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Farmacocinética do tramadol administrado pela via intravenosa e intramuscular em cadelas submetidas a ovário - salpingo - histerectomia

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Pharmacokinetics of tramadol administered by intravenous and intramuscular routes to female dogs submitted to ovariohysterectomy

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Abstract

The objective of the present study was to implant a method using a sensitive and specific system, and validate the whole analytical method to obtain an efficient tool for analyses of tramadol in plasma dogs, and to evaluate the pharmacokinetics of tramadol following intravenous (i.v.) and intramuscular (i.m.) administration of this drug in females dogs submitted to castration. The pharmacokinetics of tramadol were examined following i.v. or i.m. tramadol administration to five female dogs in each group submitted to ovariohysterectomy (dosage=2 mg/kg). In relation to intravenous administration, the half-time for the distribution process (t1/2d = 0.18 ± 0.12 h); the total body clearance was 0.60 ± 0.50 L/h/kg, half-life of elimination (t1/2b) was 1.24 ± 0.69 h. Statistically differences between parameters obtained after i.v. and i.m. was significant only to AUC0–∞: 3362.07 ± 1008 and 1604.55 ± 960.02 (ng.h/mL), respectively. The F was 48.00 ± 43.30 %. The assay for tramadol described has been demonstrated to meet all requirements for clinical PK studies. In particular, the method has satisfactory specificity, linearity, accuracy and precision range over the concentration examined.

Key words: Tramadol. Castration. Dogs. Pharmacokinetics.

Introduction

Tramadol hydrochloride, (1RS, 2RS)-[(dimethylamin) methyl]-1-(3-methoxyphenyl) cyclohexanol HCl, is a centrally acting opioid analgesic in widespread human clinical use. It is a synthetic analogue of codeine, but has a relatively low affinity for opiate receptors. Tramadol has been used for postoperative analgesia following orthopedic surgery and major gynecologic surgeries in addition to nonsurgical conditions in humans.6-8

Tramadol is well absorbed and extensively metabolized after oral administration in human beings, and its metabolites are excreted primarily in the urine.5 Unchanged tramadol and a total of twenty four metabolites, consisting of sixteen phase I metabolites and eight conjugates (seven glucuronides, one sulfate), were isolated in the urine of dogs and rats.7 Minimum effective plasma concentration in human beings for tramadol and O-desmethyltramadol, an active metabolite, have been reported to be 298 ± 171-590 ± 410 and 39.6 ± 29.5 – 84 ± 34 ng/mL, respectively in postoperative human patients.4-8

At “Veterinary Hospital of University of São Paulo”, tramadol has been used as analgesic after ovariohysterectomy (castration) of female dogs. Therefore, there is a lack of pharmacokinetics data of tramadol in this animal specie by intramuscular (i.m.) route of administration. Thus, the objective of the present work was to: (i) implant a method using a sensitive and specific system, and validate the whole analytical method to obtain an efficient tool for analyses of tramadol in plasma dogs, and (ii) evaluate the pharmacokinetics (PKs) of tramadol following intravenous (i.v.) and
intramuscular (i.m.) administration of this drug in females dogs submitted to castration.

Material and Method

Ten adult mixed breed female dogs were enrolled in this study between March and December 2005. The mean age was 2.75 years old (range: 1 – 6 years) and the mean body weight was 28.89 kg (range: 15 – 55.7 kg). All animals were considered healthy, based on physical examination, complete blood count, plasma biochemistry profile and urinalysis. All procedures related to this study were performed in accordance with The Institutional Animal Care and Use Committee at Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo.

The dogs were anaesthetized prior to and during ovariohysterectomy surgery with acepromazine, propofol and isoflurane. After the last stitch, each the dogs were randomly allocated in one of the two groups and administered a single dose of tramadol HCl commercial injection (Cristália, Brazil) (2 mg of tramadol per kg of body weight), i.v. via jugular vein or i.m. injected deep into semimembranous muscle.

A jugular catheter was placed in the right jugular vein prior to surgery. Blood samples, 10 mL per sample, were collected in tubes containing sodium heparin as anticoagulant and centrifuged at 2000 g for 10 min. The plasma was decanted, labeled, frozen at - 80 ºC until the assays were performed within 60 days of collection. This period is inferior to that established by Gan et al. 9 which is stable for more than 1 year when stored at - 20 ºC. Samples were collected immediately before tramadol administration (0) and at 10, 20, 30, 45 minutes and 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00 hours after tramadol administration.

Stock solutions of tramadol were prepared monthly by dissolving 11.38 mg of tramadol hydrochloride (Sigma®, Germany) in 100 mL of methanol (100 μg/mL) and kept stored at 4ºC. Standard curve for plasma analysis were prepared by fortifying pooled fresh canine plasma with stock solution of tramadol hydrochloride to produce a concentration range from 10 to 2000 ng/mL. The fortified calibration samples were processed and prepared exactly as described bellow for the incurred plasma samples. Tramadol concentrations for the calibration curve were: 10, 50, 125, 250, 500, 1000 and 2000 ng/mL. These working solutions were made by further dilution of the stock solutions in methanol and they were prepared fresh daily. Deionized water was produced by a Milli-Q Millipore Water System (Millipore, MA, USA).

Intra-assay precision and accuracy were determined by measuring five replicates of each of three standard concentration (100, 750 and 1500 ng/mL) prepared in fresh dog plasma and then stored. Interassay precision and accuracy were estimated by assaying three plasma concentrations on four different days. Recovery was estimated by comparing the slope of the standard curves for extract plasma with that for the corresponding unextracted standards.

Plasma concentrations of tramadol were analyzed by high-performance liquid chromatography (HPLC model LC-10AD with UV-VIS spectrophotometric detector model SPD-10AV, Shimadzu, Analytical Instruments Division, Kyoto, Japan) at Laboratório de Farmacologia from Departamento de Patologia da Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo. The HPLC method was based on previously published method 9,10,11 with modifications made to improve the efficiency of the method. For the analyses, frozen dog plasma samples were left on the bench to thaw naturally and were vortexed prior to their use. Plasma extraction was accomplished with liquid-liquid extraction. Briefly, to the plasma was added 5 drops of 0.1 M sodium hydroxide prior to the extraction. The solution was thoroughly vortexed. Then, 4 mL of ethyl acetate: hexane (1:4) (HPLC grade, Merck, Darmstadt, Germany) was added into the plasma and vortexed for 1.5 min. Afterward, it was subjected to centrifugation.

at 3500 g for 15 min. The organic layer was transferred into Cahn’s tubes. The tubes were then passed through a stream of nitrogen for drying (15 min) and 50 ml of the mobile phase was added for reconstitution before injection to the HPLC system. The analytical column was a RP-18 with particle size of 5 μm maintained at 55°C (Shimadzu, Maryland, USA). The mobile phase was constituted of 70% 0.01 M phosphate buffer adjusted to a pH of 5.9 with phosphoric acid (both of analytical reagent-grade from Merck, Darmstadt, Germany) with 0.1% triethylamine and 30% acetonitrile (HPLC grade, Merck Darmstadt, Germany). The UV detector was set to an excitation wavelength of 218 nm. The volume of each injection was 10 μL. Retention time for tramadol was 9.13 min and rate flow 1.2 mL/min.

Data analysis

Individual tramadol concentration vs. time curves was analyzed by non linear least square regression analysis using GraphPad Prism (1999). Choice of appropriate pharmacokinetic model was prepared on the basis of the lowest weighted sum of squares and lowest Akaike’s information criterion value for the individual data 12.

Following i.v. administration the final pharmacokinetic model fit the data was a two-compartment open model with first-order elimination from the central compartment in all the animals (Eqn 1):

$$C(t) = A e^{-\alpha t} + B e^{-\beta t}$$ (1)

where C(t) (ng/mL) represents tramadol plasma concentration at time t; A and B (ng/mL) are the concentration extrapolated to time 0 of the first and second phase of tramadol plasma and $\alpha$ and $\beta$ (1/h) are the distribution and elimination slopes, respectively.

Plasma tramadol distribution and elimination half-lives, $t_{1/2d}$ and $t_{1/2e}$, respectively, were calculated by Eqns 2 and 3:

$$t_{1/2d} = 0.693/\alpha$$ (2)

$$t_{1/2e} = 0.693/\beta$$ (3)

Area under the plasma curve from 0 to infinity $\langle \text{AUC}_{0-\infty} \rangle$ and area under the first moment curve from 0 to infinity $\langle \text{AUMC}_{0-\infty} \rangle$ were calculated by the linear trapezoidal method with extrapolation to infinity. The extrapolated area was estimated by Eqn 4 and 5:

$$\text{AUC}_{0-\infty} = C_{last}/\beta$$ (4)

$$\text{AUMC}_{0-\infty} = (t_{last} \times C_{last}/\beta) + C_{last}/k_{el}$$ (5)

In which $C_{last}$ is the last measured concentration, $t$ is the time of $C_{last}$, and $k_{el}$ was the elimination constant.

Total body clearance ($Cl_T$) was determined by Eqn (6):

$$Cl_T = \text{dose}/ \text{AUC}_{0-\infty}$$ (6)

Mean residence time (MRT) was determined by Eqn (7):

$$MRT = \text{AUC}_{0-\infty}/ \text{AUMC}_{0-\infty}$$ (7)

The apparent volume of distribution area was calculated by Eqn 8:

$$V_{d(area)} = \text{dose}/ (\text{AUC}_{0-\infty} \times \beta)$$ (8)

The volume of central compartment was calculated by Eqn 9:

$$V_1 = \text{dose}/ C_{p_0}$$ (9)

Where $C_{p_0} = A+B$

The micro constants were calculated by Eqn 10-12:

$$k_{21} = (\alpha B + A\beta)/A + B$$ (10)

$$k_{el} = \alpha\beta/k_{21}$$ (11)

$$k_{12} = \alpha + \beta - k_{21} - k_{el}$$ (12)

Compartmental analysis parameters
were calculated from equations published elsewhere. They are presented in table 1.

Tramadol plasma disposition curves after i.m. administration, were analyzed following the same procedure as used for i.v. analysis. Peak concentrations ($C_{\text{max}}$) of tramadol in blood and the time of peak concentration ($T_{\text{max}}$) were obtained directly from the experimental data without interpolation. Systemic bioavailability ($F$) of tramadol was calculated from noncompartmental parameters using Eqn (13):

$$F = \left(\frac{\text{AUC}_{0-\infty \text{ i.m.}}}{\text{AUC}_{0-\infty \text{ i.v.}}} \right) \times 100 \quad (13)$$

Variance analysis (ANOVA) followed by Unpaired $t$ test with Welch correction was used to analyze data from pharmacokinetic parameters. The results were presented as the mean with their standard deviation. All analyses were realized using the software GraphPad Instat and the figure by using GraphPad Prism. In all experiments, $P<0.05$ was the criterion for statistical significance.

**Results**

The linear concentration range for tramadol analysis was 10 to $> 2000$ ng/mL ($n=7$) ($r^2 > 0.999$). The limit of detection and quantification were found to be, respectively, 10 ng/mL and 50 ng/mL. The recoveries at 100, 750 and 1500 ng/mL were 87.5%, 87.7% and 86.5%, respectively.

**Table 1** - Mean ± SD values for tramadol pharmacokinetic variables following intravenous (i.v.) and intramuscular (2 mg/kg) tramadol HCl administration to five adult female dogs, in each group, after ovariohysterectomy. Plasma concentration of tramadol was measured by high-performance liquid chromatography (HPLC).

<table>
<thead>
<tr>
<th>Variable</th>
<th>i.v. route (mean ± SD)</th>
<th>i.m. route (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ (1/h)</td>
<td>3.78 ± 2.21</td>
<td>NA</td>
</tr>
<tr>
<td>$\beta$ (1/h)</td>
<td>0.56 ± 0.36</td>
<td>NA</td>
</tr>
<tr>
<td>$A$ (ng/mL)</td>
<td>4800.00 ± 2000.00</td>
<td>NA</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty \text{ i.v.}}$ (ng.h/mL)</td>
<td>$3362.07 ± 1008.60^*$</td>
<td>1604.55 ± 960.02</td>
</tr>
<tr>
<td>$\text{AUMC}_{0-\infty \text{ i.v.}}$ (ng.h/mL)</td>
<td>3621.39 ± 2107.09</td>
<td>4300.83 ± 2627.00</td>
</tr>
<tr>
<td>$B$ (ng/mL)</td>
<td>1200.00 ± 586.00</td>
<td>NA</td>
</tr>
<tr>
<td>$C_0$ (ng/mL)</td>
<td>6000.00 ± 3600.12</td>
<td>NA</td>
</tr>
<tr>
<td>$CL_{\text{T}}$ (L/h/kg)</td>
<td>0.60 ± 0.50</td>
<td>NA</td>
</tr>
<tr>
<td>$CL_{\text{T}}/F$(L/h/kg)</td>
<td>NA</td>
<td>0.59 ± 0.38</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>NA</td>
<td>625.50 ± 24.99</td>
</tr>
<tr>
<td>$%F$</td>
<td>NA</td>
<td>48.00 ± 43.30</td>
</tr>
<tr>
<td>$k_{a}$</td>
<td>NA</td>
<td>0.64 ± 0.41</td>
</tr>
<tr>
<td>$k_{12}$ (1/h)</td>
<td>1.38 ± 0.78</td>
<td>NA</td>
</tr>
<tr>
<td>$k_{21}$ (1/h)</td>
<td>1.20 ± 0.65</td>
<td>NA</td>
</tr>
<tr>
<td>$k_{el}$ (1/h)</td>
<td>1.77 ± 0.49</td>
<td>NA</td>
</tr>
<tr>
<td>$MAT$ (h)</td>
<td>NA</td>
<td>1.60 ± 0.97</td>
</tr>
<tr>
<td>$MRT$ (h)</td>
<td>1.08 ± 0.63</td>
<td>2.70 ± 1.50</td>
</tr>
<tr>
<td>$t_{1/2b}$ (h)</td>
<td>1.24 ± 0.69</td>
<td>1.82 ± 1.01</td>
</tr>
<tr>
<td>$t_{1/2a}$ (h)</td>
<td>NA</td>
<td>1.08 ± 0.62</td>
</tr>
<tr>
<td>$t_{1/2e}$ (h)</td>
<td>0.18 ± 0.12</td>
<td>NA</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>NA</td>
<td>0.75 ± 0.25</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
<td>1.06 ± 0.53</td>
<td>NA</td>
</tr>
<tr>
<td>$V_{d1}$ (L/kg)</td>
<td>0.33 ± 0.21</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Difference from i.v. and i.m. groups statistically significant, P<0.05.

Abbreviations: NA, not applicable; $\alpha$ = distribution slope; $\beta$ = elimination slope; $A$ = intercept for the distribution phase; $\text{AUC}_{0-\infty \text{ i.v.}}$ = under the curve from time 0 to infinity; $\text{AUMC}_{0-\infty \text{ i.v.}}$ = area under the first moment curve from 0 to infinity; $B$ = intercept for the elimination phase; $C_0$ = concentration at time 0; $CL_{\text{T}}$ = total body clearance; $C_{\text{max}}$ = peak plasma concentration; $F$ = systemic bioavailability; $ka$ = absorption rate constant; $k_{12}$ = rate of movement from compartment 1 to 2; $k_{21}$ = rate of movement from compartment 2 to 1; $k_{el}$ = rate of elimination; $MAT$ = mean absorption time; $MRT$ = mean resident time; $t_{1/2b}$ = elimination half-life; $t_{1/2a}$ = distribution half-life; $T_{\text{max}}$ = time of peak concentration; $V_d$ = apparent volume of distribution of the area; $V_{d1}$ = apparent volume of the central compartment central.
and inter-day precision values for quality control samples were 2.2-3.2 and 2.8-3.3% coefficient of variation (CV), respectively. In terms of stability, no significant degradation of tramadol was observed under any of the storage conditions evaluated. There were no interfering peaks from control plasma matrix, hemolyzed or not, and the presence of acepromazine, propofol and isoflurane in the plasma. Mean retention time for tramadol was 9.13 min (Figure 1).

No adverse effects were noted after i.v. or i.m. administration of tramadol HCl at 2.0 mg/kg. All twelve dogs appeared mildly sedated after administration. Blood levels of tramadol administrated by i.v. and i.m are presented in figure 2 and the PK data are presented in table 1.

Blood samples taken from all evaluated animals before tramadol administration were found to contain no measurable levels of this drug. On the other hand, they presented high tramadol levels after dosage. By i.m. the highest tramadol concentration occurred at 0.75 ± 0.25 h (625.50 ± 24.99 ng/mL). In both routes these levels were measurable until 6 hours after tramadol administration. Tramadol levels were significantly higher by i.v. than i.m at all time evaluated.

A two-compartment model best fit the plasma concentrations after intravenous tramadol in all dogs. A one-compartment model with first-order input was fit to the plasma tramadol concentrations following i.m administration.

In relation to intravenous administration, tramadol serum concentration rapidly decreased during the first hour postadministration, as reflected by the half-time for the distribution process ($t_{1/2d} = 0.18 ± 0.12$ h). Distribution was wide, with a $V_d$ of 0.33 ± 0.21 L/kg and a $V_{area}$ of 1.06 ± 0.53 L/kg. The $k_{12}/k_{21}$ ratio was 1.15 ± 0.58, indicating that the drug is returning rapidly from distribution sites for elimination from the body. Total body clearance was relatively rapidly (0.60 ± 0.50 L/h/kg). Half-life of

![Figure 1](image-url)
elimination ($t_{1/2b}$) was $1.24 \pm 0.69$ h and a MRT of $1.08 \pm 0.63$.

On the other hand, calculated parameters in relation to i.m. administration showed the same median value to the total body clearance ($0.59 \pm 0.38$ L/h/kg); the i.m. absorption was rapid as reflected by the $T_{\text{max}}$ ($0.75 \pm 0.25$ h) and $t_{1/2\mathrm{abs}}$ ($1.08 \pm 0.62$ h). Moreover, statistically differences between parameters obtained after i.v. and

![Figure 2 - Plasma concentration (ng/mL) profiles as measured by HPLC in adult female dogs after a single i.v. or i.m. administration of tramadol. Dosage = 2 mg/kg](image_url)
i.m. was significant only in the AUC$_{0-\infty}$: 3362.07 ± 1008.60 and 1604.55 ± 960.02 (ng.h/mL), respectively. The F was 48.00 ± 43.30 %.

**Discussion/Conclusion**

Our study verified if the HPLC method previously published to measure tramadol in human plasma was also appropriate to the dog plasma because this technique employs equipment and reagents available in our laboratory. The parameters analyzed showed that it is an effective technique with the advantages of being rapid, easy to perform and inexpensive.

This method has been successfully applied to the analyses of samples for a PK study in the present experiment which consisted of twelve dogs submitted to anesthesia with propofol, acepromazine and isoflurane and then submitted to castration. The dose of tramadol administered in the present investigation (2.0 mg/kg), in the end of the surgical procedure, was chosen taking into account previous studies in which this dose was verified not to produce the typical adverse effects reported for tramadol and also because this dose generates detectable blood concentrations of the compound in treated animals.

Early studies in 1999 demonstrated the analgesic effects of single-dose intramuscular tramadol 50-100 mg in human. Several studies have confirmed that repeated intramuscular administration of tramadol can provide effective and well tolerated postoperative analgesia comparable to that obtained with morphine, pentazocine and ketorolac. In this way, we elected the i.m and i.v. routes as they are the main routes of drug administration after surgical procedures and also because there isn’t any study comparing these two routes in dogs that received tramadol.

The tramadol plasma concentration vs time data after intravenous administration were best fitted to a two-compartment open model. This conclusion is in agreement with that found in previous studies of tramadol carried out in dogs. An open one-compartment model with first-order absorption best fitted the data obtained after intramuscular administration of tramadol to female dogs.

Mean residence time (MRT) reflects the difference in persistence of the drug in the body after intravenous and intramuscular administration. The prolonged MRT after intramuscular administration compared to the intravenous administration, the clearances being similar, was due to the influence of the absorption phase. Similar results have been reported in dogs that received tramadol per os and intravenous.

It was estimated that about 2% of the absorbed tramadol is excreted unchanged in the urine of dogs and more than 24 metabolites are excreted, which are almost completely eliminated through the kidneys. In healthy humans, the average elimination half-life of tramadol was estimated at 6h, whereas in patients with renal insufficiency the dose must be adjusted according to the clearance renal values. Assuming that the slower the elimination of this substance, the longer the time it will remain in the body, it could be inferred that both i.v. and i.m. dosing should expose the dogs lesser to tramadol than in human beings, as in the present study the elimination half-life of tramadol was 1.24 ± 0.69 and 1.82 ± 1.01, by i.v. and i.m., respectively.

The absorption process was rapid with a T$_{max}$ range: 0.50 - 1.00 h and corroborated by the absorption rate constant (ka) and t$_{1/2abs}$. The C$_{max}$ range: 650.49 – 600.51 ng/mL and the corresponding results after i.m. in humans was C$_{max}$ = 166 (1.24) ng/ml, which was inferior what could be in part be explained by the dose administered to human which was < 1 mg/kg. The F of the drug after i.m. administration at 2 mg/kg b.w. was 48.00 ± 43.30, in the present study. The low F values indicate that the drug was not completely absorbed from i.m. site injection in dogs. In contrast to its pharmacokinetics in humans, Ground et al. and Lintz, Beier and Gerloff founded 92.9 - 105.4%. Thus,
the results reflect the different kinetics between human and dogs.

The volume of distribution area for tramadol was 1.06 ± 0.53 and volume of distribution of central compartment was 0.33 ± 0.21 L/kg, which is consistent with a high tissue affinity. On the other hand, extrapolation of this data should be viewed with caution when considering multidose studies as it has been well determined that many differences exist in biochemical, morphological and functional changes between single and prolonged exposure to drugs.13

In summary, taken as a whole, the present data strongly support that exposition to tramadol was able to raise the levels in the plasma of dogs submitted to castration. The assay for tramadol described has been demonstrated to meet all requirements for clinical PK studies. In particular, the method has satisfactory specificity, linearity, accuracy and precision range over the concentration examined. The results from i.v. and i.m. administration of tramadol reported here provided the PK information for the design of future studies of analgesic efficacy in dogs.

Acknowledgements:
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References
5 TUNCER, S. et al. Adding ketoprofen to intravenous

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Farmacocinética do tramadol administrado pela via intravenosa e intramuscular em cadelas submetidas a ovário - salpingo - histerectomia

Resumo
O objetivo do presente estudo foi de implantar um método sensível e específico, e validar toda a metodologia para obter uma ferramenta eficiente para a análise do tramadol em plasma de cadelas, e avaliar a farmacocinética do tramadol após a administração do mesmo pelas vias i.v. e i.m. em cadelas submetidas à castração. A farmacocinética do tramadol foi examinada após a administração do tramadol por ambas as vias, em cinco cadelas em cada grupo submetidas à ovário histerectomia (dose = 2 mg/kg). Em relação à administração intravenosa, a meta-vida de eliminação (t1/2b) foi de 1,24 ± 0,69 h. Encontrou-se diferenças significativas somente nos parâmetros AUC0–∞: 3362,07 ± 1008 and 1604,55 ± 960.02 (ng.h/mL) pelas vias i.v. e i.m. respectivamente. O F foi de 48,00 ± 43,30 %. O estudo descrito neste artigo demonstrou atingir todas as exigências para os estudos clínicos em farmacocinética. Especificamente, o método apresentou especificidade, linearidade, exatidão e precisão satisfatórias no intervalo de concentrações examinadas.

Palavras-chave:
Tramadol, Castração, Cães, Farmacocinética.

References


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