LEBANESE AMERICAN UNIVERSITY

UTILIZATION AND COST EVALUATION OF TROPISETRON USE FOR CINV

MAYA O. ABDEL-RAHMAN
AND
MAYA T. REDA

June 2004

UTILIZATION AND COST EVALUATION OF TROPISETRON USE FOR CINV

by

MAYA O. ABDEL-RAHMAN
AND
MAYA T. REDA

Submitted in partial fulfillment of the requirements
for the degree of Doctorate of Pharmacy

Thesis Advisor: Dr. Shireen Nabhani

School of Pharmacy
LEBANESE AMERICAN UNIVERSITY
JUNE 2004

LEBANESE AMERICAN UNIVERSITY

GRADUATE STUDIES

I hereby approve the thesis of

Maya O. Abdel-Rahman
and
Maya T. Reda

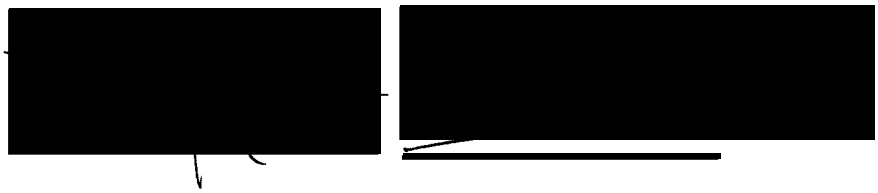
Candidates for the Doctorate of Pharmacy degree*.

Dr. Shireen Nabhani
Professor of Pharmacy
Lebanese American University

Date: June 28, 04

* I also certify that written approval has been obtained for any proprietary material contained therein.

We grant the LEBANESE AMERICAN UNIVERSITY the right to use this work, irrespective of any copyright, for the University's own purpose without cost to the University or its students, agents and employees. We further agree that the University may reproduce and provide single copies of the work, in any format other than in or from microfilms, to the public for the cost of reproduction.



UTILIZATION AND COST EVALUATION OF TROPISETRON USE FOR CINV

ABSTRACT

by

MAYA O. ABDEL-RAHMAN
AND
MAYA T. REDA

This thesis is a retrospective study on 300 medical records between January 2003 and June 2003 in Makassed General Hospital (MGH). The objective of this study is to determine if tropisetron use at MGH was appropriate, and if not, determine possible interventions for cost savings. The results showed a significant tropisetron overuse, which can be prevented by targeted interventions like seminars or pre-printed protocols for both nurses and medical doctors.

Maya O. Abdel-Rahman

To my wonderful parents, my supportive brother and my helpful friends

Maya T. Reda

To my caring family, my encouraging friends and my one and only Dany

ACKNOWLEDGMENTS

We would like to express our gratitude to Professor Shireen Nabhani for providing us with exciting and stimulating projects.

We would also like to thank Professor Habib Moallem for his help and insight in this study's statistical analysis.

Our gratitude goes to our professors and friends who have always been a joy to talk to and bounce ideas around with.

We would also like to thank our families and loved ones for their help and support through our graduate careers.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

CHAPTER 5

CHAPTER 6

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Based on several studies, it was shown that the two most common and bothersome side effects of chemotherapy are the drug-induced nausea and vomiting (N&V). Inadequately controlled N&V can lead to compliance problems as well as serious medical complications such as dehydration, electrolyte imbalances or esophageal tearing[1], which is why effort has been and still is being made to come up with ways to prevent or treat this side effect.

Chemotherapy-induced N&V (CINV) can be classified as acute, delayed, anticipatory, breakthrough or refractory. Acute N&V usually occurs within a few minutes to several hours after drug administration and usually resolves within 24 hours. It is affected by several factors[2] like the patient's age and gender, with younger patients and females being at higher risk[3]. Other risk factors include the patient's history of motion sickness, previous episodes of nausea and vomiting, the dosage of the emetogenic agent and the emetogenic potential of the chemotherapy being given. Chronic alcoholism decreases the incidence of emesis.

Delayed-onset emesis develops in patients more than 24 hours after chemotherapy administration; it occurs commonly with agents like cisplatin, carboplatin, cyclophosphamide and doxorubicin. Anticipatory N&V is the occurrence of mainly

nausea and/or vomiting before patients receive their next chemotherapy treatment (after a first cycle of chemotherapy that produced N&V). Finally, refractory emesis occurs during subsequent treatment cycles despite antiemetic prophylaxis and/or rescue.

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter that has been shown to mediate the acute N&V post chemotherapy[4], but its role in delayed emesis is still controversial[4,5] since the latter seems to respond poorly to 5-HT type III receptor blockers antagonists (5-HT_3⊥). However, since patients who were adequately managed and did not vomit in the first 24 hours post-chemotherapy were subject to fewer occurrences of delayed N&V (if any), proper prophylactic treatment of acute emesis might be the best option for the prevention of the – harder to manage – delayed N&V[1]. Therefore, the aim of antiemetic therapy is the total prevention of N&V in each chemotherapy patient[1,6]. For this purpose many agents and drug classes are available, including dopamine antagonists, antihistamines or 5-HT_3 blockers.

CHAPTER 2

BACKGROUND

There are several published guidelines on the appropriate use of antiemetic therapy in the prevention of N&V. In 2002 a consensus guideline[7] was generated by the pooled efforts of the American Society of Health-System Pharmacists (ASHP) guidelines[8], the American Society of Clinical Oncology (ASCO) guidelines[1,6], the Multinational Association for Supportive Care in Cancer (MASCC) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines. The consensus emphasized both prophylaxis and treatment options[6] (Table 2.1):

For chemotherapy with mildly emetogenic potential, clinical practice supports the use of phenothiazines, benzodiazepines, cannabinoids or low-dose metoclopramide on an "as needed" or scheduled basis[9]. As for the more emetogenic regimens, the use of a 5-HT_3⊥, with or without a corticosteroid, has shown much better results (with the best control of N&V being observed with the combination of the 5-HT_3⊥ and the dexamethasone[10]). Four major statements[7] were re-iterated in the consensus guidelines. The first one was that different 5-HT_3⊥ have similar therapeutic effects - same efficacy and side effects - at equivalent doses, both intravenously (IV) and orally (p.o.) (Table 2.2).

The other statements emphasized the use of the lowest effective dose and that no dosing schedule had been proven more effective than the once-daily regimen. Finally, the oral formulation proved to be equivalent in both efficacy and toxicity to the IV formulations.

The affinity for the 5-HT_3 receptors varies between different antagonists and might explain the differences in the doses given above [9,11] (Table 2.3).

These values might explain why low doses of 5-HT_3⊥ are sometimes enough to prevent N&V whereas metoclopramide needs to be given in higher doses to compete for the receptors effectively. Another reason for this might be the fact that tropisetron and granisetron exhibit non-competitive binding to the vagal 5-HT_3 receptor site[9,12,13], which might explain their long duration of action in humans. This also means that the same dose of antiemetic is required to block the same receptors regardless of the dose or emetogenicity of the chemotherapy regimen being given, which is not the case with ondansetron[9,13]. For ondansetron, higher doses or emetogenicity of chemotherapy need higher doses of antiemetic or more frequent administration[9]. It seems also that due to their prolonged duration of action, which is longer than their half-life would suggest, giving an extra dose of these agents within the same 24 hours would not lead to any added benefit for the patient[9]. Instead, the use of another antiemetic agent should be considered.

Published data support the use of oral ondansetron for acute emesis prophylaxis in patients taking moderate to highly emetogenic chemotherapy[14,15]. Oral route is preferred

whenever tolerated by the patient, since advantages of the oral route include ease of administration, convenience for the patient and lower cost[9]. Data also favor the use of oral granisetron or dolasetron and – even if not as studied as the other agents – of oral tropisetron as well[9].

In August 1995, the 5-HT_3 antagonist of choice in the antiemetic guidelines was revised from intravenous ondansetron to oral granisetron[16], however since all guidelines agree that if used at the appropriate dose all 5-HT_3 antagonist are therapeutically equivalent, the choice of which agent to use in the formulary is usually based on cost issues. In Makassed General Hospital (MGH), the agent used is tropisetron. Based on the amounts being consumed, it was suggested that there might be a misuse of this agent by some of the physicians or services at the hospital, thus the need for further investigations.

CHAPTER 3

OBJECTIVE

A drug utilization review (DUR) was conducted to evaluate the use of tropisetron (Navoban®) at MGH, and in case of actual inappropriate use, to intervene so as to provide cost savings for the hospital and the patients.

CHAPTER 4

METHOD

A retrospective study based on reviewing medical records was conducted using a computerized database. The study involved reviewing 300 randomly selected medical records, in which tropisetron was given between January 2003 and June 2003. The 300 medical records do not correspond necessarily to 300 patients be it that, according to the MGH patient entry system, the same patient will have a different case number every time he or she is admitted to the hospital. Evaluation was based on direct compliance with available guidelines.

To evaluate the records, a data collection sheet containing all pertinent information was used (Figure 4.1). It included the patient's case number or ID for later follow-ups, the age, gender and cancer type for population studies and the physician and the service for statistical purposes. The sheet also had a table for the chemotherapy regimen and another one for the antiemetic regimen being used, so that management could be assessed. Finally patients were checked for any oral drug intake to evaluate their p.o. tolerability.

Patient profiles were analyzed to classify tropisetron use as justified or not. Doses of 5-HT_3 blockers were considered justified if patients were on moderate to highly emetogenic chemotherapy regimens (Hesketh level ≥ 3). The use of tropisetron in patients receiving

chemotherapy with an emetogenic level of 1 or 2 was therefore considered as "non-justified".

Patients included were those who had received tropisetron for the prevention of CINV and who appeared in the hospital's database in the first 6 months of the year 2003. All patients were accepted regardless of age or unit of admission: one-day unit versus in-patients. Patients excluded were those who were sponsored by the ministry of health because these patients do not pay for their medication and consequently do not enter the database and cannot be tracked.

CHAPTER 5

RESULTS

Of the patients receiving tropisetron, 61.3% were women and patient age ranged from 1 to 86 years (Table 5.1).

Of the 300 cases that were selected, 151 (50.3%) belonged to the one-day chemotherapy service, while the rest (149, 49.7%) belonged to the other different in-services. Of the one day service records, 35 (23.2%) had non-justified use of tropisetron whereas only 5 (3.3%) of the in-patient were not justified. Therefore, the total number of unjustified doses was 40 out of the 300 cases (13.3%) ($p<0.0001$)

The Chi-square test was used for the association between physician and outcome and Fisher's Exact test was used to see if service was independent of outcome. The SAS version 8.2 (Cary, NC) was used to analyze the data. A p-value less than 0.05 was considered statistically significant. Figure 5.1 summarizes the results of this descriptive study.

Considering that one Navoban® injection (5 mg) costs 69,800 L.L. and 1 tablet costs 58,340 L.L., switching from IV use to oral use (as supported by the guidelines) would cut on costs. Specifically for MGH, 453 IV doses of prophylactic tropisetron were used, with a cumulative cost of 31,619,400 L.L. or $21,080.00. Knowing that the same number of

doses – if given orally – would have cost 26,428,020L.L or $17,619.00, the possible savings just by switching to the oral form of tropisetron would add up to 5,191,380 L.L or $3,461.00 per 300 admissions within 6 months. As for the non-justified doses of tropisetron, the 40 doses would add up to a total of 2,792,000 L.L. in savings, which corresponds to almost 9% of the total tropisetron cost for the 300 selected records.

Further scrutiny of the results showed that the chemotherapy agents mostly associated with unjustified use of tropisetron were vinca alkaloids or gemcitabine (Table 5.2), which are Level 1 and Level 2 agents respectively.

CHAPTER 6

DISCUSSION

Several neurotransmitters are involved in the pathogenesis of N&V, which is usually initiated by dopamine, opiates, histamine, acetylcholine, neurokinin1 or serotonin[8]. The main mechanisms involved in the CINV are: the chemoreceptor trigger zone (CTZ), which is located in the area postrema outside the blood brain barrier and the visceral afferents in the gastrointestinal (GI) tract[15,17] (Figure 6.1). The hindbrain CTZ was long believed to be the primary trigger site for emesis. Newer studies now seem to agree that the primary site is in fact located in the abdomen instead, with the emetic response being actually mediated by vagal transmission between the abdomen and the brain[9,18]. Circulating emetogenic substances and toxins from the blood or the cerebrospinal fluid can reach the CTZ directly thus initiating the release of various neurotransmitters that will reach the vomiting center in the brain causing emesis. Some of these toxins will also act directly on the GI lining causing irritation and release of serotonin from the enterochromaffin cells. Serotonin will then bind to the vagal afferents in the GI therefore again, stimulating the vomiting center and leading to N&V.

This theory might explain why oral serotonin receptor blockers are effective in preventing N&V in patients receiving highly emetogenic chemotherapy regimens. This theory also supports the use of tropisetron in the prevention of acute emesis since this agent was found to block the pre-synaptic 5-HT_3 receptors of the peripheral nerves in

addition to a more direct action on the CNS receptors that mediate the actions of the vagal inputs of the area postrema[15,19,20].

The following 6 different 5-HT_3⊥ are available on the market: azasetron [Serzone® (Welfide)], dolasetron [Anzemet® (Aventis)], granisetron [Kytril® (Roche)], ondansetron [Zofran® (GlaxoSmith-Kline)], tropisetron [Navoban® (Novartis)] and the newly approved palonosetron [Aloxi® (MGI pharma)] [7,21,22], which was incorporated in the NCCN guidelines on March 11, 2004.

These agents are approved for the prevention of acute N&V following moderately high or highly emetogenic chemotherapy; palonosetron is the only 5-HT_3 blocker to be approved for the prevention of delayed CINV due to its long half-life (40 hours) and high receptor binding affinity[22,23]. Since the use of these agents is not justified in patients receiving mildly emetogenic chemotherapy, it is important to classify patients' chemotherapy regimen as mild, moderate or highly emetogenic, before administering prophylactic antiemetic therapy. For single agent chemotherapy, the emetogenic potential of the drug can be known by checking its Hesketh level (Table 6.1). Level 1 (<10% N&V) and Level 2 (10-30%) agents are considered to be mildly emetogenic whereas Level 3 agents might cause N&V in 30-60% of the cases and are therefore moderately emetogenic. Finally Levels 4 and 5 are highly emetogenic and cause N&V more often than not. For combination therapy regimens, the most emetogenic agent should be identified, then the effect of the other drugs can be calculated based on the following guidelines[24]: Level 1 agents do not add to the overall emetogenic potential of the regimen. One or more Level

2 agents will increase the level of the regimen by one level above the most emetogenic agent in the regimen. Each Level 3 or 4 agents will increase the level of the regimen by one level above the most emetogenic agent in the regimen. The highest level is always 5.

Once the emetogenic level of the chemotherapy regimen is known, the use of a 5-HT_3 blocker can be classified as "justified" if the level is ≥3.

Azasetron and tropisetron are not available in the U.S. and therefore are not as studied as the other agents, however, as mentioned earlier, these agents have similar therapeutic effects and will differ only by their pharmacokinetics and pharmacodynamics.

For example, unlike granisetron, which is metabolized by the CYP3A4 subfamily[1,25], the metabolism of tropisetron is linked to cytochrome P-450 2D6 so its efficacy and tolerability may vary between poor metabolizers and extensive ones[25,26,27]. From a toxicological and pharmacokinetics point of view, it appears that the 5 mg daily dose of tropisetron can be safely administered to both poor and extensive CYP-2D6 metabolizers with poor metabolizers being at more risk of experiencing headaches than the other subgroups[26]. However, based on the study by Kaiser *et al*[25], ultra-rapid metabolizers are at higher risk of experiencing vomiting 4 hours after chemotherapy ($p<0.001$) or even within 5-24 hours after chemotherapy ($p<0.03$) when pre-treated with tropisetron. Rapid metabolizers of CYP-2D6 might therefore be inadequately protected if given tropisetron or to a lesser extent ondansetron (since it is metabolized by CYP3A4, CYP2D6, and CYP 1A2) and should be pre-treated with different doses of tropisetron or, better yet, with granisetron instead.[1,25]. In Lebanon, 10% of the people are poor metabolizers.

In a randomized crossover trial[27] comparing tropisetron (tropi) plus dexamethasone (dexa) to metoclopramide (MCP) plus dexamethasone, the tropi/dexa regimen was found to be better than the conventional MCP/dexa combination in the control of acute emesis in patients receiving cisplatin therapy. Other trials were conducted to compare different 5-HT_3⊥ doses or agents, such as a study that evaluated the efficacy of a single IV ondansetron dose (8 mg with dexamethasone) in the prevention of chemotherapy-induced N&V and showed the drug to be effective in both moderate and highly emetogenic chemotherapy[28]. Another study comparing single dose oral granisetron (1 mg with dexamethasone) to single dose oral ondansetron (16 mg with dexamethasone as well) found both regimens to be safe and effective in preventing N&V due to emetogenic chemotherapy[29]. Finally, a study conducted on children[30] (younger than 15 years old) found tropisetron to be effective and safe to use in the pediatric population.

A randomized, multi-center, double-blind study was conducted by The French Navoban Study Group to "evaluate and compare the antiemetic effectiveness and tolerability of Navoban® (tropisetron) and Zofran® (ondansetron) following high-dose cisplatin chemotherapy"[31]. 231 patients were recruited for this study and 117 received tropisetron whereas 114 took ondansetron. Tropisetron was effective in preventing acute N&V with total control of nausea in 66% of the cases and of vomiting in 54% of the cases. Ondansetron was also effective with 62% and 65% total control of N&V respectively ($p=0.052$). Results from this study showed no significant differences between tropisetron 5 mg once daily and ondansetron 32 mg on day 1 followed by 8 mg trice daily, proving

that tropisetron is at least as effective and safe as the FDA approved agent ondansetron with a more convenient dosing schedule.

Another randomized double-blind trial[32] was conducted to compare efficacy, safety and cost of 24 mg ondansetron, 3 mg granisetron and 5 mg tropisetron in patients receiving moderately and highly emetogenic chemotherapy. The 120 patients included received each three identical emetogenic chemotherapy cycles but with a different 5-HT_3 antagonist during each cycle. The three "setrons" were assigned in a random order and were all given intravenously along with dexamethasone 20 mg. The results were as follows: regarding efficacy, all 3 agents were almost as effective in complete emesis control and total acute and delayed N&V prevention ($p>0.05$). The major side effect was headache with a non-significant difference between the three agents, however patients preferred ondansetron to the other two 5-$HT_3\perp$ ($p<0.01$). Cost analysis revealed that tropisetron therapy costs 20-29 Euros per patient, versus 31-47 Euros and 23-63 Euros for granisetron and ondansetron respectively. So as a conclusion it was shown that tropisetron is as safe and effective as the other used agents while being a less expensive option.

Oral versus IV formulations of granisetron were studied in ferrets receiving 10 mg/kg of cisplatin[9,33]. In these animal studies, low dose granisetron proved to be even more potent than the IV route since at low doses (0.05 mg/Kg) "oral granisetron was associated with significantly fewer episodes of wretching"[9]. Unfortunately, there is insufficient published material to allow a direct comparison of potency between p.o. and IV tropisetron.

However, since studies and guidelines mention that the efficacy and safety of oral 5-HT_3 blockers is equal to that of the IV formulation at equivalent doses, and if the patients are healthy enough to tolerate p.o. intake before getting the chemotherapy, then the use of the oral formulation is advised based on lower cost, more convenience for the patient and ease of administration for the nurses.

During the data collection period in MGH, it appeared that all the prophylactic use of tropisetron was given by the IV route, leading to more expenses than actually needed. Also, the results from this cost and utilization evaluation, showed that most of the non-justified use of tropisetron in MGH was in the one-day service. The overuse might be due to the fact that these patients do not stay in the hospital long enough for appropriate evaluation and follow up. It might also be due to the inappropriate administration of the antiemetic. Based on a meeting with the oncologist, it appeared that N&V prophylaxis is sometimes given along with the chemotherapy or a few seconds earlier to minimize time loss and waiting periods. This suggests a more urgent need for intervention in this specific service unit as opposed to the in-patient's. Since the physicians who are responsible for the one-day unit are the same ones who take care of the in-patients, targeting this specific unit with the interventions should also take care of the in-service overuse.

Therefore suggested interventions to take care of the non-justified use of tropisetron should include on-site presentations of the guidelines and the studies regarding the appropriate use of 5-HT_3 blockers in chemotherapy induced N&V with stress on the

effectiveness of the oral formulation. A trial period of 1 month could be envisaged to test whether oral antiemetic prophylaxis is feasible in the one-day unit. Targeted intervention can also include letters to the oncologists from the ethical committee showing the extent of overuse with a brief note about the few chemotherapeutic agents that are leading to most of this overuse. Pre-printed protocols, covering the mostly used chemotherapeutic agents with their appropriate antiemetic prophylaxis, can be offered to the nurses. Finally a guideline poster can be prepared for the one-day service, including figures on how to calculate the Hesketh level and tables on the appropriate management of CINV.

CHAPTER 7

LIMITATIONS

This descriptive study had a few limitations. The study population was not representative of the whole population in the hospital since most patients in MGH belong to the middle to low income generating social classes, their expenses are covered by the ministry of health and their records were therefore not included in the study. Since these patients - and some others too – bring their own tropisetron to MGH, this drug does not appear on the database and therefore could not have been tracked or included in this study, which suggests that there might be a greater overuse than observed. Another limitation was the non-availability of some of the one-day records due to patient deaths and file transferals to the archives at a different location outside the hospital. Finally, one last limitation was due to the lack of appropriate history taking in the records, which lead to the impossibility of analyzing the presence – or absence – of N&V risk factors in the study population.

CHAPTER 8

CONCLUSIONS

There was a significant overuse of tropisetron at MGH, and most cost savings could be generated by switching to oral formulation. Targeted intervention should be able improve future management of CINV since the causes are known (mostly physician induced and with a specific group of chemotherapeutic agents). A possible solution would be staff education and pharmacists, nurses and physicians' cooperation. Another option for the future would be to actually try using tropisetron p.o. in a selected population and studying its efficacy with different chemotherapy regimens and the cost reductions that it might engender.

TABLES

Table 2.1: Management of chemotherapy induced N&V

Emetogenicity	**Day 1**	**Days 2+**
Minimal (<10%)	None	None
Low (10-30%)	Single agent (not 5-HT_3⊥)	None
Moderate (30-90%)	5-HT_3⊥ + dexa	Dexa +/or 5-HT_3⊥ or MCP
High (>90%)	5-HT_3⊥ + dexa	Dexa + 5-HT_3⊥ or MCP

Dexa = dexamethasone. MCP = metoclopramide. For acute management, 5-HT_3⊥ is oral or IV, but for delayed N&V prophylaxis it is given only orally

Table 2.2: IV and oral equivalent doses of different 5-HT_3 blockers

Drug	**IV dose**	**Oral dose**
Ondansetron	8 mg	16-24 mg
Granisetron	1 mg	1-2 mg
Dolasetron	100 mg	100-200 mg
Tropisetron	5 mg	5 mg

Table 2.3: Differences in affinity to 5-HT_3 receptors

Drug	**Affinity to receptor (5-HT_3)**
Ondansetron	184 × serotonin
Granisetron	>600 × serotonin
Tropisetron	400 × serotonin
Metoclopramide	≤ serotonin

Table 5.1: Study population

Total number of cases	300	
Age in years		
<6	9	(3%)
18-50	113	(37.7%)
>50	178	(59.3%)
Gender		
Male	116	(38.7%)
Female	184	(61.3%)
Service		
One-day unit	151	(50.3%)
In-patient	149	(49.7%)
Hesketh level		
1	10	(3.3%)
2	30	(10%)
3	49	(16.3%)
4	41	(13.7%)
5	170	(56.7%)

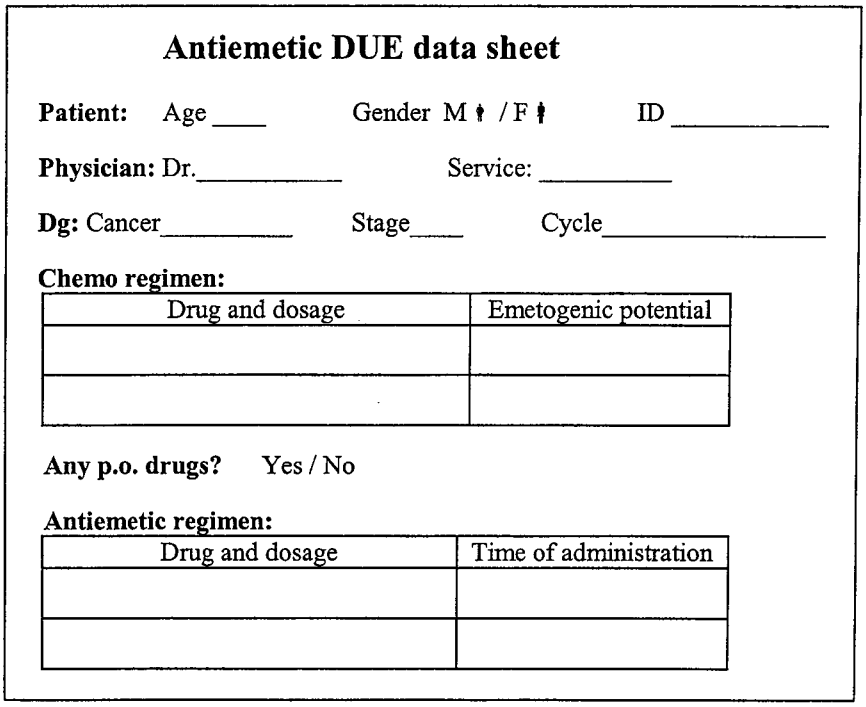
Table 5.2: Drugs used prior to non-justified tropisetron use

Chemotherapy regimen	Emetogenic potential	Number of entries
Gemcitabine	2	17
Gemcitabine/vinca	2	1
Taxanes	2	4
Topotecan	2	7
Trastuzumab	2	1
Vinca	1	9
Vinca/low dose FU (<1g/m^2)	2	1

Table 6.1: Emetogenicity of chemotherapeutic agents

Level 1	Level 2	Level 3	Level 4	Level 5
- Androgens - Bleomycin - Busulfan po - Chlorambucil p.o. - Cladribine - Corticosteroids - Fludarabine - Hydroxyurea - Interferon - Levamisole - Melphalan p.o. - Mercaptopurine - Methotrexate ≤ 50 mg/m^2 - Rituximab - Thioguanine p.o. - Tretinoin - Vinca alkaloids	- Amsacrine - Capecitabine - Cytarabine < 1000 mg/m^2 - Docetaxel - Doxorubicin < 20 mg/m^2 - Etoposide - Flurouracil < 1000 mg/m^2 - Gemcitabine - Methotrexate 51-249 mg/m^2 - Mitomycin - Paclitaxel - Porfimer - Teniposide - Thiotepa - Topotecan - Trastuzumab	- Aldesleukin - Altretamine p.o. - Asparaginase - Cyclophosphamide IV ≤ 750 mg/m^2 - Cyclophosphamide p.o. - Dactinomycin ≤ 1.5 mg/m^2 - Doxorubicin 20-60 mg/m^2 - Epirubicin ≤ 90 mg/m^2 - Idarubicin - Iphosphamide - Lomustine p.o. - Methenamine p.o. - Methotrexate 250-999 mg/m^2 - Mitoxantrone ≤ 15 mg/m^2 - Raltitrexed - Temozolomide	- Carboplatin - Carmustine < 250 mg/m^2 - Cisplatin < 50 mg/m^2 - Cyclophosphamide 751 - 1500 mg/m^2 - Cytarabine ≥ 1000 mg/m^2 - Dactinomycin 1.5 mg/m^2 - Daunorubicin - Doxorubicin > 60 mg/m^2 - Irinotecan - Melphalan IV - Methotrxate ≥ 1000 mg/m^2 - Mitoxantrone >15 mg/m^2 - Procarbazine p.o.	- Carmustine > 250 mg/m^2 - Cisplatin ≥ 50 mg/m^2 - Cyclophosphamide > 1500 mg/m^2 - Dacarbazine - Lomustine >60 mg/m^2 - Mechlorethamine - Methotrexate IT ≤ 50 mg/m^2 with Cytarabine - Nitrogen Mustard - Pentostatin - Streptozocin

FIGURES



Antiemetic DUE data sheet

Patient: Age ____ Gender M / F ID _____

Physician: Dr._____ Service: _____

Dg: Cancer_____ Stage____ Cycle_____

Chemo regimen:

Drug and dosage	Emetogenic potential

Any p.o. drugs? Yes / No

Antiemetic regimen:

Drug and dosage	Time of administration

Figure 4.1: Data collection sheet

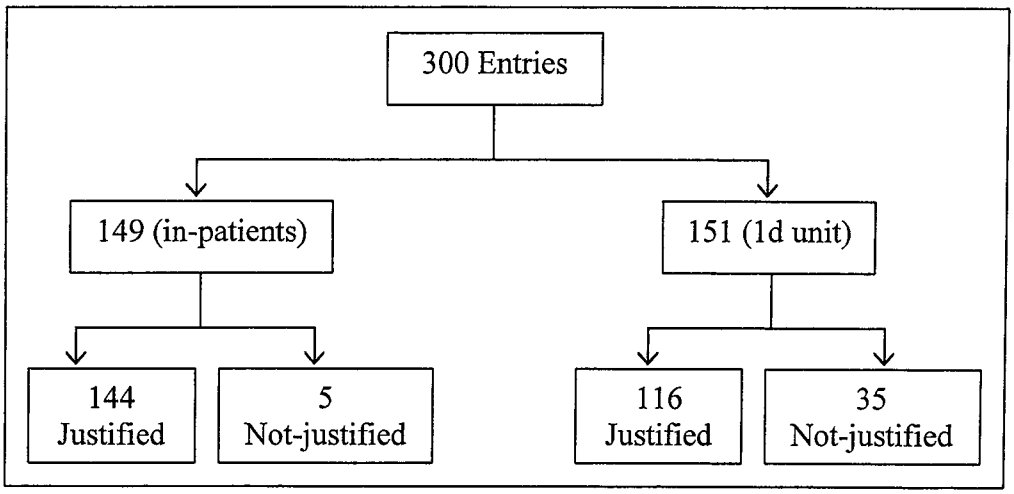


Figure 5.1: Results distribution

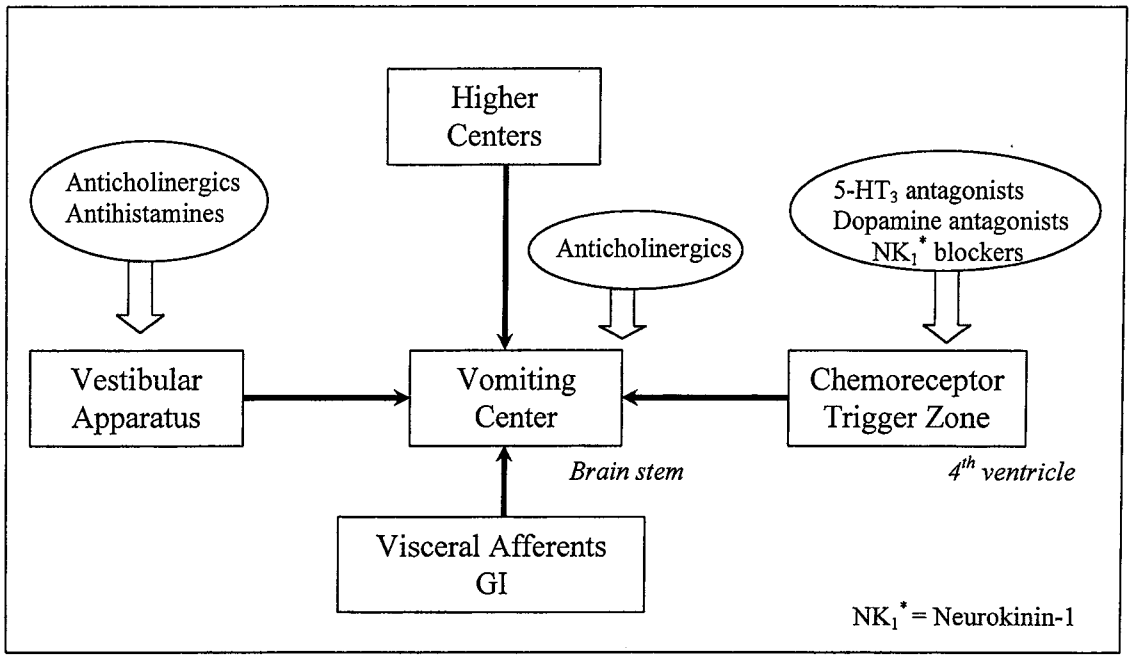


Figure 6.1: Mechanisms of N&V

REFERENCES

1. Schnell F. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. *The Oncologist. 2003*; 8: 187-198.

2. Grunberg S and Hesketh P. Control of chemotherapy-induced emesis. *N Engl J Med. 1993*; 329: 1790-1796.

3. Sorbe B. Tropisetron in the prevention of chemotherapy-induced nausea and vomiting: The Nordic experience. *Ann Oncol. 1993*; 4 (S3): S39-S42.

4. Hesketh P, Van Belle S, Aapro M *et al.* Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *European Journal of Cancer. 2003*; 39: 1074-1080.

5. Cubeddu L. Serotonin mechanisms in chemotherapy-induced emesis in cancer patients. *Oncology. 1996*; 53 (S1): 18-25.

6. Gralla R, Osoba D, Kris M *et al.* Recommendations for the use of antiemetics: evidence-based. clinical practice guidelines. *American Society of Clinical Oncology. J Clin Oncol. 1999*; 17: 2971-2994.

7. Koeller J, Aapro M, Gralla R *et al.*. Antiemetic guidelines: creating a more practical treatment approach. *Support Care Cancer. 2002*; 10: 519-522.

8. American Society of Health System Pharmacists (ASHP). ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *Am J Health Syst Pharm. 1999*; 56: 729-64.

9. Lindley C and Blower P. Oral serotonin type 3-receptor antagonists for the prevention of chemotherapy-induced emesis. *Am J Health-Syst Pharm. 2000*; 57: 1687-1697.

10. Bruntsch U, Drechsler S, Eggert J *et al.* Prevention of chemotherapy-induced nausea and vomiting by tropisetron (navoban) alone or in combination with other antiemetic agents. *Semin Oncol. 1994*; 21 (S9): 7-11.

11. Nelson D and Thomas D. [3H]-BRL 43694 (granisetron) a specific ligand for 5-HT_3 binding sites in rat brain cortical membranes. *Biochem Pharmacol. 1989*; 34: 1693-5.

12. Eliott P, Seemungal B and Wallis D. Antagonism of the effect of 5-hydroxytryptmine on the rabbit isolated vagus nerve by BRL 43694 and metoclopramide. *Naunyn Schmiedebergs Arch Pharmacol. 1990*; 341: 503-9.

13. Sweetland J, Lettis S, Fowler P *et al.* Duration of the inhibitory effect of intravenous ondansetron on intradermal 5-HT-induced flare. *Br J Clin Pharmacol. 1991*: 565P. Abstract.

14. Miguel R. Controlling chemotherapy-induced and postoperative nausea and vomiting. *Cancer Control. 1999*; 6(4): 393-397.

15. Warr D, Bramwell V, Anderson D *et al.* Use of 5-HT_3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. *Curr Oncol. 2001*; 8: 69-82.

16. McCune J, Oertel M, Pfeifer D *et al.* Evaluation of outcomes in converting from intravenous ondansetron to oral granisetron: an observational study. *Ann Pharmacother. 2001*; 35(1): 14-20.

17. McGregor E. Anti-emetics. *Curr Med Res Opin. 2001*; 17 (S1): S22-S25.

18. Andrews P, Davis C, Birgham S *et al.* The abdominal visceral innervation and the emetic reflex: pathways. pharmacology. and plasticity. *Can J Physiol Pharmacol. 1990*; 68: 325-45.

19. Kutz K. Pharmacology. toxicology and human pharmacokinetics of tropisetron. *Ann Oncol (Netherlands). 1993*; 4 (S3): S15-S18.

20. Parsad S. Revision of the antiemetic guidelines for chemotherapy-induced nausea & vomiting in adult patients. *UCH Formulary. 1998*; 40(4)
URL: http://daccx.bsd.uchicago.edu/drug/Bulletins/N0498.html. 02 Jun 2004

21. Gralla R, Lichinitser M, Van Der Vegt S *et al.* Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol. 2003*; 14(10): 1570-7.

22. Grunberg S and Koeller J. Palonosetron: a unique 5-HT_3-receptor antagonist for the prevention of chemotherapy-induced emesis. *Expert Opin Pharmacother. 2003*; 4(12): 2297-303.

23. Eisenberg P, Figueroa-Vadillo J, Zamora R *et al.* Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron. a pharmacologically novel 5-HT_3 antagonist: results of a phase III. single-dose trial versus dolasteron. *Cancer. 2003*; 98: 2473-82.

24. Hesketh P. Defining the emetogenicity of cancer chemotherapy. *J Clin Oncol. 1997*; 15: 103-109.

25. Kaiser R, Sezer O, Papies A *et al.* Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J Clin Oncol. 2002*; 20: 2805-2811.

26. Kutz K. Pharmacology. toxicology and human pharmacokinetics of tropisetron. *Ann Oncol. 1993*; 4 (S3): S15-S18.

27. Chua D, Sham J, Au G *et al.* The antiemetic effect of tropisetron plus dexamethasone as compared with conventional metoclopramide-dexamethasone combination in Orientals receiving cisplatin chemotherapy: a randomized crossover trial. *Br J Clin Pharmacol. 1996*; 41: 403-408.

28. Bernstein B and Ong C. Efficacy of a single 8-mg IV dose of ondansetron hydrochloride for preventing chemotherapy-induced emesis. *Am J Health-Syst Pharm. 2002*; 59(7): 650-652.

29. Herrington J, Kwan P, Young R *et al.* Randomized. multicenter comparison of oral granisetron and oral ondansetron for emetogenic chemotherapy. *Pharmacotherapy. 2000*; 20(11): 1318-1323.

30. Özkan A, Yildiz I, Yüksel L *et al.* Tropisetron (Navoban®) in the control of nausea and vomiting induced by combined cancer chemotherapy in children. *Japanese Journal of Clinical Oncology. 1999*; 29(2): 92-95.

31. Marty M., Kleisbauer J, Fournel P *et al.* Is navoban (tropisetron) as effective as zofran (ondansetron) in cisplatin-induced emesis? *Anticancer Drugs. 1995*; 6 (S1): 15-21.

32. Barrajon E and De La Perias R. Randomized double blind crossover study comparing ondansetron. granisetron and tropisetron. A cost benefit analysis. *Supportive Care Cancer. 2000*; 8(4): 323-333.

33. Marr H, Davey P, Boyle E *et al.* Further studies of the antiemetic activity of granisetron against whole body x-irradiation or cisplatin-induced emesis in the ferret. *Pharmacology. 1994*; 48: 283-92.