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Pharmacokinetics of acipimox and of its *N*-deoxy metabolite following single and repeated oral administration of a sustained release formulation to healthy volunteers

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Summary

Acipimox is a lipid lowering agent currently used for the treatment of hyperlipoproteinemia at a dose of 250 mg thrice daily. A sustained release (SR) formulation, containing 500 mg acipimox, has been developed with the aim of reducing the number of daily doses. We report here the pharmacokinetics of acipimox and its *N*-deoxy metabolite following single and repeated administrations of this new formulation to ten healthy volunteers. Three treatments – single-dose, once-daily administration for 1 week, and twice-daily for a second week – were evaluated over a continuous administration period, and plasma levels were monitored by HPLC following the last dose of each treatment. The pharmacokinetics of acipimox were found to be similar after single and repeated administrations of the SR formulation. All three treatments gave maximum plasma levels (mean C_{max} range 4.2–5.1 μg/ml) comparable to the currently used treatment, but with retarded maxima (mean t_{max} 5–6 h). A limited accumulation was detectable following twice-daily administration (mean R_A approx. 1.25), and some minor alterations in this plasma profile probably reflected diurnal variations in pharmacokinetic parameters. This regimen maintained, over the 12 h dosing interval, average and minimum steady state concentrations which compare favourably with 8 h dosing of the standard formulation. Plasma levels of the metabolite increased noticeably with repeated dosing and plasma profiles were more variable than for acipimox. However, maximum concentrations (mean C_{max} 0.5–0.8 μg/ml; mean t_{max} 5–11 h) remained consistently lower than unchanged drug, and average steady state concentrations over a dosing interval were about 5-fold lower.

Introduction

Acipimox (5-methylpyrazine-2-carboxylic acid 4-oxide) is a lipid lowering agent which significantly reduces plasma triglyceride levels and increases high density lipoprotein cholesterol levels (Sirtori et al., 1981; Stuyt et al., 1985; Taskinen and Nikkila, 1988). It is used clinically for the treatment of type IV and II hyperlipoproteinemia at a dose of 250 mg thrice daily (t.i.d.), administered orally as a capsule (Sommariva et al., 1985; Crepaldi et al., 1988). Acipimox is structurally related to nicotinic acid, but has considerably

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improved tolerability and potency, and its prolonged inhibition of lipolysis is more clearly correlated with dose and plasma concentrations (Fuccella et al., 1980). The absorption of acipimox is rapid and almost complete, and is followed by rapid elimination. The pharmacokinetics do not appear modified after repeated administration and no significant accumulation occurs when the drug is given thrice daily (Efthymiopoulos et al., 1992). Biotransformation of acipimox is limited, as indicated by the more than 90% dose found as unchanged drug in 24 h urine (Musatti et al., 1981). Significant plasma concentrations of the *N*-deoxy metabolite (5-methylpyrazine-2-carboxylic acid, MPCA) have however been recorded (Efthymiopoulos et al., 1992), and preclinical studies have suggested that MPCA production is primarily due to reductase activity of the intestinal microflora (Strolin Benedetti et al., 1990).

A sustained release (SR) formulation of acipimox has been developed by Farmitalia Carlo Erba with the aim of reducing the number of daily doses, whilst maintaining therapeutically useful plasma levels and limiting adverse effects such as flushing. Since acipimox has a moderate and pH-insensitive aqueous solubility throughout the acid-base range encountered in the gastrointestinal tract, it was possible to design a dosage form with long gastric residence time, releasing acipimox primarily in the stomach, and using antral sieving after a meal for delivery of dissolved drug over a prolonged period into the small intestine (Fara, 1985). The formulation comprised a non-disintegrating polymer-matrix tablet of sufficient dimensions to be retained in the stomach during digestion mode (Davis et al., 1986). In vitro tests indicated a pH-independent release rate which was initially linear with the square root of time, a profile consistent with diffusion-limited release from solid matrices (Higuchi, 1967), and reaching total release by about 10–12 h *.

* Standard dissolution testing in aqueous buffer with stirring rate 100 rpm, using basket apparatus as described in USP XXII p. 1578.

The relative bioavailability of the SR formulation and conventional immediate release (IR) capsule has been evaluated in healthy volunteers, as reported briefly elsewhere (Efthymiopoulos et al., 1990): five single-dose crossover arms allowed comparison of plasma levels for both 500 and 600 mg dose SR forms and 250 mg IR dose, and the effect of food on the IR and 600 mg SR forms. The study confirmed a satisfactory retarded delivery for the SR formulation after a meal, whilst under fasting conditions (investigated for 600 mg) considerable loss of retardation and extent of bioavailability was observed. No food effect was apparent for the IR dose. Thus food-induced gastric retention appears a necessary step for efficient and prolonged absorption of SR acipimox. The 500 mg dose allowed a plasma maximum only slightly higher than following the IR dose, and hence appears less likely than the 600 mg dose to provoke side-effects: it was in fact reported to be the best tolerated treatment.

In the present study, the 500 mg SR formulation of acipimox was used in order to evaluate the pharmacokinetics of unchanged acipimox and its *N*-deoxy metabolite following single and repeated administration to healthy volunteers. Repeated administration was evaluated for both once-daily (o.a.d.) and twice-daily (b.i.d.) regimens, studied over consecutive weekly periods. Since the altered presystemic kinetic profile following SR administration could influence exposure to bacterial reductases, predominantly active in the distal intestinal regions (Rowland, 1986), attention is given to possible changes in proportions of metabolite and parent. Preliminary indications of tolerability are also presented.

Materials and Methods

SR dosage form

A capsule-shaped, 22 mm long × 9 mm diameter, matrix tablet system was prepared using two water-insoluble but water-permeable (meth)acrylic acid ester polymers. The polymers are marketed by Röhm Pharma (Weiterstadt, Germany) as Eudragit RS-PM and Eudragit NE 30 D. The RS-PM polymer was used to construct a water-

permeable network, whilst NE 30 D served as a water-insoluble matrix binder. Acipimox powder, mixed with lactose and RS-PM polymer, was subjected to wet granulation with an aqueous suspension of polymer NE 30 D.

Subjects

Four male and six female healthy volunteers (aged between 23 and 43 years, average weight and height 64 kg and 168 cm, respectively) gave their written consent to participate in the study. Good health was ascertained by physical examination, urine analysis and haematological tests, including tests of liver function (serum bilirubin, transaminases and alkaline phosphatase) and renal function (serum creatinine). Subjects were not heavy smokers (< 10 cigarettes/day) and received no concomitant therapy or medication in the 2 weeks prior to and throughout the study. They also did not drink any alcoholic beverages during the 24 h preceding and throughout the study.

Study conduct

The study was conducted according to a protocol approved by the Ethical Committee of the Centre Hospitalier de Versailles. Each volunteer received a 500 mg SR tablet each morning for a period of 7 days; treatment continued on days 8–14 according to a twice-daily dosing regimen (500 mg SR tablet every 12 h) finishing with the morning dose on day 14. This scheme allowed assessment of pharmacokinetics from plasma levels over 24 h following a single dose (day 1) and o.a.d. treatment (day 7) as well as up to 48 h after b.i.d. treatment (days 14–15). Adverse events were monitored throughout the study: their onset, duration and intensity were recorded.

The volunteers fasted for at least 10 h before administration on days 1, 7 and 14, and received the acipimox SR dose after a standard breakfast: 200 ml tea or coffee with 10 g sugar; 1 hard-boiled egg, 250 ml orange juice, 1 slice bread (100 g) and butter (12 g); 50 g ham and 50 g Gruyère cheese. Blood samples (5 ml) were collected in heparinized tubes before administration and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after administration. Collection was through an intravenous catheter for the first 12 h, and thereafter by venipuncture. Additional blood samples were taken at 28, 32, 36 and 48 h following the last dose on day 14. The samples were centrifuged for 10 min at $1200 \times g$ and the plasma obtained was stored at −20°C until analysis.

Assay methods

Plasma concentrations of unchanged acipimox and metabolite MPCA were determined by HPLC with UV detection at 269 nm (Marrari et al., 1986; Efthymiopoulos et al., 1992). Lower quantification limits were 50 and 80 ng/ml for acipimox and MPCA, respectively.

Data analysis

For both acipimox and MPCA, non-compartmental methods were used for pharmacokinetic analysis, with the aid of the SIPHAR software (SIMED, Créteil, France) and Lotus 1-2-3 (Lotus Development Corporation, Cambridge, U.S.A.).

For unchanged drug, maximum concentrations (C_{max}) and the corresponding times (t_{max}) were read directly from the raw data. Terminal half-lives ($t_{1/2}$) were calculated by linear regression analysis of the terminal phase of log-concentration vs time curves. Areas under plasma concentration vs time curves (AUC) were calculated by the linear trapezoidal rule, and extrapolated where necessary using the terminal half-life (Gibaldi and Perrier, 1982a).

AUC(0–∞) after the single dose was compared with AUC over one dosing interval (AUC_τ, $\tau = 12$ or 24 h) following repeated administration as a test of compatibility with steady-state predictions for time-independent linear pharmacokinetics. Concentrations in each subject were also simulated over the 2 week administration period by tabular superposition of single-dose concentrations (Gibaldi and Perrier, 1982b) programmed using Lotus macro instructions: 0–12 h sampling times were repeated, and concentrations beyond 12 h after each dose digitized from extrapolation using the terminal half-life. Parameters derived from the simulated curve were compared with experimental parameters. The effect of dosing-regimen on experimental t_{max} values was also investigated.

Accumulation was evaluated from comparison of C_{max}, AUC(0–12 h) and AUC(0–24 h) between treatments. Accumulation ratios ($R_{A,C_{max}}$, $R_{A,\tau}$), were calculated as within-subject ratios of C_{max} and of AUC_τ for repeated administration v single dose.

The repeated dose profile was also described by the average concentration over a dosing interval ($C_{av} = AUC_\tau/\tau$) and, where quantifiable, a minimum concentration (C_{min}).

Analysis of variance of log-transformed parameters was used to evaluate the effect of the two or three treatment levels (single-dose, o.a.d. and b.i.d.) on the various AUC and C_{max} parameters, as well as for two-level comparisons of simulated vs experimental parameters: subject was included as a random factor. For three-level tests, significance of pairwise level contrasts was evaluated from F statistics only if a significant ($p < 0.05$) overall effect was observed. Effect of treatment on t_{max} was analysed non-parametrically by Friedman's test. Details of further calculations are described with the results.

For the metabolite MPCA, a more limited analysis was carried out on the experimental data, but following procedures similar to the above. Metabolite/parent parameter ratios were not corrected for molecular weight differences.

Results and Discussion

Pharmacokinetics

Mean (±SE) plasma levels of acipimox obtained on days 1 (single dose), 7 (o.a.d), and 14 (b.i.d.) are shown in Fig. 1, whilst the corresponding data for the metabolite MPCA are illustrated in Fig. 2. Mean (±SD) values for the pharmacokinetic parameters of acipimox and MPCA on days 1, 7 and 14 are reported in Tables 1 and 2, respectively.

Maximum acipimox plasma levels were rather similar for all three treatments, and peaked at similar times. A slight increase in plasma levels was however indicated for the b.i.d. treatment, confirmed by the significant treatment dependence of AUC(0–12 h) ($p < 0.01$ for b.i.d. vs single dose; $p < 0.05$ for b.i.d. vs o.a.d; $p > 0.5$ for o.a.d. vs single dose). Other pharmacokinetic parameters were not significantly dependent on treatment, but similar mean values of $R_{A,C_{max}}$ and $R_{A,\tau}$ were found (less than 1.1 for o.a.d., and 1.25–1.27 for b.i.d). For all subjects and treatments, concentrations of unchanged drug were quantifiable at 12 h but below the quantification limit at 24 h. Only the b.i.d. regimen gave a quantifiable C_{min}.

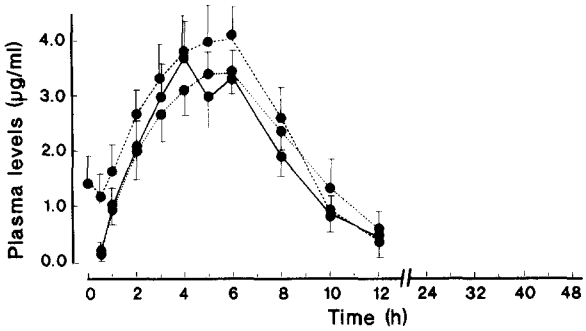

Fig. 1. Mean (±SE) concentrations of acipimox following a single dose (———), and o.a.d. (.....) and b.i.d. (------) repeated administration of 500 mg SR formulation to 10 healthy volunteers.

The repeated dose plasma curves did not deviate seriously from expectation based on linear superposition. Single-dose AUC(0–∞) did not differ significantly from experimental repeated-dose AUC_τ values, and was identical to simulated AUC_τ, confirming steady state. No significant differences were found between experimental and simulated repeated-dose parameters C_{max} and AUC_τ, and C_{av} was thus approximately propor-

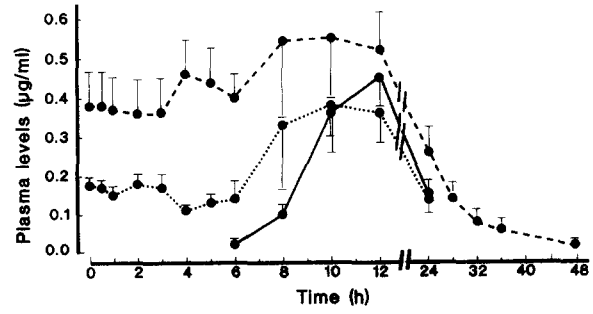

Fig. 2. Mean (±SE) concentrations of the *N*-deoxy metabolite of acipimox following a single dose (———), and o.a.d. (.....) and b.i.d (------) repeated administration of 500 mg SR formulation of acipimox to 10 healthy volunteers.

TABLE 1

Pharmacokinetic parameters (means; ±SD in parentheses) of acipimox following a single dose (day 1), and o.a.d (day 7) and b.i.d (day 14) repeated administration of 500 mg SR formulation to 10 healthy volunteers (simulated parameters in square brackets)

Parameter	Single dose	o.a.d.	b.i.d
C_{max} (μg/ml)	4.3 (±1.5)	4.2 (±0.9)	5.1 (±1.6)
		[4.3 (±1.5)]	[4.4 (±1.5)]
C_{av} (μg/ml)	–	1.1 (±0.4)	2.4 (±0.6)
		[1.1 (±0.4)]	[2.1 (±0.8)]
C_{min} (μg/ml)	–	< 0.05	0.24 (±0.12)
		[< 0.05]	[0.47 (±0.73)] [a]
t_{max} (h)	5.3 (±1.4)	5.8 (±2.0)	5.6 (±1.6)
		[5.3 (±1.4)]	[5.3 (±1.4)]
$t_{1/2}$ (h)	1.4 (±0.1) [a]	1.5 (±0.3)	1.4 (±0.2)
AUC(0–12 h) (μg h ml^{-1})	23.6 (±6.8)	24.9 (±7.3)	29.3 (±8.3)
		[23.9 (±7.1)]	[25.6 (±9.1)]
AUC(0–24 h) (μg h ml^{-1})	25.3 (±8.5)	26.3 (±8.6)	–
		[25.6 (±9.1)]	
AUC(0–∞) (μg h ml^{-1})	25.6 (±9.1)	–	–
$R_{A,C_{max}}$	–	1.04 (±0.29)	1.25 (±0.44)
		[1.00 (±0.01)]	[1.03 (±0.07)]
$R_{A,\tau}$	–	1.08 (±0.29)	1.27 (±0.27)
		[1.00 (±0.02)]	[1.08 (±0.16)]

[a] Single-dose $t_{1/2}$ for nine subjects, rejecting one outlier. Rejection of the same subject for simulated C_{min} shifts tabulated value to 0.24 (±0.10) μg/ml.

tional to dosing frequency. Simulated and experimental t_{max} values were identical. B.i.d. mean plasma levels did nevertheless appear marginally higher than expected, and a minor alteration in this plasma profile was demonstrable: concentrations at time 0 were higher than at 12 h ($p < 0.05$ by paired t-test and Wilcoxon signed-rank test: log transformation not used as some concentrations were below the quantification limit) suggesting some circadian variation in steady-state levels.

Maximum plasma levels of metabolite MPCA were consistently lower than those of the parent, but variation in individual plasma profiles was considerably greater. The metabolite generally arrived in plasma later than acipmox, peaked at later times, and remained above the quantification limit for longer periods. Following the single acipimox dose, MPCA was below the quantification limit for the first 5 h in all subjects, and up to 10 h in some: the limited data did not permit accurate determination of half-life or AUC. Plasma levels above the quantification limit were found in some subjects up to 24 h following single-dose and o.a.d. regimens, and up to 48 h following b.i.d. treatment. An increase in MPCA with repeated dosing was particularly noticeable

TABLE 2

Pharmacokinetic parameters (means ± SD) of the N-deoxy metabolite of acipimox following a single dose (day 1) and o.a.d. (day 7) and b.i.d (day 14) repeated administration of 500 mg SR formulation of acipimox to 10 healthy volunteers

Parameter	Single dose	o.a.d.	b.i.d
C_{max} (μg/ml)	0.49 (±0.24)	0.55 (±0.47)	0.79 (±0.55)
C_{av} (μg/ml)	–	0.23 (±0.14)	0.45 (±0.27)
t_{max} (h)	11.0 (±1.4)	6.7 (±5.3)	5.4 (±4.4)
AUC(0–12 h) (μg h ml^{-1})	–	2.83 (±2.33)	5.45 (±3.27)
AUC(0–24 h) (μg h ml^{-1})	–	5.59 (±3.44)	–

at early times, and AUC(0–12 h) was clearly higher ($p < 0.05$) for b.i.d than o.a.d. administration. Although a significant treatment dependence was not demonstrable for C_{max} and t_{max}, mean metabolite/parent ratios of C_{max} increased (approx. 0.12, 0.19 and 0.38 for single-dose, o.a.d. and b.i.d., respectively). MPCA AUC_τ was similar for o.a.d. and b.i.d. regimens, and similar mean steady state metabolite/parent C_{av} ratios were found, albeit with very high scatter (mean values 0.26 and 0.22, respectively; or, geometric means 0.18 and 0.17; ranges 0.03–0.70 and 0.06–0.51). Following b.i.d. administration, concentrations at the start of the dosing interval were significantly lower than at the end ($p < 0.05$).

The kinetics of SR acipimox observed in the current study were in good agreement with the single-dose SR profile reported in a previous comparative bioavailability study (Efthymiopoulos et al., 1990). The repeated dose pharmacokinetics may also be compared with those reported for the clinically used IR 250 mg t.i.d. (8 h) regimen (Efthymiopoulos et al., 1992). In that study mean ($\pm$SD), C_{max} 5.9 ($\pm$1.7) μg/ml, C_{av} 2.1 ($\pm$0.4), C_{min} 0.16 ($\pm$0.05) μg/ml, and t_{max} 1.6 ($\pm$0.6) h were obtained for unchanged drug in nine healthy volunteers after 8 days repeated dosing, and some diurnal variations in steady state plasma levels were also noticed. Both o.a.d. and b.i.d. administration of 500 mg SR formulation produced similar (slightly lower) acipimox maxima but at later times than the IR regimen, although only the b.i.d. regimen gave a comparable C_{av}. The 12 h administration also provided a C_{min} which compares favourably with thrice-daily IR dosing and with a previous proposal of 0.2 μg/ml as a minimum effective plasma concentration for acipimox (Fuccella et al., 1980).

Terminal half-life estimations for acipimox appear rather insensitive to differences between IR and SR formulations and the effect of food. Both the single-dose comparative bioavailability study and the repeated dose IR t.i.d. data (Efthymiopoulos et al., 1990, 1992) * indicated mean $t_{1/2}$ in the range 1.1–1.3 h for IR and 1.4–1.5 h for SR formulations, covering fasting and fed conditions, and consistent with the present study. The absence of a marked rate-limiting effect of absorption during the apparent terminal phase (from approx. 8 h) suggests that sustained release is practically complete by this time.

Maximum steady state concentrations of metabolite MPCA in the IR t.i.d. study (mean C_{max} approx. 0.5 μg/ml, t_{max} ca 4 h) were considerably lower on average than unchanged drug, as with the SR regimens reported here, and again with considerable variability between individual profiles. Closer examination suggested that metabolite plasma levels were even lower for the IR form, but the high variability prevented definite conclusions: for the IR repeated dose study, (arithmetic) mean steady state metabolite/parent C_{av} ratio was 0.15; range 0–0.46; geometric mean 0.09 (a highest estimate obtained by maximising unquantifiable metabolite concentrations); a comparable arithmetic mean ratio, 0.10, was found for C_{max}.

The SR formulation might be expected either to increase metabolite production (eg. by presenting acipimox in fully dissolved form throughout the intestine) or reduce production (by reducing the proportion of acipimox which reaches the distal intestinal regions). An increased production could, on the other hand, reflect inadequate gastric retention of the dosage form, resulting in an increased rather than decreased residence time in the vicinity of the microflora. This latter possibility appears to be important for fasting conditions: in the comparative bioavailability study (Efthymiopoulos et al., 1990) the previously noted poor bioavailability of acipimox SR in the absence of food (mean AUC for 600 mg dose about 60% of that under fed conditions) correlated with a marked rise in plasma levels of MPCA both in absolute terms and relative to acipimox: metabolite/parent C_{max} ratio rose to an arithmetic mean

* Comments on these studies are based on original data on file at Farmitalia Carlo Erba. Some parameters quoted in the current paper, notably acipimox C_{min} and metabolite/parent C_{av} ratios for t.i.d. IR acipimox, have been calculated directly from these data. The literature reference describing the comparative bioavailability study reports pharmacokinetics only of unchanged drug: comments in this section on MPCA plasma levels refer to unpublished data from the same study.

of 0.29 after fasting (range 0.13–0.57), compared with 0.04 (range 0–0.12) under fed conditions, and mean AUC estimates rose from poorly quantifiable values to over 60% of the parent AUC(0–∞). For the IR formulation (fasting and fed conditions) and for the SR formulation under fed conditions, C_{max} metabolite/parent ratios remained low (mean values all below 0.10). The clinical data of the present study on repeated SR administration confirm that with normal eating habits, alterations in MPCA concentrations should be of limited magnitude. The pharmacokinetics will clearly be better controlled if each dose is taken after a meal.

Tolerability

Although the aim of the present study was the evaluation of the pharmacokinetics of the new formulation, some preliminary information on tolerability was obtained. While flushing and headache prevailed in the adverse events reported after the single administration, the most common symptoms encountered during multiple dosing were recurrent nausea and other kinds of gastric discomfort. None of these adverse events was severe, therefore none of the subjects withdrew from the study because of them. However, definite conclusions on the tolerability and efficacy the new formulation of acipimox will be made only after specifically designed placebo-controlled trials.

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