May 2012

Prescribing....

Citalopram

- The MHRA has advised that Citalopram and Escitalopram are both associated with dose-dependent QT interval prolongation.
- Therefore they should not be used in patients with pre-existing QT prolongation or in combination with other treatments that prolong the QT interval.
- Escitalopram, which is not available via the States pharmaceutical scheme, has been extensively promoted as a "cleaner" drug with fewer side effects.
- However the same warnings apply, a new maximum daily dose in the elderly is recommended and crucially its effect on QT prolongation has been found to be statistically and hence **clinically insignificant** to that of citalopram.
- At current prices, Escitalopram 10mg is **thirteen times** more expensive than generically prescribed Citalopram 20mg.

Citalopram, a racemic mixture of R and S citalopram, is a selective serotonin reuptake inhibitor (SSRI) licensed for the treatment of major depressive disorder, panic disorder, and obsessive compulsive disorder.

Escitalopram is the S enantiomer of citalopram was brought to the market just before the patent on citalopram expired. It has been more extensively studied than citalopram so has broader licensed indications which include major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder, and obsessive compulsive disorder.

What is the basis of the new advice ?

The potential for both drugs to cause QT interval prolongation has been known for some time and is reflected in the product information. However recent data have further defined the risk and have clarified that their effects are dose-dependent.

For both drugs elderly patients have a higher exposure due to age-related decline in metabolism and Elimination, so the maximum doses of both have been restricted in people over 65 years.

Citalopram

The data on citalopram include double-blind placebo-controlled echocardiogram studies. A study showed a clear dose-dependant response: the change from baseline in QTc was 7.5 milliseconds (90% CI 5.9 – 9.1) at 20mg per day and 16.7 miliseconds (15.0 – 18.4) at 60mg per day.

Escitalopram

For escitalopram a dose-dependent increase in QT interval was also shown. The change from baseline was 4.3 (90% CI 2.2 – 6.4) milliseconds with 10mg per day and 10.7 miliseconds (90% CI 8.6 – 12.8) with 30mg per day.

Clearly the 90% confidence intervals (i.e. the range of values for with we can be 90% certain the true result for the entire population lies) for 10mg escitalopram and 20mg citalopram overlap. Therefore we may conclude that their effects at these equivalent doses is statistically and hence clinically similar.

Has any other advice been given ?

These drugs may have an additive effect to other drugs that prolong the QT interval. Therefore Co-administration of citalopram or escitalopram with these medicines is now contraindicated. These include Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some antimicrobials e.g. moxifloxacin, erythromycin IV , some antihistamines e.g. astemizole and some antiretrovirals e.g. ritonavir.

The new maximum daily doses of citalopram are as follows

- Adults : 40mg per day
- Adults over 65 years : 20mg
- Adults with hepatic impairment : 10mg

MHRA advice is that patients who currently take doses higher than the new recommended daily maximum should have their treatment reviewed.

The balance of risks and benefits should be considered carefully, particularly at higher doses in patients with pre-existing risk factors for QT interval prolongation, especially those with significant bradycardia, recent acute myocardial infarction or decompensated heart failure.

The following **monitoring** is recommended

- In patients with cardiac disease, an ECG review should be considered before treatment with citalopram or escitalopram.
- Electrolyte disturbances e.g. hypokalaemia or hypomagnesemia should be corrected before treatment. Monitoring of serum magnesium is advised , particularly in elderly patients who may be also taking diuretics or proton pump inhibitors.
- If cardiovascular symptoms , such as palpitations, vertigo, syncope or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia.
- If the QTc interval is > 500 milliseconds, treatment should be gradually withdrawn.
- If the QTc interval duration is between 480 milliseconds and 500 milliseconds , the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal.

Finally

Staying with antidepressants, please be aware that St John's wort has now been removed from the States prescribing list. This follows advice from NICE that doctors should not prescribe or recommend its use for mild depression. There are a number of important interactions with conventional drugs which are likely to be clinically significant. The amount of active ingredients varies between different preparations. Prescriptions for St Johns wort may be dispensed until September 1st 2012

Written by: Geraldine O'Riordan, Prescribing Advisor Tel: 01481-732460