Cardiology in the Young

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Flecainide administration in children: dosage, drug levels, and clinical effect

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Original Article

Cite this article: Thomas SAL, Ferguson R, and Wilson DG (2023) Flecainide administration in children: dosage, drug levels, and clinical effect. *Cardiology in the Young* **33**: 2072–2077. doi: 10.1017/S1047951122003729

Received: 6 September 2022
Accepted: 12 November 2022
First published online: 22 December 2022

Keywords:
Flecainide; paediatric arrhythmia; superventricular tachycardia; therapeutic drug monitoring

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Abstract

Therapeutic drug monitoring of flecainide in children using plasma concentration measurements is undertaken by some clinicians. There is very little published evidence surrounding factors which influence plasma flecainide concentration, particularly in paediatric populations. We undertook a retrospective study of 45 children receiving flecainide to identify factors that influence its plasma concentration. Patients receiving a dose of 6 mg/kg/day had a higher mean plasma flecainide concentration than those receiving lower doses. Younger age and lighter weight were also associated with higher plasma flecainide concentrations. Children aged younger than 1 year receiving flecainide three times a day had a higher mean plasma flecainide concentration than older children who received flecainide twice a day. All supratherapeutic levels occurred in children aged less than 1 year who were receiving flecainide three times a day. Supratherapeutic levels were more common in those receiving 6 mg/kg/day while subtherapeutic levels were more common in those receiving 2 mg/kg/day. A supratherapeutic level did not correlate with adverse effects or clinical toxicity. Our results would suggest the need for a change of practice from prescribing flecainide at a frequency of three times a day in children aged younger than 1 year to twice a day in line with other ages.

Flecainide is a Vaughan–Williams class Ic anti-arrhythmic drug that is used in the treatment of tachyarrhythmias in adults and children. It can be given regularly to prevent episodes of arrhythmia as well as acutely for pharmacological cardioversion. Toxicity is a rare but life-threatening potential adverse effect of the drug since it can result in ventricular arrhytmia.[1] Its narrow therapeutic index means that some clinicians monitor plasma flecainide concentration in children receiving the drug.[2]

Previous studies have shown that flecainide is effective in terminating and preventing arrhythmias of differing mechanisms.[3,4] Its effectiveness can vary depending on the mechanism. Definitions of effectiveness often vary in the published literature making comparisons between studies difficult.

The British National Formulary for Children recommends that neonates and children up to the age of 11 should receive 2 mg/kg/dose two or three times a day and that children aged 12–17 should receive 50–100 mg twice daily. The British National Formulary for Children also recommends that "doses should be adjusted according to plasma flecainide concentration" and recommends that the level should be checked "immediately before the next dose".[5]

The Noah's Ark Children's Hospital for Wales Cardiac Unit clinical guideline recommends that flecainide is used in the acute management of supraventricular arrhythmia, typically atrioventricular re-entry tachycardia, in haemodynamically stable children and for the prophylactic treatment of supraventricular arrhythmia in children with or without Wolff–Parkinson–White syndrome, either alone or in combination with other anti-arrhythmic drugs.[6] The unit practice is to check plasma flecainide concentration in all patients around 5 days following initiation of treatment and 6 hours after dose administration, rather than immediately pre-dose, as this has proved to be more practical around the standard working day. All patients have a baseline and post-initiation electrocardiogram to assess the PR interval and QRS duration.

Drug pharmacokinetics are influenced by age, disease, genetics, and other xenobiotics. Perry et al. observed mean plasma elimination half-lives of children aged less than 1 year and greater than 12 years were significantly longer (between 11 and 12 hours) than those aged between 1 and 12 years (approximately 8.5 hours).[7] Till et al. observed a strengthening in correlation between age and plasma flecainide concentration when patients with heart failure were omitted from the analysis.[4] Amiodarone, an inhibitor of CYP2D6 that metabolises flecainide, has been shown to increase plasma flecainide concentration.[8]

The published evidence surrounding how factors such as age, weight, and dose affect plasma flecainide concentration in children is sparse. The European Heart Rhythm Association and Association for European Paediatric and Congenital Cardiology Arrhythmia Working group say in their joint consensus statement on the pharmacological and non-pharmacological therapy for arrhythmias in the paediatric population that serum flecainide levels are "seldom

of use" when adjusting doses. Instead, they recommend monitoring the electrocardiogram for prolongation of the PR interval and QRS complex.[9]

This study aimed to identify factors that influence plasma flecainide concentration in our population, and whether plasma flecainide concentration was associated with clinical effect or adverse effects. We also sought to evaluate our local guideline on measuring flecainide levels. The hypothesis was that a dose of flecainide derived from an approved formulary, in this case the British National Formulary for Children, would produce a plasma concentration of flecainide within the therapeutic range.

Materials and methods

We conducted a 5-year retrospective cohort review in a tertiary paediatric cardiology unit in Cardiff, Wales. Children, defined as being under the care of the paediatric services at the time of dispensing, for whom flecainide was dispensed between 01/01/2015 and 30/09/2020 were identified using a pharmacy database. The service evaluation was registered with and approved by Cardiff and Vale University Health Board. Ethical approval was not required as all data were collected as part of the patients' routine clinical care.

Flecainide doses were prescribed in line with British National Formulary for Children recommendations, and plasma flecainide concentration values were obtained from the local electronic laboratory results system. Patient demographics including age, sex, weight, diagnoses (including arrhythmia, structural heart disease, and ventricular dysfunction), dose, response to treatment, adverse effects, history of toxicity, other anti-arrhythmic drug therapy, and date of starting flecainide treatment were collected from the electronic patient record system (Cardiobase Ltd, Derbyshire, UK), The values collected for these variables were those dated closest to the date of blood sample collection for plasma flecainide concentration measurement.

All data were anonymised and collected using an electronic spreadsheet. Statistical analysis was performed with the Statistical Package for the Social Sciences version 26.

All plasma flecainide concentration measurements were performed in the local Toxicology Laboratory (Cardiff, Wales) using high-performance liquid chromatography. The normal range used for plasma flecainide concentration was 0.15–0.90 mg/L. Subtherapeutic plasma flecainide concentration was therefore defined as less than 0.15 mg/L while a supratherapeutic plasma flecainide concentration was defined as greater than 0.90 mg/L.

Most patients had their plasma flecainide concentration measured once after it was anticipated a steady state had been achieved, the target being 5–7 days after starting the drug. These values are referred to as "post-initiation" plasma flecainide concentration and are used to determine factors that influenced plasma flecainide concentration. We recorded additional plasma flecainide concentration values after the first measurement if they were outside the normal range and these are included in analyses of subtherapeutic or supratherapeutic levels.

Analyses of how variables influenced post-initiation plasma flecainide concentration (a continuous variable) were undertaken using a two-tailed Student's *t*-test. Relative risk values are quoted (with 95% confidence intervals) when the influence of variables on the incidences of subtherapeutic and supratherapeutic levels was sought. It is not possible to calculate relative risk if the number of cases in one of the groups is zero, hence values are absent in places. A p value of <0.05 was considered statistically significant.

Results

Fifty-seven patients were identified using the pharmacy database. Six patients aged 18 years or older were excluded, one patient was excluded because flecainide had been initiated at another centre, and two further patients were excluded because they were duplicates, that is, the same patient had been initiated on flecainide on two occasions within the previous 5 years. In these cases, we used only the earliest initiation of flecainide. Of the remaining 48, 45 (94%) had at least one plasma flecainide concentration recorded and are included in our analysis.

Patient age at the time of flecainide initiation ranged from 0 days to 17.25 years. The mean age was 4.7 years. Twenty-five (52.1%) were male and 23 (47.9%) were female.

Post-initiation plasma flecainide concentration ranged from <0.05 to 1.03 mg/L, and the mean was 0.31 mg/L (SD = 0.22 mg/L). Nine (20%) of the plasma flecainide concentration measurements made post-initiation were outside the normal range. Of those, eight (89%) were subtherapeutic. The one supratherapeutic post-initiation plasma flecainide concentration of 1.03 mg/L was measured in a 17-day-old infant patient 12 days after starting treatment; there were no adverse effects nor clinical or electrocardiogram signs of toxicity in this patient.

Of the plasma flecainide concentration measurements taken as part of ongoing monitoring, for example, after a dose change, nine values were outside the normal range. Of these, five (55.6%) were subtherapeutic, and four (44.4%) were supratherapeutic.

Twenty-one patients received flecainide monotherapy, 12 of whom (57.1%) were asymptomatic after commencing treatment. Nine (42.9%) experienced breakthrough tachycardia.

Seventeen patients with atrio-ventricular re-entry tachycardia received flecainide monotherapy. Seven of these (41%) had a recurrence of their arrhythmia during monotherapy. In patients with Wolff–Parkinson–White syndrome receiving monotherapy, only 1/8 (12.5%) had a recurrence of arrhythmia during treatment compared to 6/9 (66.6%) with non- Wolff–Parkinson–White atrio-ventricular re-entry tachycardia. Flecainide and digoxin combination therapy had no effective control over the arrhythmia in one case of Wolff–Parkinson–White syndrome. The arrhythmia mechanisms in patients receiving flecainide monotherapy are outlined in Table 1. The sample sizes are not large enough to come to reliable conclusions about the effectiveness of flecainide in permanent junctional reciprocating tachycardia, atrio-ventricular node re-entry tachycardia, and ventricular ectopy.

When those with atrio-ventricular re-entry tachycardia were compared to all other arrhythmia mechanisms combined, the odds ratio for breakthrough tachycardia was 1.600 (95% confidence interval = 0.618–4.144). A Chi-squared test gave a p value of 0.35. There was no significant difference between the mean post-initiation plasma flecainide concentration in those whose arrhythmia was controlled during flecainide monotherapy and those who experienced breakthrough tachycardia (p = 0.536).

Daily dose

The mean post-initiation plasma flecainide concentration in those receiving the highest dose of 6 mg/kg/day was greater than in those receiving 4 mg/kg/day (p = 0.015). Furthermore, the mean post-initiation plasma flecainide concentration in those receiving 4 mg/kg/day was greater than those receiving 2 mg/kg/day (p = 0.071).

The incidence of subtherapeutic levels in those receiving between 1 and 4 mg/kg/day (four cases) was greater than in those

https://doi.org/10.1017/S1047951122003729 Published online by Cambridge University Press

Table 1. Mechanisms of arrhythmia where flecainide monotherapy did not result in the cessation of symptoms.

Arrhythmia mechanism	Flecainide monotherapy	Breakthrough tachycardia	% Breakthrough tachycardia
AVRT	17	7	41.0
WPW	8	1	12.5
Non-WPW	9	6	66.7
PJRT	2	1	50.0
AVNRT	1	1	100.0
VE	1	0	0.0

AVRT=Atrioventricular Re-entrant Tachycardia; WPW=Wolff-Parkinson-White Syndrome; PJRT=Permanent Junctional Reciprocating Tachycardia; AVNRT=Atrioventricular Node Reentrant Tachycardia; VE=Ventricular Ectopy.

receiving between 5 and 6 mg/kg/day (one case) (relative risk = 1.105 [95% confidence interval = 0.703–1.735]). The incidence of supratherapeutic levels in those receiving between 4 and 6 mg/kg/day (three cases) was greater than in those receiving between 1 and 3 mg/kg/day (one case) (relative risk = 1.909 [95% confidence interval = 0.340–10.718]) (Fig 1).

Age

The mean post-initiation plasma flecainide concentration in those aged younger than 5 years (0.35 mg/L, SD = 0.10 mg/L) was significantly greater than in those aged 5 years or more (0.20 mg/L, SD = 0.24 mg/L) (p = 0.033). The incidence of subtherapeutic levels in those aged younger than five (four cases) was greater than in those aged 5 years or more (one case) (relative risk = 1.628 [95% confidence interval = 0.268–9.898]). The incidence of supratherapeutic levels in those aged younger than five (four cases) was greater than in those aged 5 years or more (0 cases).

Weight

The mean post-initiation plasma flecainide concentration in those weighing less than 20 kg (0.35 mg/L, SD = 0.25 mg/L) was greater than in those weighing 20 kg or more (0.20 mg/L, SD = 0.11 mg/L) (p = 0.079). The incidence of subtherapeutic levels in those weighing less than 20 kg (four cases) was greater than in those weighing 20 kg or more (one case) (relative risk = 1.216 [95% confidence interval = 0.193–7.680]). The incidence of supratherapeutic levels in those weighing less than 20 kg (four cases) was greater than in those weighing 20 kg or more (0 cases).

Dose regime

Most patients (80%) were receiving twice-daily dosing. Eight patients (18%) were receiving three times daily dosing, all of whom were aged less than 1 year and weighed less than 10 kg. The mean post-initiation plasma flecainide concentration in those receiving three times daily dosing (0.48 mg/L, SD = 0.31 mg/L) was significantly greater than in those receiving twice-daily (BD) dosing (0.27 mg/L, SD = 0.18 mg/L) (p = 0.013) (Fig 2).

Supratherapeutic plasma flecainide concentration values were more common in those receiving three times daily dosing compared to those receiving twice-daily dosing. Supratherapeutic levels occurred in 38% of patients receiving three times daily dosing compared to 5% of those receiving twice-daily dosing (odds ratio = 2.202 [95% confidence interval = 0.748–6.480]).

There was no significant difference in response to flecainide between those receiving twice-daily dosing (sinus rhythm in 63%) and those receiving three times daily dosing (sinus rhythm in 50%) (p = 0.689).

Anti-arrhythmic drug combinations

Twenty-seven of the patients (56%) were receiving flecainide as part of combination therapy. The mean plasma flecainide concentration in those receiving flecainide monotherapy (0.24 mg/L, SD = 0.14 mg/L)) was lower than in those receiving a combination of flecainide and at least one other anti-arrhythmic drug (0.36 mg/L) (p = 0.047). The most common combination was flecainide and propranolol, used in 11 patients (22.9%). The mean post-initiation plasma flecainide concentration in patients receiving this combination was 0.37 mg/L (SD = 0.24 mg/L). The mean post-initiation plasma flecainide concentration in patients receiving amiodarone and flecainide was 0.16 mg/L (SD = 0.01 mg/L). More patients who were receiving other anti-arrhythmic drugs were on the highest dose of flecainide (6 mg/kg/day) than those receiving flecainide alone (p = 0.159). The mean post-initiation plasma flecainide concentration for all combinations which two or more patients were receiving is listed in Table 2.

Days between initiation and level check

It was possible to determine the number of days between the initiation of flecainide and the first plasma flecainide concentration measurement in 41 patients. The mean number of days between initiation of treatment and checking the plasma flecainide concentration was 8. We defined an "early level" as being between 2 and 4 days post-initiation of therapy and "late level" as being beyond 4 days. Ten patients (24.4%) had an early plasma flecainide concentration, and the mean level was 0.35 mg/L (SD = 0.18 mg/L) compared to 0.32 mg/L (SD = 0.24 mg/L) in those who had their levels measured later (p = 0.718). There was no significant association between response to flecainide treatment and early versus late post-initiation plasma flecainide concentration level (p = 0.186).

Adverse effects and toxicity

Five patients experienced adverse effects thought to be related to flecainide therapy. These included dizziness and nausea, QRS broadening right bundle branch block, lethargy, weight loss, and other unspecified side effects. The initial plasma flecainide concentration in all those experiencing side effects was within the therapeutic range, and no patient who experienced adverse effects had any supratherapeutic levels recorded at any time. There was no significant difference between the mean post-initiation plasma flecainide concentration in those experiencing adverse effects (0.32 mg/L, SD = 0.19 mg/L) and those who did not (0.31 mg/L, SD = 0.22 mg/L) (p = 0.925).

There was one case of clinical flecainide toxicity in this group. This resulted from a deliberate overdose of 500 mg of flecainide in an adolescent patient. The clinical effects were significant broadening of the QRS complex to 163 msec from a baseline of 106 msec, as well as episodes of broad complex tachycardia. This patient had an underlying ACTA1 gene alteration and a history of cardiac dysfunction with a previous out-of-hospital cardiac arrest. From their existing implantable cardioverter defibrillator, they received several life-saving appropriate shocks for ventricular arrhythmia

https://doi.org/10.1017/S1047951122003729 Published online by Cambridge University Press

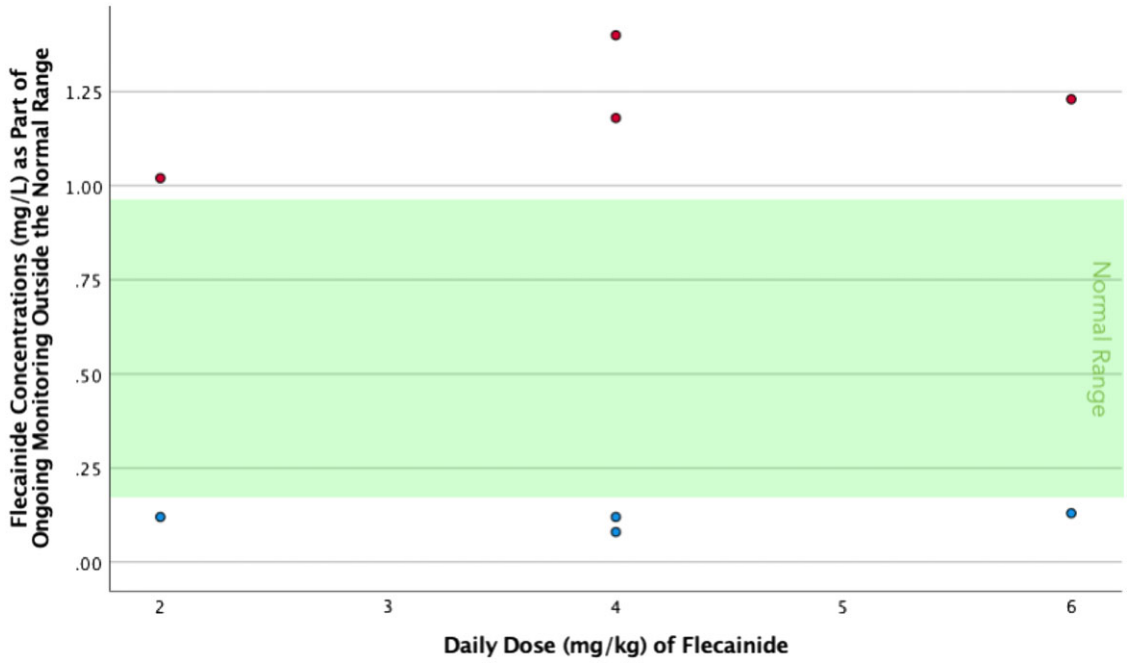

Figure 1. Subtherapeutic (blue) and supratherapeutic (red) plasma flecainide concentrations, measured as part of ongoing monitoring, by daily dose of flecainide. Green shading shows the normal range for plasma flecainide concentration.

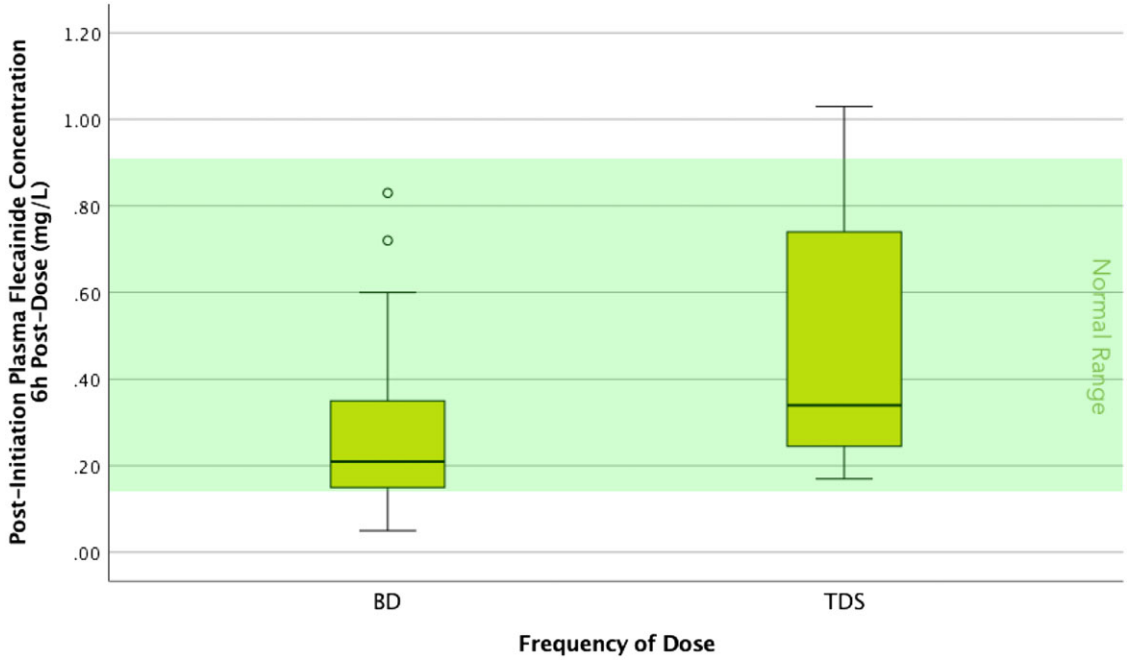

Figure 2. Mean post-initiation plasma flecainide concentration by frequency of administration of flecainide with standard deviation in yellow boxes and 95% confidence intervals shown by error bars. Green shading shows the normal range for plasma flecainide concentration. BD: bis in die (twice a day), TDS: ter die sumendus (three times a day).

triggered by flecainide toxicity. The plasma flecainide concentration sample was received by the laboratory but not processed due to a requesting error from the referring district hospital.

Study limitations

All data used in this project were collected retrospectively. Many of the parameters used in the analyses, including doses and weights, were collected from hospital correspondence dated as closely as possible to the date of the plasma flecainide concentration measurement. However, there may have been changes to weight and dose between documentation and the plasma flecainide concentration being measured.

It was assumed that all plasma flecainide concentration measurements were made 6 hours post-dose in accordance with unit practice and that all values were comparable. However, it is not

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Table 2. Mean post-initiation plasma flecainide concentration for each combination of anti-arrhythmic drugs.

Anti-arrhythmic drug combination	Mean post-initiation plasma flecainide concentration 6 hours post-dose (mg/L)	SD (mg/L)	n	Student's *t*-test (two-tailed) – combination versus flecainide only
Flecainide only	0.24	0.14	21	n/a
Flecainide + Propranolol	0.37	0.24	11	0.064
Flecainide + Amiodarone	0.16	0.01	2	0.475
Flecainide + Digoxin	0.50	0.38	5	0.016
Flecainide + Atenolol	0.22	0.07	2	0.849

SD=Standard Deviation; n=Number of patients.

always practically possible to collect a blood sample exactly 6 hours post-dose. This may be due to clinician unavailability, failed attempts at taking a blood sample, or patient refusal to have a sample taken.

We have assumed patient compliance with medication.

Discussion

Younger age, lighter weight, the highest daily dose (6 mg/kg/day), and three times daily dosing were all associated with higher post-initiation plasma flecainide concentration. Three times daily dosing was only used in children aged less than 1 year, who had lower body mass. Since these children were mostly receiving 2 mg/kg three times a day, they are also the ones who were receiving 6 mg/kg/day in total. All supratherapeutic plasma flecainide concentration values occurred in children aged less than 1 year and weighing less than 10 kg. This suggests that the use of three times daily dosing in this age group is inappropriate, or that the total daily dosage should be lowered if the drug is to be given 8 hours. The mean elimination half-life between 11 and 12 hours in children aged less than 1 year would support twice-daily dosing in this group.[7]

The range of values seen in those receiving higher doses was wider than at lower doses, making the predictability of the level more challenging for clinicians. Those receiving lower doses of flecainide were more likely to have subtherapeutic plasma levels of the drug, while those receiving higher doses were more likely to have supratherapeutic plasma flecainide concentration. However, there was one supratherapeutic level in a child receiving 2 mg/kg/day, so continuing to commence flecainide treatment at a low dose and titrating up after checking the plasma flecainide concentration seems appropriate.

We did not observe a higher mean plasma flecainide concentration in patients receiving flecainide and amiodarone related to amiodarone-mediated inhibition of cytochrome P450 2D6. In fact, the mean plasma flecainide concentration was lower in the two patients receiving this combination. This may relate to the fact that the local guideline advises a 30% dose reduction of flecainide if used in combination with amiodarone. The higher plasma flecainide concentration in those receiving a combination of flecainide and other anti-arrhythmic drugs may be explained by the fact that more patients receiving combination therapy were receiving the highest dose of flecainide compared to those not receiving combinations, likely reflecting challenges in achieving adequate rhythm control.

A higher mean plasma flecainide concentration was observed in patients receiving propranolol and flecainide compared to flecainide alone. While not statistically significant, this may result from the phenomenon described by De Giovanni whereby propranolol and flecainide are detected at similar times during high-performance liquid chromatography.[10] It is possible, therefore, that the plasma flecainide concentration values for patients receiving flecainide and propranolol are falsely higher due to propranolol interfering in the flecainide assay. Since so few patients were being administered each anti-arrhythmic drug combination, it is not possible to reliably conclude whether any other drug in particular affected plasma flecainide concentration.

There was no significant difference between the mean plasma flecainide concentration in patients who had their level checked early (i.e., within 4 days of initiation) and those who had their level checked later. Likewise, there was no difference between the incidence of supratherapeutic levels according to the timing of post-initiation plasma flecainide concentration measurement. Subtherapeutic levels were seen more commonly in patients having their plasma flecainide concentration measured later, and, while early measurement of plasma flecainide concentration may be of theoretical use in guiding changes to dosing, there was no evidence to suggest that delays in checking the plasma flecainide concentration led to ineffective treatment of arrhythmia or toxicity.

There was no association between post-initiation plasma flecainide concentration and response to treatment. Previous studies have reported a correlation between plasma flecainide concentration and clinical effect while others report incessant arrhythmia despite adequate plasma flecainide concentration and attribute this to reasons other than underdosing.[11,12] Till et al. reported a wide range of plasma flecainide concentration values, including supposedly subtherapeutic values, that were all related to patients whose arrhythmia was controlled.[4] This remains an area of uncertainty.

We had 17 patients with atrio-ventricular re-entry tachycardia receiving flecainide alone. Of 17 patients, 7 (41%) had recurrence of the arrhythmia while established on flecainide monotherapy. In those with Wolff–Parkinson–White syndrome, recurrence was seen in only 12.5% of cases. Values previously obtained in a clinical trial setting by Sanatani et al. for digoxin and propranolol suggest these two drugs are more effective in treating non-Wolff–Parkinson–White atrio-ventricular re-entry tachycardia.[13] In the Study of Anti-arrhythmic Medications in Infancy trial, the rates of supraventricular tachycardia reoccurrence were 19 and 31% for digoxin and propranolol, respectively. This trial included 61 patients, all of whom were aged less than 4 months. All had atrio-ventricular re-entry tachycardia or atrio-ventricular node re-entry tachycardia, but they excluded patients with Wolff–Parkinson–White syndrome. Our data set included patients from across the paediatric age range. There is yet to be a prospective trial of flecainide use in children.

Based on the findings of this study, we recommend that three times a day dosing of flecainide should not be used in children aged less than 1 year as standard and that twice-daily dosing is more appropriate. There are circumstances where three times a day

https://doi.org/10.1017/S1047951122003729 Published online by Cambridge University Press

dosing of flecainide is appropriate, such as in patients with ventricular dysfunction where a smaller dose given three times a day may be safer than a greater dose given twice a day. While plasma flecainide concentration measurement could identify supratherapeutic levels and prompt dose reduction, there were no cases of flecainide toxicity resulting from the accidental overdosing of a child. This study does not provide evidence to oppose a shift away from plasma concentration-based flecainide monitoring and towards electrocardiogram-based monitoring.

Acknowledgements. We would like to thank Neil Dawson, Pharmacist, for his help in obtaining an appropriate list of patients for this study.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

Ethical standards. Ethical approval was not sought due to the retrospective and observational nature of this study.

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