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# Interspecies Pharmacokinetic Comparisons and Allometric Scaling of Napsagatran, a Low Molecular Weight Thrombin Inhibitor

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**Abstract**

The objective of this work was to assess the pharmacokinetics of napsagatran, a low molecular weight thrombin inhibitor, after intravenous administration in a variety of laboratory animals, and prospectively to help design the first pharmacokinetic studies in man. Napsagatran is actively excreted into the bile and urine of various species and pronounced species-differences in its pharmacokinetics are observed. It is, therefore, an interesting compound to use in tests of the limitations of presently available inter-species scaling methods.

The present data suggest that allometric exponent values which are consistent with the values expected for physiological processes and small organic molecules are not necessarily associated with successful predictions in man when active transport processes are involved in the disposition of the compounds. For example, compared with the values observed in man, the clearance (CL), non-renal clearance ($CL_{nr}$) and the volume of distribution at steady state ($Vd_{ss}$) were over-predicted by 3-, 7- and 2-fold, respectively, by use of allometry. Of the species tested, the cynomolgus monkey seemed to be the most useful for predicting kinetics in man when the approach based on concentration-time transformations was used. Thus, for half-life ($t_{1/2}$), CL and $Vd_{ss}$, the observed mean values of 1·7 h, 459 mL $min^{-1}$ and 24 L $kg^{-1}$ in man were very close to the values predicted from the cynomolgus monkey (1·7 h, 652 mL $min^{-1}$ and 22 L $kg^{-1}$, respectively).

The results show that there are large inter-species differences for kidney and liver excretion of napsagatran. This is probably because of the involvement of active transport processes, which compromised the kinetic extrapolation from animal to man, although a more thorough investigation of the transporters involved in the disposition of napsagatran is necessary to enable better understanding of the species differences observed.

Napsagatran ([[*S*-3-[*S*-1-(aminoiminomethyl)piperidin-3-ylmethylcarbamoyl]-2-naphthalenylsulphonylaminopropionyl]cyclopropylamino]acetic acid; Ro 46-6240) is a potent, competitive, reversible and specific low molecular weight (558·6 Da) thrombin inhibitor belonging to the inverse aspartate family. It is an amphiphilic dipeptide developed mainly for treatment of deep venous thrombosis.

In the current investigation the pharmacokinetics of napsagatran have been assessed after intravenous administration to laboratory animals, including rat, rabbit, dog and cynomolgus monkey. Inter-species scaling techniques have been applied prospectively to napsagatran to help design the first pharmacokinetic studies in man.

Inter-species scaling of pharmacokinetic parameters obtained from preclinical studies has often proven useful for predicting drug disposition in man, leading to significant time savings during phase I studies (Reigner et al 1997). It has been shown that simple allometric scaling of clearance works best for renally excreted and rapidly metabolized compounds, when elimination is dependent on physiological parameters (e.g. glomerular filtration rate and liver blood flow, respectively), which themselves scale allometrically (Boxenbaum

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& D'Souza 1990). For metabolized compounds with low to intermediate extraction ratios, reliable estimates of clearance can be obtained when allometric scaling is combined with in-vitro data (e.g. hepatocyte clearance in animals and man) (Lavé et al 1995b, 1996a, b, 1997).

Few reports have dealt with inter-species scaling of compounds mostly excreted unchanged into bile and urine through active secretion mechanisms. For example, large inter-species differences in the active secretion process involved in the renal excretion of organic acids have been reported which compromised the use of the allometric approach to prediction of kinetics in man from animal data (Timchalk & Nolan 1997; Timchalk et al 1997a, b; Cherkofsky 1995). Napsagatran is actively excreted into the bile and urine of the various species and pronounced species differences in its pharmacokinetics are observed. It is therefore an interesting compound for highlighting the limitations of the methods presently available for inter-species scaling. To the best of our knowledge napsagatran is the first biliary excreted compound for which such extrapolation of kinetics from animal to man is reported. The relevance and limitations of the allometric scaling techniques in this situation are discussed.

## Materials and Methods

*Animal pharmacokinetics*

For administration to the animals, napsagatran was dissolved in 1 : 4 (v/v) DMSO-twice-distilled water. The concentration of the solution was 10 mg mL$^{-1}$ (approx.).

Male rats (230–290 g, SPF, RoRo albino; BRL, Füllinsdorf, Switzerland) were administered intravenously a single bolus dose of napsagatran (5 mg kg$^{-1}$, n = 5). To study biliary excretion, catheters were implanted into the jugular veins and bile ducts of two additional rats and napsagatran was given intravenously at 5 mg kg$^{-1}$. Bile was collected on ice for up to 2 h after administration. The test compound was administered to all rats through a catheter implanted into the jugular vein, and blood samples were withdrawn after 5, 10, 20 30, 40, 50 and 60 min. Urine samples were also collected on ice before and 0–24 h after dosing.

Male Swiss rabbits (3·4–3·7 kg, Kobu; BRL, Füllinsdorf, Switzerland) were intravenously administered a single bolus dose of napsagatran (3 mg kg$^{-1}$, n = 3) through a catheter implanted into the jugular vein. Blood samples were withdrawn 5, 15, 30 min and 1, 1·5, 2, 3, 4, 5, 6, 7 and 8 h after administration. Urine samples were collected on ice before dosing and for up to 24 h afterwards.

Male Beagle dogs (14–17 kg; BRL, Füllinsdorf, Switzerland) were given 3·5 mg kg$^{-1}$ napsagatran intravenously as a short infusion (5 min, n = 3) through a catheter implanted in a front leg vein. Blood samples were withdrawn 10, 20, 30, 45 min and 1, 1·25, 1·5, 1·75, 2, 2·25, 2·5, 2·75 and 3 h after dosing. Urine samples were also collected on ice in fractions corresponding to the time intervals 0–2, 2–4, 4–6, 6–8 and 8–24 h after administration. For one additional dog bile samples were collected on ice in fractions corresponding to the time intervals 0–1, 1–3, 3–5 and 5–7 and 7–24 h after administration of napsagatran as a 5 min infusion of 4·5 mg kg$^{-1}$.

Male cynomolgus monkeys (5·5–5·9 kg, *Macaca fascicularis*) were given napsagatran (1·63 mg kg$^{-1}$, n = 2) as a single intravenous bolus. Blood samples were collected from a brachial vein catheter 5, 15, 30 and 45 min, 1, 1·25, 1·5, 1·75, 2, 2·25, 2·5, 2·75, 3, 3·25, 3·5, 3·75 and 4 h after dosing.

On the basis of limit of quantification of napsagatran in plasma, the dosages employed in the various animal species were chosen to enable complete characterization of the pharmacokinetic profile of napsagatran in animals. The dosages were also in the range of doses used in preclinical efficacy studies.

The concentrations of napsagatran in rat and dog plasma, bile and urine were determined by HPLC. Briefly, plasma samples were deproteinized with acetonitrile and, after evaporation and reconstitution of the supernatant, the samples were analysed on a reversed-phase column and quantified by UV-detection at 225 nm. Bile and urine samples were diluted with the mobile phase, and samples were injected directly on to the column. The limit of quantification of the assay was 50 ng mL$^{-1}$ for plasma and 5 $\mu$g mL$^{-1}$ for urine and bile.

The plasma concentrations of napsagatran were determined in rabbit, cynomolgus monkey and man by means of another HPLC assay (Guenzi & Gianni 1994). Briefly, napsagatran was analysed by column switching with heart cutting and quantified by fluorescence detection ($\lambda_{exc}$ = 225 nm, $\lambda_{em}$ = 350 nm). The limit of quantification was 5 ng mL$^{-1}$ in 0·25 mL plasma or 1 ng mL$^{-1}$ in 1 mL plasma (from man).

*Pharmacokinetic analysis*

Plasma concentration–time data for each species were analysed by non-compartmental methods. The area under the plasma concentration–time curve

(AUC) and area under the moment curve (AUMC) were calculated by use of the logarithmic trapezoidal rule, and extrapolated to time infinity by adding $C/\beta$ to AUC and $tC/\beta + C/\beta 2$ to AUMC, where C is the last predicted concentration at the last sampling time t. The slope of the terminal phase, $\beta$, was determined by log–linear regression of the last three or four data points, and the terminal half-life was calculated as $t_{1/2} = 0{\cdot}693/\beta$. The systemic clearance (CL) was calculated by use of the relationship: $CL = dose/AUC^0{}_\infty$. The volume of distribution at steady state ($Vd_{ss}$) was calculated from $Vd_{ss} = CL \times AUMC^0{}_\infty / AUC^0{}_\infty$ for intravenous bolus administration and $Vdss = CL \times [(AUMC^0{}_\infty / AUC^0{}_\infty) - IT/2]$, where IT is the infusion time, for intravenous infusion. For rabbit and monkey $CL_{ren}$ and $CL_{nr}$ were calculated from $CL_{ren} = CL \times fe$ and $CL_{nr} = CL \times (1 - fe)$, where fe is the fraction of the dose administered which is excreted unchanged in urine. For rat and dog, biliary data were used to calculate $CL_{nr}$ from $CL_{nr} = CL \times fbile$, where fbile is the fraction of the dose administered which was excreted unchanged in bile.

*Allometric scaling*

For allometric scaling, the mean pharmacokinetic parameters (P) for $t_{1/2}$, CL, $Vd_{ss}$, $CL_{ren}$ and $CL_{nr}$ of napsagatran in animals were correlated with the corresponding body weight (B), using allometric equations of the form $P = aB^x$, where a is the allometric coefficient and x is the allometric exponent. The values of exponents and coefficients were estimated by least-squares fitting of log P–log B data.

By use of the allometric equations obtained for $t_{1/2}$, CL, $Vd_{ss}$, $CL_{ren}$ and $CL_{nr}$, values for a 76-kg man were estimated and compared with measured data (Jones et al unpublished data).

*Pharmacokinetic time calculations*

Pharmacokinetic times were calculated using equivalent time according to the methods of Dedrick et al (1970). The plasma concentrations were normalized by the dose administered $kg^{-1}$ and the time unit for each animal ($t_{animal}$) was converted into time for man ($t_{man}$) by use of the equation: $t_{man} = t_{animal} \times (B_{man}/B_{animal})^{0{\cdot}25}$.

## Results

The profiles of mean napsagatran plasma concentrations against time obtained for rats, rabbits, dogs and cynomolgus monkeys after intravenous administration are illustrated in Figure 1. The volume of distribution of napsagatran at steady-state ($Vd_{ss}$) was close to total body water in rat, rabbit and dog (0·6, 1·0 and $0{\cdot}7\,L\,kg^{-1}$, respectively). In cynomolgus monkey the volume of distribution was restricted to extracellular water ($0{\cdot}3\,L\,kg^{-1}$). Large inter-species differences were observed in the systemic plasma clearance of napsagatran in-vivo (Table 1). In rat, rabbit and dog most (60–97%) of the compound administered intravenously was excreted unchanged in the bile. Taking into account the fraction excreted in the bile and blood–plasma partitioning (0·5 to 0·6 in the various animal species), the biliary blood clearance values in rat, rabbit and dog were close to the corresponding liver blood flows. Similarly, renal clearance in the rat and rabbit was larger than the corresponding glomerular filtration rate (Table 1) indicating active renal secretion of napsagatran in these species. Renal clearance in the dog repre-

Table 1. Mean pharmacokinetic parameters of napsagatran in different animals after intravenous bolus administration.

| | Rat (n = 5) | Rabbit (n = 3) | Dog (n = 3) | Monkey (n = 2) |
|---|---|---|---|---|
| Weight (kg) | 0·26 | 3·55 | 14·5 | 5·7 |
| Dose ($mg\,kg^{-1}$) | 5 | 3 | 3 | 1·6 |
| Half-life (h) | 0·17 ± 0·02 | 0·43 ± 0·03 | 0·37 ± 0·08 | 0·53 ± 0·01 |
| Clearance ($mL\,min^{-1}$) | 17·0 ± 3·6 | 245 ± 126 | 405 ± 11·6 | 90·3 ± 19·3 |
| Fraction excreted unchanged in urine (%) | 25 ± 6 | 40 ± 9 | 11 ± 0·8 | ND* |
| Fraction excreted unchanged in bile (%) | 61 ± 13 | 60 ± 10 | 97‡ | ND |
| Renal clearance ($mL\,min^{-1}$) | 4·2 ± 1·0 | 98 ± 7·6 | 44·5 ± 4·6 | ND |
| Non-renal clearance ($mL\,min^{-1}$) | 10·4 ± 2·9 | 150 ± 90† | 393‡ | ND |
| Volume of distribution at steady state (L) | 0·16 ± 0·05 | 3·5 ± 1·3 | 10 ± 1·4 | 1·5 ± 0·6 |
| fu% | 33·3 ± 2·3 | ND | 51·7 ± 2·7 | ND |

Values are means ± standard deviation. *Not determined. † Non-renal clearance = total clearance − renal clearance. ‡ n = 1.

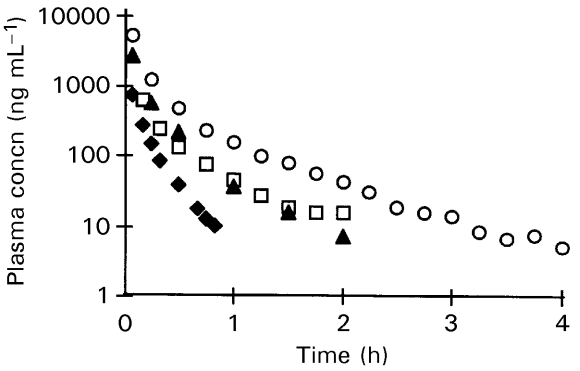


Figure 1. Mean plasma-concentration–time profiles of napsagatran for the rat (◆), dog (□), rabbit (▲) and the cynomolgus monkey (○) after intravenous bolus administration.

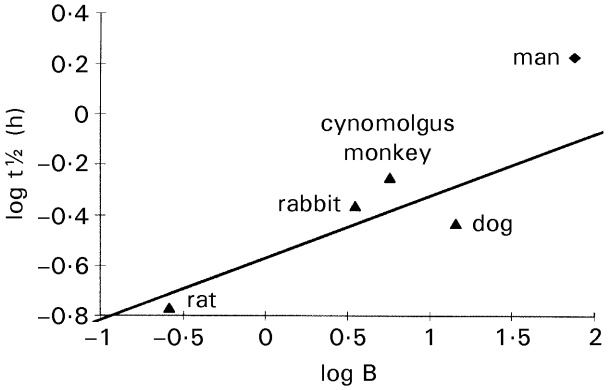


Figure 2. Allometric scaling of napsagatran half-life ($t_{\frac{1}{2}}$). Regression equation y = 0·2461x − 0·57; $R^2$ = 0·6822.

sented 50% of the renal blood flow; the unbound renal blood clearance in dog (140 mL min$^{-1}$) exceeded the corresponding glomerular filtration rate (60 mL min$^{-1}$) indicating active renal secretion of napsagatran in this species also. The urinary and biliary clearances were not determined in the cynomolgus monkey. In this species, the total blood clearance represented 60–80% (approx.) of the corresponding liver blood flow.

Napsagatran had a short elimination half-life in the various animal species—0·17 and 0·53 h in the rat and cynomolgus monkey, respectively.

Table 2 shows the results of least-squares fitting of log $t_{½}$, log CL, log $Vd_{ss}$, log $CL_{ren}$ and log $CL_{nr}$ against log B in the animals. The pharmacokinetic parameters corresponding to a 76 kg man were then estimated by use of the allometric equations obtained from the animal data. The observed parameters in man are also presented in Table 2 for comparison with predictions. The results in man were obtained after intravenous infusions of napsagatran (0·6 and 1·0 $\mu$g kg$^{-1}$ min$^{-1}$, n = 3 and n = 6, respectively) for 30 min to healthy volunteers (Jones et al unpublished data).

The regression equations for the plots of log $t_{½}$, log CL, log $Vd_{ss}$, log $CL_{ren}$ and log $CL_{nr}$ against log B, obtained using data from animals, are illustrated in Figures 2–6, with the corresponding mean values subsequently found in man.

The representations based on time transformations using equivalent time are illustrated in Figure 7. The corresponding pharmacokinetic parameters are presented in Table 3.

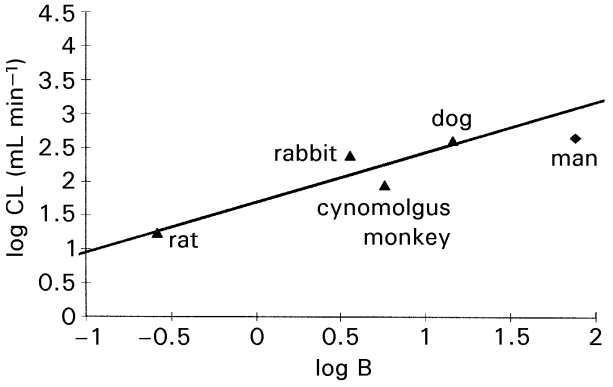


Figure 3. Allometric scaling of napsagatran clearance (CL). Regression equation y = 0·7447x + 1·6954; $R^2$ = 0·8426.

Table 2. Allometric inter-species scaling of the pharmacokinetic parameters of napsagatran in animals and comparison of values of estimated and observed parameter in man.

| Parameter | Allometric equation | Correlation coefficient ($r^2$) | Data for man | |
|---|---|---|---|---|
| | | | Estimated | Observed |
| Half-life (h) | $0·269B^{0·246}$ | 0·682 ($P$ = 0·160)* | 0·78 | 1·7 |
| Total clearance (mL min$^{-1}$) | $49·6B^{0·745}$ | 0·843 ($P$ = 0·083) | 1250 | 460 |
| Volume of distribution at steady state (L) | $0·601B^{0·974}$ | 0·901 ($P$ < 0·05) | 41 | 24 |
| Renal clearance (mL min$^{-1}$) | $14·7B^{0·636}$ | 0·645 ($P$ = 0·379) | 231 | 154 |
| Non-renal clearance (mL min$^{-1}$) | $35·0B^{0·958}$ | 0·990 ($P$ = 0·062) | 2220 | 305 |

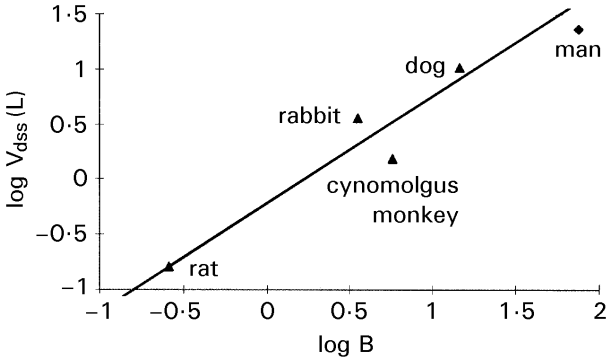


Figure 4. Allometric scaling of napsagatran volume of distribution ($Vd_{ss}$). Regression equation $y = 0{\cdot}9744x - 0{\cdot}2209$; $R^2 = 0{\cdot}9013$.

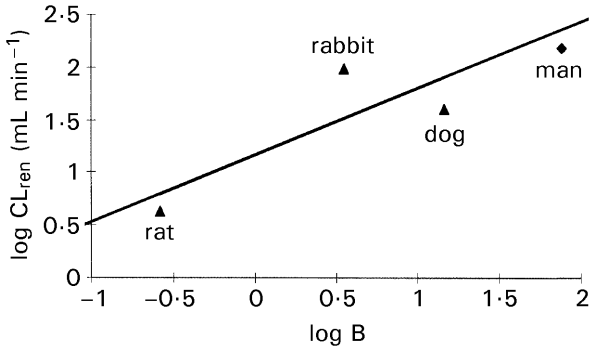


Figure 5. Allometric scaling of napsagatran renal clearance ($CL_{ren}$). Regression equation $y = 0{\cdot}6357x + 1{\cdot}1666$; $R^2 = 0{\cdot}6452$.

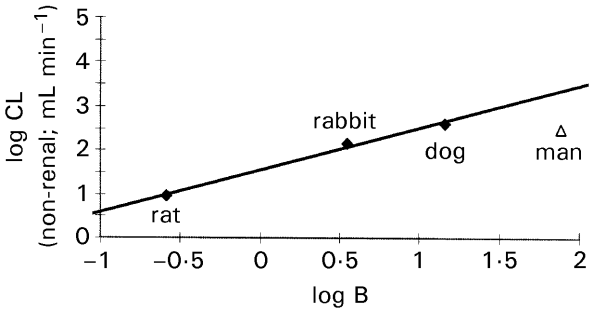


Figure 6. Allometric scaling of napsagatran clearance (CL non-renal). Regression equation $y = 0{\cdot}9585x + 1{\cdot}5438$; $R^2 = 0{\cdot}9905$.

## Discussion

Despite the high correlation coefficients (0·84–0·99) for the allometric regressions of CL, $Vd_{ss}$ and $CL_{nr}$, these parameters were not predicted adequately for man (Table 2). Compared with the values observed in man, CL, $CL_{nr}$ and $Vd_{ss}$ were over-predicted by three-, seven- and twofold, respectively. Furthermore, the allometric exponents of CL and $Vd_{ss}$, 0·745 and 0·977, respectively, were

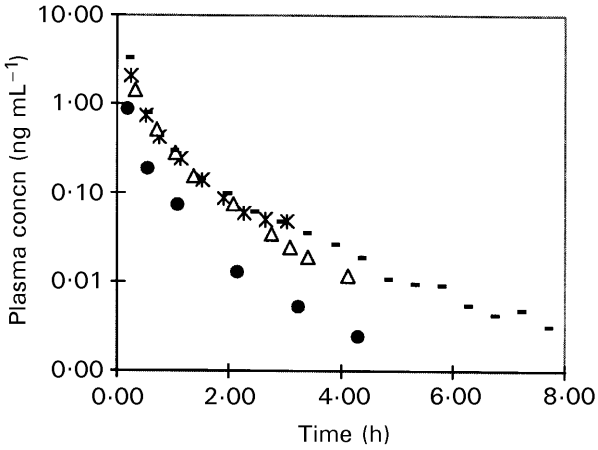


Figure 7. Concentration–time profile predicted for napsagatran in man from those obtained from dog (*), rat (△), rabbit (●) and monkey (—) by use of equivalent time.

consistent with the values expected (0·75 and 1·0) for physiological processes and small organic molecules (Mordenti 1986). This suggests that reasonable exponent values are not necessarily associated with successful predictions in man for those situation where man behaves as a unique species. Poor correlation coefficients were observed for the allometric scaling of $t_{½}$ (Figure 2) and $CL_{ren}$ (Figure 5); these did not enable reasonable prospective prediction in man.

Representations based on the concentration–time plots were also attempted and the corresponding predicted pharmacokinetic parameters in man were compared with those obtained by direct allometric scaling. By using a fixed exponent for body weight (0·25), to transform chronological time in the different species into equivalent time, the cynomolgus monkey gave the most reliable predictions. Thus, for $t_{½}$, CL and $Vd_{ss}$, the observed mean values of 1·7 h, 459 mL $min^{-1}$ and 24 L $kg^{-1}$ in man were very close to the values predicted from the cynomolgus monkey (1·6 h, 652 mL $min^{-1}$ and 22 L $kg^{-1}$, respectively). Reasonable estimates were also obtained from dogs. Use of data from the rat led to overestimates of CL by almost twofold; the rabbit led to the poorest estimates. With this last species, the clearance was overestimated fivefold (approx.) and the volume of distribution twofold. The disposition in man after the various dosage regimens was predicted on the basis of the profiles obtained after equivalent time transformation (Figure 8). These kinetic extrapolation were performed prospectively and resulted in a more efficient design of the first clinical study. The advantages of the approach based on equivalent time transformation over that based on regression analysis have been discussed (Efthymiopoulos et al

Table 3. Pharmacokinetic parameters of napsagatran predicted for man by plasma–concentration extrapolation methods (equivalent time).

| | Rat | Rabbit | Dog | Monkey | Observed |
|---|---|---|---|---|---|
| Half-life (h) | 0·93 | 0·89 | 1·3 | 1·6 | 1·7 |
| Total clearance ($mL\,min^{-1}$) | 840 | 2230 | 690 | 652 | 459 |
| Volume of distribution at steady state (L) | 27 | 53 | 26 | 22 | 24 |

1991; Lavé et al 1995a). For example, with the time transformation approach, errors in the estimation of the pharmacokinetic parameters (e.g. because of an insufficient number of points) do not interfere with the analysis (Efthymiopoulos et al 1991). In addition, the complete profile of plasma concentration against time (rather than only pharmacokinetic parameters) can be predicted in man from several or a single species using pharmacokinetic time units.

In man, napsagatran is excreted mainly unchanged in the bile and urine (60% and 40%, respectively). These fractions compare favourably with those for the rat and the rabbit, but not for those from the dog, for which biliary excretion was higher than in the other species. However, the clearances associated with renal and biliary excretion were much higher in rabbits than in man. Similarly to the dog, renal blood clearance in man (approx. $300\,mL\,min^{-1}$) represented 50% of the kidney blood flow, whereas renal blood clearance in rabbits was limited by renal blood flow. In all species, however, renal excretion of napsagatran probably involved active secretion processes as suggested by the high renal clearance values observed. In man, for example, the unbound renal blood clearance was fourfold higher (approx.) than the corresponding glomerular filtration rate.

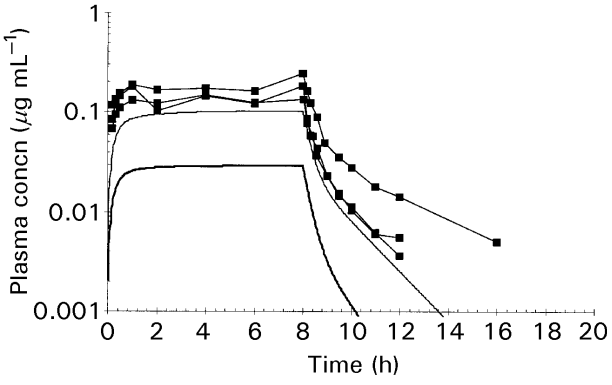


Figure 8. Comparison of predicted (—, from cynomolgus monkey; ▬, from rabbit) and observed (■) concentration–time profiles for napsagatran in man. The predicted profile was based on equivalent time transformation. The plasma concentrations in man (■) were obtained from healthy subjects (n = 3) after intravenous infusion of napsagatran (80 $\mu g\,min^{-1}$ for 8 h).

Active processes are probably also involved in biliary excretion. Non-renal clearance in dogs, rats and rabbits was close to the corresponding liver blood flow, and in man the non-renal blood clearance represented 50% (approx.) of the liver blood flow. Urinary and biliary excretion were not investigated in the cynomolgus monkey, because of practical considerations. However, because results from this species can be used for accurate prediction of the pharmacokinetics of napsagatran in man, it can be assumed that similar excretion mechanism(s) are involved in both monkey and man.

Overall, these data suggest that species differences in pharmacokinetics arise as a result of the involvement of active transport processes in both renal and biliary excretion. However, a more detailed study on the individual steps contributing to the renal and biliary excretion of napsagatran would be necessary to furnish insight into the active processes involved and identify the rate-limiting step(s). This would require, for example, the use of drugs known to interfere with hepatic uptake and biliary excretion, and in-vitro experiments on both mechanisms. Evidence for the involvement of carrier-mediated uptake by the liver has recently been reported for an amphiphilic peptidomimetic thrombin inhibitor structurally closely related to napsagatran (Eckhardt et al 1996). Furthermore, structural elements relevant for this transport process could be determined. Thus, an acidic group and an arylsulphonyl group, which are also present in napsagatran, are favourable structures for hepatic uptake (Eckhardt et al 1996).

Some preliminary indications on the rate-limiting step in the hepatic disposition of napsagatran were obtained from a quantitative tissue-distribution study in the rat (Hoffmann-La Roche unpublished data), in which concentrations in plasma and various tissues and organs were determined. Except in liver and kidney, the tissue concentrations were lower than the corresponding plasma concentrations. Furthermore, liver and kidney concentrations

tended to decrease much more slowly than plasma concentrations ($t_{1/2}$ approx. 5 h in liver and kidney compared with 0·2 h in plasma) (F. Hoffmann-La Roche unpublished data). Because napsagatran is not metabolized in-vivo or in-vitro, total radioactivity is allocated to the parent compound. These results might indicate that sinusoidal uptake is faster than biliary excretion on the canalicular membrane of the hepatocytes.

In summary, large inter-species differences were shown for both kidney and liver excretion of napsagatran, probably because of the involvement of active transport processes, which compromised the kinetic extrapolation from animal to man. These inter-species differences could not be accounted for with the allometric approach which is of limited value for napsagatran. Of the individual species, the cynomolgus monkey seemed to be the most predictive species for man for both clearance and volume of distribution. More thorough investigation of the transporters involved in the disposition of the compound is necessary to enable understanding of the species differences observed.

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