Flecainide: single and multiple oral dose kinetics, absolute bioavailability and effect of food and antacid in man

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- 1 The kinetics of flecainide after single intravenous (2 mg kg^{-1}) and oral (200 mg) dosing, absolute bioavailability, effects of food and aluminium hydroxide on flecainide absorption and steady-state kinetics following twice daily oral dosing (200 mg) have been evaluated in ten healthy subjects.
- 2 Absolute bioavailability of oral flecainide averaged 70% (range 60–86%). Rate and extent of flecainide absorption were not significantly affected by food nor by concomitantly administered aluminium hydroxide.
- 3 The apparent volume of distribution of $5.5 \pm 0.3 \text{ l kg}^{-1}$ indicates wide distribution of flecainide in tissues.
- 4 Estimated elimination half-lives from plasma data averaged 9.3 to 12.4 h (single oral dose studies), 11.8 h (single i.v. dose), and 11.5 h (multiple oral dose). Half-lives calculated from urinary excretion data corresponded well with those calculated from plasma data.
- 5 Flecainide elimination takes place both by nonrenal (metabolic) clearance and renal excretion of the intact drug involving glomerular filtration and active tubular secretion. Following i.v. dosing CL_{NR} and CL_{R} averaged respectively 3.24 ± 0.80 and $2.38 \pm 0.49 \text{ ml min}^{-1} \text{ kg}^{-1}$.
- 6 After 200 mg twice daily oral treatment steady state was reached within 3–4 days with trough and peak plasma levels on day 8 of 457 and 662 ng ml^{-1} , which are well within the therapeutic range.

Keywords flecainide bioavailability food aluminium hydroxide pharmacokinetics

Introduction

Flecainide acetate [2,5 bis (2,2,2-trifluoroethoxy)-*N*-(2-piperidylmethyl) benzamide acetate; Riker Laboratories] is a recently introduced class Ic antiarrhythmic agent (Vaughan Williams, 1984) characterized by good patient tolerance and broad spectrum of activity particularly in the treatment of ventricular arrhythmias (Anderson

et al., 1981; Duff *et al.*, 1981; Duran *et al.*, 1982; Hodges *et al.*, 1982).

A preliminary kinetic and metabolic study in man using ^{14}C -labelled drug, indicated that flecainide undergoes both renal excretion and biotransformation by oxidative dealkylation to form two major metabolites meta-*O*-dealkylated

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flecainide and meta-*O*-dealkylated lactam of flecainide, which are recovered in urine both in the free and conjugated (glucuronide/sulphate) forms (Conard & Ober, 1984; McQuinn *et al.*, 1984).

The present study was undertaken to evaluate the kinetics of flecainide in healthy volunteers after oral and intravenous administration, its absolute bioavailability, the influence of food intake and aluminium hydroxide on flecainide absorption and the accumulation and steady-state kinetics of flecainide during chronic oral treatment.

Methods

Subjects and study design

Subjects (mean age: 22.6 ± 0.5 years, mean weight: 71 ± 8 kg) were 10 male volunteers judged to be healthy on the basis of clinical examination, routine blood chemistry, urinalysis, ECG and creatinine clearance (105 ± 9 ml min⁻¹). Written informed consent was obtained according to institutional policy. Subjects participated in the following treatments:

- Five subjects received, after an overnight fast, a single intravenous dose of 2 mg kg^{-1} flecainide as a slow injection over 5 min. Breakfast was allowed 2 h post drug administration.
- Ten subjects, of which five participated in the i.v. study, received, on three occasions at least 1 week apart, a single oral 200 mg dose of flecainide under the following conditions: fasting (breakfast was allowed 2 h post-drug intake), with food and 1 h post-prandial. Nine of these subjects also received a 200 mg single dose of flecainide given with concomitant aluminium hydroxide treatment (Aldrox®, Wyeth): 15 ml (280 mg aluminium hydroxide per 5 ml suspension) 1 h before, 15 ml with and 15 ml 1 h after flecainide administration.
- Eight subjects received orally flecainide 200 mg twice daily (at 09.00 h and 21.00 h) during 8 consecutive days.

Each oral flecainide dose was administered with 200 ml of water.

Venous blood samples were collected into heparinized tubes and plasma was kept at -20°C until assay. In the single oral dose studies blood was sampled before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36 and 48 h after drug administration. In the intravenous study, additional samples were taken at the end of the 5 min injection and at 10, 20 and 45 min after the injection. During

the repeated oral dose study serial blood samples (*cfr. supra*) were obtained during one dosing interval (12 h) after the first dose and up to 72 h following the final dose given in the morning of day 8. In addition, pre-morning dose blood samples (trough levels) were taken on days 2, 3, 4 and 5. In the case of the i.v. and the single oral flecainide administrations, urine was collected at the following times: blank, 0–2, 2–4, 4–6, 6–12, 12–24, 24–36 and 36–48 h. In the multiple oral dose study, urine was collected during one dosing interval after the first dose and during 120 h following the last dose.

Drug analysis

Flecainide acetate in plasma and urine was measured by gas-liquid chromatography with electron-capture detection (Johnson *et al.*, 1984) using an analogue of flecainide (S-15531) as the internal standard. This method is specific for unchanged flecainide and is linear from 10 to 1000 ng ml⁻¹ in plasma and urine. The lower limit of detection is 10 ng ml⁻¹ using 1 ml of plasma or diluted urine. Coefficients of variation (CV%) for plasma and urine concentrations (range 50 to 1000 ng ml⁻¹) were respectively 2.5% and 3.8%. Results obtained with the g.l.c. method were found comparable to those obtained by h.p.l.c. using either UV- or fluorescence detection (Chang *et al.*, 1984; Verbesselt *et al.*, 1984).

Safety monitoring

After intravenous flecainide subjects remained supine for 1 h and were followed by serial electrocardiographic (ECG) monitoring and repeated blood-pressure measurements. Holter monitoring was performed during 12 h following drug administration and a 12-lead electrocardiogram was obtained before the study and repeated on the last day of each study period.

Pharmacokinetic analysis

Intravenous flecainide Plasma concentration-time data (C_p , t) of flecainide were analyzed by standard methods (Gibaldi & Perrier, 1982) with a curve-fitting program developed for nonlinear least squares analysis of kinetic data (von Hattingberg *et al.*, 1977). Data were fitted to a biexponential equation of the form $C_p = Ae^{-\alpha t} + Be^{-\beta t}$ where A and B are the zero time intercepts of the data plotted on semilogarithmic paper and α and β are the rapid and slow rate constants respectively. Distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) were calcu-

lated from $t_{1/2\alpha} = 0.693/\alpha$ and $t_{1/2\beta} = 0.693/\beta$. Pseudodistribution equilibrium between the two compartments was taken as the time at which f_α , given by the following equation, attained a value of 0.01 or less:

$$f_\alpha = \frac{Ae^{-\alpha t}}{Ae^{-\alpha t} + Be^{-\beta t}}$$

Area under the curve (AUC_{0-t}) was determined by the trapezoidal rule and extrapolated to infinity (AUC) by adding to AUC_{0-t} , the last measurable plasma concentration divided by β .

The volume of the central compartment (V_1) and the volume at steady state (V_{ss}) were calculated respectively from:

$$V_1 = \frac{\text{Dose}_{iv}}{A + B} \text{ and } V_{ss} = \frac{\text{Dose}_{iv} \left(\frac{A}{\alpha^2} + \frac{B}{\beta^2} \right)}{(AUC)^2}$$

The volume of distribution during the β -phase was calculated from:

$$V_\beta = \frac{\text{Dose}_{iv}}{AUC_\beta}$$

Total plasma clearance was calculated from:

$$CL = \frac{\text{Dose}_{iv}}{AUC}$$

$$\text{and renal clearance from } CL_R = \frac{A_e(\infty)}{AUC}$$

where $A_e(\infty)$ is the total amount of flecainide excreted unchanged in the urine. Nonrenal clearance was obtained from $CL_{NR} = CL - CL_R$.

Elimination half-life of flecainide from the urinary data ($t_{1/2\text{urine}}$) was estimated by the rate method (Gibaldi & Perrier, 1982).

Oral flecainide The absolute bioavailability (F) of flecainide was calculated from plasma data using the equation:

$$F_{(AUC)} = \frac{AUC_{po}}{AUC_{iv}} \times \frac{\text{Dose}_{iv}}{\text{Dose}_{po}} \times 100\%$$

and from urinary excretion data using the equation:

$$F_{(Ae)} = \frac{A_{e(\infty) po}}{A_{e(\infty) iv}} \times \frac{\text{Dose}_{iv}}{\text{Dose}_{po}} \times 100\%$$

Elimination half-life after oral dosing was determined from the terminal linear part of the log concentration time curve by linear regression analysis. For those five subjects who also parti-

cipated in the i.v. bioavailability study, plasma levels after flecainide taken in the fasting state were, for comparative purposes, also analyzed by curve fitting in the same way as they were analyzed after i.v. dosing (*cf. supra*).

Following the last (15th) dose of the multiple dose treatment, the average steady-state plasma concentration (C_{av}^{ss}) was calculated from:

$$C_{av}^{ss} = \frac{AUC_\tau^{ss}}{\tau}$$

where τ is the dosage interval (12 h).

The maximum (C_{max}^{ss}) and minimum or trough (C_{min}^{ss} 0 h and C_{min}^{ss} 12 h) drug concentrations and the time to reach peak concentration (t_{max}) were read from the individual curves. Interdose fluctuation was estimated from:

$$C_{max}^{ss}/C_{min}^{ss} \text{ 12 h}$$

Time to reach steady-state (t_{ss}) was determined by comparing the 'trough' levels at steady-state on day 8 with the 'trough' levels during the accumulation phase. The accumulation ratio (R) was estimated from:

$$R = \frac{AUC_{0-12} \text{ Dose 15}}{AUC_{0-12} \text{ Dose 1}}$$

Results and discussion

Single-dose studies

Intravenous vs oral administration Mean plasma concentration profiles following single doses of intravenous (2 mg kg^{-1}) and oral (200 mg) flecainide in five subjects are shown in Figure 1 and the corresponding kinetic data are listed in Table 1.

After intravenous dosing, the disposition of flecainide is best described by a two compartment model with an initial rapid distribution phase followed by a slow post-distribution phase. Contribution of the distribution phase component (A/α) to the total area under the curve appears very small. The mean elimination half-life (β -phase) of 11.8 h lies well within the range reported earlier by Conard *et al.* (1976, 7–15 h) and by Conard *et al.* (1979, 7–19 h).

Pseudo-distribution equilibrium was, on the average, attained within 30 min after i.v. administration. The relatively large distribution volume indicates that flecainide is widely distributed in the tissues.

Approximately 40% of the intravenous dose was excreted unchanged in the urine (Table 1, Figure 2) while 60% was eliminated by a non-

Figure 1 Mean ($\pm$ s.e. mean) plasma concentration vs time curves after 2 mg kg^{-1} intravenous ($\blacktriangle$) and 200 mg oral ($\bullet$) flecainide in five healthy volunteers.

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) of intravenous flecainide and oral flecainide in five normal subjects

Parameter	Intravenous (2 mg kg^{-1} over 5 min)	Oral (200 mg)
$C_{\max}$ (ng ml $^{-1}$)	1710 ± 788	355 ± 48
$t_{\max}$ (h)	end of inj.	2.3 ± 0.7
A (ng ml $^{-1}$)	1385 ± 780	—
B (ng ml $^{-1}$)	322 ± 25	—
α (h $^{-1}$)	15.6 ± 6.0	—
$t_{1/2\alpha}$ (min)	3.0 ± 1.2	—
β (h $^{-1}$)	0.061 ± 0.012	0.066 ± 0.014
$t_{1/2\beta}$ (h)	11.8 ± 2.8	10.9 ± 2.3
AUC_{0-36} (ng ml $^{-1}$ h)	5147 ± 1129	—
AUC (ng ml $^{-1}$ h)	6238 ± 1749	5979 ± 1598
$F_{(\text{AUC})}$ (%)	—	69.6 ± 11.0
V_1 (l kg $^{-1}$)	1.7 ± 1.6	—
V_{ss} (l kg $^{-1}$)	4.9 ± 0.4	—
V_{β} (l kg $^{-1}$)	5.5 ± 0.3	—
CL (ml min $^{-1}$ kg $^{-1}$)	5.62 ± 1.26	—
CL_R (ml min $^{-1}$ kg $^{-1}$)	2.38 ± 0.49	2.39 ± 0.43
CL_{NR} (ml min $^{-1}$ kg $^{-1}$)	3.24 ± 0.80	—
$A_e(48)$ (% dose)	38.4 ± 2.6	28.7 ± 10.4
$A_e(\infty)$ (% dose)	42.7 ± 2.9	31.0 ± 11.2
$t_{1/2 \text{ urine}}$ (h)	12.7 ± 2.8	10.6 ± 2.0
$F(A_e)$ (%)	—	72.3 ± 23.8

renal route, which according to McQuinn *et al.* (1984) is essentially metabolic. The mean renal clearance of unchanged flecainide of 171 ml min^{-1} corresponds well with the 176 ml min^{-1} reported by Franciosa *et al.* (1983) but is somewhat higher than the value of 122 ml min^{-1} obtained by Johnston *et al.* (1985). Since flecainide is approximately 40% bound to plasma proteins (Johnston *et al.*, 1982), the glomerular clearance would be

approximately 72 ml min^{-1} indicating that renal excretion of flecainide involves substantial net tubular secretion in addition to glomerular filtration.

After oral administration flecainide is rapidly absorbed. Estimates of elimination half-life and renal clearance corresponded well with those obtained after the i.v. dose. The absolute bioavailability averaged 70% based on AUC, and

Figure 2 Cumulative urinary recovery (mean $\pm$ s.d.) of unchanged flecainide after single doses of flecainide given intravenously (2 mg kg^{-1} , ●) and orally (200 mg , ○) in five healthy volunteers.

Table 2 Kinetic parameters (mean $\pm$ s.d.) of oral flecainide (200 mg): effect of food and aluminium hydroxide

Kinetic variable	Fasting n = 10	With food n = 10	1 h after meal n = 10	With antacid n = 9
$C_{\max}$ (ng ml^{-1})	341 ± 41	355 ± 62	347 ± 89	332 ± 67
$t_{\max}$ (h)	2.4 ± 1.0	2.8 ± 0.9	2.8 ± 1.5	2.5 ± 1.6
$t_{1/2}$ (h)	9.4 ± 2.6	10.6 ± 2.0	9.3 ± 2.7	$*12.4 \pm 3.8$
AUC ($\text{ng ml}^{-1} \text{ h}$)	5061 ± 1540	5723 ± 1103	4801 ± 1236	$*6118 \pm 1376$
A_e (48) (% of dose)	29.5 ± 7.5	29.5 ± 6.1	29.6 ± 5.7	29.9 ± 5.1

* $P < 0.05$. (Two-way ANOVA followed by Tukey's Multiple Range Test vs fasting)

72% based on the urinary recovery of unchanged flecainide. These values are somewhat lower than the mean absolute bioavailability of 95% (range 71–124%) reported by Conard *et al.* (1979).

Effect of food and aluminium hydroxide on flecainide absorption The kinetic parameters of flecainide in ten subjects taking the drug in the fasting state, with food, 1 h postprandial and with aluminium hydroxide are listed in Table 2 and the mean plasma concentration profiles are shown in Figure 3. Comparison of the parameters by ANOVA did not disclose statistically significant differences for either the $C_{\max}$ or $t_{\max}$ values. Single dose administration of oral flecainide on the four separate occasions resulted in a small variation in plasma half-life: from a mean value of 9.4 h in the fasting state to 10.6 h with food, 9.3 h after meal and 12.4 h with antacid, the

latter value being statistically significantly different from control although well within the range (5.8–13.0) found in the fasting state. The mean 48 h urinary recovery of unchanged flecainide was practically identical in the different treatments (Table 2).

Multiple-dose study

The plasma and urine data of flecainide after the first dose (day 1) and after the fifteenth dose (day 8) are listed in Table 3 and the corresponding mean plasma profiles are illustrated in Figure 4. A 200 mg twice daily regimen resulted in mean pre-morning dose (trough) levels of 286 ± 42 , 369 ± 91 , 442 ± 108 , 492 ± 122 and $500 \pm 128 \text{ ng ml}^{-1}$ respectively on day 2, 3, 4, 5 and 8. Potentially therapeutic trough levels of approximately 400 ng ml^{-1} were therefore reached within 3 to 4 days. Mean steady-state and peak

Figure 3 Mean plasma concentrations of flecainide in healthy volunteers after a 200 mg oral dose given fasting (●), with food (Δ) and 1 h postprandial (□) (upper panel, $n = 10$) and given with aluminium hydroxide (◇) (lower panel, $n = 9$).

Table 3 Pharmacokinetic parameters (mean $\pm$ s.d.) of flecainide following single and multiple oral administration in eight healthy volunteers

Parameters	Single dose (200 mg) Day 1	Multiple dose (200 mg 12 hourly) Day 8
$C_{\max}$	382 $\pm$ 82	901 $\pm$ 125
$C_{\min}$ 12 h	164 $\pm$ 31	457 $\pm$ 130
$C_{\max}^{\text{ss}}/C_{\min}^{\text{ss}}$		2.09 $\pm$ 0.54
$t_{\max}$ (h)	1.7 $\pm$ 1.0	1.6 $\pm$ 0.7
t_{ss} (days)		3.6 $\pm$ 0.5
AUC_{0-12} (ng ml $^{-1}$ h)	2894 $\pm$ 238	7944 $\pm$ 1753
AUC (ng ml $^{-1}$ h)	4888 $\pm$ 670	15944 $\pm$ 5623
R		2.70 $\pm$ 0.67
$C_{\text{av}}^{\text{ss}}$ (ng ml $^{-1}$)		662 $\pm$ 146
$t_{1/2}$ (h)		11.5 $\pm$ 3.0
A_e (12) (% of dose)	17.8 $\pm$ 3.5	37.0 $\pm$ 9.0

Figure 4 Mean plasma concentration profiles of flecainide after the first and final (15th) dose of a 200 mg twice daily treatment ($n = 8$). Pre-morning dose concentrations were obtained on day 2, 3, 4 and 5.

concentration on day 8 were also well within the therapeutic range of 200 to 1000 ng ml⁻¹ (Conard & Ober, 1984).

Reported side-effects

Reported adverse symptoms consisted of transient feelings of thickness of lips, tongue and palate within 10 min (after i.v. injections). Furthermore, transient headache and ocular symptoms

e.g. heavy eyelids and blurring of vision were reported after i.v. dosing and also after the last doses of multiple dose oral treatment. Excessive slowing of heart rate (to 30–40 beats min⁻¹) was observed during 5 min in one subject immediately after i.v. flecainide. At the latest 1 h post i.v. administration, all subjects were symptom free. Electrocardiograms taken before and after completion of the study were normal.

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(Received 5 February 1985,
accepted 13 March 1986)