JPP Journal of Pharmacy and Pharmacology

JPP 2005, 57: 47–51

Received July 27, 2004
Accepted September 27, 2004
DOI 10.1211/0022357055128
ISSN 0022-3573

Assessment of serum flecainide trough levels in patients with tachyarrhythmia

Masato Homma, Keisuke Kuga, Kosuke Doki, Kumi Katori, Iwao Yamaguchi, Kenji Sugibayashi and Yukinao Kohda

Abstract

The reported therapeutic range for trough flecainide concentration is 200–1000 ng mL^{-1}. Severe adverse events, such as ventricular arrhythmias, have occurred occasionally in patients whose serum flecainide exceeded 1000 ng mL^{-1}. However, the lower limit remains controversial. We have evaluated blood flecainide concentrations in patients with tachyarrhythmia who received the drug to control palpitation. We measured the flecainide trough levels and incidence and frequency of palpitation of 44 outpatients receiving oral flecainide (150–300 mg daily). Mean serum flecainide trough concentrations differed significantly between patients with (n = 14) and without (n = 30) palpitation (259.5 ± 85.2 vs 462.2 ± 197.7 ng mL^{-1}, $P < 0.01$). The frequency of palpitation decreased as the serum flecainide concentration increased. The incidence of palpitation was 65% at serum flecainide concentrations < 300 ng mL^{-1} and 11% at ≥ 300 ng mL^{-1}. QRS values were increased significantly in patients with serum flecainide ≥ 300 ng mL^{-1} compared with < 300 ng mL^{-1} (0.110 ± 0.016 s vs 0.093 ± 0.019 s, $P < 0.05$). We concluded that to control paroxysm in patients receiving flecainide for tachyarrhythmia serum flecainide concentrations should be maintained at ≥ 300 ng mL^{-1}.

Department of Pharmaceutical Sciences, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ten-nodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan

Masato Homma, Kosuke Doki, Kumi Katori, Yukinao Kohda

Department of Internal Medicine, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ten-nodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan

Keisuke Kuga, Iwao Yamaguchi

Faculty of Pharmaceutical Sciences, Josai University, Keyakidai 1-1, Sakado, Saitama 350-0295, Japan

Kenji Sugibayashi

Correspondence: M. Homma, Department of Pharmaceutical Sciences, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ten-nodai 1-1-1, Tsukuba, Ibaraki 305-8575, Japan. E-mail: masatoh@md.tsukuba.ac.jp

Funding and acknowledgements: This study was supported by research funds from the University of Tsukuba. We greatly appreciate Eisai Co. Ltd for providing flecainide and the internal standard for the assay.

Introduction

Flecainide, a Vaughan–Williams class 1c anti-arrhythmic agent, is commonly used as a strong sodium channel blocker for a variety of supraventricular tachycardia (Crozier et al 1987; Kreeger & Hammill 1987). In the Cardiac Arrhythmia Suppression Trial (CAST), flecainide failed to decrease mortality due to cardiac arrest as the toxic event of this drug (Echt et al 1991). However, these adverse events may be prevented if serum concentrations are monitored while establishing the dosage regimen of flecainide. It is well recognized that keeping serum concentration in the therapeutic range of flecainide provides relevant clinical effects without serious adverse events (Conard et al 1982).

Variation in the pharmacokinetics of flecainide has been known by changes in the clearance, which was characterized by renal and hepatic elimination including oxidative metabolism on CYP2D6 (Mikus et al 1989). The elimination half-life of this drug was reported to be 8.5–21.4 h (McQuinn et al 1984). Trough concentration monitoring, therefore, is used for the daily dose adjustment.

The reported therapeutic range for trough flecainide concentration is 200–1000 ng mL^{-1} in patients with chronic ventricular arrhythmias (Conard et al 1982). Severe adverse events, such as ventricular arrhythmias, occurred occasionally in patients whose serum flecainide level exceeded 1000 ng mL^{-1} (Morganroth & Horowitz 1984; Roden & Woosley 1986). Therefore, the upper limit of the therapeutic range of this drug is well established. The lower limit, however, remains controversial. In this study, we have evaluated blood flecainide concentrations that provided the relevant conditions without causing palpitation in patients receiving long-term flecainide for tachyarrhythmia.

Materials and Methods

Patients and sample collection

The study population comprised 44 outpatients (36 males and 8 females; Table 1) receiving oral flecainide for tachyarrhythmia. Of these 44 patients, 13 had complications such as cardiac insufficiency, hypertension, diabetes, hyperlipidaemia, and renal insufficiency requiring haemodialysis. Liver function was normal in all patients. Before the study, patients had received flecainide for 1–100 months (mean ± s.d., 18.5 ± 26.3 months). The daily dose of flecainide was 1.82–4.17 mg kg^{-1} (2.96 ± 0.58), and the patients administered flecainide twice (n = 30) or three times a day (n = 14). Other anti-arrhythmic agents, digoxin, β-blockers (carteolol, nadolol, and atenolol), Ca^{2+} antagonists (diltiazem, nifedipine, amlodipine, nisoldipine, and nicardipine), angiotensin converting enzyme inhibitors (enalapril, imidapril, and quinapril), anti-coagulants (warfarin, aspirin, and ticlopidine), H_2-blocker (famotidine), and other agents (lipid-decreasing drugs, HMG-CoA reductase inhibitors) were co-administered as needed for disease control. No drugs affecting the flecainide pharmacokinetics were co-administered to these patients.

For the determination of the serum flecainide levels, blood was drawn between 0900 and 1100 h during an outpatient visit. On the day before blood sample collection patients administered their final evening flecainide dose between 1900 and 2100 h. On sample collection days, patients postponed taking their morning flecainide dose until after blood was drawn. Informed consent was obtained from all patients, and the study was approved by the ethical committee of the University of Tsukuba.

Chemicals and instruments

Flecainide acetate and its internal standard (N-(2-piperidylmethyl)-2,3-bis (2,2,2-trifluoro-ethoxy) benzamide acetate) were supplied by Eisai Co. (Tokyo, Japan). 1-Pentanesulfonic acid sodium salt was purchased from Wako Pure Chemicals (Osaka, Japan). All other chemicals were of HPLC or analytical reagent grade. C_{18}-cartridges (Extract-Clean C_{18}, 100 mg) for solid-phase extraction were obtained from Alltech Associates (IL).

The HPLC system consisted of a pump (CCPD, TOSOH, Tokyo, Japan), UV detector (UV-8010, TOSOH), and integrator (C-R4A, Shimadzu, Kyoto, Japan). The ODS column (TSK-GEL, 4.6 i.d. × 250 mm, TOSOH) for the HPLC system was maintained at room temperature. The detection wavelength was set at 298 nm. The mobile phase solution consisted of 0.1 M 1-pentanesulfonic acid sodium salt, acetonitrile, and acetic acid (250:206:2.5 v/v) and was pumped at a flow rate of 1.0 mL min^{-1}.

Determination of serum flecainide concentration

The serum concentration of flecainide was determined by HPLC as described by Nakagawa et al (2002). Briefly, 500 μL serum was combined with 150 μL internal standard solution and was then alkalinized by addition of 100 μL 0.02 M Na_2CO_3. The mixture was loaded onto a C_{18}-cartridge pretreated with 1 mL methanol and followed by 1 mL distilled water. The C_{18}-cartridge was set at Manihold (Alltech) and subsequently washed with 1 mL water, followed by 1 mL 50% methanol when under vacuum. Flecainide and the internal standard were eluted into glass tubes by treating the cartridge with 1 mL

Table 1 Patient profile

	With palpitation	Without palpitation	Total
Age (years)	56.3 ± 15.9	61.8 ± 14.0	60.1 ± 14.7
Sex (male/female)	14/0	22/8	36/8
Weight (kg)	68.5 ± 10.1	61.3 ± 14.5	63.6 ± 13.6
Diagnosis (n)			
Atrial fibrillation	5	20	25
Atrial fibrillation and atrial flutter	4	1	5
Atrial flutter	4	3	7
Paroxysmal supraventricular tachycardia	0	2	2
Wolff–Parkinson–White syndrome	1	2	3
Supraventricular premature contractions	0	2	2
Flecainide dose (mg kg^{-1} day^{-1})	2.85 ± 0.47	3.01 ± 0.63	2.96 ± 0.58
Flecainide concn (ng mL^{-1})*	259.5 ± 85.2	462.2 ± 197.7	397.7 ± 194.1
Laboratory data			
Aspartate aminotransferase (IU L^{-1})	21.9 ± 3.9	23.1 ± 8.7	22.7 ± 7.5
Alanine aminotransferase (IU L^{-1})	19.5 ± 6.9	22.6 ± 12.9	21.7 ± 11.5
Serum creatinine (mg dL^{-1})	0.7 ± 0.1	1.0 ± 1.7	0.9 ± 1.4
Blood urea nitrogen (mg dL^{-1})	16.7 ± 3.7	17.0 ± 6.5	16.9 ± 5.7
Serum albumin (g dL^{-1})	4.1 ± 0.3	4.0 ± 0.3	4.1 ± 0.3

Values are mean ± s.d. *$P < 0.05$, significant difference was observed between the groups with and without palpitations.

methanol. The effluents were evaporated to dryness under nitrogen gas. The sample was reconstituted with 100 μL mobile phase solution, and a 20-μL sample was injected into the HPLC. The intra- and inter-day precision evaluated at the concentrations of 80 and 400 ng mL^{-1} were 1.9–2.4% and 3.6–3.7%, respectively.

Statistical analysis

All data are presented as mean ± s.d. Data for serum flecainide concentration, QRS complex, and QTc interval were analysed using unpaired Student's *t*-tests. The threshold for statistical significance was set at 0.05.

Results

Mean serum flecainide trough concentrations differed significantly between patients with (n = 14) and without (n = 30) palpitation (259.5 ± 85.2 vs 462.2 ± 197.7 ng mL^{-1}, respectively, $P < 0.01$). We could not ascertain a clear relationship between daily dose and flecainide trough concentration (Figure 1). The patients with palpitation had lower serum flecainide trough concentrations of 200–400 ng mL^{-1}, and in four patients whose palpitation was quite often, trough concentrations were < 300 ng mL^{-1}.

Inter-day variation of serum flecainide concentrations was evaluated in nine patients, from whom blood samples were taken repeatedly to enable the determination of serum flecainide. The fluctuation of daily flecainide concentrations was less than 20% (data not shown).

We compared the frequency of palpitation between the patient groups reflecting the trough concentrations of < 300 and ≥ 300 ng mL^{-1} (Table 2). The incidence of palpitation (present vs absent) differed significantly between the two groups ($P < 0.05$, Table 2). In the ≥ 300 ng mL^{-1} group, only three patients (11%) experienced palpitation, with the frequency being less than once per month. Among those with serum flecainide levels of < 300 ng mL^{-1}, 11 patients (65%) complained of palpitation, and seven of them had more than one episode per month (Table 2).

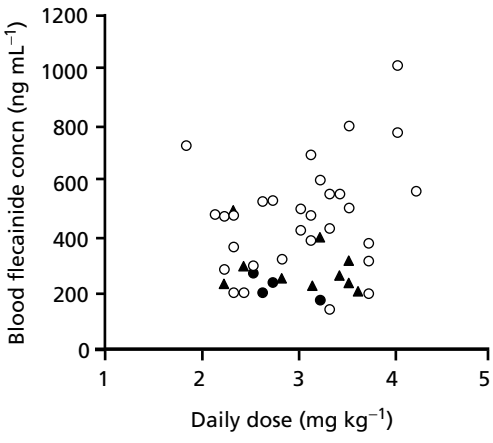

Figure 1 Relationship between daily flecainide dose and serum flecainide concentration in patients with tachyarrhythmia. ○, without palpitation; ▲, with palpitation rarely; ●, with palpitation quite often.

Table 2 Incidence and frequency of palpitation in patients receiving flecainide

Flecainide concn (ng mL^{-1})	Number of patients with palpitation (%)	Frequency of palpitation			
		Quite often	≥1 per month	< 1 per month	When taken with alcohol
< 300 (n = 17)	11 (65)	4	3	2	2
≥ 300 (n = 27)	3 (11)*	0	0	2	1
Total (n = 44)	14 (32)	4	3	4	3

*$P < 0.05$.

Table 3 QRS and QTc in patients with blood flecainide concentrations of above and below 300 ng mL^{-1}

Group	Flecainide concn (ng mL^{-1})	QRS (s)	QTc
< 300 (n = 13)	225.2 ± 40.6	0.093 ± 0.019	0.429 ± 0.018
≥ 300 (n = 12)	532.3 ± 182.4*	0.110 ± 0.016*	0.445 ± 0.060
Total (n = 25)	372.6 ± 201.5	0.101 ± 0.019	0.437 ± 0.043

*$P < 0.05$.

Electrocardiographic studies (Table 3) revealed that QRS values were significantly increased in the patients whose serum flecainide was ≥ 300 ng mL^{-1} compared with < 300 ng mL^{-1} (0.110 ± 0.016 vs 0.093 ± 0.019 s, $P < 0.05$). However, the QTc did not differ between the ≥ 300 and < 300 ng mL^{-1} groups (0.445 ± 0.060 vs 0.429 ± 0.018).

Discussion

This study assessed the incidence and frequency of a subjective symptom (palpitation) and electrocardiography data; the results indicated that the lower limit of the therapeutic range of flecainide trough levels in this population of patients with tachyarrhythmias was 300 ng mL^{-1}. Serum flecainide < 300 ng mL^{-1} was insufficient for blocking sodium channels, because QRS enlargement was not observed (Table 3), and resulted in uncontrolled palpitation in 65% of patients. However, in the patients with ≥ 300 ng mL^{-1} serum flecainide, symptoms were controlled well without increases in QTc. In addition, only 11% of this patient group had palpitation and then only rarely (< 1 episode per month). Therefore our results suggested that the therapeutic range of serum flecainide trough concentrations should be 300–1000 ng mL^{-1}.

Optimizing the daily dose of flecainide is very difficult due to large interindividual variations in the pharmacokinetics.

The poor relationship between the daily dose and flecainide trough levels highlighted the difficulty of estimating the dose of flecainide necessary to maintain serum levels within the therapeutic range without monitoring the serum flecainide concentration (Figure 1). The apparently conflicting results of the CAST study might not have materialized if the patients' serum flecainide concentrations had been kept in the therapeutic range of 300–1000 ng mL^{-1} by using a therapeutic drug monitoring system. The poor relationship between daily dose and serum flecainide was due to inter-individual variation, not intra-individual variation, in the pharmacokinetics of this drug. Of course, dose escalation increased the trough levels in individual subjects (data not shown).

Several factors are known to contribute to the large interindividual variation in serum flecainide levels, which we observed in our study. Liver and kidney dysfunction can alter flecainide pharmacokinetics (Forland et al 1988a, b; McQuinn et al 1988; Williams et al 1988); however, none of our patients had any history of liver or kidney dysfunction except for one patient, who received haemodialysis. Other possible factors are protein binding (Caplin et al 1985; Padrini et al 1993; Zordan et al 1993; Katori et al 2003), interaction with drugs concomitantly administered (Tjandra-Maga et al 1986; Munafo et al 1992), and polymorphism of CYP2D6 (Griese et al 1998; Nishida et al 2000), a main metabolizing enzyme of flecainide. This last factor is speculative as yet and is drawn from the reports of Gross et al (1989) and Mikus et al (1989), who found that the pharmacokinetics of flecainide varied according to sparteine–debrisoquine phenotype status.

The present results could be applied to therapeutic drug monitoring in the outpatient clinic for optimizing the daily dose of flecainide as follows: if the patient reported no (or rare) palpitation, the flecainide concentration could be assumed to be sufficient ($\geq$ 300 ng mL^{-1}). The patient would then undergo electrocardiography to check for side effects of the drug. If a patient reported frequent palpitation, serum flecainide levels would be required to judge whether the flecainide concentration was sub-therapeutic ($<$ 300 ng mL^{-1}) or whether flecainide was innately ineffective in that patient; in our experience, such cases account for approximately 30% of outpatients receiving flecainide. Dose escalation would be required when the serum concentration was $<$ 300 ng mL^{-1}, whereas alternative treatment for tachyarrhythmia would be considered when the serum concentration was 300–1000 ng mL^{-1}. A study of daily flecainide in the treatment of tachyarrhythmia is necessary to confirm the proposed procedures.

Conclusions

The poor relationship between daily dose and flecainide trough levels highlighted the difficulty of estimating the dose of flecainide necessary to maintain serum levels within the therapeutic range without monitoring the serum flecainide concentration. Serum flecainide $<$ 300 ng mL^{-1} was insufficient for blocking sodium channels, because QRS enlargement was not observed, and resulted in uncontrolled palpitation in 65% of patients. However, symptoms in the patients with $\geq$ 300 ng mL^{-1} serum flecainide were controlled well without increases in QTc. We concluded that the serum flecainide concentration should be maintained at $\geq$ 300 ng mL^{-1} to control paroxysm in patients receiving flecainide for tachyarrhythmia.

References

Caplin, J. L., Johnston, A., Hamer, J., Camm, A. J. (1985) The acute changes in serum binding of disopyramide and flecainide after myocardial infarction. *Eur. J. Clin. Pharmacol.* **28**: 253–255

Conard, G. J., Cronheim, G. E., Klempt, H. W. (1982) Relationship between plasma concentrations and suppression of ventricular extrasystoles by flecainide acetate (R-818), a new antiarrhythmic, in patients. *Arzneimittelforschung* **32**: 55–59

Crozier, I. G., Ikram, H., Kenealy, M., Levy, L. (1987) Flecainide acetate for conversion of acute supraventricular tachycardia to sinus rhythm. *Am. J. Cardiol.* **59**: 607–609

Echt, D. S., Liebson, P. R., Mitchell, L. B., Peters, R. W., Obias-Manno, D., Barker, A. H., Arensberg, D., Baker, A., Friedman, L., Greene, H. L. (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N. Engl. J. Med.* **324**: 781–788

Forland, S. C., Burgess, E., Blair, A. D., Cutler, R. E., Kvam, D. C., Weeks, C. E., Fox, J. M., Conard, G. J. (1988a) Oral flecainide pharmacokinetics in patients with impaired renal function. *J. Clin. Pharmacol.* **28**: 259–267

Forland, S. C., Cutler, R. E., McQuinn, R. L., Kvam, D. C., Miller, A. M., Conard, G. J., Parish, S. (1988b) Flecainide pharmacokinetics after multiple dosing in patients with impaired renal function. *J. Clin. Pharmacol.* **28**: 727–735

Griese, E. U., Zanger, U. M., Brudermanns, U., Gaedigk, A., Mikus, G., Morike, K., Stuven, T., Eichelbaum, M. (1998) Assessment of the predictive power of genotypes for the in-vivo catalytic function of CYP2D6 in a German population. *Pharmacogenetics* **8**: 15–26

Gross, A. S., Mikus, G., Fischer, C., Hertrampf, R., Gundert-Remy, U., Eichelbaum, M. (1989) Stereoselective disposition of flecainide in relation to the sparteine/debrisoquine metaboliser phenotype. *Br. J. Clin. Pharmacol.* **28**: 555–566

Katori, K., Homma, M., Kuga, K., Yamaguchi, I., Sugibayashi, K., Kohda, Y. (2003) Liquid chromatographic determination of unbound flecainide in therapeutic drug monitoring. *J. Pharm. Biomed. Anal.* **32**: 375–380

Kreeger, R. W., Hammill, S. C. (1987) New antiarrhythmic drugs: tocainide, mexiletine, flecainide, encainide, and amiodarone. *Mayo Clin. Proc.* **62**: 1033–1050

McQuinn, R. L., Quarfoth, G. J., Johnson, J. D., Banitt, E. H., Pathre, S. V., Chang, S. F., Ober, R. E., Conard, G. J. (1984) Biotransformation and elimination of 14C-flecainide acetate in humans. *Drug Metab. Dispos.* **12**: 414–420

McQuinn, R. L., Pentikainen, P. J., Chang, S. F., Conard, G. J. (1988) Pharmacokinetics of flecainide in patients with cirrhosis of the liver. *Clin. Pharmacol. Ther.* **44**: 566–572

Mikus, G., Gross, A. S., Beckmann, J., Hertrampf, R., Gundert-Remy, U., Eichelbaum, M. (1989) The influence of the sparteine/debrisoquin phenotype on the disposition of flecainide. *Clin. Pharmacol. Ther.* **45**: 562–567

Morganroth, J., Horowitz, L. N. (1984) Flecainide: its pro-arrhythmic effect and expected changes on the surface electrocardiogram. *Am. J. Cardiol.* **53**: 89B–94B

Munafo, A., Buclin, T., Tuto, D., Biollaz, J. (1992) The effect of a low dose of quinidine on the disposition of flecainide in healthy volunteers. *Eur. J. Clin. Pharmacol.* **43**: 441–443

Nakagawa, R., Homma, M., Kuga, K., Yamaguchi, I., Kobayashi, D., Morimoto, Y., Kohda, Y. (2002) High performance liquid chromatography for routine monitoring of serum flecainide. *J. Pharm. Biomed. Anal.* **30**: 171–174

Nishida, Y., Fukuda, T., Yamamoto, I., Azuma, J. (2000) CYP2D6 genotypes in a Japanese population: low frequencies of CYP2D6 gene duplication but high frequency of CYP2D6*10. *Pharmacogenetics* **10**: 567–570

Padrini, R., Piovan, D., Busa, M., al-Bunni, M., Maiolino, P., Ferrari, M. (1993) Pharmacodynamic variability of flecainide assessed by QRS changes. *Clin. Pharmacol. Ther.* **53**: 59–64

Roden, D. M., Woosley, R. L. (1986) Drug therapy. Flecainide. *N. Engl. J. Med.* **315**: 36–41

Tjandra-Maga, T. B., van Hecken, A., van Melle, P., Verbesselt, R., de Schepper, P. J. (1986) Altered pharmacokinetics of oral flecainide by cimetidine. *Br. J. Clin. Pharmacol.* **22**: 108–110

Williams, A. J., McQuinn, R. L., Walls, J. (1988) Pharmacokinetics of flecainide acetate in patients with severe renal impairment. *Clin. Pharmacol. Ther.* **43**: 449–455

Zordan, R., Padrini, R., Bernini, V., Piovan, D., Ferrari, M. (1993) Influence of age and gender on the in vitro serum protein binding of flecainide. *Pharmacol. Res.* **28**: 259–264