FLECAINIDE

01. Assay Details

CH Labs Test Reference Guide

02. Therapeutic Range

630-2100 nmol/L

How well established:
The range is well established as the dose-response relationship is linear. Drug concentration monitoring has been shown to reduce the risk of proarrhythmia. Concentrations in the lower therapeutic range have been shown to inhibit 90% of ventricular arrhythmias. The risk of adverse effects is increased at concentrations over 1500 nmol/L; some have advocated lowering the upper limit of the range to 1800 nmol/L for this reason.

03. Pharmacokinetics

F: 0.9	**Vd** (L/kg): 10	**Cl** (L/h/kg): 0.34	**t½:** 11 hrs (8-14)
Fe: 0.35-0.45	**Elimination route:** renal (unchanged drug) + hepatic metabolism (O-dealkylation, then oxidation, then conjugation)		
CYP: 2D6 substrate and inhibitor (R enantiomer only)		**Protein binding:** 0.4 (alpha1 acid glycoprotein)	

F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

- The half-life varies with age and disease as follows: mean 20 hours if ventricular arrhythmia or NYHA Class III congestive heart failure; 17-20 hours in moderate renal impairment; 26 hours if end-stage renal impairment. The mean half-life is 29 hours at birth; 11-12 hours at three months of age, 6 hours at one year, 8 hours from age 1-12 years and 14 hours after age 12.
- Mean time to peak concentration is 4 hours (for capsules) and 3 hours (tablets).
- In animal studies the metabolite meta-O-dealkylated flecainide has antiarrhythmic activity (20% activity of parent compound). This is not felt to be clinically relevant in humans.
- 5% of a dose is excreted unchanged in faeces.

04. Indications

1. Acute termination and prophylaxis of paroxysmal supraventricular tachycardia eg. AVRT, AVNRT.
2. Acute termination of paroxysmal or recent onset atrial fibrillation, prophylaxis of paroxysmal atrial fibrillation (second line therapy). Includes atrial fibrillation in the context of Wolff-Parkinson-White syndrome.

3. Termination of refractory life-threatening ventricular arrhythmia eg sustained VT (not first line therapy)
4. Other:
    - termination of non-life-threatening ventricular arrhythmia (if severe/disabling - balance against proarrhythmia risk)
    - analgesic (malignant neuropathic pain - possibly effective but poorly documented)
    - diagnosis of Brugada syndrome - very effective but risk of proarrhythmia
    - foetal supraventricular tachycardia (second line agent)

Contraindications:

1. Structural heart disease, including left ventricular dysfunction or hypertrophy, valvular heart disease, previous myocardial infarction, symptomatic ischaemic heart disease, congenital heart disease.
2. Pre-existing second or third degree heart block, or combined right bundle branch block and left anterior hemiblock (unless paced)
3. Heart failure or cardiogenic shock
4. Prolonged QT (QTc>470ms in men, 480ms in women), known congenital long QT syndrome
5. Hypersensitivity to flecainide

05. Loading dose

A loading dose is not recommended prior to long-term oral therapy due to the risk of proarrhythmia.

For cardioversion of recent onset atrial fibrillation - single oral dose 300mg (or 4mg/kg, to a maximum of 300mg).

Intravenous therapy to terminate acute ventricular arrhythmia - 2mg/kg over 10 minutes (maximum 150mg).

Intravenous therapy to terminate acute atrial/supraventricular arrhythmia - 1mg/kg over 10 minutes, then 0.5mg/kg every 30-60 minutes until arrhythmia suppressed (maximum total dose 2mg/kg or 150mg).

Intravenous infusion - 2mg/kg over 30 minutes, then 1.5mg/kg over 1 hour, then 0.1-0.25mg/kg/hr thereafter (recommend maximum duration 24 hours).

06. Maintenance dose

Supraventricular arrhythmia - starting dose 50mg bd. Titrate to effect - increasing dose by 50mg bd every 4 days. Maximum recommended dose 300mg.

Ventricular arrhythmia - starting dose 100mg bd. Titrate to effect - increasing dose by 50mg bd every 4 days. Maximum recommended dose 400mg (occasional individuals require 600mg if poorly controlled and plasma concentrations low).

After control is achieved, an attempt at gradual dose reduction can be made, and titrated to effect.

07. Notes on administration

Treatment for paroxysmal supraventricular arrhythmias could be commenced in the community. However, hospital admission and cardiac monitoring is recommended if treatment is for ventricular arrhythmia (or if risk factors such as first-degree heart block or mild QRS prolongation are present).

Flecainide can be taken with or without food.

Occasional patients are poorly controlled by (or intolerant of) the 12-hourly regimen and may benefit from 8-hourly dosing.

For intravenous infusion, dilute in 5% dextrose.

08. When to monitor

Measure the trough concentration at steady state (3-5 days after a change in dose or addition of an interacting drug).

Drug concentration monitoring is recommended if the daily dose is more than 200mg/24h, for children, if the individual has comorbid hepatic impairment, moderate renal impairment or congestive heart failure, and with concurrent amiodarone therapy.

Also measure concentration for intravenous infusion therapy of more than 24 hours duration.

Monitor clinical and electrocardiographic response also (a few weeks after commencing oral treatment).

09. Dose individualisation

Reduce doses by 50% if there is significant renal impairment (CrCl < 0.5 ml/sec). Wait 6 days before monitoring concentration in this situation, due to increased half life. With increasing renal impairment the metabolic role of CYP2D6 becomes more important (increased clinical relevance of slow metabolisers and drug interactions).

Hepatic impairment - start at the lower dose range and adjust slowly (e.g. every 6 days), monitoring concentrations.

Elderly - start at 100mg/24h.

Paediatrics - initial oral dose 50-100mg/square metre/24h (approx. 3mg/kg), increasing by 50mg/square metre/day every five days.

Paediatric intravenous dose 0.5-2mg/kg.

10. Adverse effects

The greatest concern is ventricular proarrhythmia, occurring in 4-13% of subjects (4-8% if no structural heart disease). Other potentially life-threatening cardiac effects include cardiac block,

increased pacemaker threshold and congestive heart failure due to negative inotropy (all less than 1% incidence). When used as the sole agent in atrial flutter, there is a risk of conversion to 1:1 block, with subsequent acceleration of ventricular rate.

Other adverse reactions as listed:

>10%

CNS: dizziness
EYES: blurring, dryness, corneal deposits

1-10%

CNS: headache, fatigue, sleepiness, fever, malaise, hypoaesthenia, ataxia, vertigo, tinnitus, syncope, anxiety, insomnia, depression, sexual dysfunction
CVS: palpitations, tachycardia, chest pain, oedema, sinus node dysfunction, dyspnoea
DERM: rash
EYES: diplopia
GI: nausea, constipation, abdominal pain, anorexia, diarrhoea
MUSC/SKEL: tremor, weakness, paraesthesia

<1%

CNS: amnesia, depersonalisation, euphoria, photophobia, tardive dyskinesia, neuropathy
CVS: angina, bradycardia
DERM: alopecia, exfoliative dermatitis, pruritus, angio-oedema, urticaria
GI: jaundice, cholestasis, metallic taste
GU: urinary retention
HAEM: neutropaenia, leukopaenia, thrombocytopaenia.RHEUM: arthralgia
RESP: bronchospasm, pneumonitis

11. Drug interactions

As flecainide is partly metabolised by CYP2D6 it is subject to the effects of genetic polymorphism and drug interactions. Poor metabolisers may experience elevated flecainide concentrations particularly if they also have renal impairment. Drugs inhibiting 2D6 metabolism are most likely to affect flecainide concentrations in extensive metabolisers with renal impairment.

Drugs that increase flecainide concentrations via 2D6 inhibition:

- Amiodarone doubles flecainide concentrations via 2D6 and non-2D6 enzyme inhibition. A 50% dose reduction is recommended. NB amiodarone may also interact pharmacodynamically by prolonging the QT interval.
- Cimetidine increases flecainide concentrations by 30% (inhibition of both hepatic and renal clearance). A 50% dose reduction is recommended.
- Propranolol increases flecainide concentrations by 15-30%. It is possible that other beta blockers may have similar effects, but this is unproven.
- Other proven drug interactions via 2D6 inhibition include amprenavir, ritonavir, bupropion, clozapine, quinine, quinidine, the SSRIs (fluoxetine, paroxetine, sertraline) and the tricyclic antidepressants.

- Other drugs with potential to increase flecainide concentrations via 2D6 inhibition (but without evidence/formally proven interactions) would include antipsychotics (such as fluphenazine, haloperidol, chlorpromazine and thioridazine), dextropropoxyphene, methadone, methylphenidate, moclobemide, propafenone and terbinafine.

- Urinary alkalinisers (eg antacids, bicarbonate and acetozolamide) reduce renal excretion and can increase flecainide concentrations. The clinical significance of this is unclear.

Drug-drug interactions known to decrease flecainide concentrations:

- CYP2D6 is said to be non-inducible. Studies with phenytoin suggest no change in flecainide concentrations. Other data suggest that inducers (eg carbamazepine, phenytoin, rifampicin) may increase elimination by 30% (presumably by non-2D6 mechanisms).
- Smoking increases flecainide clearance by 50% and higher doses are usually required (average dose 338mg/24h in smokers vs 288mg/24h in non-smokers)
- Urinary acidifiers (eg ammonium chloride) increase urinary excretion of flecainide and may reduce the concentrations; the clinical relevance of this interaction is not certain.

Pharmacodynamic interactions with flecainide:

- Cases of cardiogenic shock and asystole, due to combined negative inotropy, have been reported when flecainide was combined with verapamil.
- Diltiazem and beta-blockers also have potential for this effect and the combination should be avoided.

The concurrent use of drugs with potential to prolong the QT interval should be avoided due to the risk of proarrhythmia (although their use with flecainide has not been formally investigated and the potential for interaction remains theoretical). Such drugs include adenosine, antipsychotics/neuroleptics, arsenic trioxide, chloryl hydrate, chloroquine, clindamycin, cotrimoxazole, enflurane, fluconazole, halothane, lithium, macrolide antibiotics (erythromycin, clarithromycin), mefloquine, moxiflocacin, octreotide, pentamidine, tacrolimus, terfenadine and vasopressin.

Hypokalaemia as a result of diuretics may increase proarrhythmic risk.

Flecainide increases the concentrations of other drugs, mostly by competitive inhibition of CYP2D6 clozapine, SSRIs, tricyclic antidepressants and propranolol.
Increased concentrations of other 2D6 substrates (see above) when co-administered with flecainide is possible, although unproven.
Flecainide increases digoxin concentrations by 13-19% when concurrently administered, by reducing its renal clearance. Usually this is not clinically significant, but there is potential for toxicity if digoxin concentrations had been at the upper limit of the normal range or the subject is sensitive to digoxin effects.

12. Factors that may give a false assay result

None known.

13. Overdose

TOXINZ

14. Dialysability

Haemodialysis is ineffective due to the high Vd.

15. Comments

Pregnancy - Category C (teratogenicity noted in rabbits but not humans) - avoid if possible.
Lactation - milk: plasma ratio 2.5. Felt to be 'safe'.
Potential for drug-food interaction: strict vegetarian diets may result in alkalinisation of the urine, reducing flecainide clearance and elevating concentrations.

16. Key references

1. Smith W, Crozier I et al. Guidelines for the use of flecainide in patients with supraventricular arrhythmias. NZMJ 2000;113: 420
2. Campbell T and Williams K. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 1998; 46: 307-319
3. DRUGDEX. Micromedex, Inc. Denver USA 2003.
4. Medsafe - Flecainide data sheet, June 1999.
5. Dollery C (ed). Therapeutic Drugs. Churchill Livingstone 1999. (Flecainide Monograph).

17. Last updated

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