Rectal ropivacaine is absorbed proportionally to the dose, with low intraindividual variability

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Aims This study investigated the absorption characteristics and the tolerability of rectally administered ropivacaine, a local anaesthetic, intended as a new local therapy for ulcerative colitis.

Methods Thirty-two healthy volunteers participated in a randomized, placebo-controlled study. In study phase 1 ($n = 16$, double-blind, crossover) single rectal doses of ropivacaine corresponding to 50, 100 and 200 mg base were given as 20-ml gel enemas. Eight of these subjects also received an i.v. infusion corresponding to 20 mg ($^2\text{H}_3$)ropivacaine base given with the last rectal dose. In study phase 2 ($n = 16$, single-blind, crossover) the same rectal doses were given but formulated in 20, 40 and 80 ml gel, respectively. Peripheral venous plasma samples and urine were collected over 12 h after dosing and analysed for ropivacaine base by gas chromatography and ($^2\text{H}_3$)ropivacaine by gas chromatography-mass spectrometry. Ropivacaine and metabolites were analysed in urine by reversed phase liquid chromatography.

Results AUC was proportional to the dose with a point estimate [95% confidence interval (CI)] for the increase, after doubling the dose, of 1.91 (1.66–2.20) and 1.95 (1.78–2.13) in study phases 1 and 2, respectively. The increase in $C_{\max}$ was also proportional to the dose with corresponding results of 1.76 (1.52–2.04) and 1.84 (1.70–1.99). The volume of the rectal formulation had no influence on either the extent or the time course of absorption. The mean (s.d.) absolute bioavailability (% F) was 56 (18)%. AUC and $C_{\max}$ showed a two- to three-fold lower intra- than interindividual variability. Zero-order kinetics dominated the first 4 h of the absorption phase. Thereafter first-order kinetics were observed. The terminal half-lives were similar between the rectal doses and were longer than that after the i.v. administration, indicating an absorption-dependent half-life. The main urinary metabolite was 3-hydroxyropivacaine corresponding to about 23% of the dose. The subjects had no difficulties in retaining the doses and rectal administration of ropivacaine was well tolerated, both locally and systemically.

Conclusions Plasma drug concentrations were proportional to the dose after rectally administered doses corresponding to 50–200 mg ropivacaine base in a gel formulation. The drug was well-tolerated. Mean bioavailability was about 60% and not influenced by variations in the enema volume. Initial absorption seemed to follow zero-order kinetics and then first-order kinetics after about 4 h. $C_{\max}$ and AUC showed considerably less intra- compared with inter-individual variability, resulting in more consistent plasma concentrations within subjects.

Keywords: bioavailability, dose proportionality, metabolism, pharmacokinetics, rectal administration, ropivacaine, tolerability

Introduction

Ulcerative colitis (UC) is characterized by an inflammation of the colonic mucosa. Today the most widespread treatment consists of corticosteroids, ASA preparations

including sulphasalazine as well as immunomodulating agents [1]. Exploratory clinical studies have shown good results from rectal treatment with the local anaesthetic (LA) lidocaine [2, 3]. A newly developed LA, ropivacaine, has in preclinical studies shown an anti-inflammatory effect through its action on different mechanisms of the inflammatory response [4–8]. Owing to this inherent anti-inflammatory activity, ropivacaine was considered as a candidate for a new local treatment for distal UC.

The rectal route of administration of drugs can be used to achieve both local and systemic effects. The bioavailability of drugs exposed to high first-pass elimination [9] can be increased by administration via the rectal route. However, disadvantages with rectal administration could be poor local tolerability and/or the variability in absorption, both inter- and intra-individually. These factors are mainly attributed to the physico-chemical properties of the drug, as well as to the physiology of the rectum [10].

Ropivacaine [(S)-(-)-propyl-2',6'-pipecoloxylidide] is a new, long-acting local anaesthetic of the amide type [11]. It contains a single chiral centre and is used as the pure S-(-) enantiomer. *In vivo* racemization does not occur after systemic administration of the drug [12]. The physico-chemical properties of ropivacaine are as follows: m wt 274.4 (base), pK_a 8.1 and log D (pH 7.4 n-octanol *vs* buffer) 2.15. Intravenous ropivacaine shows linear pharmacokinetics [13] and the drug is almost completely metabolized, with less than 1% of the dose excreted unchanged. CYP1A2 has been shown to catalyse the major metabolic pathway *in vivo* [14, 15], producing 3-hydroxyropivacaine, whereas CYP3A4 dealkylates the drug producing PPX (2'-6' pipecoloxylidide).

The aim of this study was to investigate the single-dose pharmacokinetics and tolerability of rectal ropivacaine in the dose range 50–200 mg (doses in ropivacaine base) as well as the inter- and intra-individual variability in bioavailability in healthy volunteers. The role of enema volume was also studied.

Subjects and methods

Subjects

The study was performed in two parts involving 16 different Caucasian subjects in each (18 males and 14 females). An additional four subjects who discontinued the study have been included in the safety evaluation only. The mean $\pm$ s.d. age, weight and height were similar between the two study groups; 35 ± 5 years, 74 ± 11 kg and 176 ± 9 cm in phase 1 and 34 ± 6 , 75 ± 13 and 176 ± 12 for the corresponding parameters in phase 2. Eight subjects from study phase 1 were given an i.v. dose of ropivacaine. The characteristics of this subgroup were 37 ± 5 years, 76 ± 13 kg and 177 ± 9 cm. All subjects

were phenotyped as extensive metabolizers of mephenytoin (catalysed by CYP2C19) and debrisoquine (CYP2D6) [16].

All volunteers were judged healthy on the basis of a routine medical examination including rectoscopy, laboratory screening and electrocardiogram (ECG) investigation. Serum potassium was normal 24–48 h before each drug administration. Subjects with a history or evidence of haemorrhoids, fissures, proctitis or any other rectal or colonic disease were excluded, as were smokers.

The study was performed in accordance with the declaration of Helsinki and approved by the local Human Ethics Committee for Human Research at St Göran Hospital. All subjects gave their written informed consent.

Study design

The subjects received the four rectal doses according to a randomized crossover design with an interval of at least 7 days between each dose. Four 4×4 Latin squares were generated randomly for each part of the study. Ropivacaine hydrochloride was administered as an enema consisting of a hydroxypropylmethylcellulose gel at pH 4.4 and a viscosity between 0.8 and 1.8 Pa s^{-1} (rotation viscosimetry, 228 r s^{-1} , 20°C and 37°C) (personal communication; F. Broberg, Astra Pain Control AB, Sweden). All doses are expressed as ropivacaine base.

In study phase 1 ($n = 16$, double-blind, crossover) single rectal doses of ropivacaine corresponding to 50, 100 and 200 mg ropivacaine base were given as 20-ml gel enemas. Eight of these subjects also received an i.v. infusion corresponding to 20 mg ($^2\text{H}_3$)ropivacaine base at the same time as the last rectal dose. In study phase 2 ($n = 16$, single-blind, crossover) the same rectal doses were given in enema volumes of 20 ml (50 mg), 40 ml (100 mg) and 80 ml (200 mg) and 20 ml (placebo) gel. ($^2\text{H}_3$)ropivacaine was given as a 25-min i.v. infusion at the same time as the administration of the last rectal dose (placebo in two subjects). Bowel evacuation in the morning before rectal administration was encouraged. A nurse administered all rectal doses at approximately 5 cm above the anal verge, using plastic disposable syringes of volume 20–100 ml. The doses were checked by weighing the syringe before and after each administration, resulting in an accuracy of 5%. No immediate leakage after dosing was observed. The subjects continued fasting 3 h after dosing and were instructed not to engage in any strenuous activities during the days of administration.

The rectal mucosa and the anal canal were inspected by rigid proctosigmoidoscopy between 1 and 2 days before and at 22–26 h after each dose, by the same physician who was blinded to treatment. The rectal mucosa was inspected for the degree of hyperaemia,

redness, oedema, ulceration, tendency to bleed, fragility and vascular distribution, all of which were graded as normal, slightly changed or substantially changed, according to methods described previously [17]. Redness, epithelium defects, ulceration, the presence of fissures and mucosal prolapse were assessed in the anal canal using the same grading system. Enema retention time was also recorded, determined as the time between drug administration and the first bowel evacuation. Diagnostic ECG, blood pressure and heart rate were recorded before and 15, 30 and 60 min after drug administration. Tolerability was assessed by the open question 'Have you felt anything out of the ordinary?' at 8 h after each dose, and after the proctosigmoidoscopy.

Sampling and drug analysis

Blood samples were obtained following cannulation of a forearm vein, contralateral to that used for the infusion of ropivacaine, and transferred into heparinized test tubes (Venoject; Terumo Co., Leuven, Belgium). Plasma was separated by centrifugation for 10 min at 1188 *g* within 1 h of collection and transferred to polypropylene tubes (Cryotube; Nunc, Roskilde, Denmark). Samples were stored at -20°C until analysis. Samples were drawn immediately before and 5, 10, 20, 25, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after start of dosing.

Urine was collected in labelled plastic containers (without preservative) immediately before the dose and for 0–2, 2–4, 4–6, 6–8 and 8–12 h after ropivacaine administration. Urine volumes during each collection period were measured and aliquots were stored at -20°C until analysis (Cryotube; Nunc).

The concentration of ropivacaine base in plasma and urine was determined by gas chromatography with nitrogen-phosphorous detection. The method is based on a liquid-liquid extraction from alkalized biological fluid [18]. When both ropivacaine and ($^2\text{H}_3$)ropivacaine were determined, a gas chromatographic-mass spectrometric method was used combined with a stable isotope dilution technique. The mass spectrometer was operated in the chemical ionization mode with ammonia as reactant gas, and the selected pseudomolecular ions, $[\text{M} + \text{H}]^+$, of ropivacaine and its deuterium-labelled analogues were monitored [19].

The limit of quantification was set at 0.008 mg l^{-1} ($0.03 \text{ }\mu\text{M}$) for both methods. For validation of the analyses, quality control samples were prepared at different concentrations and assayed on each analysis run. The between-day accuracy varied between 96% and 106%. The precision expressed as the coefficient of variation was in the range of 4.5–8.1%.

In study phase 1 ($^2\text{H}_3$)ropivacaine was analysed in the urine from all subjects after the i.v. dose. Screening for

the main metabolites [3-OH-ropivacaine(3-hydroxy-1-propyl-2,6-pipecoloxylidide), 4-OH-ropivacaine, PPX (2'-6' pipecoloxylidide) and 3-OH-PPX] was performed following rectal administration in four subjects. The urine from all subjects in phase 2 of the study was analysed for ropivacaine and for 3-hydroxy-ropivacaine, the main metabolite. The concentrations of 3-OH-ropivacaine, 4-OH-ropivacaine, PPX and 3-OH-PPX were determined by reversed phase liquid chromatography with u.v. detection at 210 nm [20]. The method is based on hydrolysis of conjugated metabolites followed by a solid-phase extraction on a cationic exchanger. The accuracy varied between 94% and 113%, and the coefficients of variation ranged from 1.6% to 9.1%.

Pharmacokinetic evaluation

The pharmacokinetic parameters were estimated according to standard noncompartmental methods by using a pharmacokinetic program (PHA) written in the RS/1 command language (RS/1; BBN Software Products Corp., Cambridge, MA, USA). The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were estimated from the individual plasma concentration-time curves. The area under the plasma concentration-time curve (AUC) was obtained using the trapezoidal rule up to the last time point (t_{last}) where drug was detectable. Area under the first moment-time curve (AUMC) was calculated from the product of concentration and time at each data point. AUC and AUMC were extrapolated to infinity according to standard methods [21] by using the estimated concentration at t_{last} and the elimination rate constant (λ), as estimated by log-linear regression. The terminal half-life ($t_{1/2}$) was calculated from the expression $\ln 2/\lambda$. Plasma clearance (CL) was calculated following intravenous administration as Dose/AUC , and the distribution volume at steady state as

$$V_{\text{ss}} = (\text{Dose} * (\text{AUMC}/\text{AUC}^2)) - t_{\text{inf}}/2,$$

where t_{inf} is the i.v. infusion time.

The bioavailability (F) of the rectal dose was calculated from the equation

$$F = (\text{dose}_{\text{inf}} * \text{AUC}_{\text{rectal}}) / (\text{dose}_{\text{rectal}} * \text{AUC}_{\text{inf}}).$$

F was also calculated when the i.v. and rectal dose were given on different days but to the same volunteer, making the assumption that CL was similar between the study days. After the i.v. dose, the fraction excreted unchanged (f_e) and renal clearance, $\text{CL}_r = f_e * \text{CL}_p$, of ropivacaine were estimated. Urinary recovery of ropivacaine and metabolites after rectal administration were expressed as the percentage of the rectal dose of ropivacaine base.

For the absorption analysis a two-compartment model was fitted to the i.v. infusion data using WinNonlin (version 1.5; Pharsight, Mountain View, CA, USA). A weighting factor of $1/C_{\text{calc}}^2$, in which a constant relative error is assumed, gave the overall best fit. The goodness of fit was determined by examination of the predicted values and residual plots. The intercepts and exponents determined by model fitting were then used for the analysis of absorption data using the Loo-Riegelman method [22] (Kinetica™, Version 2.0.2; InnaPhase, Philadelphia, PA, USA). Construction of a percent unabsorbed-time plot was performed to discriminate between first- and zero-order absorption kinetics [22].

Statistical analysis

Version 6.07 of the SAS® package was used for statistical analyses. A two-sided significance level of 5% was used. All data are presented as mean $\pm$ s.d. unless otherwise stated.

Tests for carryover and period effects were performed by fitting an analysis of variance model (ANOVA) nested with subject, period, dose and carryover for the pharmacokinetic parameters C_{max} , AUC, $t_{1/2}$ and t_{max} after rectal administration. The parameters $t_{1/2}$ and t_{max} were also analysed with respect to equality between dose levels. Similarly, a reduced model (without carryover and period effects) was used for dose normalized AUC and C_{max} , to estimate the inter- and intraindividual components of the total variation [23].

Dose proportionality for C_{max} and AUC were analysed with a power model,

$$y = \alpha \times \text{dose}^\beta,$$

where α depends on subject, period and error [24]. The model assumes a linear relationship between $\log y$ and $\log \text{dose}$. Dose proportionality requires that $\beta = 1$ for dose-dependent parameters. In terms of this model, a doubling in dose is reflected in the ratio $R = 2^\beta$ of corresponding effects, i.e. $(y_2/y_1) = 2^\beta$. If proportionality holds, then this effect ratio R equals 2.

Results

Pharmacokinetics

The mean plasma concentration-time profiles were similar between the two study phases (Figures 1 and 2). After rectal administration the individual plasma concentrations of ropivacaine peaked between 1.2 h and 6.0 h and declined monoexponentially during the 12-h study period. The highest individual C_{max} were 0.62 mg l^{-1} (50 mg), 1.11 mg l^{-1} (100 mg) and 1.73 mg l^{-1} (200 mg). $t_{1/2}$ was similar over the different dose levels and the two

Figure 1 Mean $\pm$ s.d. ropivacaine and $(^2\text{H}_3)$ ropivacaine plasma concentrations after single rectal ropivacaine administration of doses corresponding to 50 (●), 100 (○) and 200 mg (■) ropivacaine base ($n = 16$, crossover). Eight of the subjects also received an i.v. infusion of $(^2\text{H}_3)$ ropivacaine corresponding to 20 mg $(^2\text{H}_3)$ ropivacaine base at the same time as their last rectal dose (□).

Figure 2 Mean ropivacaine plasma concentrations after single rectal ropivacaine administration of doses corresponding to 50 (●), 100 (○) and 200 mg (■) ropivacaine base ($n = 16$, crossover). The doses were administered in enema volumes of 20, 40 and 80 ml, respectively.

Table 1 Mean (s.d.) pharmacokinetic parameters after rectal administration of ropivacaine in a gel formulation.

	50 mg	100 mg	200 mg	20.3 mg i.v. (n = 8)
C_{max} (mg L ⁻¹)				
Phase 1	0.24 ± 0.11	0.43 ± 0.28	0.76 ± 0.39	0.70 ± 0.19
Phase 2	0.26 ± 0.13	0.44 ± 0.19	0.88 ± 0.36	
t_{max} (h)				
Phase 1	3.0 (1.2/4.0)*	3.0 (0.4/4.0)*	3.0 (0.5/4.0)*	
Phase 2	2.5 (0.8/4.0)*	3.0 (1.2/4.0)*	4.0 (1.5/6.0)*	
AUC (mg h L ⁻¹)				
Phase 1	1.39 ± 0.88	2.57 ± 1.91	5.27 ± 4.24	0.81 ± 0.35
Phase 2	1.47 ± 0.76	2.52 ± 1.17	5.48 ± 2.26	
$t_{1/2}$ (h)				
Phase 1	3.3 ± 1.6	3.7 ± 2.3	2.7 ± 0.8	1.6 ± 0.5
Phase 2	2.7 ± 1.0	2.6 ± 0.6	2.4 ± 0.3	
F (%)				
Phase 1 (n = 8)	68 ± 41	61 ± 29	55 ± 15	

Doses are expressed as ropivacaine base. The enema volumes in phase 1 were 20 ml, and in phase 2 were 20 ml (50 mg), 40 ml (100 mg) and 80 ml (200 mg). Phase 1 included a 25-min i.v. infusion of 20 mg (²H₃)ropivacaine to eight volunteers, at the same time as their last rectal dose. Values are mean ± s.d. except values denoted with *, which are median (minimum/maximum).

Table 2 Results of the power model analysis in the evaluation of dose proportionality based on single rectal administration of ropivacaine (n = 16 in each group).

	R Point estimate	95% CI	β Point estimate	95% CI
AUC, phase 1	1.91	(1.66–2.20)	0.93	(0.73–1.14)
AUC, phase 2	1.95	(1.78–2.13)	0.96	(0.83–1.09)
C_{max} , phase 1	1.76	(1.52–2.04)	0.82	(0.61–1.03)
C_{max} , phase 2	1.84	(1.70–1.99)	0.88	(0.77–0.99)

phases of the study (Table 1). T_{max} showed a nonsignificant tendency to increase with dose.

The plasma concentration-time curves were consistent with zero-order absorption up to 4 h after dosing (Figure 3a). The zero-order phase tended to be longer at higher doses. On the other hand, the absorption from about 4 h after dosing obeyed first-order kinetics (Figure 3b).

The AUC and C_{max} in both study phases appeared proportional to the dose (Figures 1 and 2, Table 1). The point estimates and their confidence intervals for C_{max} and AUC in the power model support dose proportionality, with a point estimate of β close to 1 and an R-value close to 2 (Table 2). Based on the R-values, the mean increase in C_{max} , after a doubling of the dose, was

76% in study phase 1 and 84% in study phase 2, and the corresponding values for AUC were 91% and 95%.

The bioavailability (F) of ropivacaine was reproducible within individuals (Figure 4). The variability in F between individuals seemed to decrease with the dose administered, showing a mean of about 60%, range 28–153% (Table 1). Bioavailability was estimated to be over 100% in two of the eight individuals where the i.v. and rectal doses were given on different study days, which was likely to be due to a daily variation in clearance (Figure 4). F was 56 (18)%, range 32–73%, when calculated from simultaneous rectal and i.v. administration. Quantitative analysis of the variability in AUC and C_{max} confirmed that the AUC had a considerably larger inter- than intra-individual variability. This difference in variability for C_{max} was less pronounced in phase 1 of the study (Table 3).

Overall, there was no evidence that enema retention time influenced the pharmacokinetics. Retention times after administration of ropivacaine in both phases of the study (n = 103) were <4 h (n = 8), 4–12 h (n = 17) and >12 h (n = 78). After placebo (n = 34), six subjects had a retention time shorter than 12 h.

The similarities observed in the pharmacokinetic results between the two study phases indicated no effect of the enema volume on ropivacaine pharmacokinetics (Table 1, Figures 1 and 2 and Table 2). The mean total plasma clearance, CL, after the i.v. dose was 478 ± 170 ml min⁻¹, the distribution volume, V_{ss} , was 41 ± 7 l, and the renal clearance, CL_r, was 134 ± 81 ml h⁻¹.

Figure 3 Fraction (%) of unabsorbed drug after rectal administration ropivacaine in doses corresponding to 50, 100 and 200 mg ropivacaine base ($n = 8$). Calculations were performed according to the Loo-Riegelmann method. (a) Linear ordinate; (b) logarithmic ordinate.

Table 3 The mean inter- and intra-subject variability as percentage of the total variability for AUC and C_{max} after rectal administration of ropivacaine.

	AUC, phase 1	AUC, phase 2	C_{max} , phase 1	C_{max} , phase 2
Inter (%)	80 (61–92)	75 (53–89)	59 (31–81)	72 (48–88)
Intra (%)	20 (8–39)	25 (11–47)	41 (19–69)	28 (12–52)

The associated 95% confidence intervals are given in parentheses ($n = 16$ in each group). A confidence interval lying entirely on one side of the 50% limit corresponds to a statistically significant difference between the inter- and intra-individual variances on the 5% level of significance.

In the urine from four subjects in study phase 1, 3-OH-ropivacaine was the major metabolite, accounting for 23% of the dose. 4-OH-ropivacaine represented less than 1% of the dose, and PPX and 3-OH-PPX less than 2% each. In study phase 2, only 3-hydroxyropivacaine was analysed and the amount excreted during the 12-h study period was 23 ± 6 , 23 ± 9 and $21 \pm 6\%$ following 50-, 100- and 200-mg doses, respectively. Less than 1%

of the dose was excreted unchanged after all rectal and i.v. doses.

Tolerability

Adverse events were mainly of gastrointestinal (GI) origin and of mild to moderate intensity from both the upper GI tract ($n = 7$) and from the lower part ($n = 16$). No

Figure 4 The bioavailability of rectally administered ropivacaine ($n = 8$ subjects) in doses corresponding to 50, 100 and 200 mg ropivacaine base. The i.v. dose corresponded to 20 mg ($^3\text{H}_3$)ropivacaine base and was given at the same time as one of the rectal doses, which was placebo in two subjects. Simultaneous i.v. and rectal administration is denoted by arrows ($n = 6$).

event required treatment. CNS symptoms were noted in six subjects, i.e. light-headedness (200 mg and placebo), ear buzzing (50 mg) and dizziness (50, 50 and 100 mg). The time from dosing to reporting of these events was between 2 h and 6 h. The plasma concentration of ropivacaine at the time of these symptoms were low (less than 0.6 mg l^{-1}). The relationship between plasma concentration and LA toxicity is unlikely. There were no clinically significant changes in the ECG, blood pressure or heart rate.

The proctosigmoidoscopy showed no clinically relevant findings. In addition, the enema retention time data showed that the subjects retained their doses for more than 12 h in 78/103 experimental sessions. Together, these results support good local tolerability for ropivacaine.

Discussion

The results from this study support the hypothesis of a proportional increase in C_{max} and AUC with dose after rectally administered ropivacaine. The power model essentially fulfilled the criteria for dose proportionality, especially for AUC, which is considered the more robust parameter in this respect. These results are supported by findings of a proportional uptake of intra-articular ropivacaine in single doses of 100–200 mg [25]. Furthermore, ropivacaine has been shown to follow linear pharmacokinetics after i.v. administration [13].

In this study reproducible results were obtained within individuals, a finding in agreement with the results of Gjellan *et al.* [26], involving repeated rectal administration of suppositories containing both paracetamol and

codeine with a 2-year interval between administration. Differences in the size of the rectum/sigmoideum, and thereby the area available for absorption, might contribute to the larger inter- than intra-individual variability in ropivacaine pharmacokinetics [27]. Another factor contributing to variability in absorption may be differences in the venous drainage of the rectum between individuals [9, 10].

The reason for including different enema volumes in this study was to test the hypothesis that an increased retrograde spread may be achieved with a larger volume, thereby increasing the systemic availability of ropivacaine by decreasing the first-pass effect, as earlier reported for lidocaine [28]. Additionally, the larger volume could give an increased area of absorption, leading to a higher systemic uptake. This has been shown previously for 5-aminosalicylic enema [29]. One explanation for the lack of effect of enema volume in this study is that the variation in enema volume was too small. Because of a higher viscosity in comparison with commercially available enemas, the gel may also have different spreading characteristics to other enemas [30]. A follow-up study has shown that there is a similar retrograde spread for all the enema volumes used in the present study (E. Arlander, unpublished work).

The first clinical study in UC patients given 2 weeks' treatment with 200 mg ropivacaine twice daily showed a mean decrease in AUC of 50% from treatment start to end [31]. The AUC at the end of treatment, when a healing of the mucosa was complete, was similar to the AUC in our healthy subjects. Thus, inflammation may influence the extent of intestinal absorption of ropivacaine from the rectum.

The pharmacokinetics obtained after the intravenous administration in this study are in accordance with results reported in previous studies [13, 32, 33]. Emanuelsson *et al.* also showed that the pharmacokinetics after i.v. administration of ($^3\text{H}_3$)ropivacaine are similar to those of ropivacaine [34], a prerequisite for using ($^3\text{H}_3$)ropivacaine for estimation of absolute bioavailability in this study. In comparison with i.v. administration, the terminal half-life after rectal administration was longer, which reflects an absorption-dependent elimination, as previously reported for ropivacaine after epidural administration [32].

Our study results did not demonstrate any change in the metabolic pattern for ropivacaine, with the main metabolite being 3-hydroxyropivacaine. After i.v. administration 3-hydroxy accounts for about 37% of the dose [35], whereas we obtained a value after rectal dosing of 23%. A longer collection period after dosing is required to investigate further metabolism of ropivacaine following rectal administration.

The systemic tolerability of local anaesthetics correlates to the plasma concentration [36, 37]. CNS toxicity has

been reported at a mean (min/max) threshold total plasma concentration of 4.3 (3.4/5.3) mg l⁻¹ ropivacaine [38]. This is considerably higher than that of the highest individual C_{max} found in this study, namely 1.73 mg l⁻¹. Furthermore, the plasma concentration was less than 0.6 mg l⁻¹ in all subjects reporting light-headedness, buzzing or dizziness. Hence, it seems unlikely that these symptoms are due to local anaesthetic toxicity. Light-headedness was also reported in the placebo group. Thus, ropivacaine was well-tolerated after rectal administration, with no evidence of systemic toxicity.

We conclude that plasma concentrations were proportional to the dose after rectally administered doses corresponding to 50–200 mg ropivacaine base in a gel formulation. The drug was well-tolerated both locally and systemically in our healthy subjects. The mean bioavailability was about 60% and was not influenced by enema volumes between 20 ml and 80 ml. The absorption seemed to follow both zero- and first-order kinetics. C_{max} and AUC showed considerable less intra- compared with inter-individual variability, resulting in more reproducible results within than between subjects.

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