Drug–drug interaction related to the use of pipamperon and ondansetron in a child treated for leukemia

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Abstract
Pipamperon is a potent neuroleptic drug with many side effects, including prolongation of the QT interval. We report a case of a child treated for leukemia in which prolongation of the QT interval was observed. Physicians and pharmacists should be cautious for drug–drug interactions when pipamperon is prescribed, especially in combination with other QT-prolongating agents. Alternative strategies should be used whenever possible.

Keywords
Pipamperon, ondansetron, drug–drug interaction, leukemia

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Introduction
Pipamperon is a potent neuroleptic drug belonging to the pharmacological class of butyrophenones. These drugs have lesser sedative, hypotensive and anticholinergic activity than other neuroleptics.1,2 Pipamperon is available in some European countries and is licensed for psychoses and symptomatic treatment of severe cases of excitation and agitation in adults and children. Side effects include extrapyramidal symptoms, tardive dyskinesia, endocrinological and cardiological side effects and neuroleptic malignant syndrome.1–3

The QT interval is an electrocardiogram (ECG) measure which includes both depolarization and repolarization. It starts with the onset of ventricular depolarization (Q-wave) and ends with completion of repolarization (T-wave). The QT interval shortens with increasing heart rates and is therefore usually corrected for heart rate (corrected QT (QTc)).

QT prolongation increases the risk of torsade de pointes (TdP), which is a malignant ventricular arrhythmia associated with syncope and sudden death.1,2 QTc intervals are usually around 400 ms in duration, and values lower than 440 ms are considered normal. When the QTc interval is higher than 500 ms or an increase in QTc of 60 ms or more is observed during antipsychotic treatment, it indicates significant risk for TdP.1,2

Many antipsychotics (especially haloperidol and thioridazine) and other drugs (methadone, cisapride, erythromycin, etc.) are known to prolong the QT interval.1–5 The QT prolongation is hypothesized to occur via direct inhibition of the cardiac delayed potassium rectifier (IKr) channel, which extends the ventricular repolarization process.1,2

Not all QT prolongations caused by drugs cause an increased risk for TdP. Prediction of TdP and sudden death can be improved by examining dose dependency, the percentage of QTc intervals higher than 500 ms and the risk of drug–drug interactions.6

A number of risk factors for drug-induced QT with respect to the drug regimen used have been identified.1–6 One of them is the concurrent use of more...
than one drug known to cause prolongation of the QT interval or use of QT-prolongating drugs from which the metabolism is decreased due to inhibition of hepatic cytochrome P450 enzymes.

We observed the prolongation of QT interval in a child during treatment with pipamperon and concomitantly QT-prolonging drugs, particularly with ondansetron.

Case

An 11-year-old male diagnosed with acute lymphoblastic leukemia (ALL) was treated according to the EORTC Children’s Leukemia Group guidelines (EORTC 58081).

Due to the diagnosis of a reactive attachment disorder with aggressive behavior and anger outbursts (classification defined according to the Diagnostic and Statistical Manual of Mental Disorders) at a young age, the patient was prescribed pipamperon (Dipiperon®, Eumedica, Belgium). Treatment with pipamperon started years before the diagnosis of ALL. The patient had no history of cardiac disease. Aggression dissipated under pipamperon, so its use was continued. At the age of eight, the patient stopped taking pipamperon after which anger outbursts clearly returned. From then on, pipamperon was restarted at a dosage of 10 mg in the morning and 20 mg in the evening and was continued during the entire course of ALL treatment.

During the induction course for ALL treatment, the patient received vincristine (1.5 mg/m²), cerubidine (30 mg/m²), cyclophosphamide (1000 mg/m²), uromitin (350 mg/m²) and ondansetron as anti-emetic (5 mg/m², intravenously twice daily). As ondansetron is defined as a “moderate risk” QTc-prolongating agent, the patient was on pipamperon (known as highest risk QTc-prolonging agent), a drug interaction check was performed, indicating a combination that should be avoided. However, as the ECG performed at that moment was defined as “normal” (QT/QTc 354/444 ms), ondansetron was further administered for three days after the last chemotherapy. Serum potassium and magnesium laboratory values were within normal ranges.

A few months later, the patient was readmitted to the hospital where he received a subsequent course with high laboratory values were within normal ranges. Pipamperon defined as “Highest Risk QTc-Prolonging Agent” was highly suspected to induce the prolongation, in addition to ondansetron, defined as “Moderate Risk QTc-Prolonging Agent”. As concomitant, use of highest risk QTc-prolonging agents with any other QTc-prolonging agent should be avoided, and because of the results of the ECG, the use of pipamperon was stopped immediately and the patient was cardially monitored.

Two days after the drug was stopped, a new ECG showed a decrease of the QTc interval (QT/QTc 390/477 ms). At this time, he still received ondansetron twice daily as anti-emetic treatment. Before discharge, another ECG was performed displaying a QT/QTc of 454/454 ms. Pipamperon was discontinued during the following days and a psychiatric consultation was performed during hospitalization. As the patient’s known aggressive behavior seemed to get worse without pipamperon, it was decided to restart the treatment again after 10 days.

A new ECG before start of pipamperon showed a QT/QTc of 438/459 ms. It was decided not to combine pipamperon with ondansetron during chemotherapy treatment.

A Drug Interaction Probability Scale was used to determine the causality of adverse reaction. The analysis revealed a result of 8, suggesting a probable relation of adverse event. Meanwhile, alizapride (Litican®, Sanofi Belgium, Diegem), which is not related to QT prolongation, was associated as an anti-emetic.

Discussion

QT prolongation is a rare adverse event of pipamperon, with the risk being increased when there is a concurrent use of one or more drugs known to cause prolongation of the QT interval. The concomitant use of highest risk QTc-prolonging agents with any other QTc-prolonging agent is expected to substantially increase the risk for serious toxicities, including the development of TdP or other significant ventricular tachyarrhythmias. As far as we know, there are no specific reports on the drug interaction with ondansetron, but it is known that the risk or severity of adverse effects can be increased when ondansetron is combined with pipamperon.

In this case report, the combination of pipamperon and ondansetron caused a significant prolongation of the QTc interval above 500 ms, which is associated with an increased risk for TdP. A decrease of the QTc length was observed after pipamperon was stopped. It is not clear why the QTc prolongation was observed during this chemotherapeutic cycle. Pipamperon has a half-life of about 17 h in healthy adult patients. We suggest that the prolongation might be due to the long-term therapy, the age of the patient and the combination of the other drugs are known to cause QTc prolongation.

The use of pipamperon is known to be associated with prolongation of the QT interval. A search in VigiBase, the World Health Organization’s global
database, on suspected side effects from various medicinal products retrieved 1670 records with pipamperon, from which 10 with ventricular arrhythmias and cardiac arrest (TdP).11

Although being an older molecule, the use of pipamperon could be justified in our patient. Pediatric oncologists and psychiatrists decided to continue the administration of pipamperon. Alternatives as clonidine and aripiprazole were considered but were not preferential due to their side effects. Clonidine causes hypotension, is associated with bradycardy,12 has less known effectiveness against aggressive behavior and there is the need for careful dosing. Due to a better metabolic profile, aripiprazole might be a better long-term antipsychotic for this patient. However, it was not chosen because of side effects such as dizziness, hypotension (and the need for careful dosing and the association with QT prolongation).13 Both alternative medications were not preferential as the patient is still receiving chemotherapy and suffers from frequent nausea and hypotension. Pipamperon is otherwise well tolerated by the patient and has a seemingly good effect on the patient’s aggressive tendencies. It is also not advisable to switch to other medication in a period that is emotional and unstable. The patient will be routinely followed by a pediatric psychiatrist to ensure follow-up of effectiveness and general side effects.

Ondansetron is a serotonin (5-HT3) receptor antagonist, recommended as the first-line treatment in chemotherapy-induced nausea and vomiting in adults and children.14 In vitro studies indicate that 5-HT3 antagonists block voltage-dependent sodium channels and hERG-potassium channel (cardiac ion channels).15 On the other hand, in one study the effects of intravenously infused (over 30 s) 0.1 mg/kg ondansetron was observed on ECG monitoring. There was no observed change in QTc in contrast to infusion of granisetron. A systematic review and network meta-analysis on the comparative safety of 5-HT3 receptor antagonists among patients undergoing chemotherapy or surgery is taking place in Canada.16 The primary outcome of interest is arrhythmia with QT prolongation as secondary outcome.

In case ondansetron is involved in drug–drug interactions, the use of alizapride can be justified. However, the risk of extrapyramidal symptoms being a feared and known side effect of alizapride has to be outweighed against the benefit.9

**Conclusion**

It is clear that a lot of commonly used supportive care drugs in oncology (e.g. ondansetron) are known to increase the risk of QT prolongation. We consider the prudent use of pipamperon in particular settings and advise monitoring of QT interval on a regular basis and frequent drug–drug interaction monitoring.

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