

Apomorphine and Domperidone Review



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Abstract

Apomorphine is generally a safe and well tolerated therapy used in acute and intermittent treatment of the motor symptoms, the 'off' motor state in Parkinson's disease, and there is growing evidence supporting its clinical value in non-motor symptoms. It has an excellent efficacy profile in clinical practice, though the use of the agent continues to be underutilised. One of the most common reasons of this is most likely the perception of how difficult it is to use the agent, and the management of the adverse events (AE's). The discontinuation due to AE's is not as common as it has been believed. Apomorphine is generally well tolerated by most patients and if AE's do develop, they are manageable in most cases.

The objective of this literature review was to examine the body of literature regarding the risk of Electrocardiogram (ECG) changes, and cardiac arrest in apomorphine challenges; and to look for safety parameters for people commencing and continuing apomorphine therapy. There is evidence that apomorphine can prolong a QTc interval, leading to cardiac arrhythmias. During the apomorphine challenge the drug domperidone is widely used to combat the side effects of nausea and vomiting, and vasodilation side effects of postural hypotension from the apomorphine. Domperidone has also been identified and studied as a medication with risks of QTc prolongation.

Search Strategy

A review was conducted of the published literature using Pub Med/ MEDLINE and CINAHL databases from 1995 to 2022; key words and Boolean operators were used to ensure that searches were sensitive and specific to the topic. Please see Figure 1 for search methodology.

Eligible search results included textbooks and peer reviewed journal articles, expert opinion and studies that included the keywords apomorphine, domperidone, adverse events, cardiac, cardiac events, arrhythmia, and sudden cardiac death (SCD).

Editorials, opinion pieces, newspaper articles and those not based on scientific evidence were excluded. See Appendix for the inclusion criteria.

Types of studies

Studies that will be included for the review will include randomised controlled trials, observational, cohort and qualitative studies, case studies, systematic reviews, and guidelines. The studies will all be specific to cardiac changes, in people with Parkinson's disease, which is induced by subcutaneous apomorphine therapy, and with the concomitant use of Domperidone.

Types of Participants

Participants in the studies were identified to have Parkinson's disease; where commenced or had been on apomorphine; and included a review of the use of domperidone. Participants will include all ages and disease stages. Additional studies of non-Parkinson's disease who had taken domperidone were also considered to compare risk assessment of QTc changes. The QTc interval (ventricular repolarization).

Types of interventions

Interventions will include subcutaneous apomorphine therapy including injector pens. It will exclude nasal, rectal, and oral forms of apomorphine therapy.

Types of outcome measures

Primary outcomes

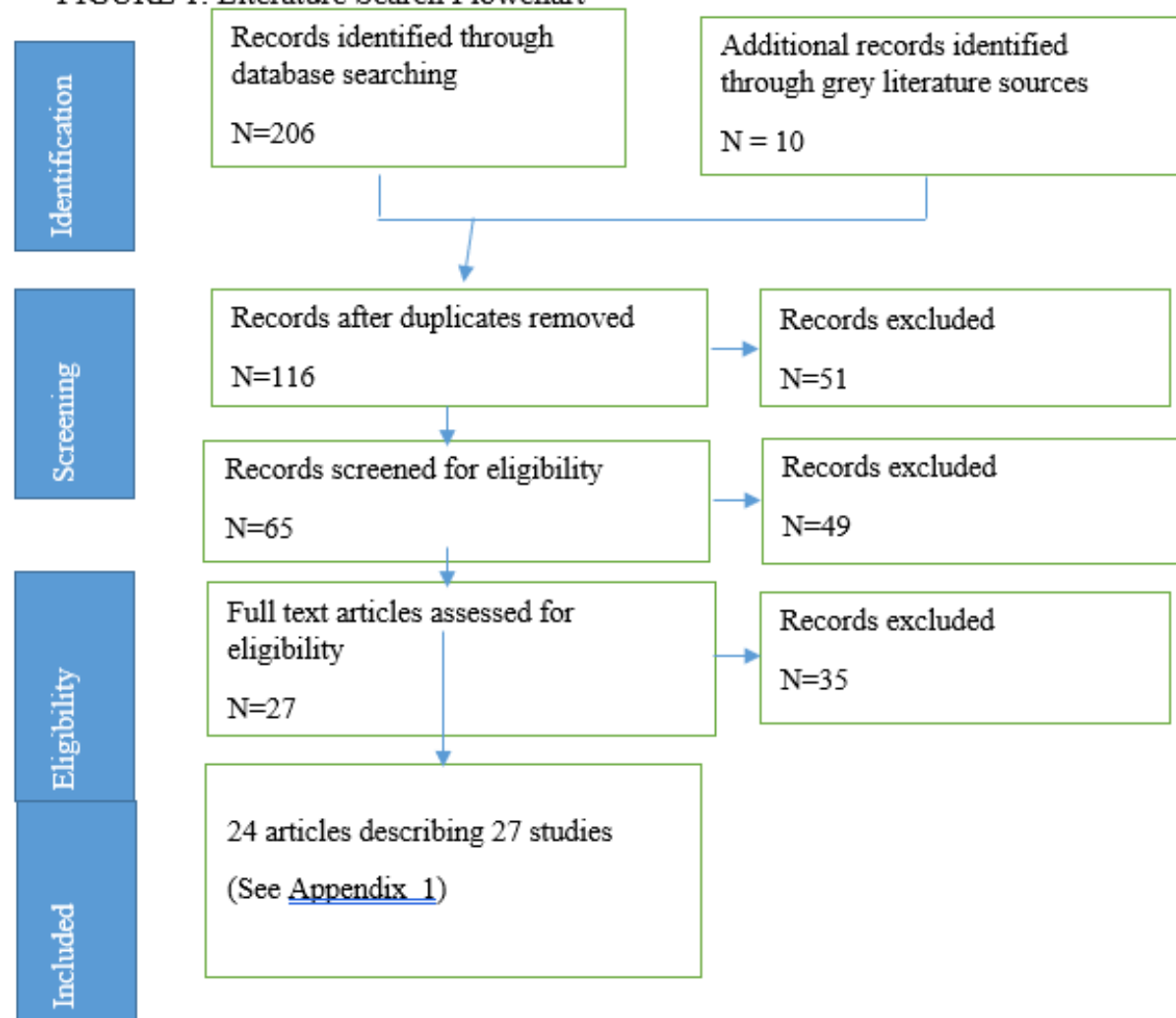
The primary outcomes included the rates of cardiac arrest during apomorphine challenges; the identification of types of ECG changes seen in subcutaneous apomorphine therapy; the identification of risk factors for developing ECG changes in apomorphine therapy; proposed pathophysiologic mechanism for ECG changes seen in apomorphine therapy, and the best management of the ECG changes.

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FIGURE 1: Literature Search Flowchart



Data Synthesis - Study Appraisal

The selected appraisal tools will be specific to the research design to improve validity, reduce measurement and information bias, and to detect the internal and external validity of the selected evidence. The appraisal tools included Quality Assessment Tool for Quantitative Studies for randomised controlled trials, cohort and observational studies (EPHPP 2010); Assessing the Methodological Quality of Systematic Reviews (AMSTAR) (Shae et al 2007); and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al 2021)

Data Collection and analysis

Two reviewers assessed the studies using the selected appraisal tools that were specific to cardiac anomalies using apomorphine / domperidone and Parkinson's disease. The reviewers were given training and education on conducting systematic reviews and both

have completed university studies at Masters level and able to review evidence synthesis.

Key words:

"Subcutaneous Apomorphine AND Domperidone"

"Subcutaneous Apomorphine AND cardiac arrhythmias"

"Subcutaneous Apomorphine AND QT"

"Subcutaneous Apomorphine AND slowed QT intervals"

"Subcutaneous Apomorphine AND Orthostatic Hypotension"

"Subcutaneous Apomorphine AND ECG OR Electrocardiogram"

"Subcutaneous Apomorphine AND Patient Safety OR Efficacy"

"Subcutaneous Apomorphine AND Long QT Syndrome"

"Subcutaneous Apomorphine AND QT Interval"

"Subcutaneous Apomorphine AND QT"

"Subcutaneous Apomorphine AND ECG OR Electrocardiogram"

AND "Parkinson's disease"

Given the scope of the literature returns it was difficult to limit to only people with Parkinson's disease, apomorphine, cardiac arrhythmias, domperidone so further scrutiny was required to include domperidone without apomorphine; and limited studies reviewing the risk of domperidone.

The Studies

The literature yielded 206 studies and grey literature yielded a further 10 articles. After the review by the two researchers only 27 studies were included the final review. Of the 27 articles, five (5) were literature reviews, several (13) expert opinions and most of these articles referred to the combination of open label, multi-centered, retrospective studies (9) or small-scale quantitative studies conducted between 2004 and up to 2018. See appendix 1.

The literature reviews were graded by the two reviewers using AMSTAR and included a review of the Journal Impact Factor. Research studies including the TOLEDO trial were reviewed using EPHPP.

Incidence of ECG changes/ QTc prolongation / adverse cardiac events with apomorphine use

The incidence of QTc prolongation in apomorphine therapy is described in several studies, but with few based on clinical evidence (Bhidayasiri, Garcia Ruiz, et al., 2016; Buffery & Strother, 2015; Gunzler, 2009; Ul Haq, Lewitt, & Fernandez, 2007), with adverse QTc prolongation at the commencement of apomorphine therapy noted in APOKYN 2006 cited by Gunzler (2009).

Menon and Stacy (2007) also make note of the propensity of apomorphine to lengthen the electrocardiographic correct QT interval based on 6mg doses or less of apomorphine without supporting evidence.

Borovac (2016) study observed the side effects of dopamine agonist therapy, listing

several studies supporting the side-effects of the ergoline-derived agonists associate with cardiac valve regurgitations and fibrotic changes in 2012. However, it is noted the better safety profile of cardiac complications in the non-ergoline derived agonists class of which apomorphine belongs to.

Borgemeester, Drent, and van Laar (2015) published a retrospective study of 125 Dutch patients on continuous apomorphine infusions. They noted a 3% occurrence of tachycardia compared with 20% occurrence of visual hallucinations and 50% skin nodules.

LeWitt, Ondo, Van Lunen, and Bottini (2009) conducted an open-label study of 546 subjects to study the safety and adverse effect profile of continued use of intermittent subcutaneous apomorphine. They reported treatment emergent serious adverse events of cardiac arrest .16%, and atrial fibrillation 1.1%. They also reported an incidence of one instance each of atrial flutter and atrial fibrillation but felt these adverse events were probably not related to the apomorphine therapy. Furthermore, they noted that, "Although statistically significant mean changes from baseline in some ECG parameters were observed at several time points, the changes were not considered clinically important, and no trends noted".

One other study reported cardiac arrhythmia was Kaminioti et al. (2013), citing a case of an 87-year-old Greek lady with ventricular bigeminy, recorded on a 12 lead ECG ten minutes after one dose of 10mg subcutaneous apomorphine, but no prolongation of the QT interval. Notably the patient was asymptomatic of dizziness, palpitations, presyncope or syncope, and was constantly cardiac monitored during the initiation treatment. The patient did not experience any further ventricular bigeminy upon withdrawal of apomorphine. This led to the consideration that cardiac arrhythmia's may be far more prevalent in the absence of cardiac monitoring during the initiation of apomorphine therapy.

Domperidone in apomorphine use

The role of the concomitant domperidone as a pre-treatment to apomorphine is to combat peripheral dopaminergic effects of apomorphine including nausea, hiccups and orthostatic hypotension (Buffery & Strother, 2015; Grandas, 2013; Zwar et al., 2016). Borgemeester et al. (2015) refers to the introduction of domperidone as successfully antagonizing peripheral and cardiovascular effects of apomorphine, this is also supported

by Auffret et al. (2018) who describes apomorphine as a valuable drug in the anti-Parkinson's armamentarium, especially when combined with domperidone to treat nausea.

The literature review yielded very little evidence of studies recommending a minimum starting dose or a minimum pre-treatment duration for domperidone prior to the commencement of apomorphine. Studies that did recommend a regimen of oral domperidone 20mg three times a day for patients 2-3 days prior to starting apomorphine infusions were based on literature from the early 1990's to early 2000's (Grandas, 2013). A later study by Henriksen (2014) suggests 10-20mg domperidone pre-treatment three times a day for 3 days before starting injection/infusion, a regimen supported by anecdotal evidence. The TOLEDO study design (Katzenschlager et al., 2018) suggests the use of 10mg domperidone given three times a day for 3 days before infusion.

A number of therapeutic guidelines recommend domperidone initiation as a pre-treatment for at least 48-72 hours from the commencement of apomorphine, these guidelines are derived from the Australian Injectable Handbook 7th Edition (Burridge, Collard, Symons, & Society of Hospital Pharmacists of Australia, 2016) and the MIMS Online (MIMS Australia, 2013).

Domperidone use in Parkinson's disease, reported adverse cardiac events and orthostatic hypotension

From the results of the literature review, only 1 study Renoux et al. (2016) describes the potential cardiac risks of the use of domperidone in the Parkinson's disease. The results from a multicentre, retrospective study revealed that domperidone may increase the risk of ventricular arrhythmias and sudden cardiac death in patients with Parkinson's disease by 22% compared with non-users though "did not reach statistical significance", but stated the risk was statistically significant in patients on domperidone who had history of cardiovascular disease. The study measured the use of anti-Parkinson's drugs, but did not specifically measure the risks amongst the different classes of anti-Parkinson's medications such as the dopamine agonist, apomorphine and concomitant use of domperidone. This is significant for future studies to review the co-administration of these two agents, of which both advise against concomitant use that prolong the QT interval and medicines that inhibit Cytochrome P450 3A4 (CYP3A4).

There were no studies that reviewed the concomitant use of apomorphine and domperidone for patients with Parkinson's disease with or without a cardiovascular history. The TOLEDO study (Katzenschlager et al., 2018) excluded patients with prolonged QT duration, and reported only one of 53 patients, 1.88% in the apomorphine group withdrew due to a myocardial infarction.

Borgemeester and van Laar (2017) study reported on orthostatic hypotension (OH) in the initiation of apomorphine, whilst a number of patients were known to be symptomatic of OH, there was no new incidence of OH, though on long term follow up 4 of 11 patients with pre-existing OH worsened necessitating 3 patients to stop the treatment. Sánchez-Ferro, Benito-León, and Gómez-Esteban (2013) study reports that up to 17.6% of patients receiving 4mg of apomorphine had OH, with the main decrease in blood pressure observed 20-40 minutes after the injection.

Domperidone and the QT Interval without apomorphine

A mini review by Buffery and Strother (2015) examining the science of QT prolongation and the clinical implications found that domperidone is not strongly associated with QT prolongation when taken at oral doses of 20mg four times a day. The study concluded that domperidone does not present as an intolerable risk to patients, and furthermore there was limited case reports that supported as association with cardiac dysfunction.

The increased risk of adverse events of QT prolongation, ventricular arrhythmias and SCD is reported with domperidone doses > 30 mg daily, when taken in combination with other medicines that prolong the QT interval and medicines that inhibit CYP3A4 (Buffery & Strother, 2015; MIMS Australia, 2013).

Domperidone has not had FDA approval in the United States (Bowron, 2004). This is in response of AE's of serious cardiac events with intravenous use of the drug (Wood, 2010). Bhidayasiri, Sringean, et al. (2016) note recommendations from the European Medicine agency is to use the lowest effective dose and discontinue as soon as possible due to adverse effects, and Wood (2010) reports no cardiotoxicity events with oral domperidone based on a 2005 study.

Monitoring electrocardiogram for domperidone and apomorphine therapy

Bhidayasiri, Garcia Ruiz, et al. (2016) recommend an ECG should be performed prior to

commencement of domperidone given the potential cardiac risks, though makes no mention of the actual risks of the agent or the need for ongoing monitoring. Two local hospital guidelines were found to recommend routine electrocardiogram (ECG) to exclude cardiac conduction problems or significant cardiac disease for patients having an apomorphine challenge procedure (NHS TRUST, 2005; Tisch & Bolitho, 2018), with Tisch and Bolitho (2018) identifying a QTc interval < 0.42 seconds as a reference point. It is noteworthy that an ECG's will be performed after patients have started domperidone at home prior to hospital admission and just prior to an apomorphine challenge. Future studies could guide clinical practice on whether an ECG should be performed prior to the commencement of domperidone and repeated prior to the start of apomorphine.

Scorza, Scorza, and Ferraz (2016) reviewed studies investigating the cardiovascular effects of domperidone in 10 individuals with idiopathic PD treated with continuous subcutaneous infusion of apomorphine in the early 2000's. They concluded that there was a demonstrated lack of published studies regarding the serious ventricular arrhythmias or sudden cardiac events associated with domperidone intake in PD patients (Lertxundi et al., 2013), and that vigilance and caution should be exercised when exceeding domperidone doses of 30mg/ day given that related cardiotoxicity can trigger a fatal cardiac event (Scorza et al., 2016).

Domperidone and intermittent versus continuous apomorphine infusion

The studies did not reveal any evidence for pre-treatment dose amounts and duration of domperidone for either intermittent or continuous infusions of apomorphine. There was an absence of any discussion regarding whether a differing regimen of domperidone would be best tailored to a continuous versus intermittent infusion, in spite of study reporting that nausea and vomiting are more commonly reported for patients having intermittent injections of apomorphine (Bhidayasiri, Garcia Ruiz, et al., 2016). Thus, there are opportunities for future research to consider investigating whether variable domperidone doses should be tailored to the use of intermittent versus continuous apomorphine infusion.

Withdrawing domperidone following apomorphine initiation

The Australian Injectable Handbook 2017 (Burridge et al., 2016) also notes that "After the patient is stabilised on apomorphine, domperidone can be slowly withdrawn or reduced to the minimum effective dose". Coupled with a lack of evidence to guide the initiation of domperidone, there was no further evidence to support recommended timeframes to taper or cease domperidone following the commencement of apomorphine.

Grandas (2013) states "many cases develop tolerance within weeks" [to Apomorphine's side effects] allowing domperidone discontinuation. Bowron (2004) recommended that tolerance to the peripheral dopaminergic effects of apomorphine "typically occur 3-6 weeks after initiation of apomorphine" for patients who receive less than four intermittent injections of apomorphine / day. Bhidayasiri, Sringean, et al. (2016) note downward titrating and cessation of anti-emetics within the first 2 months of starting treatment.

It is also known that anecdotally that patients remain on domperidone months to years after the commencement of apomorphine and that many patients stay on domperidone including continuation of domperidone after transitioning from apomorphine to levodopa-carbidopa intestinal gel, another advanced therapy in PD.

Continuation of domperidone

The use of domperidone as the preferred anti-emetic agent for people with Parkinson's is widely accepted (Lertxundi et al., 2013). The risk of developing extrapyramidal adverse effects are minimal as domperidone does not cross the blood brain barrier is widely documented. The possible basis for ongoing use of domperidone following commencement of apomorphine may be due to its general accepted role in symptomatic management of orthostatic hypotension (Sánchez-Ferro et al., 2013) and gastrointestinal dysmotility for patients with PD (Benarroch, 2014).

The use of trimethobenzamide

Several studies discussed the alternate use of trimethobenzamide in the USA where domperidone is not licensed for use in apomorphine therapy. Hauser, Isaacson, and Clinch (2014) reported in their study the good effects this drug had for nausea and vomiting during the first 8 weeks of intermittent apomorphine therapy. It is unclear as to whether trimethobenzamide provides benefit for other peripheral dopaminergic effects of apomorphine, particularly orthostatic hypotension.

Obering, Chen, and Swope (2006) note that 50% of patients in an open label study of 510 patients in 2004, were able to discontinue trimethobenzamide following initiation of apomorphine. 75% of the 50% of patients did so within 4 months of commencing a regimen of intermittent apomorphine.

Conclusions

Both apomorphine and domperidone are known to prolong the QTc interval and warn against concomitant use with the other, however these are being used together despite the risks. Few studies acknowledge or recommended performing a baseline ECG either prior to commencement of domperidone or before apomorphine and when these should be repeated. It is highly likely that the incidence of QTc prolongation and other cardiac arrhythmias such as ventricular bigeminy or atrial fibrillation directly related to the initiation of domperidone and apomorphine are not being captured in the absence of any robust cardiac monitoring. Recommendations are to study the most effective minimum doses of domperidone initiation and the shortest duration post apomorphine for cessation, and to ensure that the patient's full cardiovascular history is taken to determine risk factors, and regular ECG monitoring through apomorphine usage.

There is very little evidence to support recommended dose and duration of domperidone prior to the initiation of apomorphine, as is there very little evidence to taper or cease the medication. Future studies are warranted and should also consider whether domperidone doses should be tailored if using intermittent or continuous apomorphine. A comparison of domperidone and trimethobenzamide could also review whether the latter would be a safer agent for use in apomorphine therapy and hence recommendations for being made available in Australia.

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