |
| 6 | 30.3 ± 4.7 | 32.1 ± 5.1 | 15.8 ± 2.7 | 0.202 ± 0.026 | 1.73 |

a: the mean values of $AUC_{0-8}$ or $AUC_{0-12}$, because PMEA was not detectable beyond 8 or 12 h post-dosing in this dose. $\bar{x} \pm s$, $n = 6$.

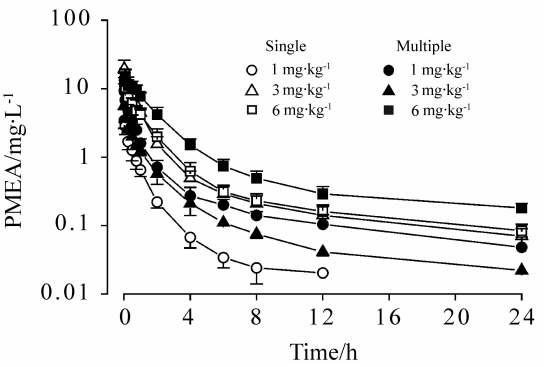


**Fig 2. Plasma concentration-time curve of PMEA-Na after single and multiple iv administrations in dogs.** $\bar{x} \pm s$, $n = 6$.

and coefficients were 0.9999 and 0.9993, respectively ($P$ value were 0.001 and 0.023, respectively). But the $c_{max}$ didn't proportioned with the dose after the 14 d dosing period.

The clearances of PMEA-Na of the single and multiple iv administrations in the dogs exceeded the glomerular filtration rate in this species (0.160 $L \cdot h^{-1} \cdot kg^{-1}$) which indicated the possibility of active tubular secretion or metabolism excretion. After the 14 d dosing period, the renal clear ability decreased obviously in all test groups. In addition, statistical analysis demonstrated there was no gender difference in kinetic parameters.

## 2.3 Urine excretion after single iv administration of PMEA-Na

The mean cumulative urine excretion-time course of PMEA-Na after single iv administration at 3.0 $mg \cdot kg^{-1}$ in dogs was shown in Fig 3. The excretion quantity of PMEA-Na within 72 h was (87.0 ± 4.8)%, which was similar with that of adefovir dipivoxil after single iv administration in monkeys at the dose of 2 $mg \cdot kg^{-1}$ (85 ± 12)% [10]. The data suggest that the majority of PMEA-Na be excreted in the urine within 24 h after iv administration, and more than half of PMEA-Na be excreted within 4 h post dosing.

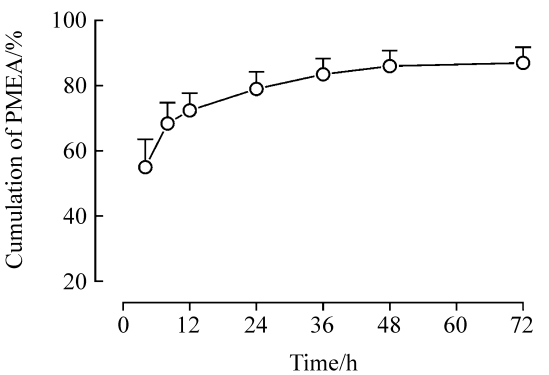


**Fig 3. Cumulative urinary excretion percentage of PMEA-Na after iv administration of PMEA-Na (3 $mg \cdot kg^{-1}$) to dogs.** $\bar{x} \pm s$, $n = 5$.

## 2.4 Serum biochemical parameters

The data of serum biochemistry tests of the dogs after multiple iv administrations of PMEA-Na were presented in the Tab 2. The data indicated that liver enzyme activity of GPT and the serum level of TBI, BUN, CRE and TG were all significantly elevated, and serum level of GLU was significantly declined in 6.0 mg · $kg^{-1}$ group compared with the control group. The activity of GOT was significantly decreased in 1.0 mg · $kg^{-1}$ group that was possibly caused by decreased the ability of hepatocellular production or release of enzyme due to initial damage of liver.

## 2.5 Pathological morphology changes

Histopathological examination showed denaturation or necrosis of tubular epithelial cells, and presence of lots of casts in lumens of renal tubule (Fig 4 C, D). There were many of denaturation in hepatocyte and eosinophilic substances that were different in size and number in the hepatocellular cytoplasm (Fig 4 D). Above pathological changes appeared in kidney and liver tissues of 6.0 $mg \cdot kg^{-1}$ PMEA-Na group, the other tissues were normal, and no pathological change was found in the control group (Fig 4 A, B).

# 3 DISCUSSION

After the repeated-doses of PMEA-Na in dogs for 14 d, the system exposures were linear with dose and almost doubled those of the single administration at each dose group, but the $c_{max}$ didn't proportioned with the dose at the last

**Tab 2.　Serum biochemical data of beagle dogs after multiple iv administrations of PMEA-Na**

| Parameter | Control | 1 | 3 | 6 ($mg \cdot kg^{-1}$) |
|---|---|---|---|---|
| GOT/$\mu mol \cdot min^{-1} \cdot L^{-1}$ | 44 ± 13 | 28 ± 8 * | 43 ± 16 | 45 ± 9 |
| GPT/$\mu mol \cdot min^{-1} \cdot L^{-1}$ | 34 ± 7 | 32 ± 56 | 63 ± 29 * | 67 ± 256 * |
| ALP/$\mu mol \cdot min^{-1} \cdot L^{-1}$ | 183 ± 25 | 205 ± 37 | 246 ± 66 | 218 ± 87 |
| TP/$g \cdot L^{-1}$ | 65 ± 7 | 61 ± 2 | 59 ± 6 | 61 ± 4 |
| ALB/$g \cdot L^{-1}$ | 26 ± 3 | 27 ± 3 | 25 ± 2 | 25 ± 3 |
| GGT/$\mu mol \cdot min^{-1} \cdot L^{-1}$ | 5.2 ± 0.5 | 4.5 ± 0.8 | 6.8 ± 2.0 | 6.0 ± 1.3 |
| TBI/$\mu mol \cdot L^{-1}$ | 4.3 ± 2.2 | 6.1 ± 1.9 * | 7.9 ± 2.6 * | 9 ± 3 * |
| BUN/$mmol \cdot L^{-1}$ | 2.5 ± 0.4 | 2.7 ± 0.7 | 2.1 ± 0.2 | 8 ± 7 ** |
| CRE/$\mu mol \cdot L^{-1}$ | 53 ± 5 | 71 ± 15 * | 57 ± 12 | 89 ± 33 * |
| GLU/$mmol \cdot L^{-1}$ | 5.5 ± 0.8 | 5.1 ± 0.4 | 4.3 ± 0.5 * | 4.0 ± 0.7 ** |
| TG/$mmol \cdot L^{-1}$ | 0.92 ± 0.10 | 1.04 ± 0.04 * | 1.21 ± 0.13 ** | 1.13 ± 0.11 * |
| CHO/$mmol \cdot L^{-1}$ | 3.2 ± 0.5 | 4.2 ± 0.8 * | 4.0 ± 0.8 | 4.0 ± 1.6 |
| CK/$\mu mol \cdot min^{-1} \cdot L^{-1}$ | 293 ± 131 | 182 ± 60 | 194 ± 56 | 190 ± 86 |

$\bar{x} \pm s$, $n = 6$. * $P < 0.05$, ** $P < 0.01$, compared with the control group.

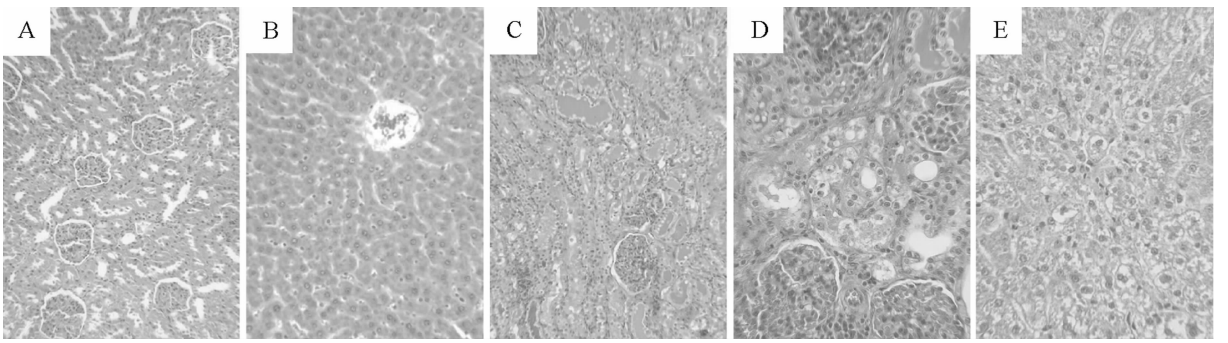


**Fig 4.　Histopathological examination of kidney and liver tissues of dogs after multiple iv administration of PMEA-Na ($6\ mg \cdot kg^{-1}$).** (HE: D, × 200; other photographs, × 120). A: normal morphology in kidney tissue of control group. B: normal morphology in liver tissue of control group. C: $6\ mg \cdot kg^{-1}$ dosage group, lots of casts appeared in lumens of renal tubule. D: $6\ mg \cdot kg^{-1}$ dosage group, denaturation or necrosis of renal tubular epithelial cells. E: hepatic tissue of $6\ mg \cdot kg^{-1}$ dosage group, cytoplasm rarity and appearance of lots of eosinophilic substances.

administration study. Furthermore, the clearance significantly declined after 14 d dosing period, which may be attributed to the renal damage that led the function of renal excretion decline. In the multiple administration of $6\ mg \cdot kg^{-1}$ group, the concentration of PMEA-Na in dog plasma declined slowly within 45 min or 1 h after dosing and the most of $T_{max}$ was the second time point of blood samping not the first time point, which showed blood flow cycle was slower. Both the serum biochemistry tests and histopathology examination showed the dysfunction of renal and liver at $6\ mg \cdot kg^{-1}$ group. Electronic microscope observation showed mitochondrial damage of tubular epithelial cells, such as vacuolated mitochondria, decreased crista, vanished membranous configuration, and presence of lysosomes and lipid droplets as-

sociated microcysts. In the clinical trial, a higher dose of adefovir dipivoxil was associated with a higher incidence of mild and reversible renal impairment[11].

Renal dysfunction may result from either the damage of glomerular filtration or active transport of the organism. For example, organic anion transporter is mainly expressed in kidney, and plays an important role in the process of tubule secreted charge molecules. When the process of tubule secretion is hindered, the drug accumulates in tubule to arouse kidney toxicity[12,13].

The liver plays an important role in the metabolism and disposition of a large number of drugs and chemicals to which animals are continuously exposed. In our study, 2 dogs died and the others showed the signs of liver damage, such as inappetence, vomit and weight loss in 6 $mg \cdot kg^{-1}$ group. In serum biochemistry tests of 6 $mg \cdot kg^{-1}$ group, the marked elevation of liver enzyme activities of GPT represented damage of parenchymal liver cells. In contrast to the liver enzyme, serum TBI concentration was significantly elevated in three test groups and increased with increase in dosage. The increase in serum TBI concentration signified the liver dysfunction as a result of cholestatic process, particularly in the dog[14]. The change in serum level of TG and GLU in 3.0 and 6.0 $mg \cdot kg^{-1}$ groups showed that lipid metabolism and carbohydrate metabolism were abnormal, and electronic microscope observation of 6 $mg \cdot kg^{-1}$ group showed the presence of distinct steatosis in hepatocytes.

In summary, the present results suggest that after iv administration of PMEA-Na in dogs, the major toxicity target organs be the kidney and liver. Because of nephritic and hepatic dysfunction, the clearance of PMEA-Na was decreased and PMEA-Na accumulated in the body, which even led animal death at 6 $mg \cdot kg^{-1}$. Because the dosing period was only 14 d, so the study couldn't recommend the safety dose in the clinics. We think that the dose should be not more than 1 $mg \cdot kg^{-1}$ in the following chronic toxicity study of PMEA-Na in beagle dogs for 9 months.

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# 9-[2-(膦酰甲氧基)乙基]腺嘌呤一钠盐在比格犬体内的毒代动力学和毒理学研究

王文艳[1]，沈子龙[1]，姚全胜[2]，姚　军[2]，白文霞[2]，潘玉英[2]
（1. 中国药科大学生物技术中心，江苏 南京 210009；2. 江苏省药物研究所药物安全评价中心，江苏 南京　210009）

**摘要：目的**　为 9-[2-(膦酰甲氧基)乙基]腺嘌呤一钠盐(PMEA-Na)重复给药的毒性研究提供毒代动力学资料。**方法**　采用液相色谱质谱联用方法测定样品中的药物浓度，数据经统计矩方法处理得到毒代动力学参数，并完成血清生化学及组织病理学检测。**结果**　比格(Beagle)犬静脉单次及多次给药(14 d，每日 1 次)后，在给药剂量范围内，AUC 均表现为剂量依赖性。在 1.0，3.0 与 6.0 mg·kg$^{-1}$ PMEA-Na 时，AUC 分别为(2.3 ± 0.5)，(8.4 ± 1.6)，(17.5 ± 3.7) mg·L$^{-1}$·h(单剂量)和(5.0 ± 0.4)，(15.9 ± 3.2)，(30.3 ± 4.7) mg·L$^{-1}$·h(多剂量)。PMEA-Na 主要经肾脏排出体外，且给药 14 d 后肾功能受损药物排泄能力降低。与对照组比较，6.0 mg·kg$^{-1}$组血清生化学检测指标丙氨酸氨基转换酶、总胆红素、尿素氮、肌酐及甘油三酯均升高，葡萄糖水平下降。6.0 mg·kg$^{-1}$组的组织病理学检查发现肝脏和肾脏有明显的病理形态学改变。**结论**　比格犬经静脉多次给 PMEA-Na 14 d 后出现毒性反应，毒性靶器官主要为肾脏和肝脏。

**关键词：** 9-[2-(膦酰甲氧基)乙基]腺嘌呤一钠盐；毒代动力学；病理学

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