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Stereoselective pharmacokinetics of ibuprofen and its lysinate from suppositories in rabbits

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Abstract

Studies were performed on the effect of ibuprofen racemate ionisation extent on the pharmacokinetics of its enantiomers following administration in suppositories to rabbits. The suppositories, containing 146.3 mg ibuprofen in acidic form (IBP) or 250 mg ibuprofen lysinate (IBPL), equivalent to the above IBP dose, were prepared using lipophilic Witepsol H-15 as a base and administered to rabbits in a crossover design. Compared with IBP, administration of IBPL was followed by faster absorption and elimination of *R* and *S* enantiomers. However, significant differences at $\alpha = 0.05$ were observed only at the stage of elimination. AUC was markedly higher following administration of suppositories containing IBP than following suppositories with IBPL and this pertained to both *R* and *S* enantiomers. Evident inversion of *R* into *S* form was noted 30 min following IBPL administration and 1 h after IBP administration. Ionisation extent only insignificantly affected the scope of chiral inversion of ibuprofen *R* into *S* form ($AUC_{S\text{-IBP}}/AUC_{R\text{-IBP}} = 1.66$, $AUC_{S\text{-IBPL}}/AUC_{R\text{-IBPL}} = 1.57$). No presystemic inversion of *R* into *S* was observed in rabbits following administration of IBP or IBPL in suppositories. IBP enantiomers were isolated from 0.5 ml serum using solid phase extraction in C_{18} columns and were quantified by HPLC using the chiral Whelk O1 column and UV detector ($\lambda = 264$ nm). © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Ibuprofen; Ibuprofen lysinate; Enantiomers; Suppositories; Chiral inversion; Bioavailability; Pharmacokinetics; Chiral HPLC

1. Introduction

2-(4-Isobutylphenyl)-propionic acid (IBP) is a nonsteroidal antiinflammatory drug (NSAID). The racemic compound is currently one of the most widely used antiinflammatory analgesics (Geisslinger et al., 1990). The IBP propionic acid side chain possesses an asymmetric α-carbon and therefore occurs as (+) and (−)-enantiomer. The (+)-enantiomer is believed to have the *S* configuration. The antiinflammatory activity, as determined by the in vitro inhibition of prostaglandin synthesis, resides almost exclusively in the *S*(+)-enantiomer (Adams et al., 1976). In

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vivo inactive $R(-)$-enantiomer (distomer) IBP undergoes a unidirectional bioinversion to the active $S(+)$-enantiomer (eutomer) via the formation of the acyl CoA tioester of 2-arylopropionate. The rate and extent of the inversion varies from species to species. Furthermore, it has been claimed that the pharmacokinetic behaviour of the two IBP enantiomers in human is different (Hutt and Caldwell, 1983; Fournel and Caldwell, 1986; Caldwell et al., 1988). The processes of absorption, distribution, tissue binding, metabolism and extraction of chiral drugs may all exhibit stereoselective differences (Hutt and Caldwell, 1983; Ariëns, 1986; Jamali et al., 1989; Tucker, 1990). Thus, it becomes apparent that the interpretation of the pharmacokinetics of IBP and other chiral profens, depends on the stereoselectivity in disposition kinetics. It is therefore necessary to measure the IBP enantiomers instead of the total IBP concentration (Ariëns, 1986; Jamali, 1988). Differences exist in defining sites of chiral R-enantiomer to $S(+)$ antipode inversion, i.e. whether it is systemic or presystemic. Jamali et al. (1988, 1992), Mehvar and Jamali (1988) have been suggesting that chiral presystemic inversion in the gut takes place, but they have not excluded the possibility of systemic IBP inversion. Furthermore greater extent of chiral inversion of IBP is associated with an extended absorption time. A significant inversion of 2-phenylpropionic acid was also found in the rat liver and kidney slices (Nakamura and Yamaguchi, 1987). Inversion of $R(-)$-IBP in the rat isolated perfused liver (Cox et al., 1985) and hepatocytes (Müller et al., 1990) was observed. Jeffrey et al., (1991) concluded that the inversion of $R(-)$-IBP to the $S(+)$ antipode occurs in the liver but it does not occur on either mucosal or serosal sides of the small rat intestine. No presystemic chiral inversion of IBP enantiomers in human is proposed (Hall et al., 1993). Until now pharmacokinetics of IBP enantiomers has been investigated mainly after oral administration (Geisslinger et al. 1990, 1993; Hall et al., 1993; Li et al., 1993; Jamali et al., 1988, 1992; Fornasini et al., 1997), rarely after intravenous administration (Ahn et al., 1991; Hall et al., 1993), and very rarely via rectal administration (Eller et al., 1989; Hermann et al., 1993; Hermann, 1995). Moreover, a disagreement exists in the literature as to the elimination half-lives of IBP enantiomers. Some studies reported a parallel decline of the plasma concentrations of enantiomers (Jamali et al., 1988; Geisslinger et al., 1990, 1993; Rudy et al., 1991; Hall et al., 1993, whereas others observed more rapid elimination of the R enantiomer (Lee et al., 1985; Cox et al., 1988; Avgerinos and Hutt, 1990).

The study aimed to determine stereoselective pharmacokinetics of IBP enantiomers from suppositories containing the acidic form IBP and its salt, IBPL, to define differences in the rate of R and S enantiomers elimination after application of a high IBP dose (47.2 mg/kg) following rectal administration, which has been used only infrequently for studies of the stereoselective pharmacokinetics of IBP enantiomers.

2. Materials and methods

2.1. Materials

Analytical standards of racemic IBP (Polfa, Pabianice, Poland), IBPL (Merckle, Blaubeuren, Germany), $R(-)$- and $S(+)$-IBP enantiomers (Ethyl Corporation, Orangeburg, SC) were obtained free of charge. Optical purity of S-$(+)$- and R-$(-)$-IBP were 99.6 and 100.0%, respectively. Racemic flurbiprofen (FB) (internal standard m.p. 110–113°C, Moffat et al., 1986: $\sim$110°C) was prepared from commercial suppositories Froben (Boots Company, UK) and further purified by recrystallisation from petrolum ether (P.O.Ch., Gliwice, Poland). Witepsol H-15 (Dynamit Nobel, Witten, Germany) was used as a suppository base. Catheters (Venocath 18) were gift from Abbot Laboratories, North Chicago, IL) and were used for drawing blood from the rabbits marginal ear veins. Methanol, n-hexane, isopropanol (Merck, Darmstadt, Germany) were HPLC grade. Glacial acetic acid (J.T. Baker, Deventer, Holland), 85% phosphoric acid (P.O.Ch., Gliwice, Poland) were of reagent grade. House tripled distilled water from silica glass equipment was always used.

2.2. Quantitation of ibuprofen enantiomers in serum

Details of the chiral HPLC procedure used to determine IBP enantiomer concentrations in serum have been published elsewhere (Główka, 1998). The method involved solid phase extraction of the IBP and FB enantiomers from 0.2 ml serum, by means of octadecyl C_{18} phase chemically bound to silica. First, columns were activated using 2×1 ml methanol and 2×1 ml triple distilled water. The compounds were washed out by methanol 2×0.5 ml under low vacuum using a water pump. Methanol was evaporated to dryness in gentle nitrogen stream. The residue was reconstituted in 150 μl of the mobile phase [hexan–isopropanol–glacial acetic acid (980:12.5:0.5 V/V/V)]; 20 μl were injected onto a chiral column and detected at 264 nm. Peaks area ratio $R(-)$- or $S(+)$-IBP to racemic FB were plotted versus either $R(-)$-or $S(+)-$IBP concentration and resulting calibration curves (range: 2.5–125.0 μg ml^{-1} of each enantiomers) were used to calculate $R(-)$-or $S(+)$-IBP concentration. Correlation coefficients (r) for all calibration curves are in the range 0.994–0.998. Inter-assay coefficients of variation were in the range 8.9–4.8 and 8.7–3.8% at 2.5–125.0 μg ml^{-1} of $R(-)$- and $S(+)$-IBP, respectively ($n = 14$ for both enantiomers concentrations). Chiral resolution of IBP enantiomers was achieved by means of the (3*S*,4*S*)-4-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenantrene chiral stationary phase chemically bound to silica gel, according to the modern Pirkle's approach (Whelk O1, 250×4.6 mm, $dp = 5$ μm, Merck, Darmstadt, Germany).

2.3. Preparation of suppositories

Suppositories were prepared by the fusion process with a metallic suppository mould. Ingredients were homogenised with Witepsol H-15, melted at 45°C, poured into a mould at 30°C and then allowed to solidify at room temperature (20–25°C). Each 2 g suppository contained IBP (0.1463 g) or IBPL (0.250 g), butylhydroxyanisole (0.0002 g), butylhydroxytoluene (0.0002 g), Aerosil 200 (0.025 g), and up to 2.0 g of the Witepsol H-15 suppository base.

2.4. Rabbit studies

Five male Albinos New Zealand rabbits, weighing 3.0 ± 0.2 kg were fasted for 20 h before rectal administration; water was given ad lib. The animals were secured in a crouching posture, and a suppository containing 146.3 mg of IBP calculated as free acid was inserted into the rectum. IBP suppositories were administered in a crossover design. A 'wash out' period of at least 2 weeks prior to the administration of each product was maintained. The anus was barricaded with surgical adhesive to prevent leakage of the melted suppository. After drug administration blood samples (2 ml) were withdrawn from the marginal ear vein at 5, 10, 15, 20 min and at 0.5, 0.75, 1.0, 1.5, 2.0, 2.5 and 3.0 h. Specimens were centrifuged immediately at $1360 \times g$ for 15 min. Serum was transferred into stoppered polyethylene tubes and stored at -20°C until analysed. The investigations were approved by Human Investigations Ethical Committee at the University of Medical Sciences in Poznań.

2.5. Pharmacokinetic data analysis

The serum IBP enantiomer concentrations (C) following administration of suppositories to rabbits were well characterised by the difference in two exponentials (Fig. 1):

$$C = B\,e^{-\lambda_z t} - A\,e^{-\lambda_1 t}$$

where A and B are the corresponding zero-time intercepts, λ_1 and λ_z are the apparent first-order fast and slow disposition rate constants and t is the time. All pharmacokinetic parameters were calculated using an open one-compartment body model. The TOPFIT 2.0 software package (Gustaw Fischer, Stuttgart, 1993) was used for calculation of pharmacokinetic parameters. The elimination rate constant (λ_z) was estimated from the linear terminal segment (four last concentrations) of the log serum drug concentration–time data. The elimination half life ($t_{0.5}$) was calculated from $\ln 2/\lambda_z$. The area under the curve ($AUC_{0\to\infty}$) were estimated by the trapezoidol rule with extrapolation to infinity using C_{last}/λ_z. T_{max} was calculated from the enantiomer concentration–time curve

and C_{max} was read at T_{max}. Serum drug clearance (Cl) was calculated by dividing the dose of enantiomer by its AUC assuming complete bioavailability. Mean residence time (MRT) was calculated from the area under the first moment curve (AUMC) divided by the AUC. MAT was calculated from equation $MAT = 1/k_a$, where k_a was estimated from the slopes of linear semiloga-

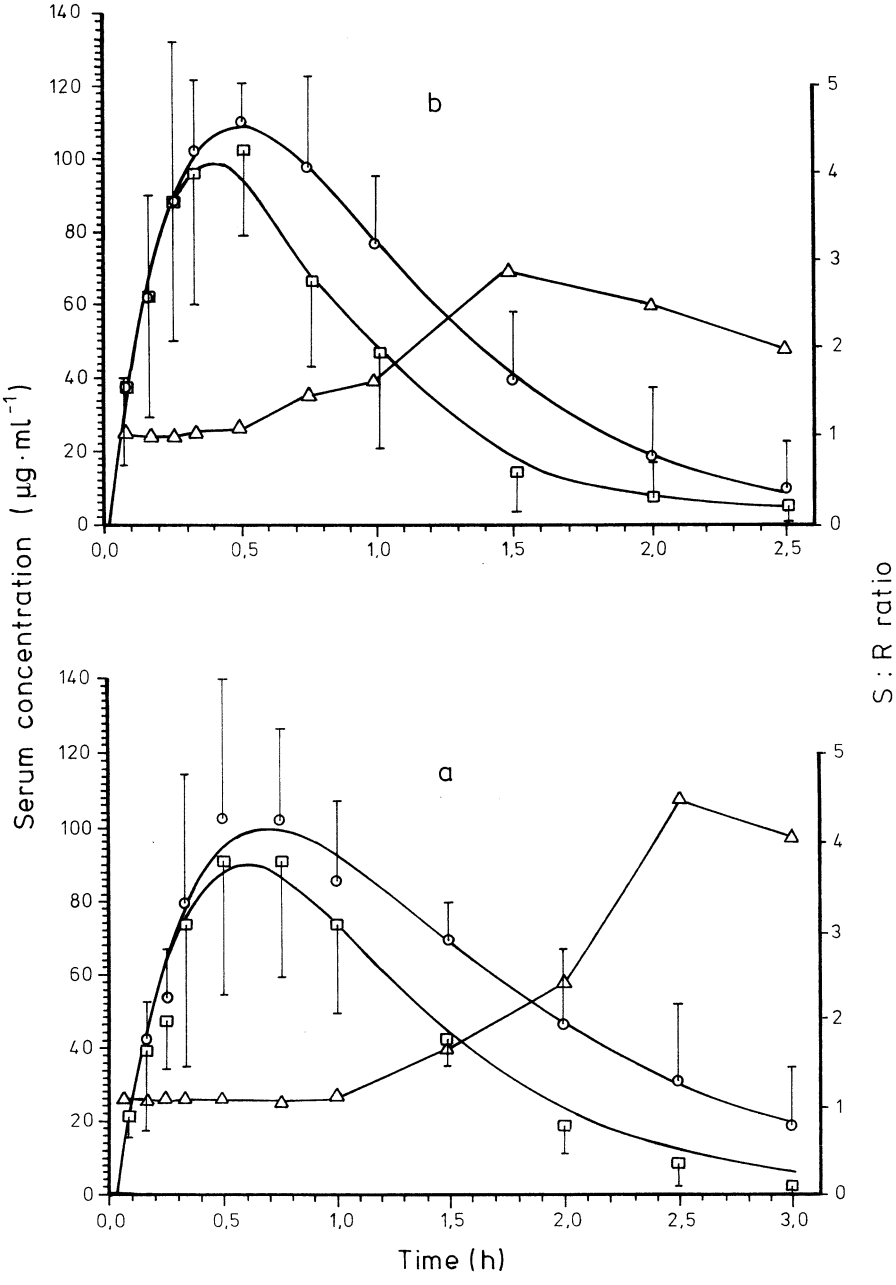

Fig. 1. Mean serum S (○)- and R (□)- ibuprofen concentrations with S.D. and corresponding S:R concentration ratios (△) vs. time after the crossover administration of racemic ibuprofen acid (a) and racemic ibuprofen lysinate (b) in supositories to rabbits.

rithmic plots of the fraction of drug unabsorbed versus time (Wagner–Nelson procedure).

2.6. Statistical analysis

Pharmacokinetic parameters of the enantiomers were analysed using ANOVA test (EXCEL 4.0 program). Differences between means were considered statistically significant if the P value was less than or equal to 0.05. The standard deviation (S.D.) was used to express the tendency of the data.

3. Results and discussion

Changes in IBP enantiomer levels in rabbit serum following administration of suppositories in its acidic form (IBP) are presented in Fig. 1a while those following administration of ibuprofen lysinate (IBPL) are shown in Fig. 1b. The suppositories were prepared in a lipophilic base (Witepsol H-15). Witepsol represents a suppository base, which does not spread out too far to the sigmoideum but remains in the rectum. The base determines the amount of active substance, which will directly penetrate to the circulation (from the rectum) or to the liver (from the large intestine). Stereoselective inversion of $R(-)$- into $S(+)$-forms was observed upon analysis of $R(-)$- and $S(+)$-IBP enantiomer concentrations following administration of either IBP or IBPL racemates. Significantly higher levels of $S(+)$-enantiomer were noted, as compared to levels of $R(-)$-enantiomer already 30 min after administration of IBPL suppositories, reaching maximum S:R value at 1.5 h. The above ratio later decreased. On the other hand, the inversion of $R(-)$ into $S(+)$ was clearly delayed for the acidic form of IBP, and started 1 h after administration, reaching maximum at 2.5 h. The faster absorption of IBPL racemate as compared with IBP racemate was noted also in the studies on bioavailability of IBP and IBPL administered in suppositories, where absolute bioavailability reached 100% (Hermann et al., 1993). The faster absorption of IBPL than that of IBP may prove advantageous to clinical practice since pain relief belongs to urgent goals under clinical conditions. According to current thinking, fast absorption and early peak plasma concentration are of clinical value in treating painful inflammatory conditions (Geisslinger et al., 1990). The results indicate that, compared to IBP, IBPL is absorbed faster and reaches higher C_{max} levels. Moreover, administration of IBPL is accompanied by milder side effects from gastrointestinal tract and, therefore, seems more suitable in treatment of painful inflammatory conditions. After administration of either IBP or IBPL suppositories to rabbits, the $R(-)$ to $S(+)$ inversion could not be clearly observed until T_{max} was passed. T_{max} values amounted to 0.49 ± 0.13 and 0.39 ± 0.09 h for $R(-)$ and $S(+)$ forms of IBPL, respectively, and were markedly shorter than those for the acidic IBP form (0.60 ± 0.05 and 0.69 ± 0.07 h, respectively). Within the studied time period of 0–2.5 (3.0) h, the S:R ratio was clearly higher for IBP than for IBPL and amounted to the maximum of 4.40 at 2.5 h and to 2.80 at 1.5 h (Fig. 1a,b) The results obtained demonstrate a significant effect of IBP lysinate or its acidic form solubility on the rates of their absorption and on S:R inversion. Compared with the acidic form, the lysinate salt showed a much higher solubility in water (Neubert et al., 1990), thus became absorbed much faster. IBPL was also more rapidly eliminated and this pertained to both enantiomers (Table 1). The average mean residence time (MRT) of the drug in rabbit body was also longer for IBP [$MRT(S) = 1.70 \pm 0.41$, $MRT(R) = 1.14 \pm 0.10$ h] than for IBPL [$MRT(S) = 1.01 \pm 0.20$, $MRT(R) = 0.76 \pm 0.16$ h] and the difference was significant (Table 1). Thus, the slower absorption and longer residence of IBP in the body significantly affected the extent of chiral inversion of R to S enantiomers. This corroborated the observation of Jamali (1988) that the slower the rate of absorption the greater seems to be the extent of inversion. Following administration of IBPL and IBP suppositories to rabbits, no progressive increase was noted in S:R ratio, which took place in humans starting at the moment of oral administration of tablets with IBP racemate (Jamali et al., 1988). The latter might indicate that the chiral R to S inversion of IBP starts already presystemically in GI-tract. The

process of drug absorption from the rectum involves diffusion through the rectal mucosa. The rectum possesses a good blood supply, no villi, a relatively low surface area, little mucus, and demonstrates a restricted buffering capacity. Moreover, it seems that rectum of rabbits like the rat small intestine (Jeffrey et al., 1991) contains insufficient enzymatic capability to invert a large dose of racemic IBP (47.2 mg/kg body weight). Results obtained in this study on rabbits clearly show a very rapid absorption of IBP and IBPL in particular, administered in suppositories, despite the relatively high doses of the drugs and indicate that the chiral *R* to *S* inversion involves mainly a systemic inversion. This conclusion seems to be consistent with the finding of Jamali et al. (1992) that in cases of rapid absorption IBP is very likely to originate from systemic inversion.

In evaluation of other pharmacokinetic parameters of *R*(−)- and *S*(+)-IBP enantiomers, the greatest differences are observed in rates of elimination. Enantiomers of the acidic IBP form are eliminated at a slower rate [$\lambda_z(R) = 1.85 \pm 0.09\ h^{-1}$, $\lambda_z(S) = 1.00 \pm 0.20\ h^{-1}$] than enantiomers of IBPL [$\lambda_z(R) = 2.85 \pm 0.21\ h^{-1}$, $\lambda_z(S) = 1.89 \pm 0.20\ h^{-1}$]. The differences can also be noted in the clearance (Table 1). The differences can tentatively be explained by saturation of serum protein bonds following administration of the high dose of the drug (47.2 mg/kg body weight of the rabbit). Administration of IBPL has been followed by higher C_{max} levels reached in a shorter time than those observed after administration of IBP. This might have been associated with a larger fraction of the free drug and, thus, with its faster elimination. IBP clearance is known to

Table 1
Mean pharmacokinetic serum parameters ($\bar{X} \pm$ S.D.) of ibuprofen enantiomers following rectal administration of suppositories in rabbits[a]

Parameter	IBP	IBPL	ANOVA test ($\alpha = 0.05$)
Dose (mg)			
As lysinate	–	250	
As free acid	146.3	146.3	
Surfactant	Witepsol H-15	Witepsol H-15	
T_{max} (h)	*R*(−)0.60 ± 0.05	0.39 ± 0.09	$P < 0.002$
	S(+)0.69 ± 0.07	0.49 ± 0.13	$P < 0.016$
C_{max} (μg ml^{-1})	*R*(−)89.6 ± 32.1	101.1 ± 28.8	NS
	S(+)99.7 ± 27.3	111.0 ± 19.7	NS
AUC (μg ml^{-1} per h)	*R*(−)129.3 ± 33.4	96.7 ± 34.4	NS
	S(+)212.4 ± 69.4	145.0 ± 41.2	NS
$t_{0.5}$ (h)	*R*(−)0.37 ± 0.04	0.27 ± 0.06	$P < 0.02$
	S(+)0.82 ± 0.38	0.38 ± 0.10	$P < 0.03$
MRT (h)	*R*(−)1.14 ± 0.10	0.76 ± 0.16	$P < 0.002$
	S(+)1.70 ± 0.41	1.01 ± 0.20	$P < 0.009$
MAT (h)	*R*(−)0.40 ± 0.15	0.22 ± 0.11	$P < 0.003$
	S(+)0.38 ± 0.15	0.33 ± 0.10	NS
Cl (ml/min)	*R*(−)10.14 ± 1.00	14.6 ± 2.73	NS
	S(+)8.25 ± 5.60	9.18 ± 2.60	NS
AUC_S: AUC_R	1.66 ± 0.22	1.57 ± 0.16	NS

[a] MRT, mean residence time; MAT, mean absorption time; $t_{0.5}$, elimination half-time calculated from terminal slope of a semilogarithmic concentration — time curve; Cl, total body clearance of ibuprofen from the serum.

be dependent upon the extent of its binding to serum proteins (Lockwood et al., 1983). Follow-ing administration of IBP, the mean AUC amounted to 129.3 ± 33.4 for the *R* form and 212.4 ± 69.4 μg ml^{-1} h for the *S* form. Administration of IBPL resulted in lower values of $AUC(R) = 96.7 \pm 34.4$ and of $AUC(S) = 145.0 \pm 41.2$ μg ml^{-1} h (Fig. 2). It should be emphasised that after administration of either IBP or IBPL the enantiomer *R* undergoes faster elimination than enantiomer *S*. A more rapid elimination of the *R* enantiomer was observed also in humans (Lee et al., 1985; Cox et al., 1988; Avgerinos and Hutt, 1990). In some studies, parallel decline in serum IBP enantiomer levels was found (Jamali et al., 1988; Geisslinger et al., 1990, Rudy et al., 1991). Differences in enantiomer elimination rates were observed also following administration of low doses of IBP (50–200 mg). The *R* enantiomer was found to be eliminated more rapidly, but the difference became insignificant with the increasing dose of the drug or even the *S* enantiomer became eliminated at a more rapid rate (Jamali et al., 1992). The situation might have reflected an inhibition of chiral inversion in presence of higher amounts of the *S*(+) enantiomer (Ahn et al., 1991). Such a situation was not noted after rectal administration of a high IBP dose to rabbits (47.2 mg/kg), which in each case was followed by faster turnover of *R* enantiomer as compared to *S* enantiomer. The observation might be explained by the more rapid drug metabolism in rabbits than in humans.

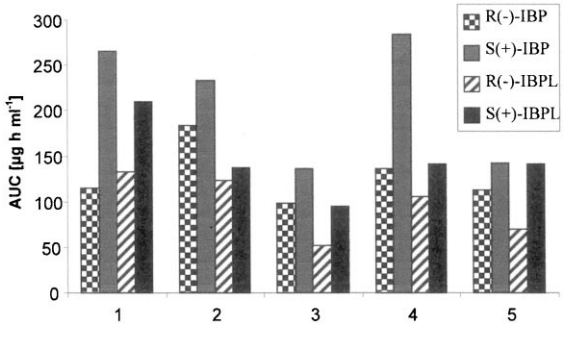

Fig. 2. Bioavailability (AUC) of *R*-ibuprofen and *S*-ibuprofen for individuals five rabbits after crossover administration of 146.3 mg racemic ibuprofen acid and 250 mg racemic ibuprofen lysinate in suppositories.

4. Conclusions

The extent of IBP ionisation (its lysinate or acidic form) has failed to significantly affect the rate of its chiral inversion, as reflected by the ratios of $AUC_S/AUC_{R\text{-IBP}} = 1.66$ and $AUC_S/AUC_{R\text{-IBPL}} = 1.57$. The lysinate salt of IBP was much more rapidly absorbed from the rabbit rectum as compared to the acidic form of IBP and has been associated with respectively earlier onset of chiral $R(-)$ to $S(+)$ inversion. A progressive increase in the form $R(-)$ to $S(+)$ inversion after rapid absorption has not been observed directly after administration of IBP acidic form or IBPL racemate suppositories to rabbits until T_{max} values have been exceeded. Therefore, the chiral $R(-)$ to $S(+)$ inversion of IBP may be regarded to represent a systemic inversion. Despite application of a high dose of IBP (47.2 mg/kg), in either lysinate or acidic form, its $R(-)$ enantiomer has been eliminated faster than $S(+)$ enantiomer and the difference has proven to be significant at $\alpha = 0.05$.

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