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Uptake and biodistribution of rizatriptan to blood and brain following different routes of administration in rats

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Abstract

The objective of the present study was to investigate the biodistribution profiles of rizatriptan in the blood and brain of Wistar rats after peroral, subcutaneous, intranasal and intratracheal administration with a particular view to determining the applicability of inhalation delivery to achieve rapid and high availability of the drug in both blood and the brain. Following the intratracheal administration of the drug (4.0 mg/kg) to the rats, the absolute bioavailability was found to be 91.2%, significantly higher than those from intranasal or peroral routes, and T_{max} in plasma and brain was attained within 2 min, significantly shorter than the T_{max} of intranasal (∼10 min in both plasma and brain), subcutaneous (16.7 min in plasma and 22.5 min in brain) and peroral (30.0 min in plasma and 45.0 min in brain) administration. In addition, other pharmacokinetic parameters associated with rapid onset of action including $AUC_{plasma/brain}$ and C_{max}, of intratracheal instillated rizatriptan appeared also to be comparable or superior to those of other delivered routes. Although AUC_{brain}/AUC_{plasma} ratios after intranasal delivery (43.4%) differed significantly from the ratios shown after intratracheal instillation (23.2%), the $AUC_{brain\,0–120\,min}$ via the latter routes was slightly but not significantly higher than that from the former routes. The results in the present study indicated that pulmonary delivery of rizatriptan may achieve maximum plasma and brain concentrations significantly more rapidly compared with intranasal, subcutaneous and peroral administration and be a promising delivery method with extremely rapid onset of action in the pain relief of migraine.

Keywords: Rizatriptan; Intratracheal instillation; Pulmonary delivery; Intranasal delivery; Subcutaneous delivery; Nose–brain drug transport

1. Introduction

Triptans belong to a class of serotonin receptor subtype-selective drugs for the treatment of migraine attack, which affects 10–20% of female and 2–8% of male population in the world. The first of such a class, sumatriptan, together with newer triptans, such as zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan and frovatriptan, were found to display high agonist activity at mainly the serotonin 5-HT1B and 5-HT1D receptor subtypes (Tfelt-Hansen et al., 2000). With the expansion of the triptan class, several administrating routes of these drugs have drawn more and more attentions to pharmacists and physicians and been utilized for the development of commercial triptan products for patients with migraine (Gladstone and Gawel, 2003). Indeed, apart from oral tablets, which have been applied to all commercial available triptans such as sumatriptan, rizatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan and eletriptan, other types of formulations such as subcutaneous injections, orally disintegrating tablets, intranasal sprays and rectal suppositories have also been developed for some triptans. In the literature, numerous clinical trials have been carried out to evaluate the efficacy of various formulations administered via oral, subcutaneous, nasal, or rectal routes (e.g. Tfelt-Hansen et al., 2000; Gladstone and Gawel, 2003).

Since patients with migraine who seek treatment relief generally consider the rapid onset of action as a top priority (Lipton et al., 2002), pharmacokinetic parameters associated with rapid onset of action, such as bioavailability and T_{max}, are of important consideration in the development of formulations. Toward this, subcutaneous and pulmonary delivery have demonstrated certain advantages over conventional oral tablets (Cady et al., 1991; Duquesnoy et al., 1998). For example, Duquesnoy et al. (1998) reported that the bioavailability for

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subcutaneous injection was greater and the T_{max} was markedly shorter than those for suppositories, intranasal sprays and oral tablets. In particular, thermally generated aerosols of rizatriptan were found to exhibit more rapid absorption kinetics and pharmacological response than subcutaneous administration in dogs (Rabinowitz et al., 2004). Therefore, pulmonary delivery of triptans might offer a more rapid pain relief of migraine attack compared to other delivery routes of formulations.

However, antimigraine activity of the triptans may involve an action both in the periphery and in the CNS (Ahn and Basbaum, 2005), for example, some studies showed that the therapeutic outcome of triptans may partially result from the central inhibitory effect within the trigeminal system (Cumberbatch et al., 1997; Goadsby and Hoskin, 1996; Goadsby and Knight, 1997). As a result, it is of particular interests to investigate the availability and the transport rate of the drug to the brain following administration. Targeting of drugs to the central nervous system is yet a difficult task to fulfill due to the tight blood–brain barrier. Nonetheless, the applicability of nasal delivery to target drugs directly to the brain has been extensively demonstrated (Illum, 2000, 2002). Vyas et al. (2006) have demonstrated that rapid and large extent of transport of sumatriptan into the rat brain could be achieved via intranasal administration. Therefore, the objective of the present study was to investigate the pharmacokinetic profiles of rizatriptan in both plasma and brain after intratracheal, intranasal, subcutaneous and peroral routes of administration to rats with a particular view to determining the applicability of inhalation delivery of rizatriptan to achieve rapid and high availability of the drug both in the blood and in the brain.

2. Materials and methods

2.1. Materials

Rizatriptan benzoate and zolmitriptan were of pharmaceutical grade, obtained from Beijing H*vs*F United Technology Co. Ltd. (Beijing, China) and all other reagents were of analytical grade or HPLC grade commercially available.

2.2. Preparation of drug solutions

Rizatriptan benzoate was dissolved in water at concentrations of 0.5, 8, 8, 8 and 50 mg/ml (w/v) for peroral, intravenous, intratracheal, subcutaneous and intranasal administration, respectively.

2.3. Animals

The study was performed in compliance with protocols required by the Animal Care and Use Committee of the Chinese Academy of Medical Sciences. SPF male Wister rats (180–220 g) were procured from Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences (Beijing, China). At the start of experiments, animals, weighing 220–310 g, were acclimated for at least 7 days bred at specific pathogen free (SPF) animal house. All animals were maintained at controlled temperature ($22 \pm 2\,^{\circ}C$), under 12 h light/dark cycles, and given diet and water *ad libitum*.

2.4. Drug administration

Groups of rats were fasted for 12–16 h before the experiments but they were allowed free access to water. Subsequently, they were administered at a bolus dose of 4.0 mg/kg of rizatriptan benzoate via intravenous, peroral, subcutaneous, intranasal or intratracheal routes. Prior to intravenous, subcutaneous, intranasal or intratracheal dosing, animals were anesthetized by an intraperitoneal injection of urethane (800 mg/kg). Followed by anesthesia, intratracheal instillation was conducted at a volume of 500 μl/kg after a curved balled needle attached on a syringe was inserted into the trachea under visual guidance (Lizio et al., 2001). After administration, the delivery device was removed and the animal was held in an upright position for 1 min to ensure deposition of the dose. Intranasal administration of the drug was carried out by delivering approximately 20 μl/rat at a concentration 50 mg/ml into the left nostril using a polyvinylchloride (PVC) tube attached to a Hamilton syringe, while the animal was fixed in a stereotaxic frame (Van den Berg et al., 2002). However, animals subject to oral administration were not anesthetized.

2.5. Blood sampling and preparation

At various time points (2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 240 min) after dosing, approximately 150 μl of blood was collected and put into the tubes with heparin. Subsequently, serum samples were prepared by centrifuging for 5 min at $5000 \times g$, and stored at $-20\,^{\circ}C$ until HPLC analysis. During the analysis, a nominal dose zolmitriptan (as internal standard) and 5 μl of 1 M sodium peroxide were added to 50 μl of serum and vortex for 30 s. The extraction of rizatriptan and zolmitriptan was subsequently carried out by addition of 400 μl of dichloromethane:acetyl acetate (1:4) and vortexing for 60 s. The mixture was then centrifuged for 1 min at $10{,}000 \times g$, after which 300 μl of the organic layer was transferred to a clean tube and evaporated to dryness using a nitrogen evaporator (HGC-12, Tianjin Hengao Ltd., China). For HPLC sample loading, 100 μl of water was used to reconstitute the residue, and an aliquot of 40 μl was injected onto a C18 reverse phase column for analysis, as described below.

2.6. Brain sampling and preparation

At each of the time points (2, 5, 10, 20, 30, 45, 60, 90, and 120 min) following dosing, three to four animals were sacrificed and decapitated, with their skulls cut open and brain tissue samples excised. Blood was collected with a syringe and a coarse needle from the trunk and put into the tubes with heparin, and subsequently, serum samples were prepared. Both brain and serum samples stored at $-20\,^{\circ}C$ prior to HPLC analysis. The analysis of serum was carried out following the protocol described in Section 2.5. To prepare the brain samples for analysis, the brain samples were homogenized with two-fold volumes

of distilled water and subsequently centrifuged at 5000 × *g* for 5 min to obtain the supernatants. An aliquot of 10 μl of zolmitriptan (2.5 μg/ml, w/v) as internal standard was added to 200 μl supernatant and equilibrated for 10 min after votex mixing. Then 10 μl of 1 M sodium hydroxide solution was added to the mixture and mixed by vortexing. The extraction of rizatriptan and zolmitriptan was subsequently carried out by addition of 400 μl of dichloromethane:acetyl acetate (1:4) and vortexing for 60 s. The mixture was then centrifuged for 1 min at 10,000 × *g*, after which 300 μl of the organic layer was transferred to a clean tube and evaporated to dryness (HGC-12, Tianjin Hengao Ltd., China). For HPLC sample loading, 100 μl of water was used to reconstitute the residue, and an aliquot of 40 μl was injected onto a C18 reverse phase column for analysis, as described below.

2.7. HPLC assay for rizatriptan

The analysis of rizatriptan was carried out using a HPLC assay reported previously (Chen et al., 2004), and performed using a Waters HPLC system, which included a Waters 717 plus autosampler, Multi λ fluorescence detector, Waters 600 Controller pump and Empower software. Each sample was injected onto a C18 Apollo column (150 mm × 4.6 mm, 5 μm, Alltech Associates Inc.) equipped with a Phenomenex guard column (Phenomenex Inc.) (4 mm × 3 mm). The mobile phase was composed of 0.05% (v/v) triethylamine in water (adjusting to pH 2.75 with 85% phosphoric acid) and acetonitrile (90:10, v/v). The flow rate was set at 1 ml/min with a run time of 15 min. The column was maintained at 45 °C. Fluorescence detection was performed at an excitation wavelength of 225 nm and an emission wavelength of 360 nm.

Stock solution of rizatriptan and zolmitriptan (used as internal standard) was prepared by dissolving the appropriate amount of powder in water, to yield the concentration of 1 mg/ml. Working solutions of rizatriptan were prepared by appropriate dilution whilst the concentration of internal standard were maintained at 500 ng/ml. All these solutions were stored in the refrigerator for less than 14 days.

The method was validated in terms of linearity, precision, recovery, limit of detection (LOD), limit of quantification (LOQ) and robustness to "fit the purpose" of analysis in the present study. The specificity was determined using the retention time of rizatriptan and zolmitriptan. The method provided good linearity ($r^2 \geq 0.999$) over a concentration range of 20–1000 ng/ml, and the standard calibration curves for rizatriptan were constructed using the analyte/internal standard peak-area ratios versus the nominal concentrations of the analyte. The precision of each assay was evaluated by determining the intra-run and inter-run relative standard deviation (R.S.D.) of six different concentrations of the standard solutions. The intra- and inter-precision were found to be less than 5.0% and 7.5%, respectively.

The recovery of rizatriptan was determined as follows: rizatriptan and zolmitriptan were spiked to blank plasma or brain homogenizer samples to give rizatriptan concentration of 20, 200 and 500 ng/ml, and maintain the concentration of zolmitriptan at 500 ng/ml. The analysis was performed using the method described above. Recovery was calculated by comparing the peak-area of the extracted sample (corrected according to the volume transferred during extraction) to that of the unextracted standard solution containing the same concentration with recovery being not less than 80%. The LOD and LOQ were calculated from the equations $\mathrm{LOD} = 3S_{\mathrm{blank}}$ and $\mathrm{LOQ} = 10S_{\mathrm{blank}}$ with value being 4.4 and 14.6 ng/ml, respectively.

The robustness tested the stability of standard solutions and the effect of extraction solvent (type and volume) and extraction procedure (mixing time) on the drug stability and recovery. The results showed that standard solutions were stable for at least 7 days at room temperature in brown volumetric flasks. The extraction protocol utilized did not significantly affect the drug stability and recovery.

2.8. Data analysis

The values of area under the plasma or brain concentration–time curve (AUC) were calculated using the trapezoidal rule, whilst the $C_{\max}$ and $T_{\max}$ values were read directly from the concentration–time profile. All AUC values and $\mathrm{AUC_{brain}/AUC_{plasma}}$ ratios were calculated for each individual animal or group animals before determining mean values. Statistic analysis was carried out using the paired Student's *t*-test (SPSS 11.0 for windows) and data are presented as mean ± S.D., unless otherwise stated.

3. Results and discussion

Studies in the literature showed that of various positive migraine treatment attributes, a rapid onset of action was regarded as a primary consideration for both clinicians and patients (Lipton et al., 2002). Towards this, different approaches have been utilized to modulate the pharmacokinetic characteristics, such as bioavailability, $C_{\max}$ and $T_{\max}$, of acute migraine therapy. These approaches include the development of new active ingredients and the utilization of drug delivery systems. The examples of the former are represented by newer triptans, such as eletriptan and rizatriptan, which conferred to high bioavailability and peak plasma concentration in shorter time relative to sumatriptan (e.g. Mathew and Loder, 2005; Milton et al., 2002; Vyas et al., 2000). Nonetheless, the latter approaches are of more interests to formulation scientists and the applicability of drug delivery systems to modulate the pharmacokinetic profiles has been well documented.

Amongst various routes of systemic drug delivery such as the pulmonary, buccal, sublingual, nasal, rectal, and vaginal cavities, pulmonary delivery has drawn considerable attention due to a larger surface area (70–140 $\mathrm{m^2}$) for systemic absorption of drugs. The onset of action following the pulmonary administration of drugs can be very rapid and could be comparable to the intravenous route. The present study aimed to compare the pharmacokinetic profiles of rizatriptan following intratracheal instillation (used as a method of pulmonary delivery), or other routes of administration (intranasal, subcutaneous, per-oral) based on the analysis of bioavailability, $C_{\max}$ and $T_{\max}$. The latter two parameters are indicative of the rate of drug absorption (Lacey et al., 1994).

Table 1
Pharmacokinetic parameters in plasma after intravenous (IV), intratracheal (IT), intranasal (IN), subcutaneous (SC) and peroral (PO) administration of rizatriptan benzoate at a bolus dose of 4.0 mg/kg in rats (mean ± S.D., $n = 6$)

	IV	IT	IN	SC	PO
$AUC_{0–240}$ (μg/ml min)	70.6 ± 5.1	64.4 ± 17.0	40.6 ± 10.2	52.3 ± 6.0	29.8 ± 7.4
Absolute bioavailability (%)	–	91.2 ± 24.1	57.5 ± 14.4	74.1 ± 8.5	42.2 ± 10.4
C_{max} (ng/ml)	>1430 ± 46	>1360 ± 324	422 ± 104	614 ± 181	234 ± 69
T_{max} (min)	<2.0	<2.0	9.5 ± 6.9	16.7 ± 4.1	30.0 ± 12.2

The absorption profiles of rizatriptan from different administered routes in rats to the systemic circulation were found to be different as shown in Fig. 1. The corresponding $AUC_{0–240}$, absolute bioavailability, C_{max} and T_{max} parameters are summarized in Table 1. Amongst the delivery routes, intratracheal instillation exhibited a very similar pharmacokinetic profile to that of IV and it produced the peak plasma concentration of rizatriptan within 2 min, which was significantly shorter than the T_{max} of intranasal, subcutaneous or peroral routes. The latter three routes of administration gave the corresponding C_{max} at 9.5 ± 6.9, 16.7 ± 4.1 and 30.0 ± 12.2 min, respectively. In addition, C_{max} of intratracheally instillated rizatriptan was found to be significantly higher than those of intranasal, subcutaneous or peroral delivered drug, also indicating a more rapid rate of drug absorption for intratracheal instillation compared to other three routes. Furthermore, intratracheal instillation of rizatriptan showed superior bioavailability in terms of $AUC_{0–240}$ to other three routes. The absolute bioavailability of intratracheal, subcutaneous, intranasal, and peroral delivery was found to be 91.2%, 74.1%, 57.5% and 42.2%, respectively. The $AUC_{0–240}$ via the latter two routes appeared to be significantly lower than that through intratracheal instillation ($p < 0.05$, paired t-test). Based on the analysis of bioavailability, C_{max} and T_{max}, it could be concluded that pulmonary delivery of rizatriptan could confer a more preferable pharmacokinetic profiles associated with the rapid onset of action relative to intranasal, subcutaneous or peroral drug delivery.

However, as described in Section 1, availability of drug in the brain might be of relevance to the pain relief of triptans. As a result, the biodistribution of rizatriptan to the brain of rats following the delivery of the different routes was investigated. Fig. 2 shows the concentration in the brain as a function of time after rizatriptan administration via the four delivery routes. Concentration of the drug in brain after intratracheal instillation was generally higher than those of the other three routes except one time point of nasal administration. Parameters including $AUC_{0–120}$, AUC_{brain}/AUC_{plasma}, relative bioavailability, C_{max} and T_{max} are summarized in Table 2. The rank order of brain bioavailability relative to that of intratracheal was: intratracheal (100) > nasal (92.8 ± 20.7%) > subcutaneous (74.3 ± 20.2%) > peroral (55.4 ± 13.8%), which was different from the order of plasma bioavailability. In addition, results showed that AUC_{brain}/AUC_{plasma} ratios after intranasal delivery (0.434 ± 0.111) were significantly ($p < 0.05$, paired t-test) higher than the ratios observed after intratracheal (0.232 ± 0.078), subcutaneous (0.218 ± 0.018) and peroral (0.248 ± 0.078) administration, whilst the latter three did not significantly differ from each other ($p > 0.05$, paired t-test).

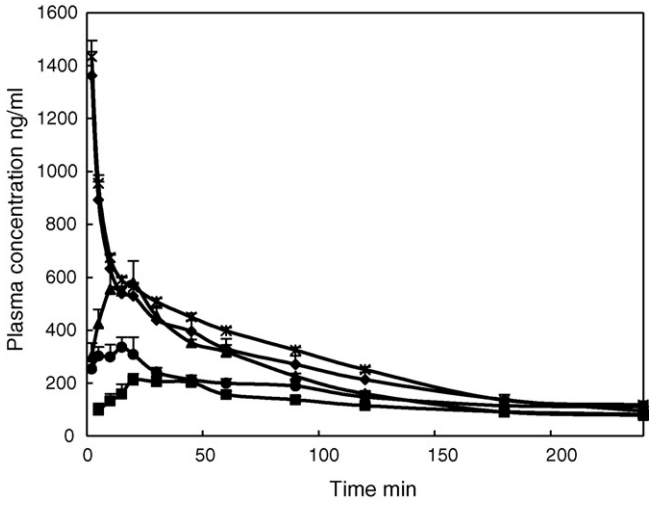

Fig. 1. Mean (±S.E.M., $n = 6$) plasma concentration–time profiles following intravenous (star), intratracheal (diamond), intranasal (circle), subcutaneous (triangle) or peroral (square) administrations of rizatriptan at a dose of 4.0 mg/kg in rats.

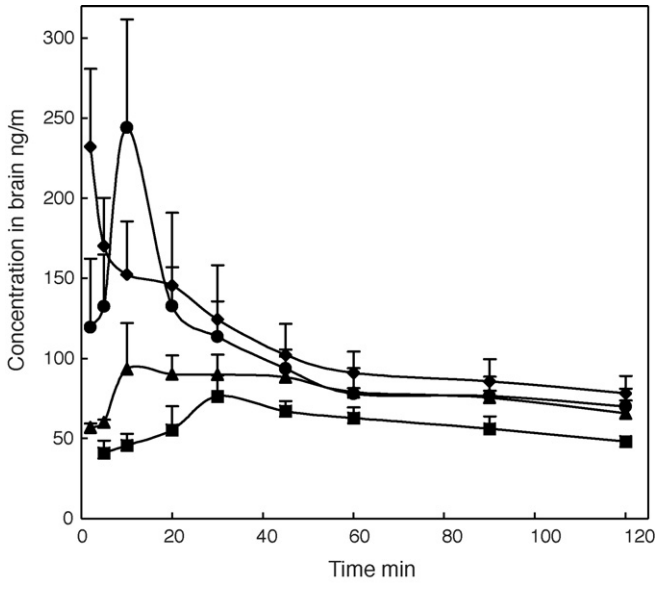

Fig. 2. Mean (±S.E.M., $n = 3$–4) concentration in brain as a function of time following intratracheal (diamond), intranasal (circle), subcutaneous (triangle) or peroral (square) administration of rizatriptan at a dose of 4.0 mg/kg in rats.

Table 2
Pharmacokinetic parameters in brain tissue after intratracheal (IT), intranasal (IN), subcutaneous (SC) and peroral (PO) administration of rizatriptan benzoate at a bolus dose of 4.0 mg/kg in rats (mean ± S.D., $n = 3–4$)

	IT	IN	SC	PO
$AUC_{0–120}$ (μg/ml min)	25.5 ± 7.7	23.6 ± 5.3	18.9 ± 5.14	14.1 ± 3.5
AUC_{brain}/AUC_{plasma}	0.232 ± 0.078	0.434 ± 0.111	0.218 ± 0.018	0.248 ± 0.078
Relative bioavailability (%)	100	92.8 ± 20.7	74.3 ± 20.2	55.4 ± 13.8
C_{max} (ng/ml)	>232 ± 97	244 ± 135	118 ± 41	87 ± 26
T_{max} (min)	<2.0	10.0	22.5 ± 9.6	45.0 ± 12.3

The capability of rizatriptan to penetrate the blood–brain barrier (BBB) has been documented previously (Williamson et al., 1997; Cumberbatch et al., 1997). The AUC_{brain}/AUC_{plasma} ratios of rizatriptan were broadly comparable to those of sumatriptan reported previously by Vyas et al. (2006), although sumatriptan was widely reported as a poor brain penetrant (Shepheard et al., 1995). In Vyas et al. work, the AUC_{brain}/AUC_{plasma} ratio of sumatriptan solution via intranasal route was found to be 0.553, which was 2.5-fold higher than those of other route of administration (ratio at ∼0.226). Whereas, this ratio for intranasally delivered rizatriptan solution in the present study appeared to be 0.434, about two-fold higher than those via other administered routes (ratios at 0.218–0.248). The higher AUC_{brain}/AUC_{plasma} ratios resulted from intranasal delivered rizatriptan might also be attributable to direct nose to brain drug transport as reported previously (Anand Kumar et al., 1974; Illum, 2000, 2002; Vyas et al., 2006).

With respect to the rate of uptake to the brain, intratracheal delivery gave the most rapid absorption with a T_{max} being less than 2 min amongst the four routes of administration. Intranasal delivery also resulted in a short T_{max} of 10 min, albeit significantly ($p < 0.05$, paired t-test) different from that of the intratracheal route. The rate absorption to the brain from the subcutaneous and peroral routes was found to be 22.5 ± 9.6 and 45.0 ± 12.3 min, respectively, which were significantly slower ($p < 0.05$, paired t-test) than that of either intratracheal or intranasal delivery. Based on the analysis of the parameters of C_{max}, the rate of uptake to the brain from intratracheal and intranasal routes appeared to be comparable, but markedly (not significantly due to large variations) higher than subcutaneous and peroral routes.

4. Conclusion

Intratracheal instillation of rizatriptan in the present study conferred superior pharmacokinetic parameters in both blood and brain of rats, associated with the rate of absorption and the onset of action, to intranasal, subcutaneous or peroral delivery. Such preferable parameters in blood include highest plasma concentration, greatest bioavailability, and shortest T_{max}, whilst those in brain contain greatest bioavailability, shortest T_{max} and almost highest C_{max}. As a result, it could be suggested that pulmonary delivery is likely to lead to an accelerated therapeutic effect compared with other previous used routes of administration of triptans such as intranasal, subcutaneous and peroral administration, and inhalation delivery of triptans is potentially promising to become an effective non-invasive route for the acute treatment of migraine attack.

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