中国药理学与毒理学杂志 2004 年 10 月; **18**(5):344 – 351
Chin J Pharmacol Toxicol 2004 Oct; **18**(5):344 – 351

Pharmacokinetic profiles of huwentoxin-1 after epidural and intravenous administration in rats

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Abstract: **AIM** To compare pharmacokinetics and tissue-distribution after epidural and iv administration of [^{125}I]labelled huwentoxin-1 ([^{125}I]HWTX-1) in rats. **METHODS** HWTX-1 was labeled by iodogen method. Single dose of 0.86, 1.7, or 2.6 MBq [^{125}I]HWTX-1 per rat was injected *via* a catheter implanted in epidural space or iv with single dose of 2.6 MBq per rat. Serum [^{125}I]HWTX-1 was determined by RP-HPLC with flow scintillation detector. Tissue radioactivity was detected by γ-counter. **RESULTS** Radioactivities detected in dural-vertebral samples was (22 ± 8)% of injected radioactivity at 10 min after epidural injection, which demonstrated successful administration into epidural space. Concentration-time curves of [^{125}I]HWTX-1 after two routes were different. Absorption phase with t_{max} at 10 min was observed after epidural injection. ^{125}I-labeled degradation products at 10 min after epidural and iv injection of 2.6 MBq were (2.1 ± 1.1) and (6.8 ± 2.5) $\mu g \cdot L^{-1}$, respectively ($P < 0.01$). c_{max} and AUC were increased with dose after epidural administration. Terminal $t_{1/2}$ after epidural or iv administration was 2.5 – 2.8 h or 2.3 h. Cl_S was 0.74 – 1.18 $L \cdot h^{-1} \cdot kg^{-1}$ after both routes. Bioavailability after epidural administration was > 82%. Distribution of [^{125}I]HWTX-1 between two routes was different, and contents in most tissues at 10 min after iv were higher than those after epidural dosing ($P < 0.05$). Excretion of radioactivity was mainly *via* urine. **CONCLUSION** The differences between vertebral and systemic biodistribution of HWTX-1, as well as degradation profiles after epidural and iv injection support the using of HWTX-1 as analgesic by epidural administration.

Received date: 2004-01-06 **Accepted date**: 2004-04-28

Foundation item: The project is supported by the National Natural Science Foundation of China(39930180)

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Key words: huwentoxin-1; pharmacokinetics; epidural administration

CLC number: R969.1
Document code: A
Article ID: 1000-3002(2004)05-0344-08

Huwentoxin-1 (HWTX-1) is a peptide toxin (with amino acid sequence of ACKGVFDACTPGKNECCPNRVCSDKHKWCKWKL) isolated and purified from the venom of the spider *Selenocosmia huwena*[1]. The structure consists of a three-stranded anti-parallel beta – sheet and three turns. The three disulfide bridges ($C^2 – C^{17}$, $C^9 – C^{22}$, and $C^{16} – C^{29}$) and three-stranded anti-parallel beta-sheet form an inhibitor cystine knot motif which is adopted by several other small proteins, such as ω-conotoxin, and gurmarin[2].

Several recently developed analgesic techniques demonstrate that neuraxial 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]. HWTX-1 caused the inhibition of the twitch response to electrical nerve stimulation in the rat vas deferens[6]. Series preclinical studies showed that epidural injection of HWTX-1 inhibited pain sensation induced by heat radiation or mechanical stimulation for 2 h in a dose-dependent manner. Its analgesic dose was less than ω-conotoxin, and its analgesic duration is longer than

morphine. Results indicated that HWTX-1 is a potential novel analgesic peptide (to be published separately). As part of preclinical studies, the pharmacokinetics profiles of [^{125}I]HWTX-1 after epidural administration at different doses in rats were investigated and compared with that after iv in this paper.

1 MATERIALS AND METHODS

1.1 Drugs and reagents

Huwentoxin-1 (purity > 99.5%, Batch No. 010620) was provided by the Institute of Life Science, Hunan Normal University. Na[^{125}I] was purchased from Perkin-Elmer Life Science [99.95% purity, 643.8 GBq·mg^{-1} (10 mCi), Batch No. NEZ033R]. Bicinchoninic acid protein determination kit was purchased from Sigma. Other reagents were all analytical or chromatographic grade(HPLC).

1.2 Animals

Wistar rats[(n = 70 of both sexes, (294 ± 56) g, Grade Ⅱ) and Kun-Ming adult male mice (n = 3, 18 – 22 g, Grade Ⅱ, Certificate D01-3024) were provided by Animal Center of Academy of Military Medical Sciences.

1.3 Intubation

Sixty Wistar rats were treated for intubation, which was performed as the method described by LoPachin, *et al*[7]. Briefly, under pentobarbital (ip 40 mg·kg^{-1}) anesthesia, the occipitoatloid membrane of rats was exposed after the dorsocervical skin and muscles incised. A PE-10 pipe was inserted and placed into the thoracic epidural space. The terminal of the pipe was sutured and fixed with the dorsocervical muscles. The rat was given benzylpenicillin 400 kU·d^{-1} per rat × 3 d after surgery. Pharmacokinetic study was performed at least 7 d after surgery.

1.4 Preparation and identification of [^{125}I] HWTX-1

HWTX-1 was labeled by iodogen method[8] and purified by a 1 cm × 50 cm Sephadex G-10 column (Pharmacia). The mobile phase was 0.4 mol·L^{-1} sodium chloride at pH 7.0 in 0.02 mol·L^{-1} phosphate buffer at a flow-rate of 0.5 mL·min^{-1}. The eluted fractions were determined for both γ-radioactivity (FT630G-4, Beijing Radio-Instrument Factory) and protein concentration (bicinchoninic acid method[9]). The determination of protein concentration followed the description in kit manual. Briefly, different concentrations of standard protein (bovine serum albumin) and unknown samples were added with bicinchoninic acid and 4% $CuSO_4$ solutions. Absorbance was assayed at 540 nm after incubation at 37℃ for 30 min. Protein concentration was estimated from calibration standard curve. The purity of [^{125}I]HWTX-1 was identified by reverse phase high performance liquid chromatography (RP-HPLC) through a column (Spherisorb C18, 300 Å, 5 μm, 4.6 mm × 200 mm) with a linear gradient from 0% – 100% of acetonitrile in double distilled water, and the flow-rate was 1.0 mL·min^{-1}. Radio-chromatograms were obtained from a HP 1100 system (Agilent Technologies, USA) online with a Radiomatic™ Flow Scintillation Analyzer (Packard 525TR, USA).

1.5 Biological assay of labeled HWTX-1

Method followed Rash, *et al*[10]. Mice were sacrificed, and the hemidiaphragms with the phrenic nerve intact were removed. Preparation were attached to tissue holders with in-built electrodes, mounted in 5 mL 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. 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 used to record the stimulation and muscle contraction.

1.6 Experimental design and sample preparation

Intubated rats were divided into 4 groups. Three groups were administrated 0.86, 1.7, and 2.6 MBq of [^{125}I]HWTX-1 per rat, respectively, (approximately equal to 25, 50, and 75 μg·

kg^{-1}) into the epidural space through a lymphatic paracentetic needle. An iv 2.6 MBq per rat (75 $\mu g \cdot kg^{-1}$) group was served as control. Rats were sacrificed at 0.17, 2, 8, and 48 h after injection (5 rats per time point), and then harvested tissues or body fluids. The sera were collected at 0, 0.02, 0.08, 0.17, 0.5, 1, 2, 4, 8, and 48 h after two routes of administration and obtained after centrifuged at 1000 × *g* for 10 min. The concentration of [^{125}I]HWTX-1 in sera and other body fluids were determined by the method of RP-HPLC combined online γ-counter. Fresh weight of tissue samples was measured with an automatic balance and homogenized. The γ-radioactivities of total, 10% trichloroacetic acid soluble and precipitated fractions of tissue samples were counted separately.

1.7 Radioactivities in epidural spaces

Vertebra was separated from the third thoracic (T3) to the third lumbar (L3). Only T3, T6, T9, T12, and L3 were dissected and divided into three parts: muscles around vertebra, spinal cord, and the dural-vertebra samples. The γ-radioactivities of them were counted separately to describe the distribution of ratioactivities of [^{125}I]HWTX-1 around the injection region. The total radioactivities in dural-vertebral or spinal cord samples were estimated by the equation of $R_T = R_{T3} + (R_{T3} + R_{T6}) + R_{T6} + (R_{T6} + R_{T9}) + R_{T9} + (R_{T9} + R_{T12}) + R_{T12} + (R_{T12} + R_{L3}) + R_{L3}$, where R_T is the total radioactivity, and the other symbols represent the radioactivities of T3, T6, T9, T12, and L3, respectively. The equation assumed the radioactivity of uncounted vertebra equals to the sum of two counted neighboring vertebrae.

1.8 Radioactivities in urine, feces and bile

Rats were placed in the metabolism cages, urine and feces were collected separately after epidural and iv administration 75 $\mu g \cdot kg^{-1}$ of [^{125}I]HWTX-1 at intervals of 0 – 8, 8 – 24, and 24 – 48 h. Bile samples were collected from 5 rats with bile duct intubation at 0 – 8 h after epidural administration with an interval of 1 h.

1.9 Pharmacokinetic parameter and data analysis

Model-independent pharmacokinetic parameters were calculated using EXCEL software. The c_{max} and t_{max} were the observed values. Other pharmacokinetic parameters were calculated as the descriptions of the non-compartmental method[8]. The bioavailabilities of 3 dosages after epidural administration were calculated by the dose normalized $AUC_{0-\infty} = (AUC_{0-\infty,epidural}/AUC_{0-\infty}, iv) \times 100\%$. 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 > 98% pure (Fig 1A), with a specific activity of 176 $GBq \cdot g^{-1}$ protein. The blocking activity on neuromuscular transmission of unchanged and [^{125}I]labelled HWTX-1 were (9.1 ± 0.4) min and (14.1 ± 2.2) min ($P < 0.05$, $n = 3$), 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 the same as that of the unlabelled peptide, and the radioactive peak eluted at (7.8 ± 0.6) min (Fig 1A, 1B). A linear regression was carried out with 5-spiked [^{125}I]HWTX-1 sera concentrations (X, in the range of 0.1 – 16 ng protein) and the radioactivities of [^{125}I]HWTX-1 peaks in radio-chromatogram (Y in Bq, three duplicated samples each concentration) were used as independent and dependent variables. The linear fit equation was $Y = 371 \times X$, with $r = 0.9984$. The relative standard deviations (RSD%) within day and between days were all less than 7%. Limit of quantitation (LOQ) was 0.02 $mg \cdot L^{-1}$. The average recovery rate from sera was 86.7%.

2.3 Radioactivities in epidural spaces

Radioactivities in dural-vertebral and spinal

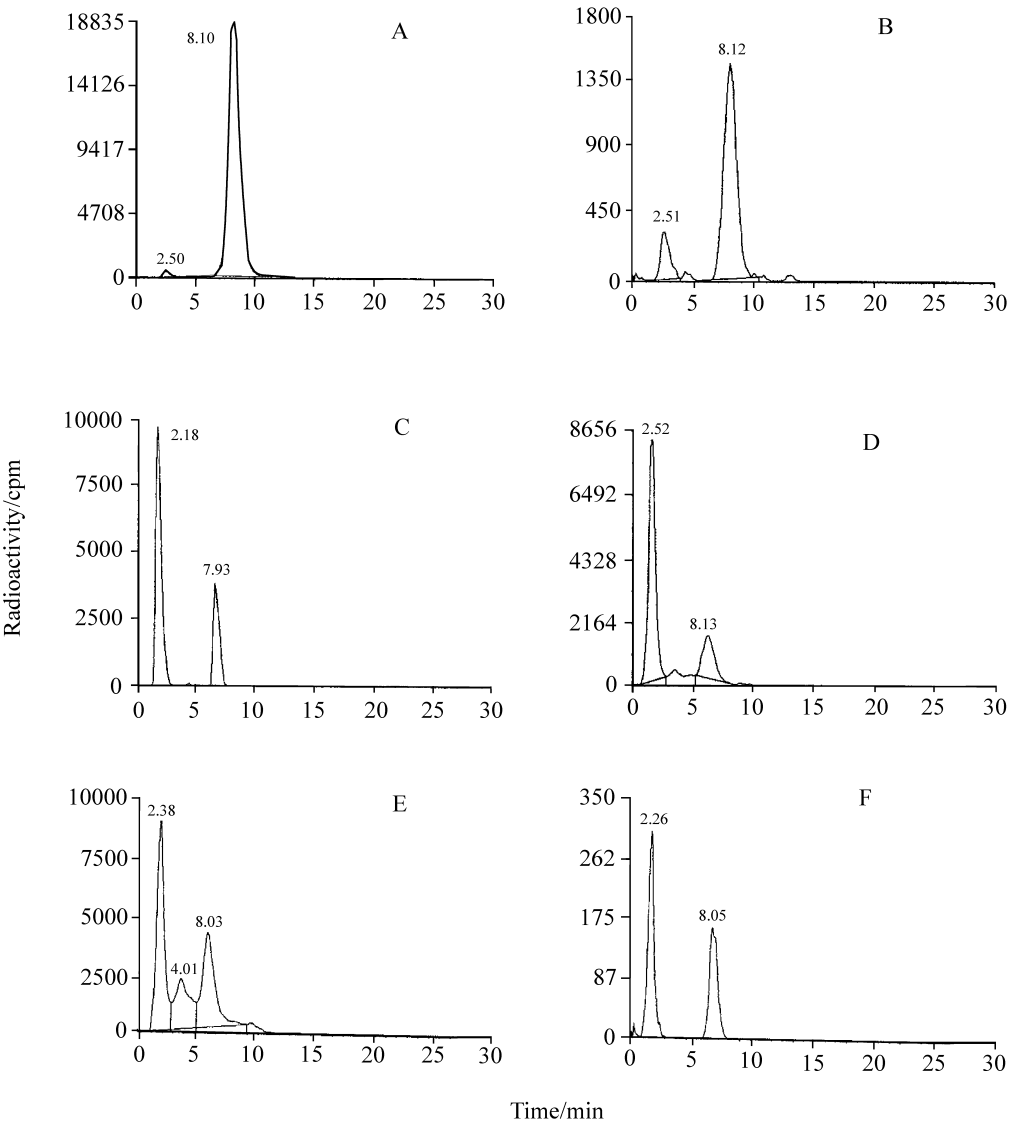

Fig 1. Representative radio-chromatogram of [^{125}I]HWTX-1 samples. HWTX-1: huwentoxin-1; A: serum spiked with [^{125}I]HWTX-1 *in vitro*; B: serum sample collected at 10 min after 2.6 MBq·kg^{-1} epidural administration; C: serum sample collected at 2 h after 2.6 MBq·kg^{-1} epidural administration; D: urine sample at 2 h after iv administration; E: urine sample at 2 h after epidural administration; F: bile sample after epidural administration.

cord samples were (22 ± 8)% and (0.12 ± 0.12)% of injected radioactivity, respectively, at 10 min after epidural administration. The result indicated that the administration of [^{125}I]HWTX-1 into the epidural spaces was successful and very few peptide penetrated the dura mater into the subarachnoid space. Levels in epidural spaces decreased rapidly to (2.1 ± 1.0)% and (0.9 ± 0.5)% of injected radioactivity at 2 h and 8 h, respectively. The radioactivities of dural-vertebral samples and spinal cord at 2 h after iv were (0.27 ± 0.09)% and (0.009 ± 0.004)% of injected radioactivity, respectively, which were lower than those after epidural administration ($P < 0.05$).

2.4 Validity of the determination of [^{125}I] HWTX-1 in tissues

Using 10% TCA precipitation method, within the ranges of 0.23 – 38.8 kBq·g^{-1} (wet tissue) or MBq·L^{-1} (body fluid) spiked concentra-

tion, there was a good linearity between the spiked concentration and TCA precipitated radioactivities ($r > 0.99$) in 11 main tissues or body fluids, including heart, liver, spleen, lungs, kidneys, brain, fat, skeletal muscles, lymph nodes, serum, and urine of rats. The limit of quantitation was 0.23 kBq·g^{-1} (wet tissue). About (80 ± 8)% radioactivities were found in TCA precipitated fraction.

2.5 Pharmacokinetic profiles of [^{125}I]HWTX-1 in serum

Radio-chromatograms showed that serum [^{125}I]HWTX-1 radioactivities decreased rapidly after iv or epidural administration, and radioactivities of hydrophilic portion increased (Fig 1B, 1C). The concentration – time curves and pharmacokinetic parameters after epidural administration of 25, 50, and 75 μg·kg^{-1} of [^{125}I]HWTX-1 were different from those after iv 75 μg·kg^{-1} (Fig 2 and Tab 1). The radioactivities at 1 min after iv and epidural injection were (189 ± 42) μg·L^{-1} and (22 ± 7) μg·L^{-1}, respectively ($P < 0.01$). The level after iv decreased rapidly to 70 μg·L^{-1} at 10 min, and followed by a slower elimination phase with terminal $t_{1/2}$ of 2.3 h. On the other hand, there was a rapid absorption phase with t_{max} at 10 min after epidural administration. At that time the radioactivities of hydrophilic degradation products after epidural injection was (2.1 ± 1.1) μg·L^{-1}, which was lower than that after iv [(6.8 ± 2.5) μg·L^{-1}, $P < 0.01$]. c_{max}, $AUC_{0-4\,h}$, and $AUC_{0-\infty}$ were increased with dose. Total body clearance (Cl_S/F) and volume of distribution at steady state (V_{SS}/F), were similar, no matter which route of administration, epidural or iv. The terminal $t_{1/2}$ and mean residence time (MRT) after iv were slightly shorter than those after epidural administration (2.3 *vs* 2.5 – 2.8 and 0.6 *vs* 0.85 – 0.91 h, respectively). Absolute bioavailability after epidural administration was > 82%.

2.6 Distribution of radioactivities in tissues

At the time of 10 min after iv 75 μg·kg^{-1} of [^{125}I]HWTX-1, the radioactivities of total (Tab 2), TCA soluble and precipitated fraction (data not shown) in most tissues were higher ($P < 0.05$ or $P < 0.01$) than those after epidural administration at the same dose, except in brain and heart muscle. The maximal radioactivities were observed at 2 h in most tissues, except serum and heart muscle, after epidural administration. The levels were approached to, or even higher than those after iv in testes, spleen, liver, lungs and heart. The highest level was found in urinary system. Radioactivities accumulated in thyroid were only 0.04% – 5.28% of injected radioactivity. The results (data not shown) of TCA soluble and precipitated fraction after epidural administration

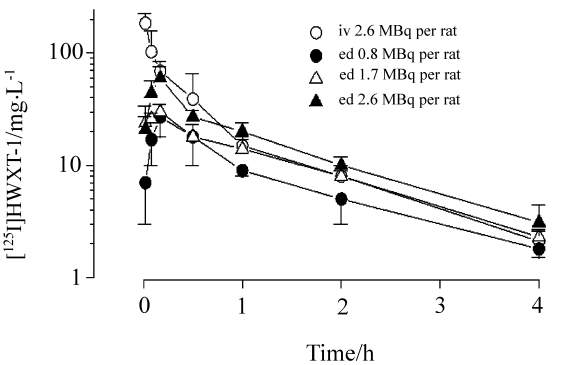

Fig 2. Concentration-time curves of [^{125}I]HWTX-1 in serum after epidural administration (ed) of 2.6, 1.7, 0.86 MBq per rat and iv of 2.6 MBq per rat of [^{125}I]HWTX-1 in rats. $\bar{x} \pm s$, $n = 5$.

Tab 1. Pharmacokinetic parameters after iv and epidural administration of [^{125}I]HWTX-1 in rats.

Parameter	Epidural			iv
	0.86	1.7	2.6	2.6(MBq)
t_{max}/h	0.17	0.17	0.17	0.02
c_{max}/μg·L^{-1}	27.1	30.8	61.8	189.5
$AUC_{0-4\,h}$/μg·L^{-1}·h	31.3	41.6	62.4	71.4
$AUC_{0-\infty}$/μg·L^{-1}·h	33.6	47.7	63.7	77.8
$MRT_{0-4\,h}$/h	0.85	0.91	0.85	0.62
Cl_S or Cl_S/F/ L·h^{-1}·kg^{-1}	0.74	1.05	1.18	0.96
V_{SS} or V_{SS}/F/ L·kg^{-1}	0.64	0.95	1.00	0.60
$t_{1/2}$/h	2.8	2.6	2.5	2.3
F/%	129$^{\triangle}$	92$^{\triangle}$	82	–

MRT: mean residence time, Cl_s: total body clearance, V_{ss}: distribution at steady state. $F = (AUC_{0-\infty,epidural}/AUC_{0-\infty,iv}) \times 100\%$. $^{\triangle}$Calculated by dose normalized AUC. $n = 5$.

Tab 2. Distribution of radioactivities after epidural and iv administration 2.6 MBq/rat of [^{125}I]HWTX-1 in rats

Tissue or body fluid	Radioactivity/MBq·kg^{-1} or MBq·L^{-1}					
	10 min		2 h		8 h	
	iv	Epidural	iv	Epidural	iv	Epidural
Serum▲	43 ± 10	13 ± 9	16 ± 5	22 ± 7	10 ± 4	6.4 ± 2.0
Urine	Lost	23 ± 20	217 ± 120	347 ± 122	89 ± 105	107 ± 34
Brain	1.0 ± 0.3	1.1 ± 0.4	0.6 ± 0.2	1.4 ± 0.6*	0.6 ± 0.3	0.51 ± 0.18
Fat	2.0 ± 0.7	0.6 ± 0.2*	0.7 ± 0.3	1.0 ± 0.2	0.48 ± 0.09	0.49 ± 0.20
Skeletal muscles	6.5 ± 1.5	2.8 ± 0.8**	3.3 ± 1.3	4.1 ± 1.2	2.2 ± 0.8	1.5 ± 0.7
Testes△	1.7	0.7	1.4	4.8	1.9	1.71
Ovaries#	17 ± 4	5.4 ± 0.6*	7.9 ± 2.6	12.8 ± 0.6*	5.1 ± 0.3	4.12 ± 0.13
Suprarenal gland	14 ± 4	6.2 ± 1.2*	4.4 ± 2.3	9 ± 4	3.9 ± 1.2	2.6 ± 0.4
Lymph nodes	5.9 ± 1.8	1.9 ± 0.5**	2.2 ± 0.9	3.9 ± 1.3*	2.8 ± 1.2	1.54 ± 0.23
Intestinal content	8.2 ± 1.6	3.8 ± 1.7**	11 ± 5	10 ± 3	7.8 ± 3.0	17 ± 7*
Feces in colon	0.8 ± 0.2	0.17 ± 0.04**	1.7 ± 0.6	2.0 ± 1.2	5.3 ± 3.2	0.9 ± 0.3*
Small intestine	17 ± 4	6.1 ± 2.1**	7 ± 4	12 ± 4	7.8 ± 2.8	10 ± 5
Spleen	17 ± 4	5.3 ± 1.6**	5.9 ± 2.7	13.1 ± 2.7**	6.0 ± 1.7	4.5 ± 1.1
Pancreas	8.8 ± 1.9	3.1 ± 1.0**	5.3 ± 2.9	6.6 ± 1.0	4.0 ± 1.2	3.2 ± 1.7
Liver	19 ± 5	7.6 ± 2.2**	5.1 ± 2.0	11 ± 3**	5.7 ± 2.3	4.0 ± 1.5
Kidneys	272 ± 130	36 ± 8*	118 ± 37	196 ± 38*	77 ± 26	47 ± 8
Urinary bladder	21 ± 6	3.6 ± 1.8**	9 ± 4	26 ± 11*	9 ± 5	10 ± 4
Submancibular gland	16 ± 4	7.2 ± 1.6**	9 ± 5	16.0 ± 2.5*	6.4 ± 1.3	7 ± 3
Eyeballs	6.0 ± 1.0	2.6 ± 0.5**	4.1 ± 1.9	6.2 ± 2.0	2.0 ± 0.5	2.42 ± 0.22
Thymus	7.2 ± 1.6	4.1 ± 1.1**	3.7 ± 1.7	6.3 ± 2.6	3.4 ± 1.4	2.6 ± 0.4
Lungs	37 ± 11	20 ± 5*	11 ± 4	22 ± 5**	10 ± 5	5.9 ± 1.6
Heart muscles	11.6 ± 2.7	12 ± 4	4.7 ± 1.5	9.8 ± 3.0*	3.9 ± 1.1	3.0 ± 0.7

▲Radioactivity of serum is calculated according to HPLC results. △$n = 2$, #$n = 3$. $\bar{x} \pm s$, $n = 5$. *$P < 0.05$, **$P < 0.01$, compared with iv group.

or iv were very similar to those of total radioactivities. The details about the tissue distribution profiles were published recently[11].

2.7 Excretion

The accumulated excretion of radioactivities in urine and feces at 48 h after iv were (82 ± 11)% and (18 ± 9)% of injected radioactivity, respectively. The values after epidural administration were (69 ± 20)% and (6 ± 2)% of injected radioactivity, respectively. The bioavailability after epidural administration estimated by radioactivities in urine plus feces was 75%. The accumulated radioactivity in bile at 8 h was (2.8 ± 0.9)% after epidural administration. The results showed that after both routes of administration, the major pathway of excretion was urinary system.

In urine and bile samples, radio-chromatogram after epidural administration showed that the radioactive component was mainly [^{125}I]labelled hydrophilic peaks and only a few unchanged [^{125}I]HWTX-1 peaks could be detected (Fig 1D, 1E).

3 DISCUSSION

In this paper, we reported the pharmacokinetics of potential novel analgesic peptide,

[^{125}I]HWTX-1, after epidural injection, an unusual administration route, and compared with that after iv in rats. The methodology was reliable with respect to the purity and no loss of biological activity of [^{125}I]HWTX-1; the RP-HPLC discrimination of unchanged [^{125}I]HWTX-1 from its hydrophilic degradation products; the successful administration of the radio-peptide into the epidural space; and minimal concentration of [^{125}I] HWTX-1 detected in the spinal cord in comparison with the high serum levels.

The most interesting result is the differences of pharmacokinetics of [^{125}I]HWTX-1 between iv and epidural administration. This can be summarized as follows: ① Very high levels and long lasting of peptide in epidural space; ② A very rapid absorption to circulation, which are similar to epidural administration of bupivacaine[12] (5 to 35 min) or morphine[13] [within (12 ± 3) min]; ③ A high bioavailability of 82%, which is similar to tramadol (83%)[14]; ④ In almost all tissues except brain, testes, and heart, 3 to 10 folds higher exposure levels were observed at 10 min after iv than those after epidural administration, which indicates that faster and higher toxic effect to those tissues by the iv route might occur and more safe is the route of epidural injection. Some of these characteristics after epidural administration are the common features of the epidural administration of chemical drugs. These features support the potential of HWTX-1 to become an analgesic by epidural administration.

The characteristics of pharmacokinetics and distribution of [^{125}I]HWTX-1 are similar to that of common small molecular peptide, *i. e.* rapidly eliminated from the circulation mainly by degradation to hydrophilic products and a few excreted in urine in unchanged form. It is worth to notice that this peptide of M_r 3750 cannot pass through the brain-blood or dural barrier.

HWTX-1 is degraded and excreted more rapidly in rats at early phase after iv than that after epidural administration. The difference of pharmacokinetic parameters in rats between epidural and iv administration, somewhat, indicates a different elimination processes between the two routes.

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

Acknowledgements This study was funded in part by China PKU Weiming Biotech Group.

We acknowledge the excellent technical assistance of Mrs. ZHU Bao-Zhen, Mrs. WANG Li-Ping, Mr. REN Jian-Ping, and Mr. ZHANG Yang.

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大鼠硬膜外和静脉注射[^{125}I]虎纹毒素-1 后的药代动力学

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摘要: 目的　比较大鼠硬膜外注射或 iv [^{125}I]虎纹毒素-1([^{125}I]HWTX-1)后的药代动力学和组织分布。**方法**　用 Iodogen 法标记 HWTX-1。大鼠经硬膜外腔插管或尾静脉注射给药。反相高效液相色谱法在线检测体液中[^{125}I]HWTX-1 浓度; γ-计数仪测定组织放射性。**结果**　硬膜-脊椎样品放射性为注射放射性的(22 ± 8)%,表明硬膜外注射成功。两给药途径的药时曲线不同: 硬膜外给药存在吸收相, 10 min 达峰; c_{max} 和 AUC 随剂量递增; 大鼠硬膜外和 iv 后, [^{125}I]降解产物的浓度分别为(2.1 ± 1.1)和(6.8 ± 2.5) $\mu g \cdot L^{-1}$ ($P < 0.01$); 末端 $t_{1/2}$ 分别为 2.5 ~ 2.8 h和 2.3 h; Cl_S 为 0.74 ~ 1.18 $L \cdot h^{-1} \cdot kg^{-1}$。硬膜外给予[^{125}I]HWTX-1 的生物利用度 > 82%。两给药途径的分布不同: iv 后 10 min, 大多数组织药物暴露水平高于硬膜外给药($P < 0.05$)。放射性主要经尿排泄。**结论**　两种注射途径的放射性在不同组织中的生物分布及药物降解等差异支持了 HWTX-1 经硬膜外注射用作镇痛药。

关键词: [^{125}I]虎纹毒素-1; 药代动力学; 硬膜外注射; 静脉注射

基金项目: 国家自然科学基金资助项目(39930180)

(本文编辑　石　涛)