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# The Site of Inversion of *R*(−)-Ibuprofen: Studies Using Rat In-situ Isolated Perfused Intestine/liver Preparations

PHILLIP JEFFREY*†, GEOFFREY T. TUCKER*, ALAN BYE†, H. KIM CREWE* AND PAUL A. WRIGHT†

*Department of Medicine and Pharmacology, University of Sheffield, The Royal Hallamshire Hospital, Sheffield S10 2JF and †Upjohn Laboratories-UK, Upjohn Ltd, Fleming Way, Crawley RH10 2NJ, UK*

**Abstract**—The site of metabolic inversion of *R*(−)-ibuprofen to the pharmacologically active *S*(+)-enantiomer has been investigated using an array of in-situ rat perfused organ preparations allowing vascular perfusion (55–60 min) of the separate or combined intestine and liver. After addition of *R*(−)-ibuprofen (20 mg $kg^{-1}$ body weight) to the closed (static) lumen of isolated 25 cm lengths of duodenum, jejunum or ileum, and single-pass vascular perfusion, both isomers were measured in the lumen and in vascular perfusate plasma (mean plasma AUC values (±s.d., μg $mL^{-1}$ min, n = 5) *R*(−)-ibuprofen: 1669 ± 115 (duodenum), 1687 ± 203 (jejunum), 2061 ± 188 (ileum); *S*(+)-ibuprofen: 23 ± 6 (duodenum), 14 ± 5 (jejunum), 26 ± 1 (ileum)). Addition of the same dose of *S*(+)-ibuprofen to the jejunum (n = 5) resulted in AUC values of 1864 ± 238 for *S*(+)-ibuprofen and 6 ± 3 for *R*(−)-ibuprofen. After addition of *R*(−)-ibuprofen (30 μg $mL^{-1}$) to the recirculating vascular perfusate (100 mL) of the entire small intestine (n = 6) AUC values were 1647 ± 34 for *R*(−)-ibuprofen and 13 ± 3 for *S*(+)-ibuprofen. The same dose of *R*(−)-ibuprofen to combined intestine/liver (n = 6) and liver only preparations (n = 6) gave AUC values of 1011 ± 25 and 1021 ± 49 for *R*(−)-ibuprofen and 220 ± 28 and 238 ± 22 for *S*(+)-ibuprofen, respectively. In all experiments, except those involving perfusion of the combined intestine/liver and the liver, the concentrations of the isomer opposite to that administered could be accounted for solely by the level of enantiomeric impurity (1·3% for *R*(−)-ibuprofen and 0·6% for *S*(+)-ibuprofen). We conclude that inversion of *R*(−)-ibuprofen to the *S*(+) antipode occurs in the liver but does not occur on either mucosal or serosal sides of the small intestine of the rat.

In common with other 2-arylpropionic acid derivatives with anti-inflammatory activity, ibuprofen is used as a racemate although most of its therapeutic action resides in the *S*(+)-enantiomer. Furthermore, in-vivo there is a significant metabolic inversion of the *R*(−)-enantiomer, mediated by stereospecific formation of a thio-ester with coenzyme A (Hutt & Caldwell 1983). The site of this unidirectional inversion has been a subject of debate since Mehvar & Jamali (1988) claimed, on the basis of a pharmacokinetic model, that inversion occurs predominantly and pre-systemically in the gut. In turn, this was suggested to account for the observation that prolonged absorption of ibuprofen from sustained-release dosage forms is associated with a greater extent of inversion. The hypothesis of an intestinal inversion site is supported by data from Meyer et al (1988) showing that *R*(−)-ibuprofen was not metabolized to the *S*(+)-enantiomer when incubated with rat or guinea-pig liver homogenates, and by the observation that *R*(−)-benoxoprofen underwent inversion in an everted rat gut preparation but not in rat liver homogenate (Simmonds et al 1980). However, against an exclusive role of the intestine are the findings of significant inversion of 2-phenylpropionic acid by rat liver and kidney slices (Nakamura & Yamaguchi 1987), and an inversion of *R*(−)-ibuprofen in the rat isolated perfused liver (Cox et al 1985) and in rat isolated hepatocytes (Müller et al 1990; Sanins et al 1990). The suggestion that the observation of the same ratio of the area under the plasma concentration-time curve of the isomers after intravenous injection and oral adminstration of ibuprofen to man precludes a significant pre-systemic inversion in the gut (Cox 1988) is weakened if it is argued that the rapid drug absorption from the conventional tablet used for administration occurred proximal to the site of intestinal inversion. Thus, the role of the intestine in the inversion of ibuprofen remains obscure. To obtain direct experimental data on this issue we have investigated the metabolism of the enantiomers of ibuprofen in an array of in-situ rat perfused intestine/liver preparations.

Correspondence: P. Jeffrey, Upjohn Laboratories-UK, Upjohn Ltd, Fleming Way, Crawley RH10 2NJ, UK.

## Materials and Methods

### *Chemicals*

*R*(−)- and *S*(+)-Ibuprofen were obtained from the Upjohn Company (Kalamazoo, USA). Their optical purities were 98·67 ± 0·07 and 99·44 ± 0·05% s.d., respectively, measured using the HPLC assay described below. *S*-(−)-1-(1-Naphthyl)ethylamine, 1-hydroxybenzotriazole, 4-chlorophenoxyacetic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were purchased from Aldrich Chemical Company Ltd (Gillingham, UK). Solvents for HPLC were purchased from Fisons Scientific Apparatus (Loughborough, UK). All reagents and chemicals were of analytical grade or better.

### *Animals*

Male Sprague-Dawley rats, 180–200 g, were obtained from the University of Sheffield colony (for jejunal, entire small intesine, small intestine/liver and liver perfusions) and from Charles River Ltd (Crl: CD(SD)BR Sprague-Dawley, Manston, UK) (for duodenal and ileal perfusions). The rats were maintained on standard small laboratory animal diets (CRM, RHM Agricultural, Christopher Hill Group, Poole, UK at Sheffield and SDS PCD No. 1, Wm. Lillico and Sons, Betchworth, UK at Crawley), and allowed free access to food and water.

*Organ Perfusions*

Four configurations were used (Fig. 1): A. Single pass vascular perfusion of a closed (static) 25 cm length of duodenum/jejunum (since the rat duodenum is approximately 10 cm long the remainder of the loop was jejunum), jejunum or ileum. The dose was introduced into the gut lumen in sufficient volume to create a lumen distension pressure preventing gut hypermotility. Serial samples of the vascular perfusate were collected. B. Recirculating vascular perfusion of the closed (static) entire small intestine. The dose was added to the vascular perfusate reservoir and serial samples were removed and replaced with blank vascular perfusate. C. Recirculating vascular perfusion of the closed (static) entire small intestine in series with the liver. The dose was added to the vascular perfusate reservoir and serial samples were removed and replaced with blank vascular perfusate. D. Recirculating vascular perfusion of the liver. The dose was added to the vascular perfusate reservoir and serial samples were removed and replaced with blank vascular perfusate.

Configuration A was used to assess any site-specific pre-absorptive inversion of ibuprofen in specific areas of the small intestine. Configuration B was used to assess any post-absorptive (systemic) inversion in the small intestine. Configurations C and D were used to assess the contributions of the small intestine and liver to the post-absorptive inversion of ibuprofen. Rats were anaesthetized with an i.p. injection of fentanyl-fluanisone (Hypnorm: Janssen Pharmaceutical Ltd, Wantage, UK) and midazolam (Hypnovel: Roche Products Ltd, Welwyn Garden City, UK) as described by Flecknell & Mitchell (1984).

*Perfused duodenum, jejunum and ileum (configuration A)*

The rat in-situ isolated perfused jejunum preparation described and validated by Castle et al (1985) was adapted for perfusion of the three segments of the small intestine. All experimental details were exactly as described by Castle et al (1985), with appropriate ligations for each segment of intestine. For duodenal perfusions the inflow lumen cannula was placed as close to the pyloric sphincter as possible. The semisynthetic vascular perfusate comprised physiological saline (Krebs & Henseleit 1932) containing 3·0% (w/v) dialysed bovine serum albumin, D-glucose (4·45 mM) and washed bovine erythrocytes to give a haematocrit of $39 \pm 2\%$. The pH was adjusted to 7·4 using saturated sodium bicarbonate solution and the flow rate was set at 1·5 mL $min^{-1}$.

*Perfused small intestine and small intestine/liver (configurations B and C)*

These preparations were similar to those described by Pang et al (1985). The rats were anaesthetized, heparinized and the abdominal organs exposed. The right and middle colic arteries and veins, the pyloric vein, the duodenum (as near to the pyloric sphincter as possible) and the ileo-caecal junction were ligated. Care was taken to ensure that blood vessels supplying the small intestine were not ligated whilst those supplying the large intestine were. The intestine was then

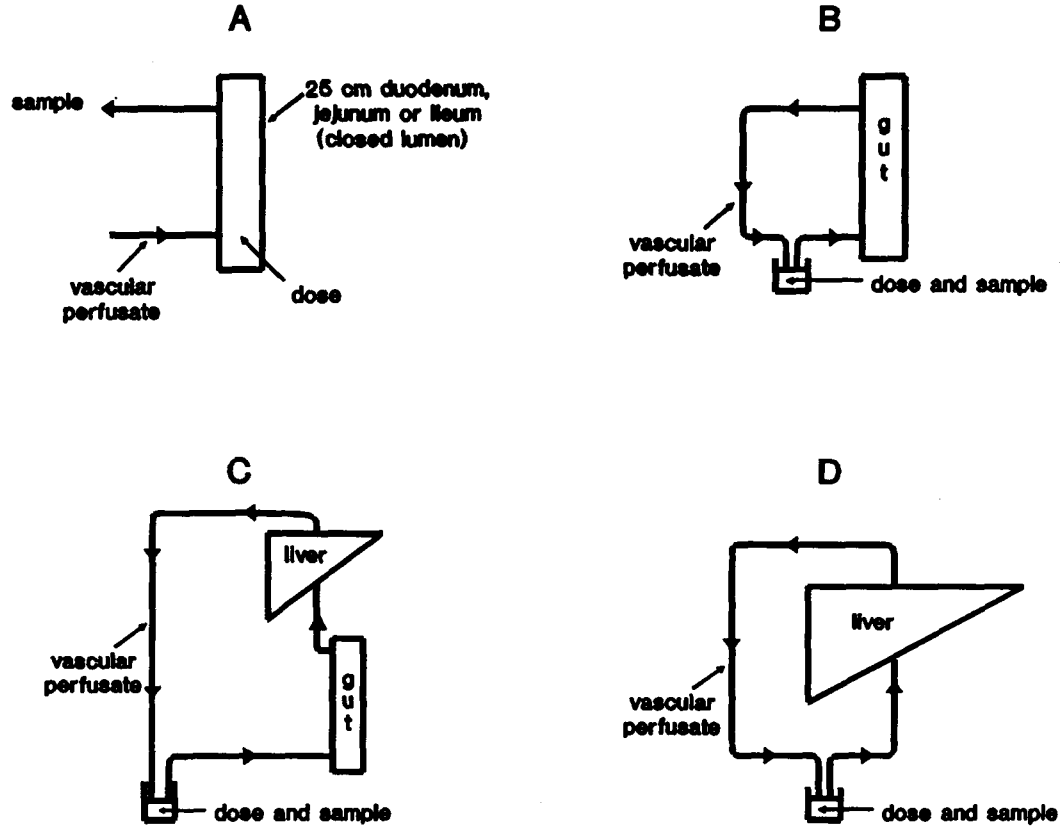


FIG. 1. Configurations of rat in-situ isolated perfused intestine/liver preparations used to investigate the site of inversion of *R*(−)-ibuprofen.

deflected to the rat's left and the superior mesenteric artery and hepatic portal vein were cannulated as described by Castle et al (1985). The composition of the vascular perfusate was as described above and it was recirculated at a flow rate of 7·5 mL $min^{-1}$ (small intestine) or 10 mL $min^{-1}$ (small intestine/liver) from a reservoir volume of 100 mL.

*Perfused liver (configuration D)*

The preparation described by Lennard et al (1983) was used. The composition of the vascular perfusate was as described above and it was recirculated at a flow rate of 10 mL $min^{-1}$ from a reservoir volume of 100 mL.

*Drug dosage*

*Configuration A.* At 5 min after the start of vascular perfusion the isolated intestinal segment was filled with a volume of solution (approximately 5 mL) sufficient to maintain a lumen distension pressure preventing hypermotility of the intestine. The solution contained R(−)- or S(+)-ibuprofen (0·80 mg $mL^{-1}$; equivalent to a dose of 20 mg $kg^{-1}$ body weight) in physiological saline with 10% (v/v) ethanol, D-glucose (3·33 mM) and 1% (v/v) Tween 80, adjusted to between pH 6·3 and 6·8 with 1 M hydrochloric acid. Samples of vascular perfusate were collected at 10, 15, 20, 30, 40, 50 and 60 min after the start of perfusion. Following centrifugation at 10 000 *g* for 1 min at room temperature (20°C), the supernatant was removed and stored at −20°C before analysis. The intestinal segment was then removed, opened, blotted, weighed and then dried to constant weight at 100°C to determine dry weight:wet weight ratios.

*Configurations B, C and D.* After an equilibration period of 5 min R(−)-ibuprofen dissolved in 100 μL ethanol was added to the vascular perfusion reservoir over 30 s to give an initial concentration of 30 μg $mL^{-1}$. Samples (3 mL) of the vascular perfusate were then taken at 10, 15, 20, 30, 45 and 60 min with replacement of the same volume of blank perfusate. Following centrifugation, the supernatant was removed and stored at −20°C before analysis. At the end of the perfusion (60 min) the intestine and/or liver was removed, blotted, weighed and dry weight:wet weight ratios determined.

*Drug assay*

Samples of vascular perfusate supernatant (hereafter referred to as perfusate plasma) were assayed for R(−)- and S(+)-ibuprofen by a modification of the HPLC method of Averignos & Hutt (1987), which involves resolution of the diastereomeric amides formed following derivatization with S(−)-1-(1-naphthyl)ethylamine using 4-chlorphenoxyacetic acid as the internal standard. Reverse-phase chromatography was performed using a DuPont Zorbax Phenyl column (250 × 4·6 m i.d., Hichrom Ltd, Reading, UK) with fluorescence detection (220 nm excitation, 350 nm emission, Perkin-Elmer LS-40 fluorescence detector, Perkin-Elmer Ltd, Beaconsfield, UK). The mobile phase was 60% (v/v) acetonitrile with 0·1% (v/v) trifluoroacetic acid at a flow rate of 1·5 mL $min^{-1}$. The sample injection volume was 5 μL. Calibration samples were prepared by adding to blank perfusate plasma known amounts of R(−)- and S(+)-ibuprofen. Each analytical run included triplicate calibration standards at four concentrations over the range 0·1–25 μg $mL^{-1}$ and four control samples. The control samples were frozen aliquots of a batch of perfusate plasma containing 5 μg $mL^{-1}$ of each enantiomer. Interassay coefficients of variation were 8·4 and 3·1% at 0·1 and 25 μg $mL^{-1}$ of R(−)-ibuprofen, respectively, and 8·3 and 3·7% at 0·1 and 25 μg $mL^{-1}$ of S(+)-ibuprofen, respectively (n = 12 for both enantiomers). Correlation coefficients (r) were greater than 0·99 for all standard curves. Based on control sample analysis, the interassay coefficients of variation were 5·4% (mean concentration = 5·17 μg $mL^{-1}$; n = 75) for R(−)-ibuprofen and 7·2% (mean concentration = 5·25 μg $mL^{-1}$; n = 75) for S(+)-ibuprofen. Because of interfering peaks on the chromatograms it was not possible to measure the ibuprofen enantiomers in intestinal lumen samples accurately.

*Data analysis*

Areas under the concentration-time curves (AUC) of the enantiomers in perfusate plasma were measured up to 55 min for duodenal, jejunal and ileal perfusions (configuration A) and up to 60 min for small intestine, small intestine/liver and liver perfusions (configurations B, C and D) using the linear trapezoidal method. A first-order rate constant, $\lambda$, was calculated from the slope of the terminal log-linear decay of the perfusate plasma drug concentration, by linear regression analysis of the last 3–4 data points. Hence a half-life ($t_{\frac{1}{2}}$) was calculated from $0{\cdot}693/\lambda$. Comparisons of AUC and $t_{\frac{1}{2}}$ values were made using one-way analysis of variance followed by Student's unpaired *t*-test on the appropriate sets of data.

## Results

Ibuprofen enantiomer concentrations in perfusate plasma during single-pass vascular perfusions of the duodenum, jejunum and ileum (configuration A) are shown in Fig. 2. The values of AUC and $t_{\frac{1}{2}}$ are summarized in Table 1. Following administration of R(−)-ibuprofen to the lumen no inversion to S(+)-ibuprofen was observed in duodenal, jejunal or ileal preparations. Observed perfusate plasma concentrations of S(+)-ibuprofen could be accounted for by the enantiomeric impurity of the R(−)-ibuprofen. Significantly more R(−)-ibuprofen was absorbed from the ileum compared with the duodenum and jejunum, as indicated by relative AUC values ($P < 0{\cdot}05$). The terminal half-life of R(−)-ibuprofen in perfusate plasma was slightly shorter after addition of the drug to the duodenal lumen compared with that after jejunal adminstration ($P < 0{\cdot}05$). Maximum perfusate plasma drug concentration ($C_{max}$) was independent of the segment of intestine that was perfused. The time of its occurrence ($t_{max}$) was 15 min for duodenal and jejunal perfusions and 20 min for ileal perfusions. Significant differences were not observed in the AUC or $t_{\frac{1}{2}}$ values nor in $C_{max}$ or $t_{max}$ (data not shown) values of the respective isomers following their addition to the jejunal lumen. In both cases, observed concentrations of the opposite isomers could be accounted for by the enantiomeric impurity of the added antipode. No S(+)-ibuprofen (other than impurity) was detected in any of the intestinal lumen samples following R(−)-ibuprofen administration.

Ibuprofen enantiomer concentrations measured in the perfusate plasma during recirculatory vascular perfusion of

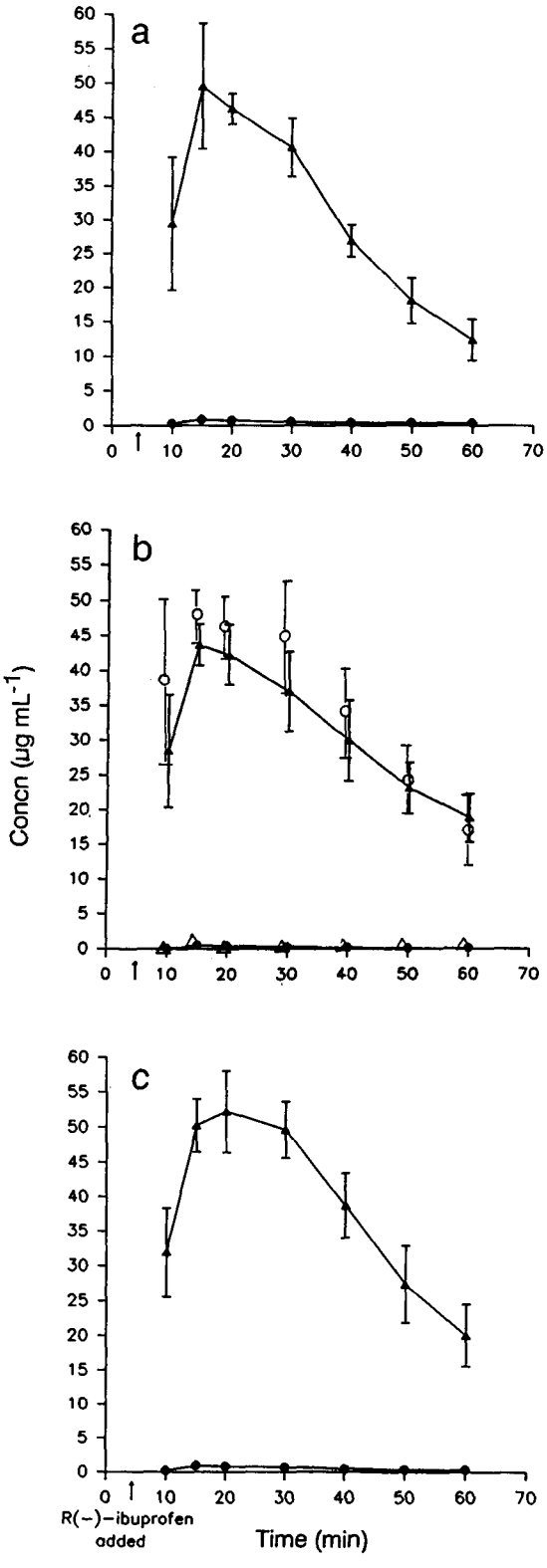


FIG. 2. Mean (±s.d.) concentrations of the enantiomers of ibuprofen in vascular perfusate plasma during single-pass vascular perfusion after addition of *R*(−)-ibuprofen (20 mg kg$^{-1}$ body wt) to the closed gut lumen (configuration A) (n = 5). A, duodenum/jejunum; B, jejunum; C, ileum. B also shows the corresponding results for the addition of *S*(+)-ibuprofen (20 mg kg$^{-1}$ body wt). ▲——▲, *R*(−)-ibuprofen; ●——●, *S*(+)-ibuprofen after addition of *R*(−)-isomer; ○——○, *S*(+)-ibuprofen, △——△, *R*(−)-ibuprofen after addition of *S*(+)-isomer.

Table 1. Mean (±s.d.) data describing the kinetics of *R*(−)-ibuprofen [*R*(−)-I] and *S*(+)-ibuprofen [*S*(+)-I] in perfusate plasma after addition of the isomers (20 mg kg$^{-1}$) to the lumen of the rat isolated perfused duodenum/jejunum, jejunum or ileum (closed loop; single-pass vascular perfusion) (n = 5 for each preparation).

| Intestinal segment/ enantiomer added | $AUC_{0-55}$ (μg mL$^{-1}$ min) *R*(−)-I | *S*(+)-I | AUC ratio (%) | $t_{\frac{1}{2}}$ (min) |
|---|---|---|---|---|
| Duodenum/*R*(−)-I | 1669±115 | 23±6 | 1·4±0·4[1] | *R*(−)-I 18·1±2·6 |
| Jejunum/*S*(+)-I | 6±3 | 1864±238 | 0·3±0·1[2] | *S*(+)-I 21·7±5·8 |
| Jejunum/*R*(−)-I | 1687±203 | 14±5 | 0·8±0·2[1] | *R*(−)-I 25·7±5·3 |
| Ileum/*R*(−)-I | 2061±188 | 27±1 | 1·3±0·1[1] | *R*(−)-I 22·0±4·1 |

[1] = Ratio: $AUC_{0-55}$ *S*(+)-I/$AUC_{0-55}$ *R*(−)-I. [2] = Ratio: $AUC_{0-55}$ *R*(−)-I/$AUC_{0-55}$ *S*(+)-I.

the small intestine, small intestine/liver and liver (configurations B, C and D) are shown in Fig. 3. AUC and $t_{\frac{1}{2}}$ values are summarized in Table 2. No inversion of *R*(−)-ibuprofen was observed during small intestine perfusions, but appreciable inversion was seen during small intestine/liver and liver perfusions. Concentrations of *S*(+)-ibuprofen observed during perfusion of the small intestine with the *R*(−)-isomer could be accounted for as enantiomeric impurity. AUC values of both isomers were similar irrespective of whether the small intestine/liver or liver alone was perfused. The $t_{\frac{1}{2}}$ of *R*(−)-ibuprofen was also independent of the configuration used.

Dry weight:wet weight ratios are summarized in Table 3 and were similar to those reported by Castle et al (1985) for the perfused intestine (0·235±0·012, n = 46) and by Cox et al (1985) for the perfused liver (0·298±0·014, n = 9).

Blank perfusion experiments (no organ present) lasting 60 min were also carried out to evaluate the stability of each enantiomer in the system. Both enantiomers were found to be chemically and stereochemically stable in vascular and lumen perfusates and they were not adsorbed to the perfusion apparatus.

Vascular pefusate flow rates were monitored throughout the experiments and did not vary by more than ±8% of initial values. Corrections for drug concentrations to account for sampling losses were not made, since they were estimated to be negligible (< 5%).

## Discussion

Inversion of *R*(−)-ibuprofen in the rat perfused liver has been confirmed, the data being virtually identical to those reported by Cox et al (1985). These findings, together with results obtained using rat isolated hepatocytes (Müller et al 1990; Sanins et al 1990) contrast with the data from studies using sub-cellular preparations (Meyer et al 1988; Knadler & Hall 1990), and emphasize the importance of maintaining cellular integrity and regulation in the experimental system.

The perfused small intestine does not appear to be able to carry out either mucosal or serosal inversion of *R*(−)-ibuprofen in the rat, as shown by experiments with the

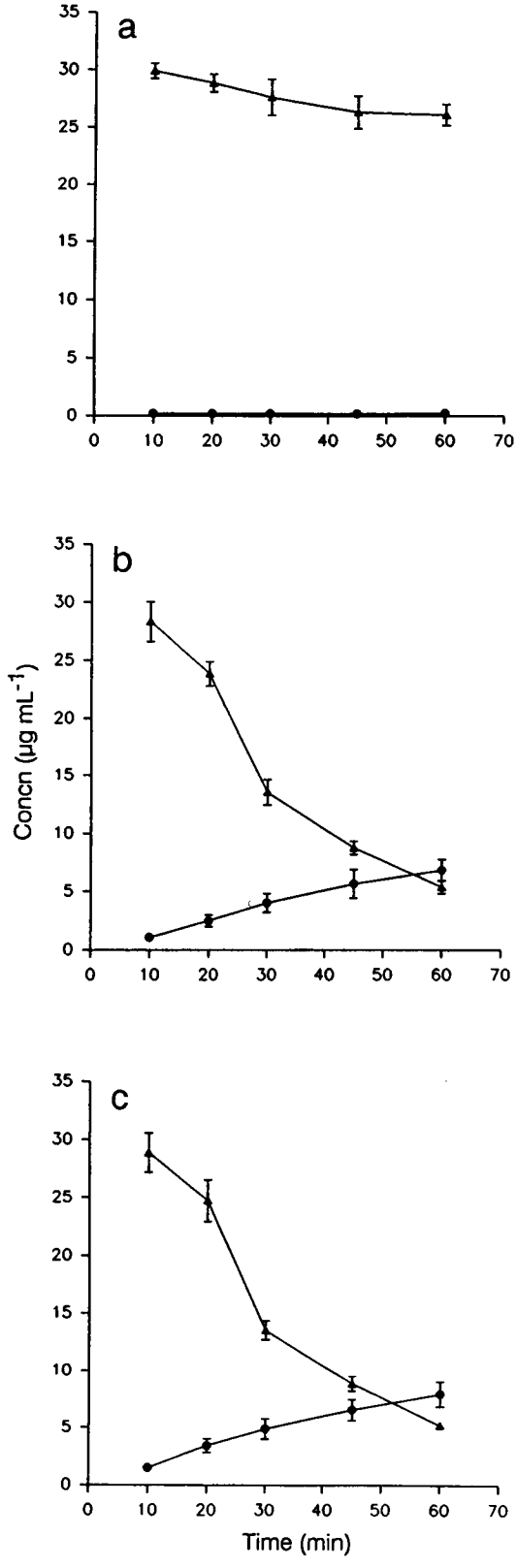


FIG. 3. Mean (±s.d.) concentrations of the enantiomers of ibuprofen in vascular perfusate plasma during recirculating vascular perfusion after addition of R(−)-ibuprofen (30 μg mL$^{-1}$) to the perfusate reservoir (configuration B) (n=6 for each preparation). A, small intestine (configuration B); B, small intestine in series with the liver (configuration C); C, liver (configuration D). ▲——▲, R(−)-ibuprofen; ●——●, S(+)-ibuprofen.

Table 2. Mean (±s.d.) data describing the kinetics of R(−)-ibuprofen [R(−)-I] and S(+)-ibuprofen [S(+)-I] in perfusate plasma after addition of R(−)-ibuprofen (30 μg mL$^{-1}$) to the recirculating vascular perfusate of rat isolated perfused small intestine/liver and liver preparations (n=6 for each preparation).

| Preparation | $AUC_{0-60}$ (μg mL$^{-1}$ min) R(−)-I | $AUC_{0-60}$ (μg mL$^{-1}$ min) S(+)-I | AUC ratio (%) | $t_{\frac{1}{2}}$ (min) |
|---|---|---|---|---|
| Small intestine | 1647±34 | 13±3 | 0·8±0·1[1] | ND |
| Small intestine+liver | 1011±25 | 220±28 | 22±4[1] | R(−)-I 19·1±1·3 |
| Liver | 1021±49 | 238±22 | 23±3[1] | R(−)-I 18·9±0·4 |

[1] = Ratio: $AUC_{0-60}$ S(+)-I/$AUC_{0-60}$ R(−)-I. ND = not determined.

Table 3. Mean (±s.d.) dry weight:wet weight ratios for all perfusions.

| Perfusion | Configuration | Dry weight:wet weight ratio |
|---|---|---|
| Duodenum (n=5) | A | 0·247±0·012 |
| Jejunum R(−)-I (n=5) | A | 0·220±0·009 |
| Jejunum S(+)-I (n=5) | A | 0·220±0·013 |
| Ileum (n=5) | A | 0·238±0·019 |
| Small intestine (n=6) | B | 0·225±0·013 |
| Small intestine | C | 0·221±0·017 |
| +liver (n=6) | | 0·283±0·021 |
| Liver (n=6) | D | 0·300±0·018 |

isolated lengths of intestine and by the almost identical extent of inversion in the liver and combined liver/intestine preparations. Although use of the latter preparation was not essential to establish this conclusion, since this was evident from the experiments with liver and intestine alone, the results were confirmatory and establish our confidence in the metabolic viability of the combined preparation. Coenzyme A plays an essential role in the inversion process (Nakamura & Yamaguchi 1987; Knihinicki et al 1989) but may not be the only enzyme contributing to arylpropionyl-CoA thioester formation. The contributions of long nd medium chain fatty acyl-CoA synthetases, as possible activating enzymes, have yet to be determined (Knadler & Hall 1990). Our findings are consistent with the suggestion that the rat small intestine contains insufficient enzymatic capability to invert ibuprofen (Knadler & Hall 1990).

Assuming that the results in rat can be extrapolated to man, they do not support the contention of Mehvar & Jamali (1988) that most of the inversion occurs in the gut. They do not exclude the possibility of some inversion in the large intestine.

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