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"**Potential drug interactions in cancer patients receiving supportive care exclusively"**

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ABSTRACT

Background: Cancer patients at the end of life often take many medications, being at risk of drug interactions. The purpose of this study was to describe the epidemiology of potential drug interactions in cancer patients receiving supportive care exclusively.

Methods: We retrospectively reviewed the charts of consecutive adult cancer outpatients attending palliative care clinics at the Princess Margaret Hospital, Toronto, Canada. Drugs were screened for interactions by the *Drug Interaction Facts* software, which classifies interactions by levels of severity (major, moderate and minor) and scientific evidence (1 to 5, with 1 = the strongest level of evidence).

Results: Among 372 eligible patients, 250 potential drug interactions were identified in 115 patients (31%, 95% CI 26 - 36%), predominantly involving warfarin and phenytoin. Most interactions were classified as being of moderate severity (59%) and 42% of them were supported by levels 1-3 of evidence. In multivariable analysis, increasing age (p<0.001), presence of comorbidity (p=0.001), cancer type (brain tumors, p<0.001) and increasing number of drugs (p<0.001) were associated with risk of drug interactions.

Conclusion: Potential drug interactions are common in palliative care and mostly involve warfarin and anticonvulsants. Older patients, those with comorbid conditions, brain tumor patients and those taking many medications are at greater risk of drug interactions.

INTRODUCTION

Drug combinations with potential to interact are common in medical practice, although their frequency in general medicine has been variable, depending on the patient population, study design and the screening methods used to identify interactions. In general medical wards, the rate of potential drug interactions has been approximately 60%.[1-3] Studies conducted in emergency departments found frequencies of potential drug interactions in the range of 16 to 47%.[4-6] Ambulatory patients with variable clinical conditions who were screened for potential drug interactions by their family physician were found to be exposed to a potential drug interaction in almost 70% of cases.[7]

Drug interactions are divided into three groups depending on the underlying mechanism of interaction: pharmacodynamic, pharmacokinetic and pharmaceutical.[8] A pharmacodynamic interaction results from combining two drugs with similar mechanisms of action, which may behave in synergistic, additive or antagonistic manner. A pharmacokinetic interaction occurs when a drug alters the absorption, distribution, metabolism (most often due to interaction with the cytochrome P450 (CYP) hepatic enzymes), and/or excretion of another medication.[8] A pharmaceutical interaction occurs when mixing chemically incompatible drugs outside the body, as for example, incompatibility of phenobarbital with opioid analgesics when mixed in the same syringe, resulting in inactivation of one or both drugs.[8] The majority of literature on drug interactions published thus far describes pharmacokinetic interactions involving the CYP enzymes, in many cases with the use of drug probes.[9]

Cancer patients often receive numerous medications including antineoplastic agents, drugs to treat comorbid conditions and supportive care medications which puts them at risk of receiving drugs with potential to interact. Furthermore, even though there are no definitive studies about the pharmacokinetic parameters in patients with cancer, a drug's pharmacokinetics may theoretically be altered in these patients because of impaired

drug absorption due to mucositis, variation in volume of distribution secondary to lower levels of serum binding-proteins and edema, and altered excretion in patients with renal and/or hepatic dysfunction. While several studies have evaluated potential drug interactions in general medicine, only a few studies have examined the frequency of potential drug interactions in patients with cancer.[10-12] An evaluation of causes of death in a Norwegian hospital identified 18% of more than 700 deaths to be associated with adverse drug reactions (including drug interactions) and 4% of all cancer related-deaths were likely to be associated with a serious interaction.[10] A retrospective study of 100 hospitalized cancer patients found that 63% were exposed to at least one drug combination with the potential to interact.[11] A recent study of 405 ambulatory cancer patients receiving cancer-directed therapy found that one third were at risk of drug interactions.[12]

Although the frequency of potential drug interactions has been examined in ambulatory cancer patients receiving cancer-directed therapy[12] and hospitalized cancer patients[11], we are unaware of studies about the epidemiology of drug interactions in the palliative care setting. Patients receiving exclusively supportive care comprise a unique population with respect to symptomatology, emotional aspects and medication profile.[13-15] We hypothesized that cancer patients at the end of life are more likely to receive drug combinations with the potential to interact and thus may be at a greater risk of drug interactions, as compared to patients in our cross-sectional study who were receiving anticancer treatment [14,16-18], because of their high burden of disease and requirements for additional drugs to treat cancer-related symptoms such as pain and cachexia . The primary objective of this study was to evaluate the epidemiology of potential drug interactions in cancer patients receiving exclusive supportive care at the Princess Margaret Hospital (PMH).

PATIENTS & METHODS

Study Design and Setting

This was a retrospective cross-sectional study conducted at PMH, the largest cancer facility in Canada, and was approved by the PMH Research Ethics Board. Approximately 1,000 new patients are seen by the PMH palliative care service each year, 80% of which are outpatients.[19] Of these, 75% are scheduled visits to the palliative care clinics, which are available five full days a week, and 25% are urgent, same-day outpatient consultations seen by the urgent consultation team. Approximately 20% of patients are referred to the clinic for pain management, 20% for control of other symptoms and 60% for palliative care planning.[15] During the initial medical visit to the palliative care clinic, which lasts approximately 90 to 120 minutes, patients are initially seen by a palliative care Registered Nurse (RN) Case Manager, who briefly assesses the patient, collects their medication list and screens them for distressful symptoms using the Edmonton Symptom Assessment System (ESAS). The palliative care physician then performs a thorough medical and psychosocial assessment. Physicians dictate clinical notes according to pre-specified guidelines: reason(s) for referral, history of present illness, symptomatology, comorbid conditions, current medications, allergies, social and family history, physical examination, summary and plan.

We reviewed the medical records of cancer patients attending the palliative care clinics at PMH. We included consecutive adult patients with solid or hematological malignancies, who were receiving supportive care exclusively and who had at least one consultation in the palliative care clinic. Patients still receiving systemic antineoplastic therapy, those seen as urgent consultations, inpatients at the time of the first consultation and those whose clinical notes lacked information on medications were excluded. Patients who were being treated with antineoplastic therapy and those who were hospitalized were

considered ineligible because they would not reflect the profile of the typical palliative care cancer outpatient; they were either too unwell (inpatients) or would represent a different cancer population, which has already been evaluated for potential drug interactions in a previous study.[12] We also excluded patients seen on an urgent basis because a comprehensive medical assessment is not performed during such consultations, which are focused on the urgent matter(s) that precipitated the referral. In contrast, during the first non-urgent consultation with palliative care at PMH, patients are initially seen by an advanced practice nurse, who collects the names of their medications and screens them for distressful symptoms; the patients are then assessed by a palliative care physician. Following the consultation, physicians dictate a thorough clinical note following pre-set guidelines: reason(s) for referral, history of present illness, symptomatology, current medications, comorbidities, social and family history, allergies, physical examination, summary and plan.

We collected data from the first consultation only because not all patients are subsequently followed by the PMH palliative care service, as they may be referred to services located in their local community. Two authors (SC and AOC) abstracted the following data from patients' medical records: age, sex, cancer type (breast, gastrointestinal, genitourinary, gynecologic, lung, brain, hematological and other), presence and number of comorbid illnesses and medications recommended by the attending palliative care physician. A comorbid illness was defined as a clinical condition that required pharmacologic therapy. Multivitamins, alternative/experimental and herbs were not considered.

Drug Interaction Screening

The medications screened for drug interactions were those that were recommended by the palliative care service in the first consultation, i.e., they consisted of drugs that patients were already using before the consultation and were continued on, in addition to those prescribed by the palliative care doctor. Drugs were screened for interaction by the *Drug Interaction Facts* software, version 4.0,[20] (available at the website: www.factsandcomparisons.com) and manually by one of the authors (RPR) for drugs not recognized by the program, using pharmacology text books**.** The software screens for potential drug interactions, provides a description of pharmacological mechanisms underlying the interaction (pharmacokinetic, pharmacodynamic or unknown when there was not sufficient evidence from the literature about the mechanism of interaction) and classifies them by level of severity and scientific evidence (Table 1). The *Drug Interaction Facts* software has both sensitivity and specificity of 97% in detecting previously known drug combinations with potential to interact[21] and has been previously utilized in cancer patients.[11,12]

Statistical Considerations

Based on previous studies[11,12], a sample of 350 patients was chosen as a compromise between reasonable size and feasibility. Approximately 800 new ambulatory patients are seen by the palliative care clinics each year[19] and, based on the Palliative Care Service internal records, we estimated that approximately 60% would be eligible, i.e., would not be receiving anticancer therapy**.** Therefore an 8-month period would suffice to achieve a sample of 350 patients. We reviewed the medical charts from November 2005 to July 2006, when the target number was achieved.

We used summary statistics to describe patient characteristics, frequency and types of potential drug interactions. The number of medications for each subject was calculated by summing all drugs. When a medication contained two or more pharmacological compounds (e.g. acetaminophen combined with codeine), each drug was considered an individual medication for analysis; when a patient was taking the same medication in different schedules (e.g., long and short acting insulin for glycemia control), the drug was counted only once.

Logistic regression was used to identify factors associated with drug combinations that have the potential to interact. The dependent variable, potential drug interaction, was defined as at least one instance of a potential drug interaction with level of evidence ≦ 4 (i.e., a drug interaction supported by at least a few case reports, excluding those of level 5 which are theoretical). Independent variables tested in the model included: age (continuous variable), cancer type (breast, gastrointestinal, genitourinary, gynecologic, lung, brain, hematological and other), presence of a comorbid illness (yes or no) and number of medications (continuous variable). Gender was not included as a risk factor for drug interactions because information that gender would contribute to the regression analysis is relevant only in certain cancer types, given that some cancer types only occur in men or women. For binary or nominal variables, the group at lower risk of the outcome was chosen as the referent. Variables with univariate *p*-values < 0.1 were entered into the multivariable model. In the multivariable model, predictors were considered statistically significant if the *p*-value was <0.05. SAS, version 9.1 was used for all analyses.

RESULTS

Study Cohort

Between November 2005 and July 2006, 633 patients were seen in the palliative care clinics and 372 patients met our inclusion criteria. Reasons for exclusion included: 150 patients were receiving antineoplastic therapy, 25 had incomplete information about their medications, 52 were seen as urgent consults, 20 were inpatients, and 14 were excluded for other reasons. For 11 patients it was noted in their chart that they remembered all but one of their medications and they were included in the study. The characteristics of the 372 eligible patients are described in Table 2. The median age was 66 years (range 22 – 94), approximately half were male, and the most common cancer type was gastrointestinal tumors. The most common pharmacological classes of drugs taken by patients were opioids (67% of patients), laxatives/stool softeners (54%), acetaminophen (40%) and corticosteroids (38%). The median number of medications per patient was 6 (range 0 – 21). The most common comorbid illnesses were cardiovascular diseases (36% of patients), diabetes (14%), musculoskeletal disorders (11%), respiratory diseases and thromboembolism (10% each), hypercholesterolemia (9%), chronic liver diseases (7%), hypothyroidism and neurological diseases (6% each) and psychiatric disorders (5%).

Potential Drug Interactions

Among the 372 patients, 250 drug combinations with potential to interact were identified in 115 patients (31%; 95% CI 26-36%, Table 3). The majority of potential interactions were classified as of moderate severity (59%) and 41.5% of them were supported by level ≤ 3 of scientific evidence (i.e. supported by at least several case

reports). The most common pharmacological mechanism underlying the potential drug interactions was pharmacokinetic. The most frequent drug combinations at risk for interaction involved phenytoin (26 cases), warfarin (16 cases) and aspirin (15 cases). The most commonly found instances of drugs with potential to interact of either moderate or major severity are summarized in Table 4. We decided not to describe the drug interactions classified as of minor severity because their clinical consequences are likely small.

Three hundred and fifty three patients were included in the logistic regression model to determine risk factors associated with drug interactions; 8 patients who were not receiving any medication and 11 who were taking only one drug were excluded from analysis because they were not at risk of drug interactions. Results of the univariable and multivariable analyses are presented in Table 5. In unadjusted analysis, advanced age, increasing number of drugs, presence of comorbid illness and cancer type were significantly associated with potential drug interactions. In adjusted analyses, all variables remained significant: increasing age (Odds ratio: 1.05 for each additional year of age, 95% CI 1.02 – 1.08; $p< 0.001$), increasing number of medications (Odds ratio: 1.3 per each additional drug, 95% CI 1.2 – 1.4; $p< 0.001$), presence of comorbid illness (Odds ratio: 6.5, 95% CI 2.1 – 19.8; $p= 0.001$) and cancer type (Odds ratio for brain versus gastrointestinal tumors: 28.5, 95% CI 7.2 – 113 and other types of cancer versus gastrointestinal tumors: 3.1, 95% CI 1.2 - 7.9; $p< 0.001$).

DISCUSSION

The present study demonstrates that one third of cancer patients receiving exclusively supportive care were exposed to at least one drug combination with the

potential to interact. These numbers raise concern because almost 70% of potential drug interactions were classified as of either major or moderate severity and almost 42% were supported by good scientific evidence (level of evidence ≤ 3). More than half of the potential drug interactions we identified in our sample were pharmacokinetic. The large majority of potential drug interactions related to warfarin and phenytoin, although the most commonly used drugs by patients were opioids, laxatives, acetaminophen and corticosteroids. Older patients, those taking more medications, those with comorbid conditions and those with brain tumors were at greater risk of drug interactions.

Patients with brain tumors were almost 30 times more likely to be exposed to drug interactions than gastrointestinal cancer patients. Anticonvulsants, which are often used by these patients, not only interact with many different medications but also are routinely prescribed in conjunction with steroids to treat cancer-related cerebral edema and seizures. There is evidence that when phenytoin is combined with dexamethasone, its plasma level may increase or decrease.[22] Likely due to a high burden of comorbidities, older patients were also at increased risk of drug interactions. Patients with comorbid conditions usually take more medications or use drugs with potential for drug-drug interactions.[12] Our previous study showed that patients taking medications to treat comorbid conditions were at greater risk of drug interactions than were patients using supportive care drugs only.[12] Similarly to other studies[2,4,11,12] an increasing number of medications was associated with a greater potential for interactions in our population.

The frequency of potential drug interactions in non-cancer populations has varied from a low of 16% among emergency room patients to a high of 70% in a population of ambulatory patients being treated by their family physician.[5,7] To date, only a few studies have evaluated drug interactions in cancer patients,[1112] and to our knowledge this is the first to report the epidemiology of potential drug interactions in patients receiving only

supportive care. A retrospective study undertaken by one of the authors of this study identified drug combinations with the potential to interact in 63% of 100 consecutive cancer patients admitted to a general oncology ward for treatment complications, supportive care or invasive procedures[11]. It is likely that the proportion of patients at risk of drug interactions was higher than in the present study because hospitalized patients are usually more acutely ill than ambulatory patients and are more likely to receive more medications. In the study of hospitalized patients the median number of drugs per patient was eight, as compared to our study, where the median number was six. In addition, infections and thromboembolic events were among the most common causes of hospital admission in the previous study;[11] both of these illnesses require pharmacological treatment with drugs that may interact, such as oral anticoagulants and antibiotics. A cross-sectional study of ambulatory cancer patients receiving anti-neoplastic therapy found that approximately one third of 405 patients were exposed to at least one potential drug interaction.[11] The similar frequency of potential interactions in this study and the previous study was not expected, since we hypothesized that cancer patients at the end of life would be at a greater risk of drug interactions when compared to cancer patients receiving anti-neoplastic therapy. In both studies, it was found that almost one third of patients were receiving drug combinations with the potential to interact. This is likely because almost 90% of potential interactions encountered in the previous study[11] involved non-anticancer agents, many of which were the same as those identified in our study (e.g. warfarin and anticonvulsants). In both studies, the majority of interactions were pharmacokinetic, and in most instances the underlying mechanism was interactions with the hepatic CYP enzymes. This is because many drugs taken by cancer patients such as proton-pump inhibitors, certain opioids and benzodiazepines, are either substrates or inhibitors/inducers of CYP enzymes.
[9]

Limitations of our study should be noted. First, the population is limited to a single institution, therefore, the generalizability to other palliative care settings is unknown. However, the patients and their medication profile were representative of other previously described palliative care cancer populations.[14,16,18,23,24] Secondly, the data were collected retrospectively, and although we were rigorous in our inclusion criteria and excluded 25 patients whose charts provided incomplete information about medications, it is possible that we missed information on medications. Thus, even though the 30% frequency of drug interactions is consistent with other studies,[12] it is possible that it has been underestimated. In addition, because of the accuracy of the screening method,[21] approximately one quarter of potential drug interactions were theoretical interactions, for which the clinical consequences are unknown. Lastly, one of the major limitations of studies examining drug interactions is the difficulty in measuring the number of potential interactions that resulted in clinical adverse events. These are difficult to ascertain retrospectively, and it would obviously not be ethical to evaluate the clinical outcomes of drug interactions in a prospective way without modifying or stopping the medications involved. We are aware that there is a growing use of herbal/dietary supplements by the general population, including cancer patients, and concerns have been raised about pharmacological interactions between drugs and herbal compounds.[25,26] However, the evaluation of herbal-drug interactions was beyond the scope of this study.

Anticonvulsants are well known to interact with other drugs. In this study as well as in two previous studies about the risk of drug interactions in cancer patients,[11,12] the association of phenytoin and corticosteroids was among the most commonly identified drug combinations with the potential to interact. In this combination, dexamethasone affects the hepatic metabolism of phenytoin, which can lead to either an increase or decrease in phenytoin serum concentrations.[22] Warfarin is metabolized by the CYP 2C6 hepatic enzyme, conferring a high risk of interactions with other drugs metabolized by this

enzyme such as acetaminophen and corticosteroids; bleeding may result from such interactions.[27,28] Although there were only three patients who were prescribed risperidone in combination with selective serotonin reuptake inhibitors, this combination is life-threatening and supported by level 1 evidence (i.e. supported by large trials).[29] An increased plasma concentration of risperidone, possibly due to inhibition of its hepatic metabolism by the antidepressant, may lead to serotonin syndrome.[29]

The best way to prevent drug interactions remains unknown. Alert guidelines such as flyers containing drug combinations with the potential to interact or electronic messages that alert physicians when entering a patient's order, and computerized programs can increase recognition of such interactions and provide an important tool for screening. We suggest that subjects at high risk, such as brain tumor patients, those with comorbidities and those receiving warfarin and anticonvulsants be routinely screened for drug interactions. This is particularly important in the palliative care setting, where patients are usually quite unwell and already have a high burden of symptoms. Palliative care physicians should be aware of possible clinical consequences of drug interactions and we suggest that health professionals who work with these patients check phenytoin serum levels when a patient develops symptoms of phenytoin toxicity (e.g. ataxia and confusion) and perform coagulation tests when a patient who takes long-term warfarin is prescribed a new medication (especially antibiotics, acetaminophen and steroids). In addition, routine re-assessment of the need of continuing certain medications at the end of life, such as statins, aspirin and angiotensin converting enzyme inhibitors, could decrease the risk of adverse drug reactions and drug interactions.

In summary, drug combinations with the potential to interact are common among ambulatory cancer patients receiving exclusively supportive care and mostly involve warfarin and anticonvulsants. Development of alert guidelines and computer-based

screening could help physicians to recognize potentially dangerous drug interactions and avoid undesirable adverse events in this already frail population. Population-based studies are warranted to evaluate the epidemiology of clinical adverse events resulting from drug interactions in oncology practice.

Table 1. *Drug Interactions Facts** software classification scheme of levels of severity and scientific evidence of drug interactions

Level of Severity	Description
1	Major: an adverse effect can cause permanent damage or life risk
2	Moderate: an adverse effect can harm and treatment is required
3	Minor: small or no clinical effect, with no treatment required
Level of Scientific Evidence	**Type of Scientific Data**
1	Established: adverse effect confirmed by large clinical trials
2	Probable: adverse effect with high likelihood of occurrence but without definitive randomized clinical trials
3	Suspect: adverse effect likely to occur; data derived from case reports
4	Possible: adverse effect may occur but data are scarce
5	Unlikely: adverse effect may theoretically occur

* Drug Interaction Facts ®, version 4.0, 2006, by Wolters Kluwer Health. Electronic source: www.factsandcomparisons.com

Table 2. Patient characteristics

Characteristic	Number	Percentage
Total number of patients	372	100
Age (years), median (range)	66 (range 22 – 94)	-
Sex		
Female	181	49
Male	191	51
Cancer type		
Gastrointestinal	112	30
Lung	59	16
Gynecologic	47	13
Genitourinary	45	12
Brain	20	5
Hematological	18	5
Breast	17	4
Other	54	14
Patients with ≥ 1 comorbid condition	247	66
Comorbid conditions, median No (range)	1 (range 0 – 7)	-
Pharmacological class of drugs taken by patients*		
Opioid	251	67
Laxative/stool softener	200	54
Acetaminophen	151	41
Corticosteroid	140	38
Antidyspeptic	136	36
Cardiovascular	128	34
Antiemetic	107	29
Benzodiazepine	87	23
Nonsteroidal anti-inflammatory drug	66	18
Antidepressant	59	16
Statin	49	13
Antidiabetic	46	12
Anticonvulsant	38	10
Antibiotic	34	9
Anticoagulant/heparin	25	7
Bisphosphonate	21	6
Drugs taken by patient, median No (range)	6 (range 0 – 21)	-

* Denominator is the total number of patients (N = 372)

Table 3. Drugs with potential to interact among ambulatory palliative care cancer patients

Potential drug interactions	Number	Percentage
Number	250	100
Number of patients with ≥ 1 potential drug interaction	115	31 (95% CI 25 - 36%)
Median (range) number of potential drug interactions per patient	0 (0-10)	
Severity of potential drug interactions		
Major	25	10
Moderate	147	59
Minor	78	31
Level of scientific evidence for identified potential drug interactions*		
1	23	9
2	66	26.5
3	15	6
4	80	32
5	66	26.5
Mechanism of identified potential drug interactions		
Pharmacokinetic	109	44
Pharmacodynamic	70	28
Unknown	71	28

* Lower number indicates greater strength of evidence in support of the drug interaction.

Table 4. Most common instances of drug combinations with potential to interact

Drugs with potential to interact	Number of cases	Description	Severity	Level of Scientific evidence *
Pharmacokinetic drug interactions				
Phenytoin + corticosteroids[22]	10	Both drugs may increase or decrease each other's liver metabolism.	moderate	2
Warfarin + corticosteroids[28]	8	Increase or decrease in warfarin anticoagulation effects. Mechanism unknown.	moderate	4
Phenytoin + statins[30]	5	Phenytoin induces statins' hepatic metabolism with consequent lower serum levels of statins.	moderate	4
Phenytoin + acetaminophen[31]	6	Phenytoin induces acetaminophen's hepatic metabolism with consequent increased hepatic toxicity.	moderate	2
Phenytoin + ranitidine[32]	5	Increased or decreased phenytoin plasma concentration, possibly because of inhibition or induction of its liver metabolism.	moderate	4
Benzodiazepine + omeprazole[33]	5	Inhibition of benzodiazepine's liver metabolism, with increased sedation	moderate	4
ASA + corticosteroids[34]	5	Reduced serum salicylate levels because of increased liver metabolism and renal elimination by steroids.	moderate	2
Risperidone + SSRI[29]	3	Increased plasma concentration of risperidone, possible due to inhibition of its liver metabolism; risk of serotonin syndrome	major	1
Pharmacodynamic drug interactions				
Warfarin + acetaminophen[27]	8	Increased vitamin K antagonism by acetaminophen, with risk of bleeding.	moderate	2
Prochlorperazine + ACE inhibitor[35]	7	Additive hypotensive effects.	moderate	4
NSAID + SSRI[36]	5	Increased risk of upper gastrointestinal bleeding. Mechanism unknown, possible additive effects.	moderate	2
ASA x ACE inhibitor[37]	5	Hypotensive effects of ACE inhibitors may be reduced because of inhibition of prostaglandins synthesis by ASA.	moderate	2

Abbreviations: ASA, acetylsalysilic acid; SSRI, selective serotonin reuptake inhibitor; ACE inhibitor, angiotensin converting enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug.

* Lower number indicates greater strength of evidence in support of drug interaction.