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Review

Drug-drug interactions between antiemetics used in cancer patients☆

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ABSTRACT

Drug interactions are common in cancer patients as they use many drugs concurrently. Most drug interactions have been reported to be among supportive care medications. Antiemetics are one of the commonly used drugs in these patients for the management of disease and therapy related nausea and vomiting and they are sometimes used in combinations. The objective of this review is to determine and compare potential drug interactions among these drugs using Micromedex and Lexicomp drug interaction checkers. There is an increase in the risk of extrapyramidal activities and neuroleptic malign syndrome accompanying the concurrent use of olanzapine and metoclopramide and thus this combination should be avoided. Another important consequence of interactions is QT prolongation associated with 5-HT_3 receptor antagonists. Care must be taken especially in patients with risk factors. The NK_1 receptor antagonist reduce the metabolism of dexamethasone and increase its exposure, therefore the dose of dexamethasone when used as an antiemetic should be reduced when used in combination with these agents. No dose adjustments are recommended when dexamethasone is used as an adjuvant in chemotherapy regimen, but patients should be monitored for side effects. It should not be forgotten that these interactions may also be present with other medications, all medications taken by cancer patients should be adequately reviewed to reduce drug interaction related problems in these patients.

1. Introduction

Drug interactions occur in different forms as: drug-drug, drug-food and drug-disease interactions. Unsuitable drug combinations may result to alterations in the effect or side effects of one or more drugs. Drug combinations that have direct consequences on a patients outcomes are referred to as clinically significant interactions.[1] The outcome of interactions are frequently clinically insignificant, sometimes beneficial or occasionally harmful.[2] The estimated rate of clinically significant drug interactions is between 3% and 20%.[3]

Patients treated for cancer are usually at risk of drug interactions as they use multiple drugs concurrently.[4] Most anti-cancer drugs are metabolized via the CYP450 liver enzymes.[4–6] As such they are liable to most metabolic interactions. Metabolic interactions involve mostly the cytochrome (CYP) 450 enzymes and these interactions present as competition for a particular metabolic enzyme or the induction or inhibition of an enzyme by a drug. In the latter, a drug can induce or inhibit its own metabolism.[3] Induction of metabolic enzymes develops and wears off in 2–3 weeks while inhibition lasts only a few days. These imply that metabolic interactions may continue even after the related drug has been stopped.[2]

Drug interactions can reinforce or intensify side-effects already present with cancer pharmacotherapy.[7] Detection and evaluation of drug interactions in cancer patients is essential for the optimal management of pharmacotherapy in these patients. A routine systematic review of patient's medications is necessary to prevent interactions.[7,8] The high incidence of drug-drug interactions has been reported in previous studies and most interactions involve supportive care medications.[8–12] This may be due to the continuous use of these medications in cancer patients. Supportive care medications especially anti-emetics and opioid analgesics cannot be avoided in cancer patients and they are mostly used in combinations.

In patients receiving highly emetogenic chemotherapy, antiemetics are used in combinations as the effectiveness of single

☆ The simultaneous use of antiemetics is inevitable in cancer patients. This review was done to evaluate the potential drug interactions among these drugs. Caution must be taken when olanzapine and metoclopramide are used concurrently. Patients taking 5-HT3 receptor antagonists should be monitored in terms of QT prolongation particularly those at risk and those taking concurrent medications known to prolong QT interval.

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agents reduces as the emetogenic capacity of chemotherapy agents increases. Antiemetics recommended for the prophylaxis and treatment of chemotherapy induced nausea and vomiting in the ASCO guidelines[13] based on the chemotherapy and radiation risk are given in Table 1.

2. Antiemetics

2.1. Dopamine receptor antagonists

2.1.1. Metoclopramide

Metoclopramide is a benzamide prokinetic antiemetic agent. It causes central and peripheral dopamine D_2 antagonism at low doses, and weak 5-HT_3 blockade at the higher doses used for emesis caused by cytotoxic drug therapy.[14] It is used for its prokinetic effect in addition to its antiemetic effect in cancer patients. Some side effects of metoclopramide are anxiety, depression, restlessness, hyperprolactinemia and QT prolongation.[15] Irreversible tardive dyskinesia is associated to high doses and long-term use of metoclopramide. Metoclopramide has only moderate antiemetic effects at low doses so higher doses are required for chemotherapy induced emesis. Although it has been replaced with the 5-HT_3 receptor antagonists due to their superior efficacy and safety, it is still used as an add on agent for the prevention of cisplatin-induced delayed emesis and with emesis failing first-line treatment.[15] It is commonly used as rescue therapy in patients receiving radiotherapy.[13]

Clinically significant drug interactions related to metoclopramide may necessitate dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Drug interactions may increase the risk of some serious central nervous system toxicity of metoclopramide like neuroleptic malign syndrome and tardive dyskinesia especially when metoclopramide is used in combination with serotonin modulator drugs (e.g. tramadol). Metoclopramide may increase the QT prolongation effect of QT prolonging agents (e.g. granisetron). It is advisable to avoid such combinations, but in cancer patients were these combinations are inevitable caution must be taken. Patients should be monitored for any evidence of QT prolongation or other alterations of cardiac rhythm (Micromedex drug reference, Access date: metoclopramide: drug information Lexicomp, Access date: 15/02/2018).

The other two benzamides trimethobenzamide and domperidone are not used as antiemetics in chemotherapy receiving patients due to their weak antiemetic effects in these patients.[14]

2.2. Serotonin receptor antagonists

2.2.1. 5-Hydroxytryptamine (5-HT_3) receptor antagonist

The 5-HT_3 receptor antagonists with their high therapeutic index for prevention of chemotherapy related nausea are the antiemetics of choice in the prevention and treatment of acute emesis associated with moderate to high emetogenic chemotherapy agents.[14,15] Some studies also support their use in delayed emesis prophylaxis, but this is not recommended in the ASCO guideline.[13] They are also used for the prevention and treatment of cancer disease related nausea. The six serotonin antagonists (ondansetron, granisetron, dolasetron, palonosetron, tromesetron and ramosetron) recommended by ASCO are similar in terms of efficacy or tolerability with palonosetron having a higher receptor binding affinity and much longer half-life. Palonosetron has been shown to be superior to first-generation 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron) in the prevention of both delayed and acute emesis,[14,15] but this is not certain for antineoplastics with moderate emetic risk.[13] Electrocardiogram (ECG) interval changes are common with the first-generation 5-HT_3 antagonists. Most of these changes appear in the early hours after administration of a dose and are mostly small with no clinical significance and return to baseline within 24 h. Yet, torsade de pointes and other potentially fatal cardiac arrhythmias have been linked to QT prolongation caused by these agents.[14] The US Food and Drug Administration recommends ECG monitoring in patients taking concomitant medications that prolong the QT interval. Many risk factors that may increase a patient's risk for TdP development associated with the use of QT-prolonging drugs have been identified. Some factors include female sex, age (>65 years), hypokalemia, bradycardia, underlying heart disease, hypomagnesemia, higher concentrations of one or more QT-prolonging medications and genetic predisposition.[17–20]

2.2.2. Olanzapine

Olanzapine blocks dopamine D_2 and serotonin 5-hydroxytryptamine (5-HT_2) receptors. It may be exceptionally useful in preventing both nausea and vomiting in contrast to other conventional antiemetics that successfully prevent emesis but not nausea. The superiority of olanzapine inclusive antiemetic regimens has been shown in different studies.[13,15] Olanzapine was shown to be superior to metoclopramide in another randomised trial.[21]

Most data suggest that olanzapine is superior to metoclopramide alone. Though the optimal dose of olanzapine is yet to be definitively established, the use of lower doses (5 mg versus 10 mg) may provide comparable efficacy with lesser risk of side effects.[22] Olanzapine is a substrate of the metabolic enzymes CYP1A2 and CYP2D6, as such it is subjectable to drug interactions.

2.3. Neurokinin-1 (NK_1) receptor antagonists

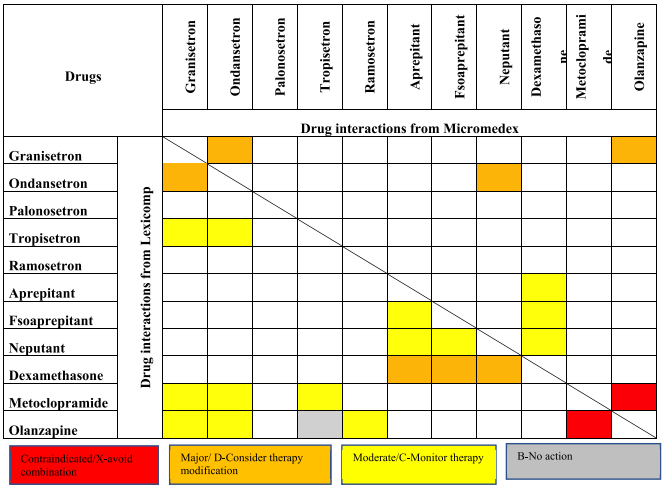
The emetogenic effects of substance P which is a mammalian neuropeptide found in neurons that innervate the brainstem areas intimately involved in the induction of vomiting are mediated through the neurokinin-1 (NK_1) receptor, a member of the G protein receptor superfamily.[14] NK_1 receptor antagonists include the oral agent aprepitant and its parenteral version fosaprepitant, netupitant (which is available in a fixed-dose combination with palonosetron [NEPA]), and rolapitant. Although they are more efficient than first-generation 5-HT_3 receptor antagonists in preventing both delayed and acute emesis caused by highly emetogenic antineoplastic drugs (cisplatin), these agents appear to work best when used in conjunction with serotonin receptor antagonists and dexamethasone.[14]

All agents except rolapitant are moderate inhibitors of the CYP3A4 metabolic pathway, and dose reduction may be needed for drugs that are primarily metabolized through CYP3A4 when used concurrently. The doses of glucocorticoids when used as antiemetics may routinely be reduced when administered with these NK_1 receptor antagonists. Aprepitant has a theoretical effect of

Table 1
Antiemetics used in cancer patients based on chemotherapy and radiotherapy risk category.

Risk category	Chemotherapy	Radiotherapy
High	• NK_1 receptor antagonist • 5-HT_3 receptor antagonist • Dexamethasone • Olanzepine	• 5-HT_3 receptor antagonist • Dexamethasone
Medium	• 5-HT_3 receptor antagonist • Dexamethasone	• 5-HT_3 receptor antagonist • Dexamethasone
Medium/Low	• 5-HT_3 receptor antagonist • Dexamethasone	• 5-HT_3 receptor antagonist • Dexamethasone • Metoclopramide

Table 2
Drug-drug interaction among antiemetics recorded from Micromedex and Lexicomp.



reducing the elimination of drugs metabolized by CYP3A4 (cyclophosphamide, etoposide, docetaxel, vinca alkaloids, irinotecan) but this effect is yet to be clinically confirmed.[14,15] Rolapitant on the other hand inhibits CYP2D6. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been reported in patients that received intravenous rolapitant emulsion as a result of drug interactions.[14]

2.4. Glucocorticoids

Glucocorticoids are used in cancer patients for their different effects including antiemetic effect. They are effective and well-tolerated antiemetics for chemotherapy-induced emesis. They are used as single agents with mildly emetogenic chemotherapy, in combination with 5-HT_3 receptor antagonist with moderately emetogenic chemotherapy and in a triple combination with a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist with highly emetogenic chemotherapy and in patients receiving a combination of an anthracycline and cyclophosphamide. Glucocorticoids are effective with both cisplatin and non-cisplatin-based chemotherapy for delayed emesis prophylaxis. Dexamethasone is the most extensively evaluated and used steroid.[14]

3. Method

Potential drug-drug interactions were checked using the Micromedex online drug interaction checker (Access date: 17/02/2018) and the Lexicomp drug interactions checker (Access date: 15/02/2018). Drug-drug interactions are classified based on their severity. Micromedex classifies them as contraindicated, major, moderate and minor. The Lexicomp classification is similar but groups the interactions based on the recommendations as X-avoid combination, D-consider therapy modification, C- monitor therapy, B-no action needed and A-no known interaction.

4. Results

The Micromedex drug interaction tool revealed one contraindication, three major and three moderate interactions while Lexicomp drug interaction tool revealed two X, four D, ten C and two B recommendations. The distribution of interactions is given in Table 2. The summary of interactions from Micromedex is given in Table 3. No interactions were recorded for tropisetron and ramosetron as these drugs were not available on Micromedex. The summary of interactions from Lexicomp is given in Table 4.

5. Discussion

The drug interactions among antiemetics were similar in both tools although the Lexicomp drug interaction checker revealed more interactions than the Micromedex drug interaction checker. The concomitant use of metoclopramide and antipsychotics like olanzapine was rated as a high-risk interaction and concomitant use should be avoided as suggested in the metoclopramide product information.[23] The combination of these drugs is associated with the development of extrapyramidal activities and neuroleptic malign syndrome. These side effects of metoclopramide are exacerbated with the use of drugs that affect the central dopaminergic activity directly or indirectly. In cases where use is unavoidable patients should be monitored adequately.[16,23–25]

The dose of dexamethasone when used for its antiemetic effect should be reduced when used with NK_1 receptor antagonists. NK_1

Table 3
Summary of drug interactions from Micromedex.

Drug combinations	Severity of interactions	Documentation	Onset	Summary
Olanzapine – Metoclopramide	Contraindicated	Fair	Not specified	Increased extrapyramidal reactions and NMS risk
Olanzapine – ondansetron	Major	Fair	Not specified	Increased QT prolongation risk
Ondansetron – granisetron	Major	Fair	Not specified	Increased QT prolongation risk
Netupitant – ondansetron	Major	Fair	Rapid	Increased ondansetron exposure as netupitant inhibits CYP3A4
Dexamethasone – Aprepitant and Fosaprepitant	Moderate	Excellent	Rapid	Increased dexamethasone exposure
Dexamethasone – Neputant		Good		

Table 4
Summary of drug interactions from Lexicomp.

Drug Combinations	Severity/risk rating	Reliability Rating	Summary
Olanzapine – Metoclopramide	Major/Avoid combination	Fair	Increased risk of extrapyramidal reactions and NMS
Aprepitant – Netupitant	Major/Avoid combination	Fair	Decrease in aprepitant clearance by CYP3A4 Inhibition
Dexamethasone – Aprepitant and Fosaprepitant	Major/Consider therapy modification	Fair	Increase in serum concentrations of dexamethasone
Dexamethasone – Neputant		Good	
Granisetron – Ondansetron	Major/Consider therapy modification	Fair	Increased QT prolongation risk
Olanzapine –Ondansetron and Granisetron	Moderate/Monitor therapy	Fair	Increased QT prolongation risk
Olanzapine – Tropisetron	No action		
Olanzapine – Ramosetron	Moderate/Monitor therapy	Fair	Increase in constipation risk of ramosetron by Anticholinergic activity
NK_1 Receptor Antagonists	Moderate/Monitor therapy	Excellent	All are CYP3A4 substrates, they may increase the serum concentration of each other.
Metoclopramide - 5-HT_3 Receptor Antagonists Except Palonosetron and Ramosetron	Moderate/Monitor therapy	Fair	Increased QT prolongation risk
Granisetron – Tropisetron	Moderate/Monitor therapy	Fair	Increased risk of QT interval prolongation
Ondansetron – Tropisetron	Moderate/Monitor therapy	Fair	Increased risk of QT interval prolongation

receptor antagonists as CYP3A4 moderate inhibitors reduce the metabolism of dexamethasone and increase its serum concentrations.[26–30] This increase is sustained for up-to 8 days after a single dose of netupitant.[26] But dose reduction is not suggested when dexamethasone is used as part of a chemotherapy regimen.

The outcome of interactions between 5HT receptor antagonists adds up to their risk of prolonging QT interval. Ondansetron and granisetron have a moderate risk, tropisetron has an intermediate risk while palonosetron and ramosetron show no risk. Metoclopramide and olanzapine have an intermediate risk for prolonging QT interval and there is possibility of additional effects on the QT interval when used in combination with drugs with moderate risk.[31] Olanzapine may also add up to the constipation side effect of ramosetron. This interaction is anticipated based on the independent constipating effects of ramosetron and anticholinergic agents. As a substrate of CYP3A4 the serum concentration of ondansetron may be increased by netupitant (a moderate inhibitor of CYP3A4). If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate.[26]

The use of multiple drugs from the same group is not recommended but it may be necessary to give additional anti emetics for breakthrough emesis or as a premedication prior to a chemotherapy administration in patients previously on antiemetics. In such cases, care must be taken as these agents may interact leading to exacerbations in side effects. Granisetron and ondansetron have a moderate risk of prolonging QT interval. Due to the potential for additive effects on the QT interval, ECG monitoring is recommended if concomitant therapy is required.[31–33] Other 5 N receptor antagonist except palonosetron have intermediate QT prolonging risk, so there may be risk when they are combined with those with moderate risk. Palonosetron may be safer choice when necessary. Netupitant should also not be administered with aprepitant as both are moderate inhibitors of CYP3A4 enzyme. This interaction may also be applicable to other drugs that inhibit this enzyme.[34]

6. Conclusion

Antiemetics are commonly used medications in cancer patients among. Even though it is necessary to use them concurrently, care must be taken especially in patients liable to their side effects. Drug interactions may be present between antiemetics and other drugs like pain relievers, antipsychotics and chemotherapy agents used in these patients. Patients' medications must be frequently reviewed in terms of interactions and monitoring must be employed in patients when serious interactions are inevitable.

Conflicts of interest

None.

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