Domperidone safety: a mini-review of the science of QT prolongation and clinical implications of recent global regulatory recommendations

Pamela J Buffery, R. Matthew Strother

ABSTRACT

AIMS: In New Zealand, domperidone is approved for gastrointestinal motility and nausea and vomiting. The European Medicines Agency (EMA) recently concluded that domperidone poses a significant risk of sudden cardiac death (SCD) and has restricted use in Europe. This paper reviews the risk of QT prolongation and cardiac adverse effects with domperidone and provide information to allow prescribers to make informed decisions on usage.

METHODS: A search of two bibliographic databases, the European Medicines Agency (EMA) website, Micromedex, Lexicomp and reference texts was undertaken for domperidone related reports of QT prolongation, cardiac arrhythmias and/or SCD. The New Zealand Centre for Adverse Drugs Reaction Monitoring was also contacted for cardiac adverse event reports with domperidone.

RESULTS: Over 30 published papers, EMA documents and other information sources were collated, including two studies that met thorough QT study (TQT) criteria (ICH-E14). The first TQT was negative while the second was marginally positive. Reports of QT prolongation, ventricular arrhythmias and SCD were located (predominantly high/very high–dose IV domperidone). With oral domperidone, a Dutch case–controlled study reported an adjusted odds ratio of SCD of 11.4 (95% CI 1.99-65.2), based on only three patients out of 1,366 cases of SCD. A second nested case–controlled study calculated an odds ratio of ventricular arrhythmia or SCD of 1.59 (1.28–1.98) vs. placebo.

DISCUSSION: Based on the results of the two TQT (the regulatory agency gold standard for assessment of QT prolongation) domperidone does not appear to be strongly associated with QT prolongation at oral doses of 20 mg QID in healthy volunteers. Further, there are limited case reports supporting an association with cardiac dysfunction, and the frequently cited case-control studies have significant flaws. While there remains an ill-defined risk at higher systemic concentrations, especially in patients with a higher baseline risk of QT prolongation, our review does not support the view that domperidone presents intolerable risk.

Introduction

Domperidone is licensed in New Zealand as a treatment for nausea, vomiting, and dyspepsia. In practice, it is used as a pro-kinetic, an adjunct in Parkinson's disease, treatment of chemotherapy induced nausea and vomiting, and off-label as a galactagogue. Domperidone is a preferred medication by several practice groups across New Zealand because it is believed to be both efficacious and have a relatively limited side-effect profile, particularly compared to other dopamine receptor blockers (eg, metoclopramide), insofar as incidence of extrapyramidal side effects. However, the recommendations recently published by the European Medicines Agency (EMA) and a subsequent review by MedSafe's Medicines Adverse
Reactions Committee (summarised in Table 1), may change the way New Zealand practitioners use this drug. In this paper we explore the background for concern by global drug regulatory agencies and critically examine the strength of the evidence behind their recommendations.

Domperidone is a peripheral dopamine D2-receptor antagonist with prokinetic and antiemetic properties that has been available since 1978. Studies have explored a variety of indications: nausea and vomiting (both related and unrelated to chemotherapy); dyspepsia; bowel motility disorders, and control of the gastrointestinal side effects of anti-Parkinson medications. Initial reports of QT prolongation and cardiac events started to appear in the 1980s and related to administration of high-dose intravenous (IV) domperidone. As a direct consequence of these case reports domperidone was never approved in the US and the IV formulation was withdrawn globally. However, oral domperidone remains available in many countries, including New Zealand.

In 2013 the EMA, at the request of the Belgian drug regulatory agency, undertook a review of the clinical use and safety of domperidone. The report from the Pharmacovigilance Risk Assessment Committee, released in March 2014, found that domperidone posed a significant risk of QT prolongation, cardiac dysrhythmias, and sudden cardiac death (SCD). Citing this risk, and concerns over efficacy data, the EMA made the following recommendations: maximum doses of domperidone in adults and children should be reduced to 30 mg/day and 0.75 mg/kg/day, respectively; use should be restricted to less than 1 week; domperidone should only be used for treatment of nausea and vomiting; and use in high risk groups (hepatic dysfunction, the elderly (≥60 years), those with pre-existing QT prolongation, and in those on other QT prolonging agents) should be curtailed. These regulatory restrictions are consistent, though less onerous, with the American approach, where domperidone is only available via special application to the Food and Drug Administration (FDA) as an investigational agent.

### Table 1: Medicine Adverse Reaction Committee (MARC) Recommendations June 2014

<table>
<thead>
<tr>
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<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>The Committee recommended that Medsafe request the sponsors of domperidone to update the indications, contraindications and warnings and precautions sections of the data sheets.</td>
</tr>
<tr>
<td>2</td>
<td>The Committee recommended that Medsafe request the sponsors of domperidone to update the data sheets with a reduced recommended daily dose for use in children.</td>
</tr>
<tr>
<td>3</td>
<td>The Committee recommended that Medsafe communicate the results of this review to healthcare professionals by including an article on domperidone in a future edition of Prescriber Update.</td>
</tr>
<tr>
<td>4</td>
<td>The Committee recommended that Medsafe communicate the results of this review directly to nurses and midwives through the New Zealand Nurses Organisation (NZNO) and New Zealand College of Midwives.</td>
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</table>

Sudden cardiac death and QT prolongation

The concern driving drug regulatory agencies is an association between domperidone and SCD. While the exact aetiology of SCD frequently cannot be determined, regulators believe domperidone leads to progressive prolongation of the QT interval. The QT interval is considered a biomarker for SCD because it has been observed with prolongation, the cardiac depolarisation/repolarisation cycle becomes more chaotic, increasing the likelihood of a depolarisation occurring concurrently with repolarisation, leading to ventricular dysrhythmia Torsades de Pointes (TdP), which has a high risk of SCD. Indeed, families with genetic mutations of cardiac ion channels reveal that individuals with persistent QT prolongation have a significantly higher risk of TdP and SCD, as can electrolyte abnormalities, other medical conditions, and importantly, medications.

The molecular mechanism of drug-induced QT prolongation has not been fully elucidated, but is linked to the potassium efflux channel, human Ether-a-go-go-Related Gene (hERG). A drug can bind to the hERG
channel effectively closing it, thus delaying cardiac repolarisation and lead to QT prolongation. Unfortunately, the transmembrane portion of hERG is promiscuous, binding to many drugs, and thus hERG-mediated QT prolongation has been associated with many drugs. Non-trivial risk for QT prolongation exists for many drugs and potential drugs and significant investment has been put into the pre-clinical and clinical quantification of this risk. A number of pre-clinical in vitro and in vivo models have been developed, and extensive reviews of advances in this area can be found in the literature. For purposes of this review, however, it is significant to note that while regulatory guidance has been non-directive on species selection, generally dog is considered the in vivo model of choice in relation to humans for QT prolongation assessment.

Clinically, the gold standard for determining a drug's risk for QT prolongation and SCD is unambiguously the ‘thorough QT’ study (TQT). The International Committee on Harmonisation (ICH) E14 Guidance on Clinical QT Studies has been adopted by all major drug regulatory bodies. This guidance recommends a basic study design including a positive control (ie, a fluoroquinolone) that will increase the QTc by about 5ms in most subjects, sufficient dose levels to allow assessment of a dose-response curve to QTc prolongation, and defines the negative TQT as a study in which the largest baseline-subtracted, time-matched, mean difference between drug and placebo is ≤ 5 ms with an upper bound of the 95% confidence interval of ≤ 10 ms. While there remains significant debate around aspects of the TQT—the impact of sex, cross-over versus parallel design, and methodologies/algorithms for QT interval determination and rate correction (determining the QTc)—the negative TQT is generally accepted that the drug imparts minimal risk for TdP and SCD.

Methods

A literature search of Embase (1947 to present) and Medline (1946 to present) was conducted using various Medical Subject Headings (MeSH) terms that included: domperidone; QT prolongation; heart arrhythmia; QT prolongation.mp; and arrhythmias-cardiac. In addition, several databases and reference texts were searched for any relevant data regarding domperidone and QT prolongation, cardiac arrhythmias and/or sudden cardiac death. We also browsed and searched the EMA website for documents relating to their recent recommendations regarding domperidone. Lastly, we contacted the New Zealand Centre for Adverse Drugs Reaction Monitoring for the numbers of reports received by the centre relating to the use of domperidone and reports of QT prolongation, cardiac arrhythmias and SCD.

Domperidone and SCD: initial reports

Concerns over the cardiac effects of domperidone arose in the 1980s when five cases of cardiac arrest were reported with use of high–dose IV domperidone. The initial report was of a single patient in a small dose-escalation trial for chemotherapy-induced nausea and vomiting who developed fatal ventricular fibrillation following a 200 mg IV bolus of domperidone. In spite of this death, the study reported on a further three patients administered between 0.94 mg/kg and 13.4 mg/kg given divided between an initial IV bolus followed by a 13-hour infusion. The authors reported tolerance and good efficacy at 1.2 mg/kg IV bolus followed by 1.6 mg/kg IV infusion. A subsequent series of four case reports occurred at more moderate doses of 50 mg (one over 2 hours and repeated after chemotherapy, the other a single dose over 15 minutes) and 20 mg (both as IV bolus). However, it was noted that three of these patients had hypokalaemia, a known risk factor for ventricular dysthymias, all were successfully resuscitated, and one of the patients went on to receive further IV domperidone with no sequelae. However, based on these concerns the regulatory authorities removed IV domperidone from global markets, and formal studies of cardiac risk with domperidone were initiated.

Oral domperidone in the thorough QT study

Two TQT studies have been performed to assess the risk of oral domperidone.

The first, cited in the EMA report, was a
well-designed four-way crossover study with placebo and moxifloxacin as an active control in 44 healthy volunteers. Two dosage regimens of domperidone were compared, 10 mg four times a day (40 mg/24 hours) and 20 mg four times a day (80 mg/24 hours), with drug concentration monitoring of both domperidone and moxifloxacin conducted during the study. Three methods were used to determine QTc. No clinically relevant dose-QTc response and exposure QTc response effects were observed in this study. This was a negative study according to the ICH-E14 criteria with oral domperidone at single or multiple doses of 10 to 20 mg, or multiple doses of 40 to 80 mg in 24 hours.

The second study, not cited by the EMA, was a pharmacokinetic and TQT double-blind crossover study in 24 healthy volunteers. Study arms were: domperidone (10 mg four times a day); ketoconazole (200 mg twice daily); and a combination of domperidone and ketoconazole with placebo. Monitoring and determination of QTc was similar to that of the first study. QT prolongation greater than 470 ms was not observed with any single drug or combination. The highest mean increase in QTc from baseline compared with placebo was the combination at 15.9 ms (95% CI, 12.47 to 19.33, \( p < 0.001 \)); ketoconazole alone was 9.24 ms (5.85 to 12.63, \( p < 0.001 \)); and domperidone was 4.2 ms (0.77 to 7.63, \( p = 0.017 \)). Therefore, this study is borderline positive for domperidone monotherapy (maximum mean increase in QTc compared with placebo was > 5 ms at some time points but never exceeded 12 ms). It should be noted, however, that this increase is in the same range as the accepted positive control, anazole antifungal, where the risk is felt to be minimal enough that these medications are routinely prescribed not just in illness, but in healthy volunteers in TQT studies.

Case-controlled studies

Three case-control studies have reported an increased risk of ventricular arrhythmias (VA) or SCD associated with domperidone use, summarised in Table 2. Van Noord et al. identified 1,336 cases of VA or SCD of which 10 (0.75%) had a current prescription for domperidone at the time of their event. Matched against 20 or 40 controls, depending on whether the event was fatal the odds ratio (OR) for VA/SCD due to domperidone was just under four. Further subgroup analysis of the three cases with domperidone doses >30 mg/day had an adjusted OR (aOR) of 11.

The second study matched 140 cases with 560 controls not on QTc prolonging drugs and found an aOR of 2.1 (1.2–3.5) for patients on any medication associated with QTc prolongation, and 4.7 for domperidone specifically. This compares to aORs of 3.87 (1.6–9.2), 2.6 (1.4–6.4), 2.0 (0.5–8.1), and 1.4 (0.2–8.6), for haloperidol, cotrimoxazole, amitriptyline, and clarithromycin, respectively. Taking more than one drug associated with QTc prolongation had an aOR of 4.8 (1.6–14), and specifically taking drugs that inhibited metabolism of a concurrently prescribed QTc prolonging drug had an aOR of 4 (1.2–13).

A Canadian nested case-controlled study using a healthcare database of just under 1 million residents compared the risk of proton pump inhibitors (PPIs) and domperidone for SCD. The 83,212 individuals prescribed domperidone, a PPI, or both were matched with up to four controls, and 1,608 cases of VA or SCD were identified. Of these, 169 (10% of those having VA/SCD) had active domperidone prescriptions at the time of their event. Compared to current PPI use domperidone had an OR of 1.44 (1.12–1.86), and compared to placebo 1.59 (1.28–1.98).

The New Zealand Pharmacovigilance Centre has received a total of 32 spontaneous reports of any type of adverse effect associated with the use of domperidone submitted by various health professionals around New Zealand. Only one of these reports related to QT prolongation, from which the patient was reported to recover from (no further details known). There were no other reports for QT prolongation and none for SCD, TdP, or arrhythmia of any kind. From a global perspective, as of June 2014, the World Health Organization adverse drug event database had a total of 67 reports (six fatal) of domperidone associated with QT prolongation, 34 of TdP (6 fatal), 21 of arrhythmia (one fatal) and 41 of cardiac arrest (29 fatal).
**Discussion**

Domperidone has been available for prescribing in New Zealand since 1984, and in that time CARM has had no reported cases of VA or SCD associated with its use. However, domperidone has received the attention of global drug regulatory agencies because of association with these very serious risks.

Before summarising the clinical literature, it is worth noting that a significant component of the EMA recommendation was based on pre-clinical data. This is remarkable because the E14 guidance preferences clinical data above preclinical. In fact, E14 specifically states that only in the case of an ambiguous TQT and significant clinical concern should animal data be used to guide clinical decisions. It is therefore discordant that the EMA cites a negative TQT, but based a significant portion of their recommendations on animal model data performed in rodents, a non-preferred model for human hERG. So, this review focuses on the available clinical information to help the clinician interpret these data.

The clinical literature defining this risk with oral domperidone is comprised of a negative TQT, a marginally positive TQT and three case control studies. It is worth remarking on some aspects of these studies to address the concerns raised by the EMA and subsequently New Zealand Medsafe.

First, the case reports that prompted the initial concern over SCD were associated with high-dose IV domperidone. Indeed, given that domperidone has oral bioavailability of 13–17% the reported cases would have occurred at oral doses in excess of 1000 mg in the initial case, or at bolus doses of 150 mg to 380 mg. Second, the two presented TQT studies give a mixed picture—one is negative, with dosing up to 80 mg/24 hours and the second is marginally positive, with dosing up to 40 mg/24 hours. It is interesting that the marginally positive study was not cited in the EMA literature, but it is worth noting that the QTc prolongation associated with domperidone was similar to that of routinely prescribed fluoroquinolones and many other QT prolonging drugs not associated with extensive regulatory restrictions on their use. The case-control studies using retrospective databases do consistently identify a risk of VA/SCD with domperidone—although the extent of that risk varies wildly with the more extreme estimates being driven by a very small number of cases. Finally, it is important to note that in New Zealand there is one report potentially associating domperidone with QT prolongation (non-fatal); globally, only 67 spontaneous reports (42 fatalities) are on record associating domperidone with cardiac events from 1984 to 2014—bearing in mind that these data are not extensively validated and prone to over-association.

**Table 2: Case control studies of domperidone and VA or SCD**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Control Population</th>
<th>Number of Cases on Domperidone</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Electronic primary care record with 1 million patients [van Noord C, et al, 19]</td>
<td>Patients without VA or SCD</td>
<td>10 with domperidone&lt;br&gt;3 with domperidone &gt; 30mg/24 h</td>
<td>3.72 (1.7.2–8.08)&lt;br&gt;11.4 (1.99–65.2)</td>
</tr>
<tr>
<td>Single institution database of cardiac arrest and SCD over 8 years [De Bruin ML, et al, 20]</td>
<td>Patients with cardiac arrest or SCD not on any QTc prolonging medications</td>
<td>140 cases on a QTc prolonging drug&lt;br&gt;7 cases on domperidone</td>
<td>4.7 (1.4–16)</td>
</tr>
<tr>
<td>Electronic database of approximately 1 million patients [Johannes CB, et al, 21]</td>
<td>Patients without VA or SCD with or without PPI</td>
<td>69 cases on domperidone</td>
<td>1.44 (1.12–1.86) compared to PPI&lt;br&gt;1.59 (1.28–1.98) compared to no exposure to either domperidone or a PPI</td>
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</table>
In summary, this literature is mixed, and therefore, as with the many approved and routinely prescribed medication associated with QT prolongation (the reader is referred to CredibleMeds, www.crediblemeds.org), prescribing clinicians should be aware of this potential risk and work to mitigate this or pursue alternatives. Limiting risk means knowing the other clinical contributors to QTc prolongation, including: baseline QTc prolongation (genetic, structural, or drug-induced); electrolyte imbalances (hypo and hyper-kalemia); concurrent prescription with other QTc prolonging drugs; or concurrent prescription with drugs inhibiting the metabolism of domperidone (cytochrome p450 3A). Indeed, it was notable that the second TQT study presented observed significantly greater domperidone exposure (2.9 and 3.6 fold higher Cmax and AUC, respectively) as a result of the CYP3A inhibition by ketoconazole. If however, the clinician is uncomfortable with this risk, they should look to alternatives.

Alternatives to domperidone as an antiemetic or as a prokinetic, the two indications licensed in New Zealand, are presented in Table 3. Given that both nausea/vomiting and motility disorders have presently available alternatives, prescribing clinicians must weigh the risks and benefits of prescribing domperidone and select this as the drug of choice. A regulatory restriction on maximum dosage will mandate prescribers choose either a less effective dose or an alternative, regardless of whether they feel the risks and benefits are in favour of domperidone. We would argue given the relative weakness of data driving the decisions of the EMA and the FDA, that New Zealand prescribers should acknowledge a possible risk, but have the ability to weigh this risk both in the context of the clinical decision and in light of alternatives, rather than be forced into avoiding domperidone.
### Table 3: Alternative agents to domperidone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (QT prolongation risk)</th>
<th>Selected serious ADRs (%)</th>
<th>Selected common ADRs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aprepitant</strong>&lt;br&gt;(NO)</td>
<td>neutropenia (up to 9%)&lt;br&gt;bradycardia (4%)&lt;br&gt;sinus tachycardia (cr)&lt;br&gt;TEN (cr)&lt;br&gt;neutropenic sepsis (cr)</td>
<td>alopecia (24%)&lt;br&gt;fatigue (22%)&lt;br&gt;anosmia (20%)&lt;br&gt;headache (18%)&lt;br&gt;nausea (13%)&lt;br&gt;constipation (12%)</td>
<td>hiccup (≤11%)&lt;br&gt;diarrhoea (≤10%)&lt;br&gt;anosmia (≤10%)&lt;br&gt;hypotension (≤6%)&lt;br&gt;puritus (5%)&lt;br&gt;fever (≤6%)</td>
</tr>
<tr>
<td><strong>Cyclizine</strong>&lt;br&gt;(NO)</td>
<td>raised ventricular filling pressures (ind)&lt;br&gt;pallpitations (ind)&lt;br&gt;tachycardia (ind)</td>
<td>bradycardia (4%)&lt;br&gt;sinus tachycardia (cr)</td>
<td>alopecia (24%)&lt;br&gt;fatigue (≤22%)&lt;br&gt;anosmia (≤20%)&lt;br&gt;headache (≤18%)&lt;br&gt;nausea (≤13%)&lt;br&gt;constipation (≤12%)</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong>&lt;br&gt;(NO)</td>
<td>bradyarrhythmia (ind)&lt;br&gt;cardiac dysrhythmia (cr)&lt;br&gt;cardiomyopathy (ind)&lt;br&gt;thromboembolic disorder (ind)&lt;br&gt;pancreatitis (ind)&lt;br&gt;psychiatric symptoms (inn ind convulsions (ind)</td>
<td>hypotension (ind)&lt;br&gt;skin thinning (ind) &lt;br&gt;hyperglycaemia (ind)</td>
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<tr>
<td><strong>Droperidol/Haloperidol</strong>&lt;br&gt;(YES)</td>
<td>cardiac arrest (ind)&lt;br&gt;tachycardia (ind)&lt;br&gt;TdP (ind)&lt;br&gt;extrapiramidal symptoms (ind)&lt;br&gt;hallucinations (ind)&lt;br&gt;hyperactivity (ind)&lt;br&gt;NMD (cr)&lt;br&gt;psychiatric symptoms (ind)&lt;br&gt;haematological effects (ind)</td>
<td>hyperpolarisation (ind)&lt;br&gt;hyperpolarisation (ind)&lt;br&gt;hyperprolactinaemia (ind)&lt;br&gt;hyperprolactinaemia (ind)&lt;br&gt;somnolence (ind)</td>
<td></td>
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<tr>
<td><strong>Erythromycin</strong>&lt;br&gt;(YES)</td>
<td>TdP (ind)&lt;br&gt;Sudden cardiac death (ind)&lt;br&gt;ventricular arrhythmia (ind)&lt;br&gt;convulsions (ind)&lt;br&gt;erythema multiforme (rare)&lt;br&gt;SJS/TEN (rare)&lt;br&gt;C.difficle colitis</td>
<td>diarthrosis (≤16%)&lt;br&gt;dizziness (≤16%)&lt;br&gt;anorexia (≤10%)&lt;br&gt;skin thinning (≤10%)&lt;br&gt;hypertension (≤6%)&lt;br&gt;impairment (≤6%)&lt;br&gt;osteoporosis (≤5%)&lt;br&gt;tetraparesis (≤4%)&lt;br&gt;</td>
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<tr>
<td><strong>Lorazepam</strong>&lt;br&gt;(NO)</td>
<td>extrapiramidal symptoms (&lt;1%)&lt;br&gt;hepatotoxicity (&lt;1%)&lt;br&gt;cerebral oedema (&lt;1%)&lt;br&gt;cardiac arrest (&lt;1%)&lt;br&gt;convulsions (&lt;1%)&lt;br&gt;psychiatric symptoms (&lt;1%)&lt;br&gt;GI haemorrhage (&lt;1%)&lt;br&gt;haematological effects (&lt;1%)&lt;br&gt;NMS (&lt;1%)</td>
<td>sedation (&lt;10%)&lt;br&gt;dizziness (≤7%)&lt;br&gt;headache (≤5%)&lt;br&gt;</td>
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<tr>
<td><strong>Metoclopramide</strong>&lt;br&gt;(NO)</td>
<td>dystonia (≤29%, dose dependent)&lt;br&gt;psychiatric symptoms (cr)&lt;br&gt;cardiac arrest (cr)&lt;br&gt;cardiac dysrhythmia (cr)&lt;br&gt;malignant hypertension (cr)&lt;br&gt;supraventricular tachycardia (ind)&lt;br&gt;extrapiramidal symptoms (ind)&lt;br&gt;haematological effects (ind)</td>
<td>dizziness (≤70%, dose dependent)&lt;br&gt;fatigue (≤10%)&lt;br&gt;nausea (≤8%)&lt;br&gt;headache (≤6%)&lt;br&gt;dizziness (≤8%)&lt;br&gt;</td>
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<tr>
<td><strong>Ondansetron</strong>&lt;br&gt;(YES)</td>
<td>bradycardia (&lt;1%)&lt;br&gt;cardiac arrhythmia (&lt;1%)&lt;br&gt;cardiac arrest (&lt;1%)&lt;br&gt;extrapiramidal symptoms (&lt;1%)&lt;br&gt;hepatic failure (&lt;1%)&lt;br&gt;hepatic necrosis (cr)&lt;br&gt;NMS (&lt;1%)&lt;br&gt;TEN (&lt;1%)&lt;br&gt;TdP (cr)&lt;br&gt;anaesthesia (cr)</td>
<td>headache (≤27%)&lt;br&gt;fatigue (≤13%)&lt;br&gt;constipation (≤13%)&lt;br&gt;dizziness (≤12%)&lt;br&gt;hyperglycaemia (≤11%)&lt;br&gt;diabetes (≤10%)&lt;br&gt;fever (≤8%)&lt;br&gt;xerostomia (≤5%)&lt;br&gt;</td>
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<tr>
<td><strong>Prochlorperazine</strong>&lt;br&gt;(YES)</td>
<td>cardiac arrest (ind)&lt;br&gt;sudden cardiac death (ind)&lt;br&gt;NMS (ind)&lt;br&gt;haematological effects (ind)&lt;br&gt;hepatotoxicity (ind)&lt;br&gt;extrapiramidal symptoms (ind)&lt;br&gt;tardive dyskinesia (ind)&lt;br&gt;convulsions (ind)&lt;br&gt;psychiatric symptoms (ind)</td>
<td>dizziness (ind)&lt;br&gt;somnolence (ind)</td>
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</table>

**Key:**
- **ADR**: adverse drug reaction
- **cr**: case reports
- **ind**: incidence not defined
- **SJS**: Stevens-Johnson Syndrome
- **TEN**: toxic epidermal necrolysis
- **NMS**: neuroleptic malignant syndrome
- **GI**: gastrointestinal
- **TdP**: Torsades de Pointes
- **LFT**: liver function tests

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