FLUOXETINE

01. Assay Details

Assay method: HPLC
Limit of sensitivity: 5 ug/L
Assay Cost: $100

02. Therapeutic Range

Not applicable.

How well established:
A range of 60-500 ug/L for fluoxetine, and 50-500 ug/L for the active metabolite norfluoxetine, has been found in patients taking 20-60 mg daily. In these studies, a correlation between concentration and therapeutic effect has not been found. However, it is not clear from the data whether compliance was good and there is little description of depression sub-types, severity and statistical techniques.
Monitoring is not usually indicated except perhaps to check compliance or in cases of suspected overdose and toxicity.

03. Pharmacokinetics

F: 0.9 (0.8-0.95)	**Vd** (L/kg): 33 (20-43)	**Cl** (L/h/kg): 0.15	**t½:** 4-6 days; 4-16 days for norfluoxetine
Fe: 0.025	**Elimination route:** hepatic		
CYP: 2D6 to norfluoxetine, then metabolised by 3A4. Fluoxetine also inhibits 2D6, 2C9 & 2C19 (minor).			**Protein binding:** 0.96 (0.94-0.98)

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:

- Fluoxetine is metabolised to the active metabolite desmethylfluoxetine (t1/2=7 days (range 4-16).
- PK is not affected by renal impairment, but clearance is reduced in cirrhosis.

04. Indications

1. Major depressive episode
2. Binge eating and vomiting in patients with moderate to severe bulimia nervosa
3. Obsessive-compulsive disorder

05. Loading Dose

Not required

06. Maintenance Dose

20mg po daily in single (morning) or divided doses (if larger than 20mg/day doses). The dose may be increased after several weeks by 20mg/day increments. The maximum daily dose is 80mg.
The usual dosage range is 20-80mg/day for depression and OCD, 20-60mg/day for obesity, and 60-80mg/day for bulimia. Lower doses of 5mg/day have been used as initial treatment. Elderly should start at 10mg/day.

07. Notes on Administration

Food has no effect on the AUC.

08. When to Monitor

At the trough, just prior to the next dose.
Monitoring is not usually indicated except perhaps to check compliance or in cases of suspected overdose and toxicity.

09. Dose Individualisation

Monitoring is not usually indicated except perhaps to check compliance or in cases of suspected overdose and toxicity.

10. Adverse Effects

>10%
CNS: headache, nervousness, insomnia, drowsiness
GI: nausea, diarrhoea, xerostomia

1-10%
CNS: anxiety, dizziness, fatigue, sedation, tremor
DERM: rash, pruritus
ENDO: SIADH, hypoglycaemia, diaphoresis, hyponatraemia (elderly or volume-depleted patients)
GI: anorexia, dyspepsia, constipation

<1%
CNS: extrapyramidal reactions, visual disturbances, suicidal ideation
GI: deranged liver function tests
MISC: anaphylactoid reactions, allergies, abnormalities of platelet function

11. Drug Interactions

Fluoxetine is a substrate for the CYP 2D6 and inhibits this enzyme and 2C9

Drugs that may increase the fluoxetine concentration:
Tricyclic antidepressants (2-fold increase in fluoxetine), amiodarone, cimetidine, flecainide, haloperidol, imidazoles/triazoles, methylphenidate, metoprolol, moclobemide, SSRIs, propranolol, saquinavir, quinidine, thioridazine, macrolide antibiotics, diazepam, lithium.

Fluoxetine may increase the concentration of the following drugs:
Alprazolam, tricyclic antidepressants, trazadone, carbamazepine, clozapine, dextromethorphan, diazepam, digoxin, diltiazem, haloperidol, phenytoin, ritonavir, perhexiline.

Fluoxetine may decrease the concentration of the following drugs:
Valproate

Serotonin syndrome may occur with the following concurrent drugs:
Dextromethorphan, fenfluramine, fluphenazine, sumatriptan, selegiline, MAOIs, lithium, tryptophan.

MAOIs - This combination should be avoided due to toxicity (hyperpyrexia, tremors, seizures, coma, delirium). At least 14 days should elapse between stopping a MAOI and starting fluoxetine and 5 weeks should elapse before stopping fluoxetine and commencing a MAOI.

Lithium - Fluoxetine may increase (or decrease?) lithium and the lithium concentration should be monitored. Serotonin syndrome may also occur with this combination.

Warfarin - increased INR with fluoxetine.

12. Factors that may give a False Assay Result
Nil known.

13. Overdose
TOXINZ

14. Dialysability
Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be helpful due to the large volume of distribution of fluoxetine

15. Comments
Fluoxetine should not be administered if GFR<10ml/min, nor in lactation where the WAMD is 6-13%. Relative contraindication include patients with unstable angina or post MI (as there is little evidence regarding its use in these situations), in cirrhosis or hepatic failure as it reduces clearance of fluoxetine and its active metabolite, and in diabetes, as fluoxetine may cause hypoglycaemia. Large studies on the elderly have not been completed. Avoid alcohol. Pregnancy Risk Factor B

16. Key References
1. Drugs Vol 32(6) pg 481-508 Dec 1986
2. Drug Information Handbook 5th Edition 1997-98 ed. Lacey et.al.
3. Selective Serotonin Reuptake Inhibitors Ed Boyer WF, Feighner 1991 pg 99-100.
4. Kelly, MW Perry et al. "Serum fluoxetine and norfluoxetine concentrations and antidepressant response." Therapeutic Drug Monitoring 11:165-179 1989

17. Author/Date
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