PHARMACOKINETICS AND ABSOLUTE BIOAVAILABILITY OF IBUPROFEN AFTER ORAL ADMINISTRATION OF IBUPROFEN LYSINE IN MAN

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ABSTRACT

The lysine salt of \textit{d,l-2-(4-isobutylphenyl)}-propionic acid (ibuprofen lysine) was administered as a single oral dose of 500 mg by means of commercially available coated tablets (Imbun®).* To assess the absolute bioavailability of ibuprofen after its oral application as a lysine salt, intravenous injections of ibuprofen solutions containing 200 mg and 400 mg of the drug served as reference application. In a partially randomized cross-over design, 8 healthy male volunteers received three different single dose administrations which were separated by wash-out periods of 4 days each. Ibuprofen plasma concentrations were determined by HPLC using direct injection, pre-column enrichment and column switching techniques. From the results of intravenous injections one can deduce linear ibuprofen pharmacokinetics within the considered dosage range, with corresponding AUC\textsubscript{0-\infty} values of 3786 µg \textbullet min ml\textsuperscript{-1} and 7260 µg \textbullet min ml\textsuperscript{-1} for the 200 mg and 400 mg doses, respectively. The values of plasma clearances as well as those of different volumes of distribution showed remarkable constancy after evaluation from both intravenous injections. The absorption of orally administered ibuprofen lysine proved to be rapid, resulting in a mean peak plasma level (C\textsubscript{\text{max}}) of 31 µg ml\textsuperscript{-1} ibuprofen and in a mean time to peak (t\textsubscript{\text{max}}) of 45 min. The absolute bioavailability of ibuprofen amounts to 102.7 per cent, indicating a complete absorption of ibuprofen when administered as its lysine salt. Drug tolerability was excellent for the oral administration of ibuprofen lysine as well as for the intravenous treatments with ibuprofen free acid. Only mild and transient adverse drug reactions such as mild burning or dragging sensation during injection or mild redness at the site of injection were reported.

KEY WORDS Ibuprofen Ibuprofen lysine Pharmacokinetics Absolute bioavailability Dose linearity

INTRODUCTION

The lysine salt of \textit{d,l-2-(4-isobutylphenyl)}-propionic acid (ibuprofen lysine) is widely used as an analgesic, anti-inflammatory, and antipyretic drug. Like ibuprofen which is well known for its good gastrointestinal tolerability and for

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its low incidence of adverse drug reactions, ibuprofen lysine proved to be a valuable therapeutic tool during analgesic treatment of rheumatic disease states in a clinical trial.¹

The pharmacokinetics of ibuprofen from orally administered ibuprofen lysine are mainly characterized by a more rapid onset of absorption from the gastrointestinal tract as opposed to that observed with ibuprofen free acid.²

Recently Geißlinger et al.³ conducted a bioequivalence trial with oral administrations of ibuprofen lysine (Imbun®) as test preparation and another commercial formulation containing ibuprofen free acid as a reference. By this study ibuprofen lysine was clearly demonstrated to be absorbed with a higher rate than was ibuprofen free acid: the time to reach peak plasma concentration ($t_{\text{max}}$) was significantly shorter with the lysine salt.

The present study was performed in order to get knowledge about the absolute bioavailability and dose-linearity of ibuprofen from ibuprofen lysine in man. Furthermore data received after intravenous administration of ibuprofen in man should supply additional pharmacokinetic parameters of the drug, because up to now all literature data are still based on results coming from comparisons with orally administered ibuprofen solutions.

**METHODS**

*Subjects*

Eight healthy male volunteers participated in the study after they had given informed consent. They had a mean age of $29.8 \pm 6.5$ years, a mean weight of $70.1 \pm 8.2$ kg, and a mean height of $175.5 \pm 5.5$ cm. The volunteers were checked according to standard methods of clinical chemistry and haematology before and after the study. ECGs were performed before the study start as well as after each treatment.

None of the participants had received any form of medication 2 weeks prior to the experiments.

*Experimental design*

Three different single dose administrations were investigated in this study which was designed and performed as a partially randomized cross-over trial. The administrations were separated by wash-out periods of at least 4 days each. The study was approved by an Ethical Committee and conducted according to German law and the Declaration of Helsinki.

The three study treatments were:

1. *Treatment A*: slow i.v. (3 min) of a sterile solution containing 200 mg of ibuprofen/3 ml, Lot No. V211 186.
2. *Treatment B*: slow i.v. (3 min) of a sterile solution containing 400 mg of ibuprofen/3 ml, Lot No. 290 585/1.
3. **Treatment C**: oral application of coated tablets* containing 500 mg of ibuprofen lysine (equivalent to 292.6 mg ibuprofen free acid), Lot No. 23 956.

After an overnight fast, the volunteers received their respective administration in the morning. Breakfast was 2 h after drug administration.

With treatments A and B blood samples were taken immediately before administration and then after having finished the slow injections (\(=t_0\)). Further blood samples were withdrawn at 1, 2, 3, 4, 6, 10, 20, 30, 40, 60, and 90 min and 2, 3, 4, 6, and 8 h after i.v. injection.

After oral administration blood samples were taken before administration and 10, 20, 30, 40, 60, and 90 min and 2, 3, 4, 6, and 8 h after drug intake.

Blood samples being anticoagulated during collection were centrifuged; the resulting plasma layers were separated, stored at \(-20^\circ\), and shipped in dry ice.

**Drug assay**

Plasma levels of ibuprofen were determined by HPLC, using a Hewlett Packard HP 1090 apparatus and a diode array detector HP 1040 A together with a HP-LAS system HP 3357 for computerized data handling.

Before analysis plasma specimens were acidified with 40% phosphoric acid and then centrifuged during 10 min at 13 000 g. The cleared supernatants were applied to the HPLC system which worked with a special column switching technique.

Ibuprofen was extracted on line from plasma by enrichment on pre-columns (15 mm \(\times\) 4.6 mm i.d.), filled with Lichroprep RP18, 25–40 \(\mu\)m. After spilling with 0.1 mmol l\(^{-1}\) KH\(_2\)PO\(_4\) (pH 5.0) for 2 min at a flow rate of 1·5 ml min\(^{-1}\), automatical column switching caused a backflush of enriched ibuprofen to the analytical column (125 mm \(\times\) 4.6 mm i.d.), filled with Nucleosil C18, 5 \(\mu\)m particles. Elution was performed isocratically with methanol/5 mmol l\(^{-1}\) (NH\(_4\))\(_2\)SO\(_4\), pH 3·0 = 71/29 (v/v). Additional separation conditions were: flow rate 0·5 ml min\(^{-1}\), oven temperature 50°, UV detection wavelength 220 nm, injection volume 500 \(\mu\)l or 50 \(\mu\)l.

HPLC chromatograms were evaluated by the external standard method using drug-spiked plasma specimens as standards. Two calibration ranges were used and checked for linearity between concentration and detector response by daily recalibration. They proved to be highly linear within the concentration ranges 25–1000 ng ml\(^{-1}\) and 1–50 \(\mu\)g ml\(^{-1}\), respectively.

A detection limit of 17 ng ml\(^{-1}\) of ibuprofen was calculated. The within-day imprecision was 5·7 per cent at 25 ng ml\(^{-1}\) and 0·9 per cent at 50 \(\mu\)g ml\(^{-1}\) ibuprofen.

Day-to-day imprecision as validated by the coefficient of variation of the slope of the daily calibration curves of a 2-months period was 7·95 per cent.

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*Imbun®, manufacturer: Merckle GmbH Blaubeuren, FRG.*
The recovery of pre-column enrichment was:

\[ 92.2 \pm 3.9 \text{ per cent at } 50 \text{ ng ml}^{-1}, \]
\[ 97.6 \pm 7.6 \text{ per cent at } 250 \text{ ng ml}^{-1}, \text{ and} \]
\[ 102.2 \pm 2.1 \text{ per cent at } 500 \text{ ng ml}^{-1}. \]

Quality assurance measurements were done by analysing plasma samples spiked with known amounts of ibuprofen and comparing found vs nominal values. Thus the accuracy of the method can be indicated as \( 103.9 \pm 1.5 \text{ per cent} \) in the concentration range between 141 and 22 500 ng ml\(^{-1}\).

**Pharmacokinetic calculations**

Pharmacokinetic modelling was carried out with a Hewlett Packard computer (model HP 1000) using a selfmade program for iterative curve approximation (ITER, FORTRAN 77).

Coefficients and exponents of functions (1) and (2) were used to present the results of curve fitting:

**Oral administration**

\[
C = A \times e^{-\alpha t} + B \times e^{-\beta t} - (A + B) \times e^{-k_s(t-t_{in})} \tag{1}
\]

**Intravenous administration**

\[
C = A \times e^{-\alpha t} + B \times e^{-\beta t} \tag{2}
\]

Unless otherwise stated summarized results comprising values of all 8 subjects are given as arithmetic means with standard deviations \((x \pm SD; n = 8)\)

The plasma concentration vs time data were fitted on the basis of a two-compartment open model in the case of the orally applied drug, while intravenous data were fitted to an intravenous open two-compartment model.

The \( \text{AUC}_{0-\infty} \) was calculated using the trapezoidal rule. Extrapolation to infinity was performed according to equation (3),

\[
\text{AUC}_{0-\infty} = \text{AUC}_{0-t} + C_{\text{last}}/\beta \tag{3}
\]

with \( t \) = time of the last measured concentration \( C_{\text{last}} \) and \( \beta \) = hybrid constant of equations (1) and (2).

A completely model-dependent calculation of the area under the curve based on equation (4) was also performed,

\[
\text{AUC} = A/\alpha + B/\beta \tag{4}
\]

where \( A \) and \( B \) are constants resulting from equations (1) and (2) of the curve fitting procedure.

Total body or systemic clearance of ibuprofen was calculated from intravenous data according to equation (5),

\[
\text{Cl}(t) = D/\text{AUC}_{0-\infty} \tag{5}
\]
with D = applied dose of ibuprofen.

\[ V_{d,area} = D/\beta \times \text{AUC}_{0-\infty} \]  \hspace{1cm} (6)

\[ V_c = D/(A + B) \]  \hspace{1cm} (7)

\[ V_{pc} = (k_{12}/k_{21}) \times V_c \]  \hspace{1cm} (8)

\[ V_{ss} = V_c + V_{pc} \]  \hspace{1cm} (9)

The microconstants \( k_{12} \) and \( k_{21} \) were determined as described in (4).

To investigate the absolute bioavailability of ibuprofen after oral application of the drug as its lysine salt, the resulting AUC values from both i.v. experiments were used to calculate the area corresponding to a theoretically applied i.v. dose of ibuprofen equivalent to the drug amount applied via the oral route, i.e. 292.6 mg of ibuprofen.

RESULTS

Figures 1, 2, and 3 depict mean plasma concentration vs time data (±SEM) of all three treatments, whereas Figure 4 summarizes these concentration–time courses in one single diagram.

Ibuprofen i.v. injections resulted in mean peak plasma values of 40.4 ± 6.4 \( \mu g \) ml\(^{-1}\) (treatment A, 200 mg i.v.) and 83.0 ± 22.2 \( \mu g \) ml\(^{-1}\) (treatment B, 400 mg i.v.) immediately after injection. The measured mean \( t_{max} \) values were 1.1 ± 0.6 min (treatment A) and 1.1 ± 0.8 min (treatment B).

Ibuprofen from orally administered ibuprofen lysine peaked at a mean \( t_{max} \) of 45.0 ± 9.2 min, with a mean \( C_{max} \) of 31.0 ± 6.9 \( \mu g \) ml\(^{-1}\).

The corresponding mean AUC\(_{0-480}\) values were:

\[ 3623 \pm 906 \mu g \times \text{min ml}^{-1} \text{ (treatment A),} \]
\[ 6963 \pm 1615 \mu g \times \text{min ml}^{-1} \text{ (treatment B), and} \]
\[ 5093 \pm 1253 \mu g \times \text{min ml}^{-1} \text{ (treatment C).} \]

From these i.v. data one can deduce linear ibuprofen pharmacokinetics, with a 2.05-fold greater \( C_{max} \) and a 1.92-fold greater AUC\(_{0-480}\) for the 400 mg dose as compared with the 200 mg application.

Table 1 lists harmonic means of pharmacokinetic time parameters \( t_{0.5}(a) \), \( t_{15}(a) \) and \( t_{0.5}(\beta) \). Intravenously injected ibuprofen shows a mean terminal half-life \( t_{0.5}(\beta) \) of 94 min, whereas ibuprofen applied as ibuprofen lysine is absorbed with a mean half-life \( t_{15}(a) \) of 11 min and eliminated with a mean \( t_{0.5}(\beta) \) of 122 min.

Extrapolation of the areas under the curve (AUC\(_{0-480}\)) to infinity yields AUC\(_{0-\infty}\) values of 3786 ± 973 \( \mu g \times \text{min ml}^{-1} \) and 7260 ± 1745 \( \mu g \times \text{min ml}^{-1} \) for the 200 mg and 400 mg intravenous injections, respectively.
Figure 1. Time course of the plasma concentrations of ibuprofen after treatment A. Each point represents the mean ± SEM of 8 determinations.
PLASMA CONCENTRATIONS OF IBUPROFEN
AFTER I.V. APPLICATION OF
400 MG IBUPROFEN-SOLUTION
LOT NO.: 290 585/1

Figure 2. Time course of the plasma concentrations of ibuprofen after treatment B. Each point represents the mean ± SEM of 8 determinations.
Figure 3. Time course of the plasma concentrations of ibuprofen after treatment C. Each point represents the mean ± SEM of 8 determinations.
Figure 4. Combined presentation of mean plasma concentration vs. time curves of treatments A–C (without mean errors)
Table 1. Characteristic half-lives ($n = 8$; harmonic means) of ibuprofen after treatments A–C. The data were calculated from an iterative computer approximation technique, using the two-compartment model (either its complete open form or its intravenous open version).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$t_{1/2} (a)$ (min)</th>
<th>$t_{1/2} (a)$ (min)</th>
<th>$t_{1/2} (b)$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A (200 mg ibuprofen i.v.)</td>
<td>—</td>
<td>5·5</td>
<td>94·8</td>
</tr>
<tr>
<td>Treatment B (400 mg ibuprofen i.v.)</td>
<td>—</td>
<td>3·8</td>
<td>94·3</td>
</tr>
<tr>
<td>Treatment C (500 mg ibuprofen lysine p.o.)</td>
<td>11·4</td>
<td>33·6</td>
<td>121·7</td>
</tr>
</tbody>
</table>

Table 2. Individual and mean AUC$_{0-\infty}$ and corresponding 400 mg/200 mg ratios after treatment A and B, together with their statistical evaluations.

<table>
<thead>
<tr>
<th>Subject</th>
<th>200 mg</th>
<th>400 mg</th>
<th>400 mg/200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5212</td>
<td>7536</td>
<td>1.45</td>
</tr>
<tr>
<td>2</td>
<td>3379</td>
<td>6051</td>
<td>1.79</td>
</tr>
<tr>
<td>3</td>
<td>3901</td>
<td>7667</td>
<td>1.97</td>
</tr>
<tr>
<td>4</td>
<td>4686</td>
<td>9395</td>
<td>2.00</td>
</tr>
<tr>
<td>5</td>
<td>3409</td>
<td>7294</td>
<td>2.14</td>
</tr>
<tr>
<td>6</td>
<td>2303</td>
<td>4461</td>
<td>1.94</td>
</tr>
<tr>
<td>7</td>
<td>2911</td>
<td>6025</td>
<td>2.07</td>
</tr>
<tr>
<td>8</td>
<td>4488</td>
<td>9648</td>
<td>2.15</td>
</tr>
<tr>
<td>Mean</td>
<td>3786</td>
<td>7260</td>
<td>1.94</td>
</tr>
<tr>
<td>SD</td>
<td>973</td>
<td>1745</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The AUC$_{0-\infty}$ after orally applied ibuprofen lysine amounts to $5093 \pm 1253 \mu g \cdot \text{min mL}^{-1}$.

The mean ratio of AUC$_{0-\infty}$ after i.v. application of 400 mg and 200 mg ibuprofen is $1.94 \pm 0.23$, whereas the model-dependent calculation of AUC results in a mean ratio of $2.24 \pm 1.22$. No statistically significant difference exists between these ratios (paired t-test).

Table 2 lists individual and mean values of AUC$_{0-\infty}$ resulting from treatments A and B, as well as individual and mean ratios of the 400 mg:200 mg comparison. A striking dose dependency between the two intravenous data sets is again clearly visible.

The absolute bioavailability of orally administered ibuprofen as ibuprofen
Table 3. Individual and mean AUC\textsubscript{0-\infty} after injection of a mathematically interpolated theoretical i.v. dose of 292.6 mg ibuprofen, together with the AUC\textsubscript{0-\infty} after oral application of 500 mg of ibuprofen lysine, corresponding to 292.6 mg of free drug. The right column contains individual and mean values of absolute bioavailability.

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC 292.6 mg i.v.</th>
<th>AUC 292.6 mg p.o.</th>
<th>AUC (p.o.)/AUC (i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6288</td>
<td>6215</td>
<td>98.85</td>
</tr>
<tr>
<td>2</td>
<td>4616</td>
<td>5220</td>
<td>113.08</td>
</tr>
<tr>
<td>3</td>
<td>5645</td>
<td>6180</td>
<td>109.48</td>
</tr>
<tr>
<td>4</td>
<td>6866</td>
<td>8246</td>
<td>120.09</td>
</tr>
<tr>
<td>5</td>
<td>5208</td>
<td>5743</td>
<td>110.28</td>
</tr>
<tr>
<td>6</td>
<td>3302</td>
<td>3066</td>
<td>92.85</td>
</tr>
<tr>
<td>7</td>
<td>4353</td>
<td>3817</td>
<td>87.69</td>
</tr>
<tr>
<td>8</td>
<td>6877</td>
<td>6179</td>
<td>89.85</td>
</tr>
<tr>
<td>Mean</td>
<td>5394</td>
<td>5583</td>
<td>102.77</td>
</tr>
<tr>
<td>SD</td>
<td>1272</td>
<td>1595</td>
<td>12.05</td>
</tr>
</tbody>
</table>

Table 4. Arithmetic means (n = 8) of different ibuprofen distribution volumes and total body clearance, calculated from intravenous pharmacokinetic data of treatment A and B, respectively. (\(V_c\) = volume of central compartment; \(V_{\infty}\) = volume of peripheral compartment; \(V_{ss}\) = volume at steady state; \(V_{d,area}\) = volume calculated from AUC).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(V_c) (l)</th>
<th>(V_{p0}) (l)</th>
<th>(V_{ss}) (l)</th>
<th>(V_{d,area}) (l)</th>
<th>Cl(r) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (200 mg ibuprofen i.v.)</td>
<td>4.8 ± 0.8</td>
<td>5.4 ± 2.9</td>
<td>10.3 ± 3.6</td>
<td>11.7 ± 4.3</td>
<td>56.2 ± 15.9</td>
</tr>
<tr>
<td>B (400 mg ibuprofen i.v.)</td>
<td>5.0 ± 1.4</td>
<td>5.1 ± 2.0</td>
<td>10.1 ± 2.8</td>
<td>11.4 ± 3.6</td>
<td>58.2 ± 15.6</td>
</tr>
</tbody>
</table>

Lysine in relation to the i.v. applied drug is shown by Table 3. Therein the individual ratios AUC (p.o.)/AUC (i.v.) of each subject are listed after mathematical interpolation of the i.v. data into values equivalent to the dose of free ibuprofen administered orally.

Table 3 reports an absolute bioavailability of ibuprofen from orally administered ibuprofen lysine of 102.77 ± 12.05 per cent, suggesting complete absorption of the drug through the gastrointestinal mucosa.

From intravenous data additional pharmacokinetic parameters such as different volumes of distribution and total body clearance of ibuprofen were calculated according to equations (5)–(9). Table 4 lists arithmetic mean values of these parameters. A clearcut dose independence of these pharmacokinetic parameters of ibuprofen is intriguing, if one compares the results of both i.v. experiments to each other.
DISCUSSION

Most pharmacokinetic data of ibuprofen are based on the assumption that the orally applied drug is completely absorbed and systemically available. Pharmacokinetic parameters such as different volumes of distribution, total body clearances or absolute bioavailabilities were therefore evaluated by data sets from orally applied ibuprofen solutions as references.

Intravenous data of ibuprofen are only published from studies with dogs and rats. Human i.v. pharmacokinetics have not been reported until now.

The height of drug plasma concentrations obtainable by treatments A and B correspond well with those resulting from therapeutic oral dosage. From the intravenous data a central volume of distribution of the drug of about 5 l is calculated, a value which nearly equals $V_{\text{pc}}$, the peripheral volume of distribution. This indicates the high plasma protein binding of the drug which amounts to 99 per cent, because ibuprofen theoretically should show a higher peripheral distribution volume according to its lipophilic properties. The total body clearance of plasma ibuprofen which occurs primarily via hepatic metabolization and subsequent renal elimination of conjugated metabolites was determined to be 56.3 ml min$^{-1}$ and 58.3 ml min$^{-1}$ for the 200 mg and 400 mg dosage, respectively.

Compared with literature data, where an 'apparent oral clearance' of 0.046 1 h kg$^{-1}$, corresponding to 53.7 ml min$^{-1}$ is reported, our study reveals identical results.

A terminal half-life $t_{0.5} (\beta)$ of 94 min for both injections furthermore demonstrates an excellent congruence of results. Pharmacokinetic data obtained after 200 mg and 400 mg i.v. ibuprofen are characterized by linear relationships between the parameters AUC or $C_{\text{max}}$ and the administered dose, whereas volumes of distribution and the clearance remain constant.

In contrast to this Lockwood et al. published data indicating nonlinear ibuprofen pharmacokinetics at doses exceeding 800 mg p.o. They argued that saturation of plasma protein binding might contribute to this effect. Otherwise they showed that unbound ibuprofen could be described by linear pharmacokinetics over the concentration range of 400–1200 mg of orally applied drug.

In each case 500 mg oral doses of ibuprofen lysine generate drug plasma levels lying within the range of linear pharmacokinetics.

The pharmacokinetic behaviour of ibuprofen after oral application as ibuprofen lysine in man can be described as follows, using a two compartment open model for data fitting: the drug is absorbed from the gastrointestinal tract with a mean half-life $t_{0.5} (a)$ of 11.43 min, a value which agrees well with that of 5.9 min (calculated from $k_a = 7.06$ h$^{-1}$) of an orally applied ibuprofen solution.

Ibuprofen lysine shows an essentially higher water solubility than does ibuprofen free acid. Conclusions drawn from animal studies with intraduodenal application of ibuprofen lysine, that this salt might act as a type of drug solu-
ibuzifer, therefore get essential confirmation.

The absolute bioavailability of ibuprofen from orally applied ibuprofen lysine is 102.7 ± 12.0 per cent. This means that the drug bioavailability is essentially the same one as known for the free acid form. With respect to data obtainable with oral solutions of the drug, ibuprofen was shown to be fully bioavailable.6,7 In addition, the findings of Geißlinger,3 who demonstrated complete bioavailability of ibuprofen from ibuprofen lysine (Imbun®) compared with ibuprofen free acid after oral application as commercial drugs, confirm our results.

From a given complete absolute bioavailability of ibuprofen after oral application as its lysine salt, an apparent oral clearance for the substance of 52.4 ml min⁻¹ can be calculated which is virtually identical with the data of both i.v. experiments. Therefore the pharmacokinetic equivalence between orally applied ibuprofen lysine and ibuprofen free acid is further demonstrated. Pharmacokinetic data of ibuprofen from ibuprofen lysine exhibit a prolonged phase of distribution (t₁/₂(a) = 33.6 min). The terminal half-life too is longer than evaluated by i.v. injection, with a mean value of 121.7 min. However, the reasons for these differences between oral and intravenous data are not yet clearly understood.

Together with findings reported on better gastrointestinal tolerability of the lysine salt as opposed to that of the free acid,2 the investigated drug modification appears to be an effective and safe substitute of the parent drug.

From the clinical point of view both application routes did not cause any significant adverse drug reaction during the study. The drug tolerability after i.v. application of the free acid as well as after oral application of ibuprofen lysine proved to be excellent.

Therefore and because of its considerable better solubility in water the use of ibuprofen lysine offers considerable advantages together with the possibility of additional routes of application.

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REFERENCES
