ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 5, 2016

Online - 2455-3891
Print - 0974-2441

Research Article

DRUG UTILIZATION EVALUATION AND COST ANALYSIS OF ANTIEMETIC DRUGS PRESCRIBED IN ONCOLOGY WARD IN A QUATERNARY CARE HOSPITAL

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Received: 28 April 2016, Revised and Accepted: 11 May 2016

ABSTRACT

Objective: Drug utilization is defined by the World Health Organization as the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences. Our study is done to obtain the variation of drug use and costs of drug therapy, from which medical and social qualitative consequences can be found. Our study emphasizes on knowing the drug utilization and cost included for antiemetics in patients undergoing chemotherapy in oncology ward.

Methods: It was observational, prospective and non-interventional study.

Results: Total of 141 patients were studied, out of which 77 (54.6%) patients were female and 64 (45.4%) patients were males. The majority of the patients in this study belong to the age group of 40-49 (29%) and 60-69 (20%) years. The comparison with the standard protocol was made according to the use of antiemetics in the patients. Out of which, 137 (97%) patient profiles were found to be deviating from standard protocol, and 4 (3%) patient profiles were found following the standard protocol because of including prochlorperazine which is not mentioned in the standard protocol.

Conclusion: As of future approach, education to physician for rational drug use and review of medication chart with patient consideration can give better health care and also cost effective treatment.

Keywords: Drug use evaluation, Antiemetics, Chemotherapy.

 DOI: http://dx.doi.org/10.22159/ajpcr.2016.v9i5.12464

INTRODUCTION

Drug use evaluation is a system of ongoing, systematic, criteria-based evaluation of drug use that will help ensure that medicines are used appropriately (at the individual patient level) [1,2]. Drug utilization studies are mainly of types, quantitative, or qualitative [3]. Drug utilization review (DUR) in pharmacist education has traditionally stressed the importance of the 3 R's (right drug, right dose, and right time). DUR focuses on to reduce serious preventable drug-related morbidity and complicated regimens. It mainly compares the particular drug advice by the physician with the widely used given standard practice guidelines and quality assurance with therapy [4,5] and quality of therapy and cost development of drug use [6]. Drug utilization studies, depending on settings and underlying priorities, may be used for a variety of purposes. It can be used for the pattern of drug use, quality of drug use, determinants of drug use, outcome of drug use [7], monitoring and evaluating the effects of undesirable drug use. Following the changes made, cost variation and alternative to the drug use. Assessing the spread of knowledge on the indicative drug use relative to the disease [8].

Rational drug use help adheres to prescribing policies which prevents unsatisfactorily treatment and high overall health cost. DUR analyzes the rational use of drugs by studying the patterns of drug prescribed [9]. Data on drug costs are important in managing policy related to drug supply, drug pricing, and drug use [10]. Cost-effectiveness (CE) analysis indicates whether the health expected to be gained or lost where the health-care activities are displaced and represents quality-adjusted life-years, and it is measured in "lives saved" and "life years gained" [11]. It provides the basis for its empirical estimation and to define the CE threshold [10]. Clinicians should give the effective therapy related to less cost. The study can help create clinical guidelines for clinicians that will help them to prescribe in appropriate manner [12].

Chemotherapy-induced nausea and vomiting (CINV) is linked as an adverse reaction with chemotoxic agent. Delayed nausea and emesis were reported in discharged after few days of chemotherapy [13]. Nausea and vomiting are the major side effects for 70-80% of patients receiving chemotherapy [14] and with 10-44% experiencing anticipatory type of emesis [15]. Even one or two emetic episodes can lead to unsatisfactorily in the quality of life, physical and cognitive functioning [16]. Nausea can be measured by numerical rating scale-11 scale were with being no distress and 10 is the worst distress imaginable. It is mainly divided into four levels as shown in Table 1 [17].

Three main types of pathophysiology are central mechanism-activating chemoreceptor trigger zone, peripheral mechanism-acting on gastric mucosa causing irritation and damage with the release of various neurotransmitters, and combined mechanism - acting both by peripheral and central [18].

Treatment guidelines are useful tools used by the physicians to integrate the clinical research into the practices. The importance of antiemetics use was given in the antiemetics guidelines of USA base such as ASCO, MASCC, and others as NCCN. They give the general practice to carry out the prescription pattern for antiemetics usage in the chemotherapy and radiation based NV. Prophylactic use of antiemetics is most important to reduce NV in during chemotherapy [19].

Optimal antiemetic use in chemotherapy has the potential to lower the overall health-care cost by providing cost-effective treatment. Utilization characteristics of antiemetic drugs will be assessed and made clear whether its use is optimal based on their therapeutic efficacy [5,20]. Antiemetics can be used depending on the patient characteristics, able to withstand the cytotoxic drugs and individual risk for the clinical outcome [21]. Physicians should be careful in the selection of these antiemetics which might help to reduce the overall cancer regimen cost [22-24].

Table 1: Emetic risk groups

High	Risk in nearly all patients (>90%)
Moderate	Risk in 30-90% of patients
Low	Risk in 10-30% of patients
Minimal	Fewer than 10% at risk

The four emetic risk groups of chemotherapeutic drugs (ASCO/MASCC/NCCN) Perugia Guidelines 2004, NCCN Guideline Update 2006

Table 2: Variables

Variables	Cases (%)
Gender	
Female	77 (54.6)
Male	64 (45.39)
Range in years	
1-9	1 (1)
10-19	3 (2)
20-29	8 (7)
30-39	24 (17)
40-49	40 (29)
50-59	25 (17)
60-69	28 (20)
70-79	11 (8)
80-89	1 (1)

Impact of antiemetics

Fosaprepitant and aprepitant acts by sending noxious sensory information to the brain [25-28]. Studies have demonstrated that the addition of an NK1RA to standard antiemetic therapy with corticosteroid (dexamethasone) appears to have a significant effect in controlling cisplatin-induced emesis; in addition, aprepitant regimen was more effective in highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) [29-31]. One study has been resulted for recommendation of aprepitant for anthracycline and cyclophosphamide chemotherapy that is due to the emetogenic property of the chemo drugs. In the same study, the triple combination (ondansetron, dexamethasone, and aprepitant) was used in the first 24 hrs of therapy, and then, aprepitant for next 2 days gave a satisfactory result in next 5 days regimen [13].

All three guidelines recommend granisetron 1 mg (0.01 mg/kg) for intravenous (IV), 2 mg orally by MASCC and ASCO, and 1-2 mg orally by NCCN.

ASCO guidelines recommend ondansetron at dose 24 mg (orally) and 8 mg or 0.15 mg/kg (IV). In one of the meta-analysis studies, it stated that high dose (24 mg or 32 mg) of ondansetron was highly effective than low dose (8 mg) ondansetron with cisplatin chemotherapy of HEC [32].

Dexamethasone dose ranges from 8 to 20 mg. The dose of steroid is reduced when Aprepitant/Fosaprepitant is given in the treatment regimen according to Antiemetic Subcommittee of the MASCC [33,34]. It is used for acute and delayed CINV [35]. This was explained in the study of Warr *et al*. [12] in patients receiving MEC.

Metoclopramide is no longer recommended due to its side effects such as sedation, diarrhea, and extrapyramidal symptoms. It is effective when given in combination with steroid for delayed CINV [36]. Cannabinoids such as dronabinol and nabilone are recommended for MEC [37]. It is used in combination with weak antiemetics so that sedation and euphoria can make them imply to the regimen therapy of antiemetics [35]. Benzamides class of drugs is rarely used due to side effects such as sedation, acute dystonic reactions, and akathisia [37]. Butyrophenones group of drugs such as haloperidol also have antiemetic activity by antidopaminergic action, but the efficacy is less as compared to metoclopramide [38,39]. Antihistamines such as diphenhydramine or hydroxyzine in the treatment of CINV have not shown activity [40]. Olanzapine from the class of an antipsychotic drug, with a dose of 2.5-5 mg has antiemetic actions. It mainly acts on multiple receptor sites which controls CINV [41].

METHODS

The study was done at a quaternary care Hospital, Bengaluru. It was a prospective and non-interventional observational study. The study was carried out for a period of 6-month. It includes 141 patients undergoing chemotherapy who are prescribed with antiemetics. IEC was obtained from the institute to carry out this study.

Inclusion criteria includes

- Patients who are prescribed with antiemetics and admitted to chemoward.
- Patients of all age groups were considered.
- All co-morbidity conditions and other conditions, such as obese, smoker, and alcoholics, are included.

Exclusion criteria includes

- Patients who do not receive any antiemetics.
- Pregnant women.

Methods

Those patients, who meet the study criteria, will be enrolled into the study. Relevant data such as demographic details, drug name, dose, route, frequency, duration of therapy, total pills per day, and laboratory data will be collected from medical records of the patient and by patient interview where ever required. Changes to drug therapy if any will be noted on daily basis and documented. Results and cost analysis was done using Microsoft Excel.

RESULTS AND DISCUSSION

ASCO guidelines are the widely used standard protocols for antiemetic drugs to be used in CINV worldwide, and so we have considered this as standard.

Antiemetics for high emetic risk, moderate emetic risk, and low emetic risk are given as per the Table 3.

In our hospital set up, granisetron 1 mg oral is prescribed twice a day for 3 days or once a day for 5 days which results in the same cost for granisetron per each cycle. Ondansetron 8 mg oral is prescribed twice a day for 3 days which results in the lesser cost than granisetron. IV granisetron 3 mg is prescribed once a day per each cycle.

Granisetron use

In another study, IV granisetron 3 mg was administered to the patient having HEC for the protocols like EC. Around 84% of patients experienced zero or two episodes of emesis and on the 4th day the control increased to 90% [43]. Oral ondansetron 8 mg thrice a day has shown zero emesis in 92.3% of patients on the 2nd day of chemotherapy with EC schedule [44]. Granisetron 1 mg and 3 mg IV showed the similar rate of complete protection from nausea and vomiting. As recommended by the guidelines of Japan for the reduction of economic burden and medical care expenses, prophylactic administration of granisetron 1 mg may be appropriate for acute CINV in cancer patients [45,46].

Ondansetron use

In one study, they have stated that ondansetron have the lowest receptor occupancy at the time of administration, in which the occupancy at 24th hr was 20% for iv injection, whereas <10% for oral administration; therefore, they have explained that dose of ondansetron that is 4 mg is approved in Japan when compared to other clinical guidelines stating 16-24 mg for oral and 8-12 mg for IV is recommended. It is assumed that $5HT_3$ receptor occupancy required to produce sufficient antiemetic results at 12th hr administration is more than or equal to 70% [47].

Table 3: Emetic risk of IV antineoplastic agents [42]

Emetic risk	Agent	
High	Carmustine	Dactinomycin
	Cisplatin	Mechlorethamine
	Cyclophosphamide - 1,500 mg/m^2	Streptozotocin
	Dacarbazine	
Moderate	Azacitidine	Daunorubicin
	Alemtuzumab	Doxorubicin
	Bendamustine	Epirubicin
	Carboplatin	Idarubicin
	Clofarabine	Ifosfamide
	Cyclophosphamide - 1,500 mg/m^2	Irinotecan
	Cytarabine - 1,000 mg/m^2	Oxaliplatin
Low	Fluorouracil	Methotrexate
	Bortezomib	Mitomycin
	Cabazitaxel	Mitoxantrone
	Catumaxomab	Paclitaxel
	Cytarabine - 1,000 mg/m^2	Panitumumab
	Docetaxel	Pemetrexed
	Doxorubicin HCL liposome injection	Temsirolimus
	Etoposide	Topotecan
	Gemcitabine	Trastuzumab
	Ixabepilone	
Minimal	2-chlorodeoxyadenosine	Pralatrexate
	Bevacizumab	Rituximab
	Bleomycin	Vinblastine
	Busulfan	Vincristine
	Cetuximab	Vinorelbine
	Fludarabine	

Dexamethasone use

Dexamethasone is prescribed in different doses at different frequencies for the different durations of days depending on the patient condition and severity of cancer. Usually for IV 4 mg, 8 mg, 16 mg, and 20 mg are administered, whereas in oral dosage form 2 mg to 4 mg are widely used. Variation in the cost of dexamethasone use is different for different patients depending on their disease condition. Dexamethasone 8 mg single IV dose is effective as similar to that of 24 mg single IV dose and 8 mg followed by 4 mg orally for 4 times a day [48].

Prochlorperazine use

Prochlorperazine is prescribed with the uniformity of 5 mg thrice a day for 5 days per each cycle which cost about Rs. 61.72. In one study, oral granisetron was more effective than prochlorperazine in preventing nausea and vomiting for up to 48 hrs in MEC. In the group of patients receiving granisetron and prochlorperazine, granisetron had no significant high rate of emesis than compared to prochlorperazine. Nausea and vomiting were not observed at the 48th hr with the patient receiving granisetron than prochlorperazine [49].

Aprepitant use

Aprepitant is prescribed in a kit containing 3 tablets of 125 mg/80 mg per each cycle which cost about Rs. 1215 for the complete kit. For patient receiving AC schedule, aprepitant regimen was more effective than the controlled regimen of $5HT_3$ and corticosteroid in the prevention of CINV [50] with two study groups each with $5HT_3$ and corticosteroid and other with aprepitant alone. The complete response of no emesis was found with aprepitant [51,52]. Addition of aprepitant to the standard antiemetic treatment affords improved prevention for cinv during multiple-day chemotherapy administration [53].

Combination therapy

In a study combination of oral dexamethasone and oral granisetron gives the high control of emesis about 86%. Results have shown that this combination was effective than high dose of ondansetron and dexamethasone [54]. Therefore, we state that the combination of oral

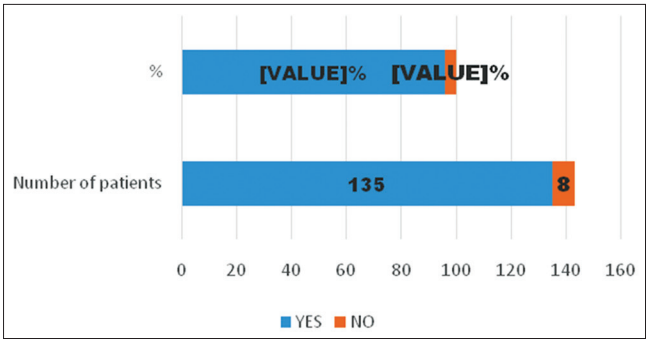

Fig. 1: Comparison with standard showing deviation

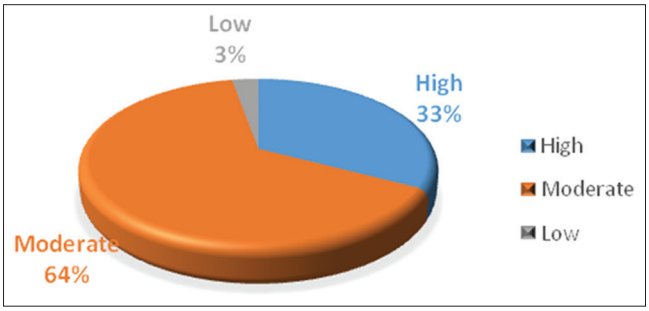

Fig. 2: Risk of emesis depending on chemotoxic agent used

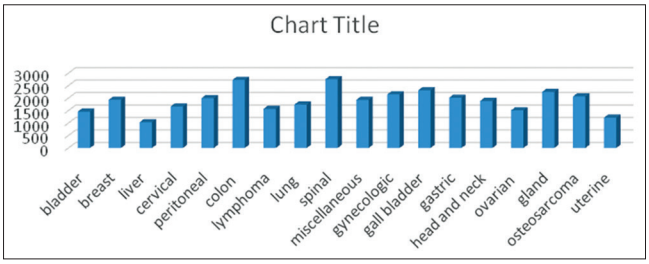

Fig. 3: Total cost for antiemetics for complete cycle

Risk Category	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
High emetic risk*		
NK_1 antagonist		
Aprepitant	125 mg oral	80 mg oral; days 2 and 3
Fosaprepitant	150 mg IV	
$5\text{-}HT_3$ antagonist		
Granisetron	2 mg oral; 1 mg or 0.01 mg/kg IV	
Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral; 0.25 mg IV	
Dolasetron	100 mg oral ONLY	
Tropisetron	5 mg oral; 5 mg IV	
Ramosetron	0.3 mg IV	
Corticosteroid†		
Dexamethasone	12 mg oral or IV	8 mg oral or IV; days 2-3 or days 2-4
Moderate emetic risk‡		
$5\text{-}HT_3$ antagonist		
Palonosetron	0.50 mg oral; 0.25 mg IV	
Corticosteroid		
Dexamethasone	8 mg oral or IV	8 mg; days 2 and 3
Low emetic risk		
Corticosteroid		
Dexamethasone	8 mg oral or IV	

Fig. 4: Antiemetic dosing by chemotherapy risk category [42]

dexamethasone and granisetron is more effective than the high dose combination of ondansetron and dexamethasone. Frakes *et al.* studied the combination of oral dosage form of three antiemetics, which are granisetron, prochlorperazine, and dexamethasone, are very effective for acute control of emesis, but sizeable percentage of the patient had late onset of emesis.

Cost analysis

Cost calculation was done for individual different classes of antiemetics in oral and IV dosage forms. Cost analysis of antiemetics was calculated per each cycle and complete cycle. The total number of patients in the study were 141, out of which, 77 (54.6%) were female and 64 (45.4%) were male who are undergoing chemotherapy and are prescribed antiemetics. The comparison with the standard protocol was made according to the use of antiemetics in the patients.

Out of which 137 cases were found to be deviating and 4 cases to be not with the percentage of 97% and 3%, respectively. Deviation of cases without considering prochlorperazine was found to be 74% as deviating and 26% as not deviating compared to the results where prochlorperazine was included. The different chemotherapy regimens were compared with the standard protocols and the risk of emesis which categorized as high, moderate, and low were found to be 62%, 33%, and 5%, respectively. Out of 141 patients, HEC contributes to 88 patients out of which 86 (61%) were found to be deviating, and 2 (1.41%) patients were not deviated from the standard protocol. Moderate emetogenic chemotherapy contributes to 46 patients, out of which, 44 (31%) were found to be deviating, and 2 (1.41%) patients were not deviated from the standard protocol. Low emetogenic chemotherapy contributes to 7 (5%) patients. The average cost analysis was done for all different antiemetics used in all the classes of cancer for complete cycles. Among which, the average cost was high for spinal cancer (Rs. 2757.57), colon cancer (Rs. 2729.32), and gallbladder cancer (Rs. 2314.90).

CONCLUSION

In our study, utilization of antiemetic drugs in the chemotherapy undergoing patients was granisetron, dexamethasone, prochlorperazine, lorazepam, and aprepitant. As per ASCO guidelines, 137 (97%) cases, out of total 141 cases, were deviating from the standard protocol for the antiemetics used in CINV.

Our study suggests that oral dosage form of ondansetron 4 mg can be used instead of ondansetron 8 mg which results in CE. IV 8 mg dexamethasone can be prescribed instead of 4 mg dexamethasone which shows better efficacy. We also found that 1 mg granisetron IV is appropriate for acute CINV instead of 3 mg granisetron IV, which reduces the overall health care cost. The use of prochlorperazine in our study is widely used which increases the health-care cost while the granisetron is more effective than prochlorperazine in MEC. Combination of aprepitant with $5HT_3$ and corticosteroid is a good tolerability profile in control and prevention of CINV.

Regular medication chat review by the clinical pharmacist will help reduce the cost of therapy with the appropriate use of drug which in-turn helps improving the patient care. In future, approach should be taken to update the knowledge of nurses, pharmacist, and physicians for the rational antiemetic drug use in the oncology ward. All these observations may have important implication for improving prescribing practice by the implementation of standard guidelines, which result can be cost saving and better quality of life.

ACKNOWLEGMENTS

The authors of the article would like to acknowledge PESCP principal, head of the department and BGS global hospital for their support.

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