Drugs prolonging the QTc interval and palliative care

A prolonged QTc interval is a pro-arrhythmic state predisposing to ventricular arrhythmia, particularly *torsade de pointes* (TdP). The risk grows as QTC interval increases, particularly >500msec.

Palliative care patients in general may be at a higher risk of a prolonged QTc interval given the high prevalence of polypharmacy and metabolic disturbance.

Table 1: Drugs used in palliative care which may affect QTc interval

Definite risk	Possible risk	Conditional risk*
Ciprofloxacin	Buprenorphine	Amitriptyline
Citalopram/escitalopram	Capecitabine	Esomeprozole
Domperidone	Granisetron	Fluoxetine
Macrolide antibiotics e.g. erythromycin	Mirtazepine	Ketoconazole
Fluconazole	Nortriptyline	Lansoprazole
Haloperidol	Risperidone	Loperamide
Levomepromazine		Metocopramide
Methadone		Metronidazole
Ondansetron		Olanzapine
		Paroxetine
		Quetiapine
		Sertraline

*These drugs are associated with TdP **but** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalaemia or when taken with interacting drugs) **or** by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QTc-prolonging drug or by causing an electrolyte disturbance that induces TdP)

Table 2: Main additional risk factors

Female gender	Cardiac disease, e.g.:
Congenital long QT syndrome	• Bradycardia <50 betas/min
Baseline prolonged QT interval	• Left ventricular hypertrophy
Electrolyte imbalance:	• Heart failure
• hypokalaemia	• recent conversion from AF
• hypomagnesaemia	• ventricular arrhythmia

Implications for practice

Of 300 patients referred to a specialist palliative care unit who were not imminently dying, although 48 (16%) had a prolonged QT interval, only 2 (0.7%) had a severely prolonged uncorrected QT interval of >500msec. Both patients had ischaemic heart disease.

The risk is dose dependent. Doses of methadone used for analgesia in palliative care tend to be lower than that used in addiction services. Although QTc interval

prolongation has been reported at doses as low as 30-40mg of methadone per day, other studies found it to be unchanged at less than 100mg per day. For those on lower doses, multiple other risk factors were present (see above). Doses of antipsychotic drugs such as haloperidol and levomepromazine used for nausea also tend to be lower than when used for psychosis.

In view of this:

- When dealing with palliative care patients, prescribers should be aware of drugs that may affect the QTc interval.
- The lowest effective dose should be used.
- Evaluate the potential benefit against potential risk for each individual patient
- Explain to the patient and family the risk involved and the reason for using the drug(s) in question to allow an informed decision to be made.
- At the end of life a commonsense approach should prevail, and the benefit of drugs such as haloperidol is likely to far outweigh any risk and an ECG is not required.
- Drugs metabolised via CYP450 may interact; enzyme inhibitors will increase levels of other substrate drugs. Drugs which risk increasing QTc interval **AND** inhibit CYP450 will increase levels of a co-prescribed substrate drug also known to affect QTc interval. Therefore, the increase in risk will be over and above that expected from merely adding a second drug. In the case of methadone, this increased drug level may cause respiratory depression as well as increasing the risk of TdP. Important examples that may be found in palliative care are found in table 3.

Table 3: Drugs which may interact via CYP450 to cause increased TdP risk

CYP450 enzyme	Substrate with TdP risk	Inhibitor with TdP risk
CYP1A2	Amitriptyline Mirtazapine Olanzapine	Ciprofloxacin Erythromycin (weak) Fluoxetine (weak) Paroxetine (weak) Sertraline (weak)
CYP2C8/9	Amitriptyline	Fluconazole Metronidazole
CYP2C19	Amitriptyline Citalopram Fluoxetine Lansoprazole Omeprazole Sertraline	Esomeprozole Fluoxetine Ketoconazole Lansoprazole Omeprazole
CYP2D6	Amitriptyline Fluoxetine Haloperidol	Fluoxetine Haloperidol Levomepromazine

	Mirtazapine Ondansetron Sertraline	
CYP3A4/5	Amitriptyline Erythromycin Loperamide Methadone Mirtazapine Omeprazole	Clarithromycin Erythromycin Fluconazole Fluoxetine Itraconazole Ketoconazole Omeprazole

Prescribing hints in palliative care

- Symptom relief is paramount at the end of life, and it may not be possible to avoid combinations of drugs which predispose to TdP
- Prescribers need to be mindful rather than avoidant.
- Prescribe with caution in patients with ischaemic heart disease
- Use Nystan® rather than a conazole to treat oral candidosis if patients are on drugs in the 'definite risk' group, particularly methadone. If an oral agent is required consider **terbinafine** (unlicensed use).
- Methadone will be initiated in palliative care patients only in the hospice inpatient setting. Perform an ECG prior to starting methadone, and take all risk factors into account
- Consider duloxetine over a tricyclic for neuropathic pain; there is currently insufficient data to show an association between duloxetine and TdP
- Avoid escitalopram and citalopram. Again, duloxetine may be a better choice for depression, particularly if patients also have troublesome pain
- Advice from Specialist Palliative Care prescribers is available 24/7 via the hospice on 01226 244244

References

- Palliative Care Formulary Fifth Edition. Twycross, R, Wilcock, A and Howard, P (eds.) palliativedrugs.com
- crediblemeds.org

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