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Use of Prescription and Non-Prescription Medications and Supplements by Cancer Patients during Chemotherapy; Questionnaire Validation

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Abstract

Background—Cancer patients take medications for coexisting disease and self medicate with over-the-counter drugs (OTCs). A complete analysis of the use of prescription drugs, OTCs and supplements during cancer treatment has never been done.

Methods—The study developed and validated a self-administered questionnaire on the use of concomitant medications by patients undergoing treatment with chemotherapy. The questionnaire listed 510 prescription medications, OTCs, and supplements (including vitamins, minerals and herbs). Fifty-two subjects completed the questionnaire while visiting the infusion clinic to receive chemotherapy. On a subsequent visit the subjects brought their medications to the clinic and a pharmacist reviewed their completed questionnaire.

Results—Ninety-six percent of the subjects reported taking prescription medications within three days prior to chemotherapy, 71% reported taking OTCs and 69% reported use of supplements. The subjects took an average of 5.5 (range 0-13) prescription drugs, 2.2 (0-20) OTCs and 1.9 (0-11) supplements. Twenty-one drugs were each taken by at least 10% of the subjects. Acetaminophen was taken by 59.6% of the subjects. One subject reported taking five acetaminophen-containing drugs. The questionnaire's sensitivity was 92.0%, specificity 99.9%.

Conclusion—Within 3 days prior to chemotherapy, subjects took an average of 9.6 concomitant medications, many of which alter drug metabolism and or disposition. In clinical trials, multivariate analysis of all concomitant medications could add to clinically relevant data to identify drug interactions that negate or potentiate the efficacy of cancer treatment regimens. In some instances, apparent resistance of tumors to chemotherapy may be the result of drug interactions.

Keywords

Chemotherapy; concomitant medications; drug interactions; over-the-counter medications

INTRODUCTION

Cancer patients undergoing treatment with chemotherapy often take additional medications for coexisting medical conditions. In addition to prescribed drugs, many cancer patients self-medicate with over-the-counter medications (OTCs), vitamins, dietary supplements, herbs and other items (1-3). Sensitivity or resistance of a tumor to a chemotherapeutic regimen is often assumed to be due to inherent properties of the tumor. However, concomitant medications can alter the efficacy of the chemotherapeutic regimen (4).

Use of prescription drugs or alternative medications by cancer patients have been reported, but no comprehensive study describes the use of prescription drugs, OTCs and supplements by patients receiving chemotherapy. One deterrent to such studies is the lack of a validated questionnaire that collects data on the use of all concomitant medications. We have designed and validated a questionnaire for use in prospective studies of drug interactions. The half-life of most drugs is within 72h providing for significant interaction between the concomitant drug and the absorption, distribution, metabolism or excretion of the chemotherapy (5). Induction of drug metabolizing enzymes such as cytochrome P450s also occurs within 72h (6;7). In addition, in dietary studies, questionnaires requiring a 72h recall have been shown to provide valid data (8). Therefore, we collected data on concomitant drug use within 3 days prior to chemotherapy, the optimal timeframe for drug interactions. Herein we detail the questionnaire's development and its validation in a population of patients receiving intravenous or intraperitoneal chemotherapy, and report the use of prescription drugs, OTCs, vitamins, supplements and herbs by these patients.

METHODS

Questionnaire

A questionnaire was developed that contained an exhaustive list of the most commonly used prescription medications, OTCs and supplements. A list of prescription medications was compiled from the list, published by RxList.com, of the "Top 300 Prescriptions for 2004 by Number of US Prescriptions". The top 207 drugs from this list were included. On the questionnaire, drugs were categorized according to the ailment for which they were most commonly prescribed [Heart Medications (Blood Pressure), Pain Relief, Allergy etc.]. Following Phase I of content validation, a separate section containing the fifteen anti-nausea medications most commonly used by chemotherapy patients was included in the questionnaire. Lopressor HCT® (metoprolol with HCTZ) was also added. The questionnaire instructed subjects to indicate whether in the previous 10 days they had taken any of five drugs that are formulated for slow release [Fosamax® weekly (Alendronate), Actonel® weekly (Risedronate), Procrit® (Epoetin Alfa), Neulasta® (Pegfilgrastim), Aranesp® (Darbepoetin Alfa)]. The final questionnaire included a total of 228 prescription drugs.

The questionnaire included all OTCs ranked by Drugtopics.com, in terms of dollar sales, as the "Top 200 OTC/HBC Brands in 2004." For popular brands of OTCs such as Tylenol®, Robitussin®, Sudafed®, the questionnaire included all of the combination formulations in the manufacturer's product line. The OTCs were categorized according to the ailment for which they were most commonly used. The questionnaire also asked about the use of deodorants with antiperspirants and deodorants without antiperspirants. All antiperspirants contain aluminum which can be absorbed through the skin (9). A total of 211 OTCs were included on the questionnaire. The questionnaire included 75 vitamins, minerals, supplements and herbal remedies that were compiled from lists of the "Top-Selling Herbal Dietary Supplements," "Common Herbs useful for Cancer and Chemotherapy," and other sources (10-12).

The questionnaire was designed as a self-administered, paper document of eleven pages. It began with three demographic questions (sex, age, race) and three questions regarding use of tobacco, alcohol and special diets. The medications sections provided, to the left of each listed medication, a box that subjects could check if they had taken that medication within the past 3 days. Each medication was listed with both its brand names and generic names. At the end of the prescription drug list, and on the last page of the questionnaire, sections were provided that asked subjects to write the names of medications they were taking that they had not found among those listed. All medications that were written in by the subjects were included in the analyses.

The first of several steps in the validation of an instrument such as a questionnaire is face validation: “the extent to which an instrument (in this case the questionnaire) seems in the opinion of experts to measure what it purports to measure.”(13). The questionnaire was reviewed by three nationally known pharmacy faculty with expertise in survey development. Revisions to the instrument were made based on their comments and feedback. Content validation of the questionnaire with subjects is detailed below. The questionnaire is available from the corresponding author.

Subjects

All subjects were recruited from patients receiving chemotherapy for cancer at the Hematology/Oncology Chemotherapy Clinic or the Gynecologic Oncology Clinic at the University of Oklahoma Health Sciences Center. The subjects were invited to participate in the study after their chemotherapy infusion had started. Written informed consent was obtained from each subject at the time of enrollment. The study was approved by the IRB at the University of Oklahoma Health Sciences Center.

Phase I and Phase II Validation: The questionnaire was administered to two patient groups. In Phase I, the study coordinator recorded the amount of time the subject required to complete the questionnaire. After completing it, subjects were asked if they had questions or suggestions to improve the questionnaire. Investigators modified the questionnaire on the basis of the subjects' responses.

Subjects enrolled in Phase II of the validation completed the modified questionnaire twice. They first completed the questionnaire when they enrolled in the study (Phase IIA). After completing the questionnaire, they were asked to bring all their medications, including OTCs, supplements and herbal remedies to their next scheduled chemotherapy appointment. The study coordinator called patients the day before the visit to remind them to bring their medications. Each subject completed the questionnaire a second time (Phase IIB) when they returned. Then, a pharmacist reviewed the subject's medications in an individual interview and compared them with the subject's questionnaire responses, noting medications that were incorrectly reported and medications that were not marked.

Data Analysis

A database was constructed, using Microsoft Access, and the data were entered and verified by trained individuals. Data analysis considered each combination drug such as Glucovance® and separately considered individual components such as glyburide and metformin. Acetaminophen is a component of 40 different medications listed on the questionnaire. Acetaminophen is one of 24 drugs that were components of more than one listed medication.

Fisher's exact tests investigated differences in the race, smoking behavior, alcohol use or special diets between the groups of subjects recruited for Phase I and Phase II. An unpaired t-test investigated differences in the mean age of the two subject groups. Analyses were done

with GraphPad Prism 4 (GraphPad Software, San Diego, CA). Statistical analyses of the reporting errors evaluated in Phase IIB included estimates of the percent of total medication reports that were erroneous, along with 95% confidence intervals for these estimated error percentages. The questionnaire's sensitivity and specificity were calculated and adjusted for clustering using generalized estimating equations (GEE) in connection with a logistic regression model(14). Sensitivity was modeled as the predicted probability (adjusted for within-subject associations among 26 patients) that subjects stated they used a drug, given that the pharmacist verified they used it. This logistic regression approach is analogous to dividing the number of drugs that subjects correctly reported (true positives) by the sum of this number plus the number of drugs they took but did not report (true positives plus false negatives). Similarly, cluster-adjusted specificity was derived using GEE to predict the probability that patients correctly did not report using a drug, given that the pharmacist also did not record their using it. The approach is analogous to dividing the number of true negatives by the sum of this number plus the number of drugs that subjects actually took but did not report (true negatives plus false positives).

RESULTS

Data Collection

Twenty-nine subjects were asked to participate in Phase I of the study. Only three refused. Table 1 shows the demographics of the 13 men and 13 women who enrolled in Phase I. The average time to complete the Phase I questionnaire was 19.2 ± 9.2 minutes (median 15.5 min). Only one subject took longer than 32 minutes. That subject took 51 minutes. Based on comments from subjects in Phase I, a separate subsection entitled "Anti-Nausea Medications", was included in the prescription drug section and several additional drugs were listed on the questionnaire. In both Phase I and Phase II the subjects had the opportunity to write in any drugs they were taking but did not find on the list. A new group of 13 men and 13 women, non-overlapping with the subjects enrolled on Phase I, was recruited and enrolled in Phase II of the study. The Phase I and Phase II patient groups did not differ significantly with regard to race, age, smoking behavior, alcohol use or special diets (Table 1).

Subjects in Phase II completed the updated questionnaire upon enrollment (Phase IIA). Table 2 shows the use of concomitant drugs reported by subjects in Phase I and Phase IIA. Fifty subjects (96%) reported taking prescription medications prior to chemotherapy. The subjects reported taking between 0 and 13 prescription drugs within the three days prior to chemotherapy. Thirty-seven subjects (71%) reported taking OTCs. OTC use ranged from 0 to 6, except one subject who reported taking 20 OTCs. Thirty-six subjects (69%) reported using vitamins, herbs or supplements prior to chemotherapy. One subject reported using 11 items, including high doses of vitamin C, vitamin E, zinc, ginko, ginseng, lecithin, melatonin. The only medication uses not included in Table 2 involve the use of deodorants (with and without antiperspirants) and non-medicated chapstick. The percentages of subjects using deodorants with antiperspirants (all of which contain aluminum) was 57.7%, while 15.3% reported using deodorants alone.

Reporting Errors and Validation

Subjects in Phase IIB brought their medications, including OTCs, supplements and herbal remedies to their scheduled appointment for chemotherapy. They completed the questionnaire, then a pharmacist went through their medications with them and reviewed their responses on the questionnaire. Table 3 summarizes the findings of the pharmacist's evaluations. The pharmacist discovered 25 prescription drugs that subjects failed to report, representing a 15.6% omission error [95% Confidence Interval(CI): 10.0, 21.3%]. Included among the 25 were 2 drugs for which the subjects had marked an incorrect form of the drug. The pharmacist also

found that two subjects falsely reported a total of three prescription drugs (reported taking a drug when they were not), representing a 1.9% false reporting rate (95% CI: 0.0, 4.0%). In addition, three subjects had marked an incorrect form of a drug. One subject marked Lisinopril® with HCTZ but was taking just Lisinopril®. A second subject marked Enalapril® but was taking Enalapril® with HCTZ. The third subject marked three forms of metoprolol (one form was correct, the other two were incorrect), then added a note to the questionnaire that they did not know what form they were taking. These four incorrectly marked drugs represent a misreporting rate of 2.5% (95% CI: 0.1, 4.9%).

Fewer reporting errors occurred for OTC medications and for vitamins, minerals, supplements and herbs. Subjects failed to report 8 of the 61 OTC medications that the pharmacist discovered, a 13.1% omission rate (95% CI: 4.6, 21.6%). Subjects correctly marked all OTC medications that they were taking. Among the vitamins, minerals, supplements and herbs, subjects failed to report 1 of the 33 substances that the pharmacist reviewed, a 3.0% omission rate (95% CI: 2.8, 8.9%). Subjects correctly marked all items among the vitamins, minerals, supplements and herbs.

Across all categories (Prescription Drugs, OTCs, Vitamins, Minerals, Supplements and Herbs), subjects failed to report 34 of the 254 for a combined omission rate (false negative rate) of 13.4% (95% CI: 9.2, 17.6%). Overall, three drugs were incorrectly reported for a 1.2% false reporting (false positive) rate (95% CI: 0.0, 2.5%). In four instances incorrect forms of the drugs were reported for an overall misreporting rate of 1.6% (95% CI: 0.0, 3.1%).

The questionnaire listed 510 prescription medications, OTCs, Vitamins, Minerals, Herbs and Supplements (not including deodorants and non-medicated chapstick, 4 items total). In Phase IIB the subjects failed to report 34 items (false negatives), correctly reported 227 items (true positives), reported taking 7 drugs that they were not taking (false positives) and correctly did not mark 13260 items (true negatives). Adjusted for clustering (within-subject associations among 26 patients), the questionnaire's sensitivity was 92.0% and its specificity was 99.9%. Given that a patient was taking a drug, as confirmed by the pharmacist's review, the probability of it being reported was 0.920. Given that a patient's non-use of a drug was confirmed, the probability of the drug not being reported was 0.999.

We did not attempt to determine the reliability of the paired responses that we obtained from the patients in Phase II who completed the questionnaire twice. The time between a subject's enrollment in the study and his or her return visit varied from 14 days to 49 days. Several subjects were hospitalized in the interim between completing the questionnaire the first and second time. We could not evaluate whether discordance in responses between the first and second questionnaire was due to errors or omissions by subjects, or whether it accurately reflected changes in their use of medications.

Commonly used Medications, Vitamins and Supplements

The use of individual drugs was evaluated. For example, to determine whether subjects had taken aspirin within the past three days, we evaluated their reports on the use of Alka-Seltzer®, prescription strength aspirin (acetylsalicylic acid), aspirin, Bayer Back and Body Pain®, Bayer Nighttime Relief®, Bayer Rapid Headache Relief®, Bayer Women's Plus Calcium®, Ecotrin®, Ecotrin Arthritis Relief®, Excedrin Extra Strength®, Excedrin Migraine® or St. Joseph's Aspirin®. Table 4 lists the medications taken by at least 10% of the subjects in Phase I or Phase IIA. All of the commonly used medications were taken by both men and women with the exception of tamsulosin (Flomax®) which was only prescribed to males. Twenty-three percent of the males were taking tamsulosin.

Sixty-seven of the medications listed contained acetaminophen. Sixty percent of the patients took acetaminophen or some medication containing it within three days prior to chemotherapy. Four subjects had each taken three different drugs containing acetaminophen. One subject took five medications containing acetaminophen (Alka-Seltzer Plus Cold®, Robitussin Night Relief®, Tylenol®, Tylenol with codeine®, and Tylenol Cold Relief Nighttime®).

Analysis of the data for the 26 patients in Phase IIB, which were collected after the pharmacist reviewed the questionnaires, revealed commonly used medications in addition to those included in Table 4. Other medications taken by at least 10% of the 26 subjects in Phase IIB included oxycodone and lorazepam, each of which was taken by 7 (27%) of the subjects. Prochlorperazine (in the form of Compazine®) was taken by 6 (23%) of the subjects. Furosemide and iron supplements were each taken by four (15.4%) and HCTZ by three (11.5%) of the subjects. Acetaminophen was the most commonly used medication among Phase IIB subjects. The pharmacist confirmed that within three days of chemotherapy one subject in Phase IIB took four medications that contained acetaminophen (oxycodone with APAP, Tylenol®, Benadryl Allergy Cold Caplet® and Tylenol Arthritic Pain®).

DISCUSSION

We collected data on use of concomitant medications. The sensitivity and specificity of our questionnaire was 92.0% and 99.9% respectively. The data revealed that 96% of the subjects used prescription medications within three days prior to chemotherapy, 71% took OTCs and 69% used vitamins, herbs or supplements. Riechelmann and colleagues' study of prescription drug use by cancer patients reported an average of 5 drugs prescribed per patients (range 0-23) which is in close agreement with our findings of 5.5 prescriptions drugs per patient (range 0-13) (4). Our data are also similar to those of McCune and colleagues who reported that 78% of adult cancer patients receiving chemotherapy at a university-based outpatient clinic used vitamins and herbal supplements (15). Many studies report that more than half of cancer patients use herbs and vitamins during cancer treatment (1;2;15-18).

Our study is the first to include a comprehensive study of all medications including prescription, OTC, vitamins, minerals, herbs and supplements. Many drugs, such as acetaminophen, are available in both prescription and OTC formulations. We observed that five of the subjects had taken three or more medications that contained acetaminophen within three days. These data are alarming in light of a recent study by Larson et al. who reported that the primary cause of acute liver failure in the United States was acetaminophen-induced (19). Their study noted that a high level of ingestion of acetaminophen was often unintentional and the result of patients taking multiple medications containing acetaminophen. The extent of acetaminophen use would not have been revealed unless data on use of both prescription medications and OTCs had been collected. We also included deodorants (with and without antiperspirants) on the questionnaire as all antiperspirants contain aluminum which can be absorbed through the skin (9). We did not include the data on deodorants or medicated lip gloss in the validation of the questionnaire because they are distinct from all the other items which are ingested. But, aluminum is neurotoxic and induces pro-inflammatory genes and the data may be of value in future analyzes (20).

Riechelmann and colleagues investigated prescription drug use in cancer patients and found that 27% of the patients were at risk for at least one potential drug interaction (4). Among the potential prescription drug/chemotherapy interactions were: quinolines with cyclophosphamide; ondansetron, phenytoin or furosemide with cisplatin; cimetidine or phenytoin with fluorouracil (4). McCune and colleagues identified 27% of patients as being at risk of a detrimental interaction between their chemotherapy and the herbs or vitamins that they were taking (15). These interactions included antioxidants which can inactivate some of

the most widely used chemotherapy drugs (15;21-23;23;24). Concomitant medications can also alter the side effects of chemotherapy. A study by Shord and colleagues of interactions between prescription drugs and the nephrotoxicity of cisplatin, found that use of albuterol, atenolol, hydrochlorothiazide or multivitamins correlated with increased incidence of nephrotoxicity while dexamethasone and ondansetron correlated with reduced incidence of nephrotoxicity (25).

Use of the questionnaire has several advantages in obtaining information on concomitant medications. The questionnaire groups medications according to the ailment for which they are used. Previous studies have shown that recall is higher for questions about drug use for a specific indication than for an open ended question about drug use (26). Providing a list can be helpful to the patient in recalling all of their medications. The questionnaire is self-administered and does not require that a physician or nurse complete a detailed, time-consuming medication history. Several classes of over-the-counter medications such as hair growth treatments and nasal sprays may not be considered medications by patients and therefore would not be reported on a medication history. Finally, the questionnaire requests information about the consumption of vitamins and herbs which are rarely included in a medication history, but have been shown to alter metabolism of chemotherapy drugs (15).

The goal of the current study was to identify the prescription drugs, OTCs and supplements taken by patients within 3 days prior to chemotherapy. We developed and validated a self-administered questionnaire that can be used to gather this information. We did not collect information on the chemotherapy regimen. The sensitivity (92.0%) and specificity (99.9%) of our questionnaire compares favorably to other self administered questionnaires including those designed to collect data on use of hormone therapy (84.9% and 97.7%) or dietary supplements (78% and 93%) (27;28). The questionnaire is a reliable tool for studies of drug interaction.

The data obtained as part of the validation of this questionnaire reveal wide-spread use of concomitant medications by patients under going treatment with chemotherapy. Data on concomitant drug use should be collected and analyzed in all studies evaluating the safety or efficacy of chemotherapy drugs. We plan to use this questionnaire in prospective studies of the interaction between concomitant medications and the efficacy and/or toxicities of chemotherapy and radiation.

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Table 1**Demographic Information**

	Phase I	Phase II	Total
Male	13	13	26
Female	13	13	26
White	23	24	47
Black	3	2	5
Age in years (range)	68 ± 8.3 (53-85)	63 ± 10.4 (44-79)	
Smoker	2	1	3
Non-smoker	24	25	49
Alcohol (past 3 days)	2	2	4
Vegetarian diet	0	1	1

Table 2**Summary of Concomitant Medications**

	Phase I	Phase IIA	Total
Number Prescription Drugs	157	128	285
Average # Drugs per Subject (median, range)	6.0 (5, 0 -13)	4.9 (4.5, 0 - 11)	5.5
Number OTCs	67	47	114
Average # OTCs per Subject (median, range)	2.6 (1, 0-20)	1.8 (2, 0-6)	2.2
Number Vitamins, Supplements, Herbs	63	35	98
Average # Vit etc. per Subject (median, range)	2.4 (1, 0-11)	1.3 (1, 0-6)	1.9
Total	287	210	497

Table 3**Reporting Errors**

	Phase IIB Subject Responses	Phase IIB After Review by Pharmacist
Number Prescription Drugs	142	160
Average # Prescription per Subject (range)	5.5 (1-16)	6.2 (1-16)
Number OTCs	53	61
Average # OTCs per Subject (range)	2.0 (0-9)	2.3 (0-10)
Number Vitamins, Supplements, Herbs	32	33
Average # Vit. etc. per Subject (range)	1.2 (0-6)	1.3 (0-6)
Total	227	254

Table 4
Medications taken by more than 10% of Subjects within 3 days prior to Chemotherapy

Medication	# Subjects	% taking Medication
Acetaminophen	31	59.6
Multivitamins	21	40.4
Hydrocodone	15	28.8
Calcium supplements	14	26.9
Tamsulosin	6 (all male)	23.1 (% of males)
Amlodipine	11	21.2
Aspirin	11	21.2
Diphenhydramine	11	21.2
Potassium	10	19.2
Ibuprofen	9	17.3
Magnesium	8	15.4
Metoprolol	8	15.4
Omeprazole	8	15.4
Promethazine	8	15.4
Esomeprazole	7	13.5
Levothyroxine	7	13.5
Pseudoephedrine	7	13.5
Dextromethorphan	6	11.5
Glipizide ER	6	11.5
Pantoprazole	6	11.5
Ranitidine	6	11.5