ORAL VERSUS RECTAL IBUPROFEN IN HEALTHY VOLUNTEERS

Rolanda Vilenchik[1], Matitiahu Berkovitch[2,3], Azaria Jossifoff[4], Zvi Ben-Zvi[1], Eran Kozer[3,5]

[1]Department of Clinical Pharmacology, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel; [2]Clinical Pharmacology & Toxicology Unit; [3]Assaf Harofeh Medical Center, Zerifin, Sackler School of Medicine Tel Aviv University, Israel; [4]Super-Pharm Laboratories, Israel; [5]Pediatric Emergency Unit Assaf Harofeh Medical Center Zerifin, Israel

Corresponding Author: erank@asaf.health.gov.il

ABSTRACT

Objective
Ibuprofen is a safe and effective non steroidal anti-inflammatory drug (NSAID). Ibuprofen suppositories are marketed in Europe; but data regarding pharmacokinetics of rectal vs. oral ibuprofen in humans is scarce. The objective of this study is to compare the pharmacokinetics of single-dose rectal vs. oral ibuprofen in healthy adult volunteers.

Methods
Ten healthy adult male volunteers, aged 20-37 years, received in a non-blind, cross-over setting, two formulations of ibuprofen. First, a 400 mg (about 5 mg/kg) of racemic ibuprofen suppository; second (after a three week washout period) the same dosage of ibuprofen syrup. Blood samples were collected before dosing and for 12 hours after administration. Pharmacokinetics analysis was preformed.

Results
Mean peak plasma concentration (C_{max}) of rectal ibuprofen was considerably lower, and the mean time to peak (T_{max}) considerably longer, compared to oral ibuprofen. Absorption of rectal ibuprofen was considerably lower than oral ibuprofen, with a relative bioequivalence of 63%. Rectal ibuprofen reached therapeutic plasma concentration (>10 µg/ml) 45 minutes after dosing and remained in that range for four hours. The values of Vd/F and CL/F also differ significantly after rectal and oral administration, while no difference was found in the elimination rate constant (K_{el}) or half-life elimination ($t_{1/2}$).

Conclusions
Racemic ibuprofen suppository has lower bioavailability compared with ibuprofen syrup. Therapeutic plasma concentrations of ibuprofen were reached 45 minutes after dosing and remained in that range for 4 hours. Ibuprofen suppositories can contribute to the management of fever and pain when the oral route is not available.

Key Words: *Ibuprofen, pharmacokinetics, rectal, oral, adults*

Ibuprofen is one of the most commonly used NSAIDs which serves as an analgesic, antipyretic and anti-inflammatory agent.[1] It is also combined with opiates to prevent the development of severe pain and inflammation after surgery.[2,3] Ibuprofen acts by inhibiting cyclooxygenase (COX) activity, and therefore reducing synthesis of prostanoids both in the periphery and central nervous system.[1,4] Ibuprofen is a chiral 2-arylpropionic acid that is usually marketed and administrated as the racemic mixture of S-(+) and R-(-) enantiomers. Its pharmacology activity is attributed only to the S-(+) enantiomer.[1,5,6]

Ibuprofen's safety and efficacy has been demonstrated in children and adults.[7-10] It was found as efficacious (some studies suggest more efficient) as acetaminophen in fever reduction in children, with the advantage of having anti-

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inflammatory properties.[11] Oral administration of ibuprofen is occasionally impossible, especially among infants and small children who vomit or refuse taking the drug. In such cases, a rectal formulation may serve as an alternative. In light of this, ibuprofen suppositories for children were developed, and are being marketed in several European countries. Although ibuprofen suppositories are being frequently used, in some countries, for pain and fever management, the pharmacokinetics of rectal ibuprofen is lacking.

To our knowledge, there is only one study presenting the pharmacokinetics of ibuprofen after rectal administration in humans.[12] Furthermore, we are not aware of any study comparing the pharmacokinetics of rectal vs. oral ibuprofen in humans. The objective of the present study was to compare the pharmacokinetics of rectal vs. oral ibuprofen in healthy adult volunteers after a single therapeutic dose.

METHODS

Two single dose formulations of ibuprofen were investigated in a non-randomized cross-over study. The study was conducted in Assaf-Harofeh Medical Center, Israel. The hospital ethics board approved the study.

Study Population

Ten healthy male volunteers were enrolled and were gave a written informed consent. Subjects having allergy to ibuprofen or any other NSAIDs, existing peptic ulcer/bleeding, or renal/liver/heart disease, were excluded. We also excluded subjects who had taken any over the counter (OTC) medication or consumed alcohol 48 hours prior to the beginning of the study, or any prescription medication 14 days before the beginning of the study.

Study Design

After an overnight fast of ten hours, all subjects received, in a cross-over setting, two formulations of ibuprofen. On the first occasion, a single suppository containing 400 mg of racemic ibuprofen (Super-Pharm Professional, Yarkonim, Israel) which was self inserted by every subject. After a three week wash-out period they received the same dose of ibuprofen syrup (Nurofen®, Reckitt Benckiser, Slough, UK). The syrup was diluted in 200 ml of water to ensure full consumption. After dosing, all subjects remained in an upright position for at least 20 minutes. The dose of ibuprofen chosen is the accepted therapeutic dosage for fever and pain management in adults. Both formulations contained ibuprofen in the form of free acid. After dosing, the subjects kept fasting for one more hour before having breakfast.

Blood samples and Analysis

Blood samples (~ 4 ml) were collected through an indwelling catheter inserted in the upper arm. Samples were collected immediately before (time 0) and 10, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after dosing. All blood samples were collected in heparinized test tubes, which were immediately centrifuged for 10 minutes at 4000 rpm. The resulting plasma was separated and kept frozen at -80ºC until the analysis.

Preparation of Suppositories

Ibuprofen suppositories were prepared and donated by Super-Pharm Professional laboratories, Yarkonim, Israel by a technique previously described.[13] In brief, powdered ibuprofen was mixed with Propylene Glycol in a glass vessel. To this mixture, two lipophilic suppository bases, Witepsol H15 and Witepsol H35, were added. The mixture was continuously stirred to ensure uniform dispersion of the drug in the suppository base. Finally, the homogeneous mixture was transferred to a suppository mold which was placed in a freezer to allow hardening and shaping of the suppositories.

Analysis of Plasma Ibuprofen Concentration

Plasma concentration of racemic ibuprofen was determined by high performance liquid chromatography (HPLC) method previously described[14] and slightly modified to our needs. In brief, about 200µl of plasma sample were transferred to an eppendorf tube and mixed with 250µl of acetonitrile and 20µl of naproxen solution (10µg/ml), which served as the internal standard (IS).

The tubes were vortex mixed for 15 seconds and kept at room temperature for 15 minutes. Vortexing was repeated for 15 seconds and the tubes were centrifuged for 15 minutes at 3200

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rpm. Finally, 20µl of the supernatant were injected to the HPLC.

Ibuprofen concentration in plasma were determined by using HPLC model 1100- Hewlett Packard (HP), Ramsey, MN USA, equipped with universal liquid chromatographic injector, UV absorbance detector (215 nm), and a C-18 RF Beckman column (25cm X 4.6mm) with a particle size of 5µm. The mobile phase consisted of methanol/water (80:20) and 1ml of orthophosphoric acid per 1000 ml of the solvent (pH=3). It was delivered at a flow rate of 1ml/min in room temperature. Data was processed using HPLC data analysis software, Chemstation (version 6.01) Hewlett Packard (HP), Ramsey, MN USA. Area under the peaks was used to quantify the concentration of ibuprofen in plasma. Stock standard solutions of ibuprofen in methanol (2.5mg/ml) and naproxen in water (100µg/ml) were used to prepare working standards for the calibration curves. Working standards were prepared by adding measured aliquots of these solutions to 200µl of human plasma (ibuprofen free) to yield a concentration of 1-80µg/ml. Stock standard solutions and working standards were freshly prepared on each assay day. The calibration curves were linear over the concentration range of 1-80 µg/ml with a regression coefficient (R^2)>0.99. The lower limit of quantitation (LOQ) was 0.082µg/ml. Retention times for naproxen and ibuprofen were approximately 4.5 and 7 minutes, respectively.

Pharmacokinetic Analysis

For each subject we calculated several pharmacokinetic parameters. Peak ibuprofen plasma concentration (C_{max}) and time to attain this concentration (T_{max}) were observed directly from each plasma concentration vs. time curve. The area under the plasma concentration vs. time curve from 0-12 hours (AUC_{0-12}) was calculated by applying the linear trapezoidal rule. AUC from 12 hours to infinity ($AUC_{12-\infty}$) was calculated as the last concentration measured (Cplast) divided by the elimination rate constant -K_{el}.

$K_{el,}$ was calculated by a logarithmic regression analysis of the terminal linear phase of the plasma concentration vs. time curve. The terminal half life, $t_{1/2}$, could then be calculated using the equation $t_{1/2} = \ln 2/K_{el}$. The total body clearance, CL/F, was calculated using the equation CL/F=Dose/AUC and total volume of distribution Vd/F, using the equation Vd/F= CL/K_{el}. Because in this study the absolute bioavailability of the drug (F) was not determined, the latter parameters are presented as depending on F.

Bioequivalence Testing

Another goal of this study was to assess whether ibuprofen suppository is bioequivalent to syrup. In order to do so, a comparative bioavailability study was performed where ibuprofen suppository (test formulation) was compared to ibuprofen syrup (reference formulation). According to the FDA criteria, two formulations are considered bioequivalent if the 90% coefficient interval (CI) of the relative mean, C_{max} and $AUC_{(0-\infty)}$ of the test to reference lies in the range of 0.8-1.25.[15,16]

Statistical Analysis

Data processing was carried out using the Microsoft Office Excel and SPSS (version 14) programs. All results are presented as mean±SD with the fitting 95% CI. To verify whether the pharmacokinetic measurements are normally distributed, we used the Kolmogorov-Smirnov test (data not shown). To compare the measurements after oral and rectal ibuprofen, we used two-tailed paired t-test. Differences were regarded as statistically significant if p-value was less than 0.05.

RESULTS

Ten healthy male volunteers were qualified to participate and completed the study successfully. Each received a single 400mg suppository and a single 400mg dose of syrup ibuprofen. No adverse effects were noted during or after the study. The study group had a mean age of 26.9±6 years, mean weight of 78±10.8 kg and mean height of 180±5.3 cm.

The mean concentration vs. time curves of ibuprofen after oral and rectal administration is presented together in Figure 1. Values of pharmacokinetic parameters measured after oral and rectal administration of ibuprofen are summarized in Table 1. The results are presented as mean values ± SD and 95% CI. Results of the bioequivalence test are summarized in Table 2.

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From the concentration vs. time curve (Fig.1) it can be seen that after oral administration, the absorption of ibuprofen was rapid and efficient. Therapeutic concentration (>10µg/ml) was detectable in the plasma of most subjects 20 minutes after dosing (39.5±22µg/ml) and remained above this concentration (11.4±4.28µg/ml) for 4 hours after administration. After rectal administration, ibuprofen reached therapeutic concentration (>10µg/ml) in plasma of most subjects 45 minutes after dosing (12.08±3.94µg/ml) and remained above this concentration for 4 hours (10.29±4.18µg/ml) (for most of them).

TABLE 1 Summary of mean (±SD) and 95% CI values of the pharmacokinetic parameters measured after oral and rectal administration of 400 mg ibuprofen, n=10 healthy volunteers.

Method of administration / **parameter**	**Rectal**	**Oral**	**Two-tailed paired t-test p-value**
C_{max} (µg/ml)	22.6± 5.6 (17.9,23.3)	48.4±15.9 (34.9 ,61.9)	p<0.05
T_{max} (min)	111±20.2 (93.8 ,128.2)	40±17.6 (25,55)	p<0.05
AUC $_{0}$- ∞ (µg*min/ml)	5216±1734 (3744 ,6688)	8254±3120 (5604 ,10903)	p<0.05
$t_{1/2}$ (min)	113±30.6 (87 ,139)	108±24.6 (87.5 ,129.5)	p>0.05
K_{el} (1/min)	0.0066±0.0016 (0.0053 ,0.0079)	0.0067±0.0013 (0.0056 ,0.0078)	p>0.05
VD/F (L)	13.2±3.8 (10,16.4)	8.7±4 (5.3 ,12.1)	p<0.05
CL/F (ml/min)	84.3±26.3 (61.95 ,106.7)	55.5±21.2 (37.5 ,73.5)	P<0.05

TABLE 2 Relative bioavailability of ibuprofen suppositories compared with ibuprofen syrup

Parameter	**Relative mean values (Rectal/Oral)**	**90% CI**
C_{max}	0.5	0.39-0.6
T_{max}	3.3	2.22-4.48
AUC $_{0}$- ∞	0.66	0.54-0.78

Statistical compression of the relative mean values of pharmacokinetic parameters following administration of 400 mg of ibuprofen – Rectal/Oral; n=10 healthy volunteers

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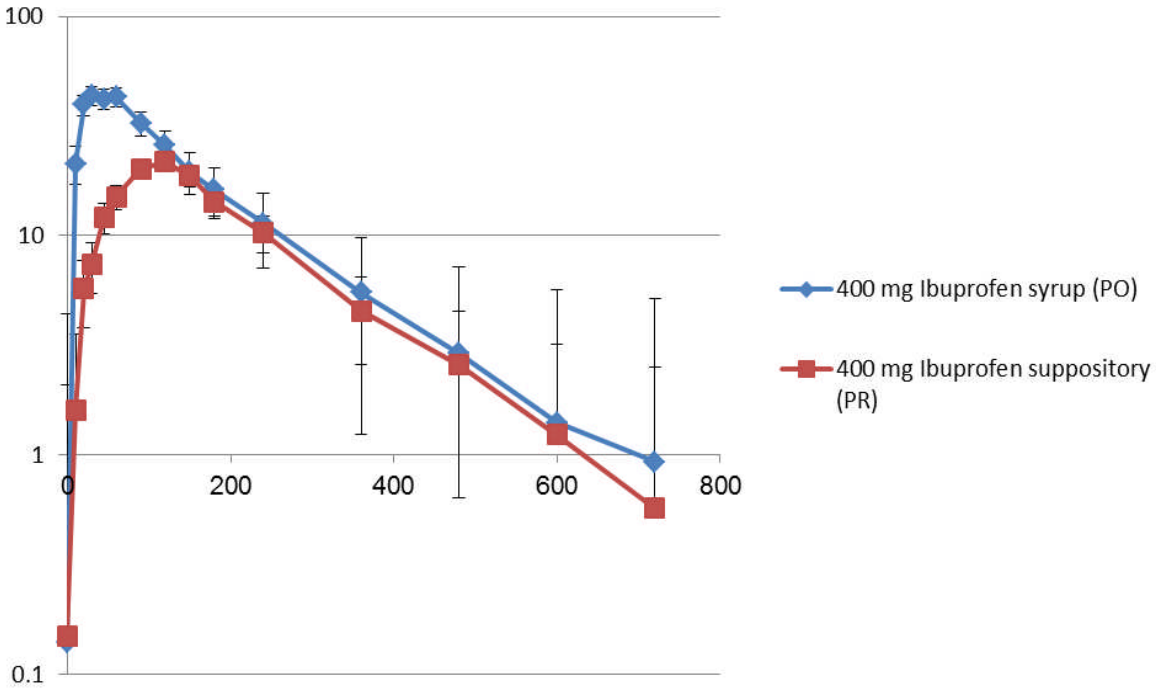
FIG. 1 Combined presentation of mean plasma concentration (log-scale) vs. time curves after oral and rectal administration of 400 mg ibuprofen*



*Error bars are the standard error of the mean

After oral administration, the mean peak plasma ibuprofen concentration (C_{max}) was 48.4±15.9µg/ml, significantly higher than the value measured after rectal administration - 22.6±5.6µg/ml (p=0<0.05). Mean time to reach peak plasma concentration (T_{max}) after oral administration was 40±17.6 minutes, significantly shorter than the corresponding value after rectal administration, which was 111±20.2 minutes (p<0.05).

Mean $AUC_{0-\infty}$ values were calculated as 8254±3120µg*min/ml and 5216±1734µg*min/ml after oral and rectal ibuprofen, respectively (p<0.02). Terminal half-lives, $t_{1/2}$ after oral and rectal administration were 108±24.6 and 113±30.6 minutes, respectively (p>0.05). The elimination rate constants (K_{el}) were also almost identical with values of 0.0067 ±0.00131 1/min and 0.0066 ±0.0016 1/min after oral and rectal ibuprofen, respectively (p>0.05).

After oral ibuprofen, mean CL/F was 55.5±21.2 ml/min, compared with 84.3±26.3 ml/min after rectal ibuprofen (p<0.05). Vd/F after oral and rectal administration were 8.7±4 and13.2±3.8, respectively (p<0.05) (Fig 1, Table 1).

DISCUSSION

Our results demonstrated that compared to oral ibuprofen, the administration of a single dose rectal ibuprofen resulted in lower C_{max},T_{max}, and $AUC_{0-\infty}$, Ibuprofen suppositories reached therapeutic concentration (>10 µg/ml) 45 minutes after administration, and remained above this concentration for 4 hours.

Ibuprofen is widely used in both adults and children. In light of the understanding that oral treatment with ibuprofen is occasionally not viable (for example with infants and small children who vomit, refuse oral treatment, are

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after surgery or in the intensive care unit), suppositories were developed and are being used routinely in several European countries. Ibuprofen pharmacokinetics after oral and intravenous administration was studied extensively in adults[1,17,18] and children.[19,20] However, information after rectal administration is scarce. To our knowledge, there are only two studies which presented the pharmacokinetics of ibuprofen after rectal administration in humans.[12,21] Kyllonen et al[12] investigated high dose ibuprofen and did not present the pharmacokinetics after oral administration. Eller et al[21] compared the pharmacokinetics of orally and rectally administered ibuprofen. They used solution or suspension as rectal forms and used extensive bowel cleansing including enemas before administrating the drug rectally. This approach may have theoretical benefits but it is not practical for clinical use.

Our objective was to study and compare the pharmacokinetic of a single therapeutic dose of rectal vs. oral ibuprofen in healthy adult volunteers. We found that after oral administration, ibuprofen was rapidly absorbed and detectable in plasma within 10 minutes after dosing. Relatively high peak plasma concentration was obtained shortly after administration. These results are in agreement with previous studies.[1,6] After rectal administration, ibuprofen was also rapidly detectable in plasma, though in significantly lower concentration. Peak plasma concentration was significantly lower and more slowly obtained, compared to oral administration. The extent of ibuprofen absorbed through the rectal mucosa was also significantly lower compared to oral ibuprofen, with relative bioavailability of 63%.

The lower C_{max} T_{max} and AUC of ibuprofen suppositories compared with oral solution may indicate that dose adjustments are needed when ibuprofen suppositories are used. The inferior absorption profile (rate and extent) of rectal ibuprofen can stem from several factors such as small surface of the rectal mucosa, scarcity of liquids there, presence of stool in the rectum, pH of the rectal contents and factors related to the suppositories formulation[22].

Contrary to our findings, in a rabbit model, Hermann et al[23] showed that high dose rectal ibuprofen was completely absorbed (F=100%). Their suppositories contained lysine or free acid ibuprofen and both hydrophilic and lipophilc bases were used. Kaka et al[24] showed that after rectal administration of four different formulations of ibuprofen suppositories (hydrophilic and lipophilic) to rats, the extent of absorption was lower compared to oral ibuprofen while the rate of absorption was similar. Kyllonen et al[12] described the pharmacokinetics of rectal ibuprofen in humans. After administrating high dose (20 mg/kg) ibuprofen suppositories (Burana®, Orion Pharma, Finland), the drug reached plasmatic therapeutic concentration, 40 minutes after dosing and remained above this concentration for 8 hours, significantly longer compared to our results (4 hours). C_{max} and $AUC_{0-\infty}$ values were also significantly higher than the values measured in our study while $t_{1/2}$ was similar. The differences found between both studies are expected since there is a linear relationship between drug concentration and dose. Therefore, if we normalize the results according to dose then there is a strong similarity between both study results. These studies along with our own indicate that although the oral route seems to be the superior method for ibuprofen administration, rectal administration is also viable and may offer a good alternative when oral treatment is not possible.

The study was conducted on adult healthy volunteers yet, we believe the results are applicable for children. We choose ibuprofen syrup as the oral preparation since young children do not take medications as tablets and there are no significant differences between adults and children in C_{max}, AUC and T1/2 of ibuprofen suppositories[12]. In our study, values of Clearance and Volume of Distribution are presented with a dependency on F, since we were not able to study the pharmacokinetics after intravenous administration and therefore could not determine the absolute bioavailability (F) of oral or rectal ibuprofen.

The values of CL/F and Vd/F after oral administration were similar to those previously reported[1,6]. CL/F and Vd/F after oral and rectal administration were significantly different. These results are in accordance with our expectations since AUC, which is used to calculate CL and Vd, was significantly different. If we could calculate F, we would not expect to find a significant

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difference between CL and Vd after oral and rectal administration, as they are independent of dose or formulation. As expected, we did not find any significant difference in terminal half life, $t_{1/2,}$ and K_{el} as they are as well independent of formulation or route of administration.

The 90% CI for the relative mean values of all parameters (C_{max}, T_{max} and $AUC_{0-\infty}$) are outside the required bioequivalence range (Table 2). Therefore, 400 mg ibuprofen suppository (at the formulation tested in our study) is not bioequivalent to the commercially available ibuprofen syrup (Nurofen® for children) when given at the same dosage. The question remains whether the different pharmacokinetic profiles will have clinical consequences?

Ibuprofen has both central and peripheral effects.[25-27] Therefore, the interpretation of the clinical response to ibuprofen is complex. The effect of ibuprofen may not be directly related to blood concentration. Concentration in the effect compartment (CSF) probably better correlates with the therapeutic effects yet, it is not feasible to routinely conduct pharmacokinetic studies on the CSF. Some studies found that antipyretic activity of ibuprofen correlates with plasmatic concentration greater than10µg/ml.[28-30] Other studies have shown a clear linear relationship between ibuprofen plasma concentration and pain relief beginning at 10µg/ml, with maximal effect at concentration greater than 30µg/ml.[31,32] In our study, 45 minutes after suppository administration most subjects had ibuprofen concentration exceeding 10µg/ml for 4 hours after dosing.

Acetaminophen, similarly to ibuprofen, is used for fever and pain management and is also marketed in suppositories formulation. Most studies comparing oral and rectal pharmacokinetics of acetaminophen showed inferior absorption profile after rectal administration, where in some cases rectal administration resulted in a sub therapeutic concentration.

Nevertheless, Goldstein et al[33] found no clinical implications of the observed pharmacokinetic differences between oral and rectal acetaminophen on fever deduction. Therefore, the clinical implications of the different pharmacokinetic profile of ibuprofen suppositories and syrup should be further evaluated.

In conclusion, absorption of ibuprofen syrup is better compared with suppositories. Ibuprofen suppositories can contribute to the management of fever and pain in infants, children and adults, mainly when the oral route is not available.

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