Pharmacokinetics of [^{125}I]Huwentoxin-1 after epidural and intravenous administration to rhesus monkeys*

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ABSTRACT **AIM** To study and compare pharmacokinetics (PK) after epidural or intravenous (iv) administration of [^{125}I]labeled Huwentoxin-1 ([^{125}I]HWTX-1) in rhesus monkeys. **METHODS** Huwentoxin-1 was labeled by iodogen method and was administered at a dose of 0.388 MBq·kg^{-1} by lumbar puncture at the third lumbar (L_3) and the forth lumbar (L_4) interspaces using a 12-gauge paracentetic needle into epidural space of rhesus monkeys or iv at the same dose. Reverse Phase High Performance Liquid Chromatography (RP-HPLC) determined serum [^{125}I]Huwentoxin-1 with an automatic gamma counter. **RESULTS** The puriation of [^{125}I]Huwentoxin-1>96% and with the same bio-activity as unlabeled Huwentoxin-1; Radioactivity detected in epidural space was 38% of injected radioactivity at 10 min after epidural injection, which demonstrated successful administration into epidural space; The maximum serum concentration after epidural or iv administration of [^{125}I]labeled Huwentoxin-1 were determined to be (0.70±0.04) MBq·L^{-1} and (4.98±0.58) MBq·L^{-1}, respectively, at the maximum serum concentration times of 30 min and 2 min. Terminal $T_{1/2}$ after epidural or iv administration were (10.36±0.27) h or (11.03±1.16) h, respectively. Cls was (1.29±0.07) L·h^{-1}·kg^{-1} or (1.25±0.23) L·h^{-1}·kg^{-1}, respectively. Bioavailability after epidural administration was (95±5)%. **CONCLUSION** Concentration-time curves of [^{125}I] labeled Huwentoxin-1 after two routes were different. The degradation profiles after epidural and iv injection supported the using of HWTX-1 as analgesic by epidural administration.

KEY WORDS huwentoxin-1; pharmacokinetics; epidural administration

Huwentoxin-1 (HWTX-1) is a peptide neurotoxin (with amino acid sequence of ACKGV FDACT PGKNE CCPNR VCSDK HKWCK WKL) isolated and purified from the venom of the Chinese bird spider Selenocosmia huwena[1]. The structure consists of a three-stranded anti-parallel beta-sheet and three turns. The three disulfide bridges($C^2 \sim C^{17}$, $C^9 \sim C^{22}$, and $C^{16} \sim C^{29}$) and three-stranded anti-parallel beta-sheet form an inhibitor cystine knot motif which is adopted by several other small proteins besides huwentoxin-1, such as ω-conotoxin, and gurmarin[2].

Several recently developed analgesic techniques demonstrate that neuratoxial analgesia by spinal administration (epidural or intrathecal) of local anesthetics and opioids provides the highest level of pain control after major surgery and trauma injuries[3,4]. Recent data indicated that ω-conotoxin has a favorable risk/benefit ratio with advantages over several currently available intrathecal therapies for pain and was recommended for approval by the FDA for the management of chronic pain[5]. As an analgesic, HWTX-1 has the similar structure and mechanism to those of ω-conotoxin. Series preclinical studies showed that epidural injection of HWTX-1 inhibited pain sensation induced by heat radiation or mechanical stimulation for 2 hours in dose dependent manner. Its analgesic dose was less than ω-conotoxin, and its analgesic duration was longer than morphine. The results indicated that HWTX-1 is a potential novel analgesic peptide (to be published separately). As part of preclinical studies, the pharmacokinetics (PK) profiles of [^{125}I]HWTX-1 after epidural administration in rhesus monkeys were investigated and compared with those after iv in our studies.

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1 MATERIAL AND METHODS

1.1 Drugs and reagents Huwentoxin-1(purity＞99.5 %,batch 010620) was provided by the Institute of Life Science, Hunan Normal University. Na ^{125}I was purchased from Perkin-Elmer Life Science (99.9% purity and 10 mCi or 647.0 GBq·mg^{-1}, NEZ033R). Dicinchona acid protein determination kit was purchased from Sigma. Other reagents were all analytical or HPLC grade.

1.2 Animals Rhesus monkeys(n=8 of both sexes, 6.0±0.5 kg) and adult male mice (Kun-Ming strain, n=6 of both sexes, 18～22 g, Grade II, Certificate D01～3024) were provided by Animal Center of Academy of Military Medical Sciences.

1.3 Preparation and identification of [^{125}I]HWTX-1 HWTX-1 was labeled by Iodogen method[6] and purified by a column of 1×50 cm filled with Sephadex G-10(Pharmacia). The mobile phase was a 0.4 mol·L^{-1} sodium chloride at pH 7.0 in 0.02 mol·L^{-1} phosphoric buffer at a flow-rate of 0.5 ml·min^{-1}. The eluted fractions were determined for both γ-radioactivity by Automatic gamma counter (1470 WIZARD^{TM}, Wallac) and protein concentration by commercial dicinchona acid method kit. The purity of [^{125}I]HWTX-1 was identified by RP-HPLC (C_{18}, 300Å, 5 μm, 4.6 mm×250 mm, CAT. #218TP54, Vydac^{TM}), with a linear gradient of 0～100% acetonitrile in double distilled water, and the flow-rate was 1.0 ml·min^{-1}. Radiochromatogram was obtained from a HP 1100 system (Agilent Technologies, USA) online with a detector of Radiomatic^{TM} Flow Scintillation Analyzer (Packard 525TR, USA).

1.4 Biological assay of labeled HWTX-1 Method followed Rash LD *et al*[7]. Mice were killed, and the hemidiaphragms with the phrenic nerve intact were removed. Preparation were attached to tissue holders with in-built electrodes, mounted in 5 ml·L^{-1} of Tyrode's solution and maintained at 37℃ under 1 g resting tension. The incubation solution was saturated with 95% O_2 plus 5% CO_2. The tissue was then equilibrated for at least 30 min before the addition of venom (0.01 g·L^{-1} in Tyrode's solution). Hemidiaphragms were stimulated via the phrenic nerve at supramaximal voltages (0.2 Hz, 0.5 ms) using a Nihon Kohden Sen3201 stimulator. A recorder (Shanghai Da-Hua Instrumental Company) was use to record the stimulation and muscle contraction.

1.5 Administration and sampling [^{125}I]HWTX-1 was epidurally administered by the anesthesiologist at a dose of 0.388 MBq·kg^{-1} weight of monkey (approximately equals to 11.2 μg·kg^{-1}), with a lumbar puncture at the third lumbar(L_3) and the forth lumbar(L_4) interspace using a 12-gauge epidural paracentetic needle (B72～05, 1.2× 55 mm)into epidural space. The epidural space was identified using the loss-of-resistance technique with saline. Provided that neither cerebrospinal fluid nor blood was obtained on aspiration. An iv group with the same dose was served as control. Blood 1.5 ml was collected before administration and 2, 4, 7, 10, 15, 20, 30 min, and 1, 2, 4, 6, 8, 12, and 24 hour after administration of [^{125}I]HWTX-1. The blood was collected into centrifuge tubes and centrifuged at 1 000(×g) for 15 min. The samples of serum stored at 0～4℃ until required for assay.

1.6 Radioactivity in epidural spaces Two rhesus monkeys of both administrations were sacrificed at 10 min after injection by a large dose of thiopentone. The third lumbar (L_3) and the forth lumbar (L_4) were separated from vertebra of two monkeys, respectively. The samples were split into two parts respectively. The spinal cord and the dura mater were removed clearly and carefully, and then the exposed epidural space was washed with saline twice. All the spinal cord, the dura mater, the washed saline and the remained vertebra were collected, and γ-radioactivity was counted respectively.

1.7 Analytical technique Measurement of [^{125}I]HWTX-1 in serum was performed with an injection of 100 μl serum onto chromatograph by RP-HPLC (C^{18}, 300 Å, 5 μm, 4.6 mm×200 mm, CAT. #218TP54, VYDAC^{TM}), with a linear gradient of 0～100% acetonitrile in double distilled water within 20 min, and the flow-rate was 1.0 ml·min^{-1}. Radio-chromatogram was obtained from a HP 1 100 system (Agilent Technologies, USA) with

an Automatic gamma counter (1470 WIZARD™, Wallac). The radioactivity of [^{125}I]HWTX-1 in serum was determined by calculating the area under the curve (AUC) of it's radio-chromatogram which eluted at the same time as pure [^{125}I]HWTX-1 did.

1.8 Pharmacokinetic parameter and data analysis Model-independent pharmacokinetic parameters were calculated. All of pharmacokinetic calculations were performed on individual data. The C_{max} and T_{max} were the observed values. The elimination half-lives of the drug were calculated using the following equation:

$$T_{\frac{1}{2}} = \frac{0.693}{Ke}$$

Where the Ke is apparent elimination rate constant of [^{125}I]HWTX-1 from serum. The area under the curve (AUC) from time zero up to time of the last quantifiable sample(T_{24h}) was calculated using the linear trapezoidal rule. $AUC_{0\sim\infty}$ was extrapolated to infinity by adding C_{24h}/λ_Z, where C_{24h} is serum concentration of [^{125}I]HWTX-1 at 24 h after administration and λ_Z is elimination constant of each of the compounds calculated from the slope of the end part of the serum concentration curves. The apparent total clearance (Cls/F) was calculated as dose/$AUC_{0\sim\infty}$. The volume of distribution at steady state (V_{SS}) and the mean residence time (MRT) were calculated by the non-compartmental method. The bioavailability after epidural administration was calculated by the dose normalized $AUC_{0\sim\infty}$($AUC_{0\sim\infty}$, epidural/$AUC_{0\sim\infty}$, iv×100). The computation and statistical infer were obtained by EXCEL and Microcal Origin software.

2 RESULTS

2.1 Purity, specific activity and biological activity of [^{125}I]HWTX-1 The radio-chromatogram of the purified [^{125}I]HWTX-1 demonstrated that the labeled peptide was>96% pure (Fig 1A), with a specific activity of 34.6 GBq·g^{-1}(protein). The blocking activity on neuromuscular transmission of unlabeled and [^{125}I]labeled HWTX-1 were (9.1

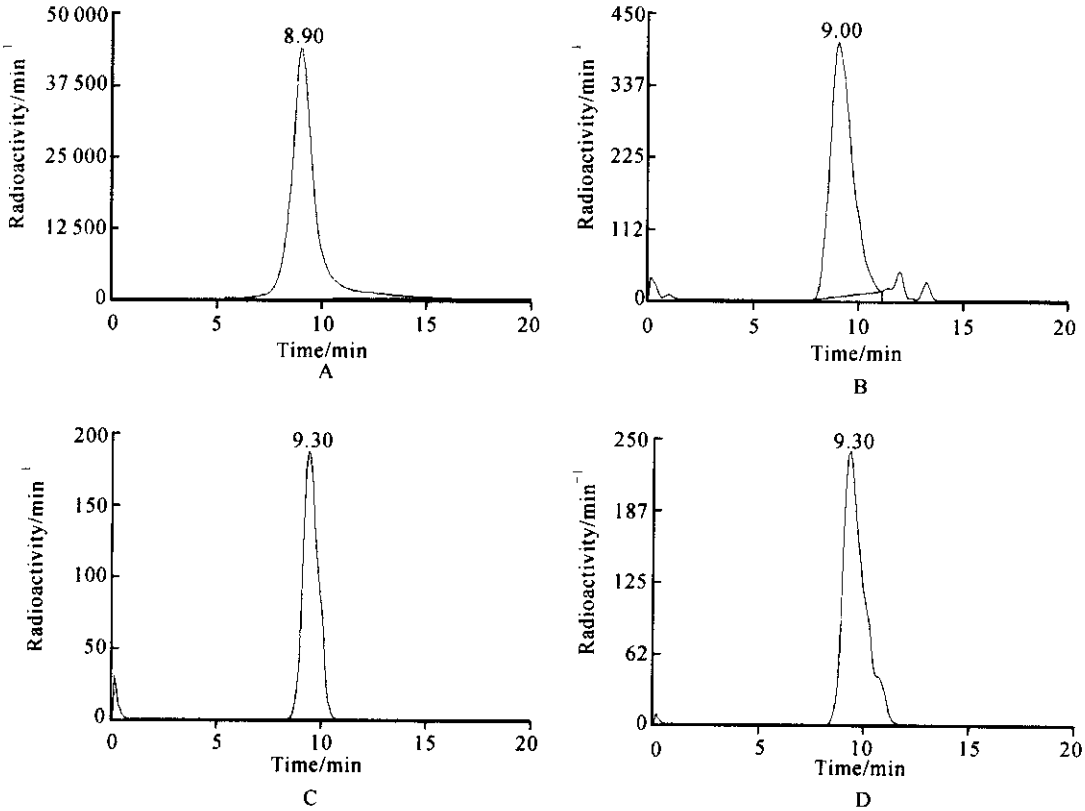

Fig 1 Representative radio-chromatogram of [^{125}I]HWTX-1 samples

A:[^{125}I]HWTX-1 in buffer; B: serum spiked with [^{125}I]HWTX-1 *in vitro*; C: serum sample collected at 15 min after 0.388 MBq·kg^{-1} iv administration; D: serum sample collected at 1 hour after 0.388 MBq·kg^{-1} iv administration

±0.4) min and (14.1±2.0) min ($n=3$, $P>0.05$), respectively.

2.2 Validity of the determination of [^{125}I]HWTX-1 in serum by RP-HPLC The chromatographic behavior of [^{125}I]HWTX-1 was same as the unlabeled peptide, the radioactive peak eluted at (9.3±0.7) min (Fig 1A,B). A linear regression was carried out with 6-spiked [^{125}I]HWTX-1 serum concentrations (X, in the range of 0.38～12.24 MBq·L^{-1}) and the radioactivity of [^{125}I]HWTX-1 peaks in radio-chromatogram (Y in the area under curve (AUC) of Radio-chromatograms, three duplicated times each point) was used as independent and dependent variables. The resulting equation was Y=664.25+2547.66×X, with $r=0.9992$. The relative standard deviations (RSD %) within day and between days were all less than 7%. Limit of quantitation (LOQ) was 0.1 MBq·L^{-1}. The average recovery rate from serum was 71.3%.

2.3 Pharmacokinetic profiles of [^{125}I]HWTX-1 in serum The principle pharmacokinetic parameters of [^{125}I]HWTX-1 were summarized in Table 1. Radio-chromatograms showed that serum [^{125}I]HWTX-1 radioactivity decreased rapidly after iv administration, with radioactivity of hydrophilic and hydrophobic [^{125}I]labeled peak increased (Fig. 1C,D).

The concentration-time curves and PK parameters after epidural administration of 0.388 MBq·kg^{-1} of [^{125}I]HWTX-1 were different from those after iv at the same dose. (Fig 2 and Tab 1).

The radioactivity at 2 min after iv and epidural injection were (4.98±0.58) MBq·L^{-1} and (0.18±0.01) MBq·L^{-1}, respectively ($P<0.01$). The level after iv administration decreased rapidly to (1.21±0.52) MBq·L^{-1} at 30 min, and followed by a slower elimination phase with terminal $T_{1/2}$ of (11.03±1.16) h. On the other hand, there was a rapid absorption phase with T_{max} at 30 min after epidural administration followed a rapid disposition phase with the $T_{1/2}$ (Ka) was (0.52±0.27) h. Cl_S/F and V_{SS}/F were similar after the same dose of epidural or iv administration. The terminal $T_{1/2}$ and MRT after iv were similar to those after epidural administration (11.03±1.16) h *vs* (10.36±0.27) h and (15.92±1.68) h *vs* (14.94±0.38) h, respectively. The mean Absolute bioavailability after epidural administration was (95±5)%.

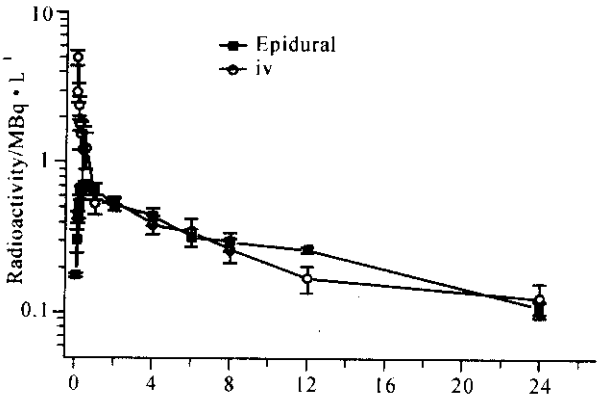

Fig 2 The concentration-time. The average concentration-time curves of [^{125}I]HWTX-1 in serum after *iv* and epidural administration of 0.388 MBq·kg^{-1} in rhesus monkeys

Tab 1 Pharmacokinetic parameters after iv and epidural administration of [^{125}I]HWTX-1 in rhesus monkeys. ($\bar{x}\pm s$, $n=3$).

Parameters	iv	epidural
T_{max}/h	0.03**	0.50
C_{max}/MBq·L^{-1}	5.0±0.6**	0.7±0.1
$AUC_{0\sim24\,h}$/Bq·μl^{-1}·h^{-1}	6.8±0.9	6.9±0.3
$AUC_{0\sim\infty}$/Bq·μl^{-1}·h^{-1}	9.1±1.6	8.7±0.4
$AUMC_{0\sim24\,h}$/Bq·μl^{-1}·h^{-1}	51±11	58±4
$AUMC_{0\sim\infty}$/Bq·μl^{-1}·h^{-1}	147±38	130±10
MRT/h	15.9±1.7	14.9±0.4
K_e	0.063±0.007	0.067±0.002
K_a	—	1.6±0.9
$T_{1/2(Ka)}$/h	—	0.52±0.27
Cl_S or Cl_S/F/L·h^{-1}·kg^{-1}	1.25±0.23	1.29±0.07
V_{SS} or V_{SS}/F/L·kg^{-1}	19.7±1.5	18.4±0.9
Terminal $T_{1/2}$/h	11.03±1.16	10.36±0.27
$F(AUC_{0\sim\infty,epidural}/AUC_{0\sim\infty,iv}\times100)$/%	—	95±5

** $P<0.01$ *vs* epidural administration

2.4 Radioactivity in epidural spaces Radioactivity in epidural space and spinal cord samples were 38% ID (percentage of injected dose) and 0.01% ID, respectively, at the time of 10 min after epidural administration and 0.06% ID and 0.004% ID after iv administration, respectively. The result indicated that a successful administration of [^{125}I]HWTX-1 into the epidural spaces and very few peptide penetrate the dura mater into the subarachnoid space.

3 DISCUSSION

In this paper, we reported the phamacokinet-

ics of the potential novel analgesic peptide-HWTX-1 after epidural injection, an unusual administration route, and compared with that after iv in rhesus monkeys. The methodology was reliable respect to the purity and biological activity of [^{125}I]HWTX-1; the RP-HPLC discrimination of unchanged [^{125}I]HWTX-1 from its degradation products.

The concentration-time curve of epidural administration, as may be seen in Fig 2B, shows that [^{125}I]HWTX-1 which be injected into epidural space can be transferred rapidly into blood. The maximum concentration in serum was reached in a fairly short time (30 min), which are similar to epidural administration of bupivacaine[8] (5 to 35 min) or ketamine[9] [within (26.4±14.4) min]. However, the retention of [^{125}I]HWTX-1 in epidural space (38% ID, 10 min after epidural administration) reduced the maximum concentration of [^{125}I]HWTX-1 in plasma [(0.70±0.04) MBq·L^{-1}, much lower than that of iv administration, (4.98±0.58) MBq·L^{-1}, $P<0.01$]. The time course of the serum concentration of [^{125}I]HWTX-1 revealed no statistically significant differences between the elimination phase of epidural and that of iv administrations. Their $T_{1/2}$, Cl_S, V_{SS}, and K_el are similar ($P>0.05$), so a high mean bioavailability of 95%, which is similar to tramadol (83%)[10], was observed. The findings suggest that [^{125}I]HWTX-1 in serum has a different absorption and disposition procedure but the same elimination process after epidural or iv administration.

The results of this study are helpful for understanding the mechanism and toxicity of HWTX-1, and useful for the design of clinical trial of HWTX-1 in the future.

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猕猴硬膜外及静脉注射[^{125}I]虎纹毒素-1的药代动力学*

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摘要 **目的** 研究与比较猕猴硬膜外(ed)及静脉(iv)注射虎纹毒素-1后的药代动力学过程。**方法** Iodogen法标记虎纹毒素-1,按0.388 MBq·kg^{-1}的剂量向猕猴第3和第4腰椎之间硬膜外腔及静脉注射标记后虎纹毒素-1,用反相高效

◇实验方法学◇

基于重心频率和复杂度分析的大鼠睡眠分期比较*

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摘要 **目的** 研究能对大鼠睡眠进行准确快速分期的技术途径。**方法** 通过慢性埋置电极采集自由活动大鼠的皮层脑电和海马电位,原始信号经过去噪声重采样以后进行重心频率和复杂度分析,然后根据其分布直方图,结合睡眠各时相特点,对睡眠成分进行分析。**结果** 利用重心频率和复杂度分析可以很好的区分出大鼠清醒期(Waking)、非快动眼(NREM)睡眠期和快动眼(REM)睡眠期三种生理状态,与人工分析比较符合率达85%以上,并且后者的分期结果更为准确。**结论** 基于重心频率和复杂度分析的方法可以很好的对大鼠睡眠进行准确快速的分期。

关键词 皮层脑电;海马电位;重心频率;复杂度

睡眠质量的好坏对人类身体健康有着直接或间接的影响。催眠药物的研究要有好的实验方法。对睡眠进行分期是催眠药物开发和评估的重要手段,是睡眠状况分析和睡眠质量评价的前提和基本内容。大鼠为夜行性动物,睡眠呈多相性,脑电活动及成分与人类很接近。找到较为简便的大鼠睡眠分期方法对建立高效的催眠药物药效和药理实验方法具有重要的意义。

觉醒和睡眠是人和高等动物普遍的生理现象,其脑电信号(EEG)具有不同的特征波形。在觉醒期,EEG表现为去同步的低幅快波;在慢波睡眠,又称非快动眼(non rapid eye movement, NREM)睡眠期,EEG表现为同步化的高幅慢波;进入异相睡眠,又称快动眼(REM)睡眠期,EEG又表现出较高频率的快波。1968年,Rechtschaffen提出了人体睡眠各期的划分规范,为睡眠的各期划分提供了客观标准。探寻和建立新的睡眠状态区分的定量分析方法是该领域的重要研究课题。

EEG中包含了丰富的频域信息,由几种频率不同的波混合在一起,在不同的生理状态下具有典型特性。这些特性常用功率谱方法进行分析,它可以反映EEG能量在不同频率上的分布情况[1]。

近年来随着非线性科学的发展,一些研究者采用复杂性测度(Complexity Measure)方法分析脑电,从EEG波形的复杂性上反应其变化特征。如文献[2]报道觉醒期和REM睡眠期的脑电复杂度比NREM睡眠期高,在麻醉、癫痫发作等状态下,脑电复杂度显著降低[3]。

这些报道所分析的都是头皮或皮层脑电,主要是反映近皮层部位神经结构的电活动性。深部脑组织的自发电位在不同生理状态下的变化如何呢?海马是大脑深部中枢神经系统边缘组织的一部分,被认为是情感、行为和学习记忆等高级神经活动的重要部位,尤其是作为神经突触可塑性机制研究的重要部位,近年来海马电位变化特性的研究受到广泛的关注[4]。

文献[5,6]报道了联合采集EEG、EMG、EOG进行睡眠自动分期的方法,本文利用慢性埋置电极同时检测大鼠大脑皮层和海马的自发电位,探索采用重心频率和复杂度的方法对睡眠进行准确快速的分期。

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液相色谱检测猴血清中的药物放射性活度;γ-计数仪检测猴第3和第4腰椎硬膜外腔的药物放射性活度。**结果** 制备了具有生物活性的[^{125}I]虎纹毒素-1。硬膜外给药10 min后,给药部位局部硬膜外腔的药物放射性占总给药量的0.38,说明硬膜外给药是成功的.硬膜外及静脉给药后,血药浓度分别在30 min和2 min达峰,分别为(0.70±0.04) MBq·L^{-1}和(4.98±0.58) MBq·L^{-1}。两种给药途径的药时曲线不同:猕猴硬膜外和静脉给药后,末端$T_{\frac{1}{2}}$分别为(10.36±0.27) h和(11.03±1.16) h;Cl_S分别为(1.29±0.07)L·h^{-1}·kg^{-1}和(1.25±0.23) L·h^{-1}·kg^{-1},硬膜外给予[^{125}I]HWTX-1的绝对生物利用度(95±5)%。**结论** 硬膜外和静脉两种给药方式下,[^{125}I]虎纹毒素-1在猕猴体内的药代动力学过程具有差异性,两种给药方式下[^{125}I]在猕猴体内的分布与吸收特点对于虎纹毒素-I的临床药效学和毒理学研究提供了参考数据。

关键词 虎纹毒素-1;药代动力学;硬膜外注射