Cost-effectiveness analysis of tropisetron vs. chlorpromazine-dexamethasone in the control of acute emesis induced by highly emetogenic chemotherapy in children

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ABSTRACT

Objective. To perform a cost-effectiveness analysis (CEA) between a standard antiemetic regimen -chlorpromazine + dexamethasone (CPM-DEX)- and a 5-HT_3 receptor antagonist -tropisetron (TROP)- in the control of acute emesis induced by highly emetogenic chemotherapy in children, considering two analytic perspectives: hospital and patients.

Methods. The CEA was performed by constructing a decision tree, for both analytic perspectives, of the possible outcomes of treatment with TROP (single 0.2 mg/kg i.v.) or CPM (5-15 mg i.v. infusion for 3 doses) plus DEX (2 mg/m^2 i.v. bolus i.v. x 2). The patients were stratified by age in two groups (2-12 and 13-17). To estimate the probability of each endpoint at the decision tree we have taken as a base a trial developed in the Department of Pediatrics. Direct medical cost of primary therapy, failure, complications and side effects were included in the cost calculations.

Results. From patients' analytic perspective, TROP was more cost-effective than CPM-DEX for both groups of patients. Discrepancy between both analytic perspectives in 13-17 year-old patient's group was resolved in favour of the option chosen from the patients' analytic perspective (TROP). Sensitivity analysis showed the reliability of the results.

Conclusions. 1. TROP was more cost-effective than CPMDEX. 2. Taking into account the patients' analytic perspective is essential when we compare antiemetics pharmacoeconomically. 3. It seems necessary to increase the effectiveness of TROP in pediatric patients receiving highly emetogenic chemotherapy

KEYWORDS

Acute emesis; Antiemetics; Cancer chemotherapy; Chlorpromazine; Cost-effectiveness analysis; Dexamethasone; Pediatric; Tropisetron.

INTRODUCTION

Of the standard antiemetic regimens (ARs), chlorpromazine (alone or in combination) has been the most widely used in infantile oncology because of its favourable safety/efficacy relationship [1]. The growing complexity of chemotherapy treatments and the appearance of new antiemetics (5-HT_3 receptor antagonists) has resulted in a gradual increase in the number and quality of clinical trials of antiemetics in children [2-9]. Parallel to this, the need to develop pharmacoeconomic evaluations as a complement to these safety and efficacy studies has been seen.

The aim of this study is to carry out a cost-effectiveness analysis (CEA) between a standard antiemetic regimen (AR)-chlorpromazine + dexamethasone (CPM-DEX)- and a 5-HT_3 receptor antagonist -tropisetron (TROP)- in the control of acute emesis induced by highly emetogenic chemotherapy in pediatric patients with cancer, considering two analytic perspectives: hospital and patients.

A pharmacoeconomic comparison was made between one alternative of proven effective [10-11] and low cost -CPM-DEX- and an option which is apparently more efficient clinically [5 6 9] but with higher costs -TROP-. The inclusion of a nil alternative in the study was not considered because of the high incidence of acute chemotherapy-induced emesis in pediatric patients who do not receive antiemetic prophylaxis prior to the administration of highly emetogenic chemotherapy [12].

METHODS

The CEA was performed by constructing a decision tree for both analytic perspectives (Figures 1 and 2) of the possible outcomes of treatment with TROP (single 0.2 mg/kg; 30 minutes; i.v. infusion prior to chemotherapy) or CPM (5-15 mg; 120 minutes; i.v. infusion prior to chemotherapy and 2 doses repeated every 6 hours) plus DEX (2 mg/m^2; bolus i.v. prior to chemotherapy and repeated 12 hours later).

The therapeutic options were evaluated in terms of effectiveness. The results of effectiveness were evaluated in natural units related to the final health outcome. Therefore the parameter/unit of effectiveness (common health outcome) was established taking into account the antiemetic response and the tolerability of both ARs.

From the hospital's analytic perspective the parameter/unit of effectiveness was established as follows: "day of chemotherapy with total control of acute emesis without probable or definitive collateral adverse effects produced by AR or with probable or definitive adverse effects induced by AR but not requiring treatment".

From the patients' analytic perspective the parameter/unit of effectiveness was established as follows: "chemotherapy cycle in which the evaluation of antiemetic response and AR tolerability on the part of the patient, or his or her caregiver, is satisfactory". These are therefore positive end-points of the decision trees: T2, T3, CD2 and CD3 from the hospital's analytic perspective and Ta, Tb, CDa and CDb from a patients' analytic perspective.

PROBABILITY CALCULATIONS

To estimate the probability of each end-point at the decision trees we have introduced the appropriate changes in a randomized, double blind, serially crossed, prospective efficacy and safety study of TROP vs. CPM-DEX to adapt it to the associated economic evaluation and to the real clinical situation. The study was carried out by the Department of Pediatric Oncology of the University Hospital of Navarra (UHN) in collaboration with the Pharmacy Service of the aforementioned hospital.

Data of the antiemetic response and the tolerability of both AR in 30 patients (16 male and 14 female) aged between 2 and 17 years (mean age 11.5 years) was collected in the period between April 1995 and April 1996. Prior to the study the informed consent of all patients (or their legal representative) was obtained as was the approval of the ethics committee of the hospital.

All the patients had been diagnosed as having a solid malignant tumour. The patients received highly emetogenic chemotherapy:

- Combinations of iphosphamide $\geq$ 1 g/m^2 with another highly emetogenic cytotoxic (cisplatin $\geq$ 30 mg/m^2 or dactinomycin $\geq$ 0,3 mg/m^2 or carboplatin $\geq$ 150 mg/m2) ± a moderately or slightly emetogenic cytotoxic.
- Combination of 1 highly emetogenic cytotoxic (iphosphamide $\geq$ 1 g/m2, methotrexate $\geq$ 1 g/m2, dacarbazine $\geq$ 100 mg/m2, cisplatin $\geq$ 30 mg/m2, doxorubicin $\geq$ 45 mg/m2, dactinomycin $\geq$ 0,3 mg/m2, carboplatin $\geq$ 150 mg/m2, cyclophosphamide > 1 g/m2) ± a moderately or slightly emetogenic cytotoxic.

From the hospital's analytic perspective, data were collected over 221 days of highly emetogenic chemotherapy, corresponding to a total of 87 cycles. For 110 of these days the patients received CPM-DEX as AR and TROP for the other 111 days. The number of emetic episodes experienced in the 24 hour period following the start of the administration of chemotherapy, as well as the verbal evaluation of nausea in this same interval of time were recorded by the patient or caregiver. The definitive or probably attributable adverse effects of the ARs and/or the complications due to poor emetic control were recorded by the researcher. Information regarding adverse effects treatment and a possible increased hospitalisation time of the patient (as a consequence of adverse effects or as a consequence of the poor emetic control) was taken from a review of the clinical history. From the patients' analytic perspective data was collected from a total of 87 chemotherapy cycles. The patients received CPM-DEX as AR in 43 of the cycles and TROP in the remaining 44. The antiemetic response and tolerability to the adverse effects and/or complications were evaluated by the patient or carer once the cycle had concluded.

COST ESTIMATES

Direct medical costs of primary therapy, failure, complications and side effects were included in the cost calculations of each end-point at the decision tree. Data of direct medical cost were collected from over 221 of highly emetogenic chemotherapy (Hospital's analytic perspective), corresponding to 87 cycles (patients'analytic perspective). However neither direct nonmedical costs or indirect costs were considered.

Intangible costs were not studied implicitly although they were studied explicitly when evaluating the antiemetic response and the tolerability of the ARs from the patients' analytic perspective. We have considered that the percentage payment made by the patient is in the 100% range (no capitation, no copayment, no coinsurance).

The quantification and the economic valuation of each identified resource are shown in Annex 1 from the hospital's analytic perspective and in Annex 2 from a patients' analytic perspective. The specific units of quantification of each identified potential cost and the sources of information about these units are shown in Table 1. The corresponding monetary value assigned to each identified potential cost was based on the following sources of information: Biochemical Laboratory, UHN Personnel Department, UHN Analytical Accounting, UHN Internal Administration and UHN Pharmacy Service.

SUBGROUPS OF ANALYSIS

The age of the patients defined the limits of the two subgroups on this CEA: patients 2-12 years of age (n=16) and patients 13-17 years of age (n=14).

UPDATING COSTS AND EFFECTS

It was not necessary to discount either the costs or effects with regard to the time at which the pharmacoeconomic evaluation was carried out, given that the temporal horizon was less than one year. Costs and effects were produced in the same time horizon.

ANALYSIS OF THE RELATION COSTS-EFFECTS

Cost-effectiveness ratio (CEr) for both ARs, incremental cost (IC), incremental effectiveness (IE) and incremental cost-effectiveness (ICE) were established from the two analytic perspectives in both age groups.

The values of IE (difference between the probability in percentage of obtaining as a result of treatment with TROP one unit of effectiveness and the probability of obtaining the same result with CPM-DEX) and their relationship with IC (cost of treating 100 days or 100 cycles of chemotherapy with TROP minus the cost of treating the same number of days or cycles of chemotherapy with CPM-DEX) have given rise to the following two situations:

1. The values for IE are lower than -4,9%. In this case CPM-DEX is more effective and cheaper than TROP and therefore considered the most cost-effective alternative.
2. IE is higher than + 4,9%. In this case TROP is more effective than CPM-DEX, but has higher costs. Thereby in order to determine the more cost-effective AR it is necessary to establish hospital's and patients' willingness to pay per extra effectiveness unit.

It was assumed that the hospital would be willing to pay 50% more than CPM-DEX cost-effectiveness ratio (CEr CD) per extra effectiveness unit; TROP would therefore be chosen as the most cost-effective option if:

$$ICE - CEr\ CD \leq \frac{CEr\ CD}{2}$$

Patients' willingness to pay per extra effectiveness unit was determined by a function based on a theoretical model. The function correlates the percentage increase -which incremental effectiveness supposes for the percentage CPM-DEX effectiveness (X)- with the higher percentage over CEr CD which the patients or relatives are willing to pay for such an increase in effectiveness (Y).

$$Y = f(X);\ \frac{(CEr\ T\ -\ CEr\ CD)}{CEr\ CD}\ X\ 100\ =\ f\left(\frac{IE\ x\ 100}{\%\ Effectiviness\ CD}\right)$$

$$Y = X + PIF$$

PIF being a proportional incremental factor which in the base case has the value:

$$PIF = \frac{X^2}{75}$$

The graph of the function of the theoretical model (figure 3) divides the first quadrant of the plane into two areas: A and B. From the patients' analytic perspective TROP is more cost-effective than the alternative CPM-DEX if the point:

$$(X, Y) = \left(\frac{IE\ x\ 100}{\%\ Effectiviness\ CD}\ ,\ \frac{(CEr\ T\ -\ CEr\ CD)}{CEr\ CD}\ X\ 100\right)$$

is found in area A of the graph in Figure 3.

6. SENSITIVITY ANALYSIS

From the Hospital's analytic perspective we studied the impact on the results of the pharmacoeconomic evaluation of variations in the following key variables: Tropisetron acquisition cost, Human Resources in AR CPM-DEX and Hospital willingness to pay per extra effectiveness unit (Table 2a).

From patients' analytic perspective we studied the impact on the results of the pharmacoeconomic evaluation of variations in the following key variables: Tropisetron acquisition cost, AR CPM-DEX acquisition and preparation costs and patients' willingness to pay per extra effectiveness unit (Table 2b).

RESULTS AND DISCUSSION

Table 3 shows TROP and CPM-DEX effectiveness, average cost and cost-effectiveness ratios from both analytic perspectives and for each subgroup of patients. The probability and the total cost associated with each of the end-points at the decision trees are available upon request from the authors.

Probability calculations

The difference in TROP effectiveness found between the two age groups (50% vs. 33.30% and 76% vs. 57.20%, hospital's and patients' analytic perspectives, respectively) could be explained by the more complicated control of emesis in adolescent patients than in younger children [13].

If anxiety is the cause whereby emetic episodes and nausea are perceived as more frequent and acute in adolescent patients [14], its reduction as a consequence of the somnolence induced by CPM could explain the higher percentage of effectiveness of CPM-DEX in patients > 12 years of age (44.3%, hospital's analytic perspective) with respect to patients ≤ 12 years of age (34.7%, hospital's analytic perspective).

The higher TROP effectiveness found in patients' analytic perspective with respect to their equivalents in the hospital's analytic perspective (76% vs. 50% and 57.20% vs. 33.30%, 2-12 and 13-17 year-old patients' respectively) could be explained by the different way in which hospital and patients evaluate TROP antiemetic response and tolerance. Therefore, for example, the total of the adverse effects of TROP which require treatment (not complying with the criteria of effectiveness from the hospital's analytic perspective) are valued as tolerable by patients, fulfilling in this way the criteria of effectiveness from the patients' analytic perspective.

The difference of effectiveness of CPM-DEX found between the two analytic perspectives could be explained in 2-12 year old patients by the different way in which hospitals and patients evaluate CPMDEX antiemetic response and tolerance, and in 13-17 year old patients by the intolerance which an important group of these patients shows towards somnolence and dizziness induced by chlorpromazine, intolerance which is not commonly found in very young children.

Cost estimates

The CPM-DEX/TROP average cost relation is 1:1.35 (patients' age 2-12) and 1:1.51 (patients' age 13-17) from the hospital's analytic pespective and 1:3.19 (patients' age 2-12) and 1:2.66 (patients' age 13-17) from the patients' analytic perspective. The difference in ratios found between the two analytic perspectives could be explained by the different degree of compensation of the higher acquisition cost of TROP (with regard to CPM-DEX). While from the patients' analytic perspective the only compensating feature of the higher cost of purchase of tropisetron in the total costs are the associated costs of the TROP preparation, from the hospital's analytic perspective this higher price is compensated for by the lower associated costs of the antiserotoninergic drug prescription, preparation, administration and surveillance.

Analysis of the relation costs-effects

The CEr T is lower than the CEr CD only in the sub-group of patients ≤ 12 years of age from the hospital's analytic perspective (CEr T = $66.19 and CEr CD = $70.72). In this case the ratio CEr CD: CEr T is 1:0.94, thus inverting the relationship CPM-DEX/TROP established for the average cost (1:1.35). This inversion is due to the higher percentage of effectiveness of TROP compared to CPM-DEX (50% vs. 34.70%) and to the lower percentage of failures (12.8% vs. 38.8%) that quantitatively are reducing the costs associated with therapeutic failure and clinical complications.

The simultaneous cost-effectiveness relationship between the two alternatives is shown in Table 4, where the most cost-effective AR for each case is highlighted. The most cost-effective alternative in the subgroup of patients ≤ 12 years of age who receive highly emetogenic chemotherapy is the TROP from both analytic perspectives.

The no coincidence of the most cost-effective alternative from both analytic perspectives in the subgroup of children > 12 years of age who receive highly emetogenic chemotherapy is resolved in favour of the option chosen from the patients' analytic perspective (TROP). The previous decision takes into account not only the cost of the drug but also its impact on the physical, social and emotional well-being of the patient (ECHO model [15]). In this subgroup of patients to select CPM-DEX as the most favourable pharmacoeconomic alternative is unacceptable in spite of the economic advantages from either analytic perspectives and the advantages of effectiveness from the hospital's analytic perspective, given that in 66.70% of the chemotherapy cycles in which it is administered the above mentioned AR is not evaluated as good by the patients. Other considerations which support this decision are:

- 25% of patients belonging to this subgroup of the study refuse to receive CPM-DEX in the following chemotherapy cycle.
- CPM-DEX has disadvantages which cannot be evaluated by patients given the design of the study from which the probabilities of each end-point are calculated. For example:
  - CPM is administered three times a day, in such a way that one or two of these may coincide with night-time schedules.
  - CPM tends to precipitate in alkaline solutions. When CPM is administered in high dosage cycles of methotrexate it is necessary, in addition to washing the via, to stop administering concomitant alkaline fluidotherapy for 6 hours with the added risk of eliminating the antimetabolite incorrectly.

Sensitivity analysis

Sensitivity analysis showed the reliability of the results:

- The CEA are not affected by modifications in the values of the key variables reviewed in table 2 in the subgroup of patients ≤ 12 years of age from the hospital's analytic perspective and in the subgroup of patients > 12 years of age from the patients' analytic perspective.
- In the subgroup of children ≤ 12 years from the patients' analytic perspective the cost-effective subanalysis is sensitive to modifications in the key variable "patients' willingness to pay per extra effectiveness unit". When the mentioned variable takes on its worst theoretical value, and on the condition that the price

of TROP does not undergo modifications with regard to its base value, CPM-DEX will be more cost-effective than TROP. This change does not affect the final result of the CEA given that when faced with the results of both analytic perspectives TROP will still be chosen as the most cost-effective.

- The CEA in the subgroup of patients > 12 years of age from the hospital's analytic perspective is only sensitive if the values of the three key variables (Table 2a) are modified at the same time. In this subgroup of patients from the hospital's analytic perspective TROP is more cost-effective than CPM-DEX only when the acquisition cost of TROP is reduced by 60% and the associated costs of CPM-DEX human resources take on their worst estimated value and the hospital is willing to pay 100% more than CEr CD per additional unit of effectiveness.

Although the pharmacoeconomic evaluation has been carried out in the environment of the Department of Pediatric Oncology of the University Hospital of Navarra, the results are applicable to Pediatric Oncology Departments of other Spanish hospitals. First of all because the data of effectiveness on which the study is based can be extended to the whole of the pediatric oncological population which receives highly emetogenic chemotherapy, and secondly, because the foreseeable interhospital differences in the values taken on by the key cost variables do not modify the final results of the present study as we have proved in the sensitivity analysis.

Finally, the need to increase the effectiveness of tropisetron with strategies such as the addition of a corticoid should be noted, given that in pediatric patients who receive highly emetogenic chemotherapy with an antiemetic regimen based only on TROP the percentage of effectiveness does not surpass the 50%.

CONCLUSIONS

- TROP was more cost-effective than CPM-DEX in the control of acute emesis induced by highly emetogenic chemotherapy in children.
- When antiemetics are evaluated pharmacoeconomically it is important to take into account the patients' analytic perspective in addition to the hospital's analytic perspective, as it is possible in this way to avoid giving more importance to the cost of the drug compared to the relevance of its impact on the physical, social and emotional well-being of the patient.
- It seems necessary to increase the effectiveness of TROP in pediatric patients receiving highly emetogenic chemotherapy with strategies such as the addition of a steroid.

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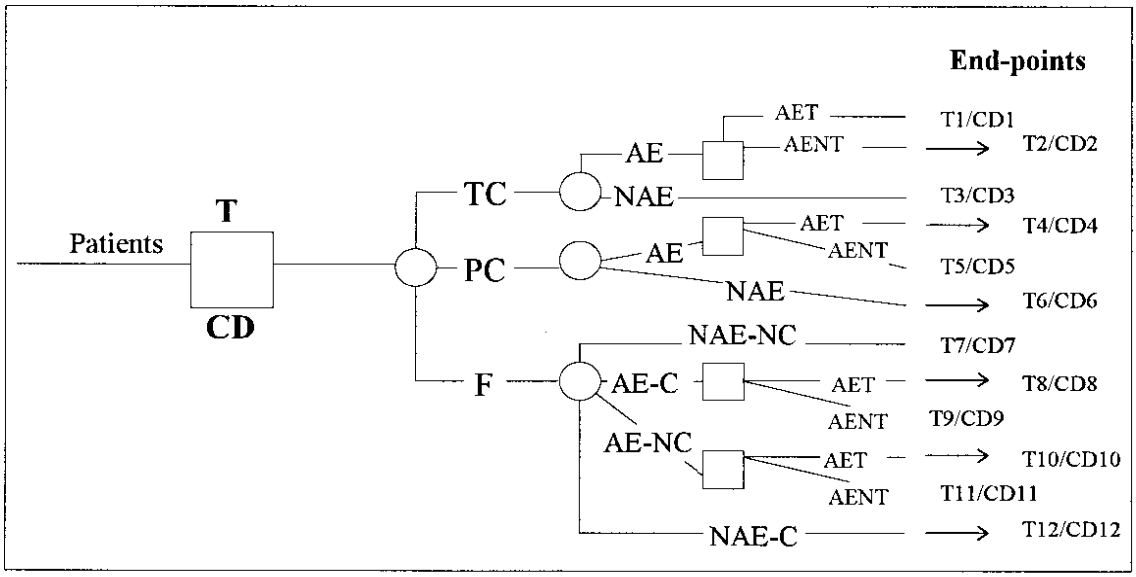


Initial choice: **T** = TROP; **CD** = CPM-DEX.

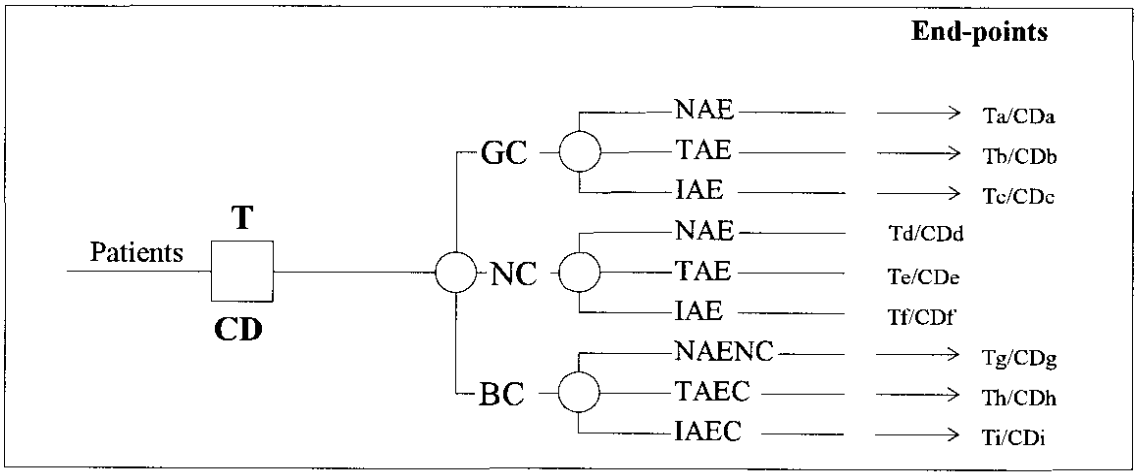
Control of daily acute emesis: **TC** = total control (no emetic episodes, no nausea); **PC** = partial control (no emetic episodes + medium-moderate nauseas or 1-5 emetic episodes + null-medium-moderate nauseas); **F** = failure (0-5 emetic episodes + extreme nauseas or more than 5 emetic episodes ± nauseas).

Emetic episode: 1 episode of vomiting or 1-5 retching in 5 minutes.
Medium nausea: does not interfere with the daily activities of the patient.
Moderate nausea: interferes with the daily activities of the patient.
Extreme nausea: obliges the patient to stay in bed.

Yatrogenia: **AE** = adverse effects definitely or probably attributable to ARs; **NAE** = no adverse effects definitely or probably attributable to ARs. *Adverse effects treatment:* **AET** = adverse effects treated; **AENT** = adverse effects not treated.

*Clinical complications in patients with **F**:* **C** = complications due to a lack of acute emesis control; **NC** = no complications due to a lack of acute emesis control. *Clinical complications treatment*: it is estimated that the total of clinical complications are treated.

Figure 1. Decision tree, hospital's analytic perspective



Initial choice: **T** = TROP; **CD** = CPM-DEX.

Evaluation by the patient or carer of:

1. The control of acute emesis during the chemotherpy cycle: **GC** = good control; **NC** = normal control; **BC** = bad control.

2. The adverse effects definitely or probably attributable to ARs in patients with GC or NC: **NAE** = no adverse effects (positive evaluation is implied); **TAE** = tolerable adverse effects; **IAE** = intolerable adverse effects.

3. The adverse effects definitely or probably attributable to ARs and the clinical complications due to a lack of acute emesis control in patients with BC: **NAENC** = no adverse effects and no complications (positive evaluation is implied); **TAEC** = tolerable adverse effects and/or tolerable complications; **IAEC** = intolerable adverse effects and/or intolerable complications.

Figure 2. Decision tree, patients' analytic perspective

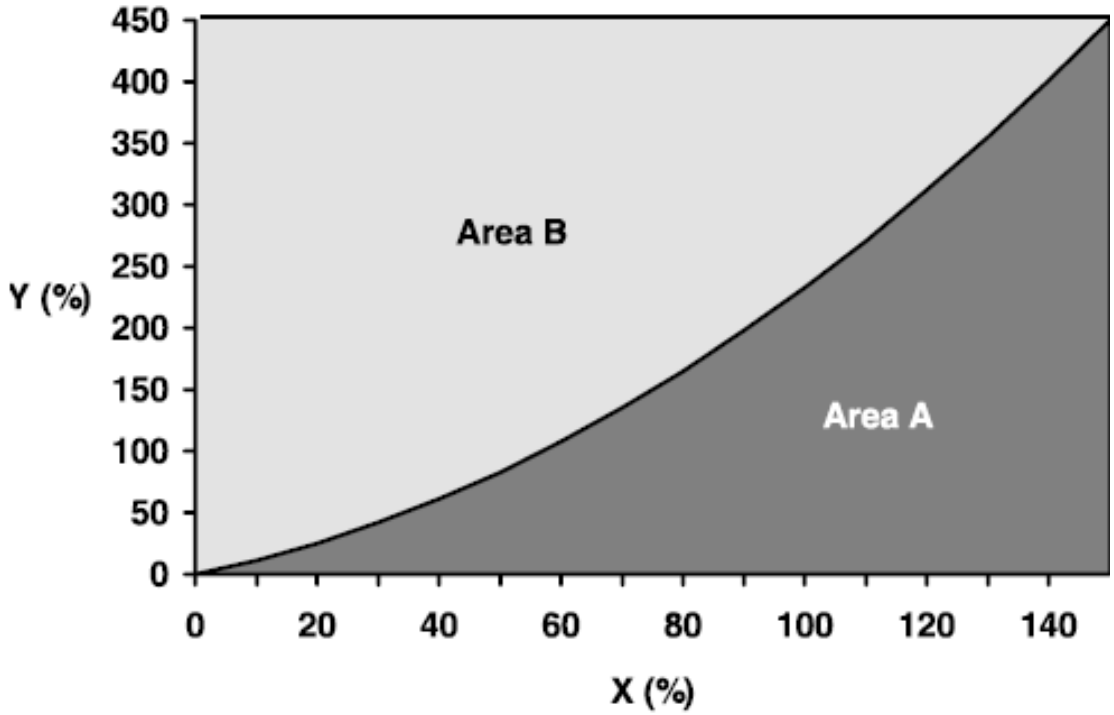


Figure 3. Graph representing the function of the theoretical model

Table 1 *Specific units of quantification and information sources about them. Hospital and patients' analytic perspectives*

Costs	*Specific units of quantification*	*Information sources*
Clinical tests	Number of times carried out	Hospital patient record Pediatrician interview
Human resources	Minutes taken for specific tasks	Stop watch studies and staff interviews: ($\bar{X} \pm SD$) Literature review (median and extreme values)
AR drugs	Number of ampoules administered per chemotherapy day or cycle	Hospital computerised data base ARs administration schedule
Antiemetic rescue therapy	Number of doses administered, number of ampoules per dose	Hospital computerised data base Hospital patient record
Supplies Diluting solutions	Units consumed during the preparation and administration of each dose of: AR, rescue antiemetic, pharmacological treatment of adverse effects and clinical complications	Questionnaire to nursing staff of the pediatric ward Hospital computerised data base
Treatment of clinical complications and/or adverse effects	Units (bottles, vials, ampoules, tablets) of the drug, nutrition or fluidotherapy consumed	Hospital computerised data base Hospital patient record
Laundry	Number of sets of sheets and pyjamas washed and ironed as a consequence of emesis	Questionnaire to nursing staff of the pediatric ward Estimations
Increased hospitalisation time	Days	Hospital patient record

Table 2 *Key variables to modify in the sensitivity analysis*

a. Hospital's analytic perspective

Variable	*Justificatión of choice*	*Variable modifications*
Tropisetron acquisition cost	78-88% of total modifiable costs of AR TROP	20 ,35 ,50 and 60% reduction[1]
Human resources in AR CPM-DEX	1. 54-59% of total modifiable costs of AR CPM-DEX 2. High grade of uncertainty due to the system of quantification	1. Worst case Stop watch studies and staff interviews: $(\bar{X} + 2SD)$ Values from medical literature: highest extreme value 2. Best case Stop watch studies and staff interviews: $(\bar{X} - 2SD)$ Values from medical literature: lowest extreme value
Hospital willingness to pay per extra effectiveness unit	Base value of the variable based on atheoretical model	Increased, the hospital willing to pay 100% more than CEr CD per additional unit of effectiveness

b. Patients' analytic perspective

Variable	*Justificatión of choice*	*Variable modifications*
Tropisetron acquisition cost cost	92-96% of total modi-fiable costs of AR TROP	20 ,35 ,50 and 60% reduction[1]
AR CPM-DEX acquisition and preparation costs	Almost 100% of the total modifiable costs of AR CPM-DEX for 71% of patients	A 25% reduction in the forecast of possible reductions in the price of diluting agent or in the forecast of generic products commercialization
Patients' willingness to pay per extra effectiveness unit	Base value of the variable based on atheoretical model	• Worst estimated theoretical value: $PIF_{worst\ case} = 0,75 \times PIF$; $Y_{worst\ case} = X + X^2/100$ • Best estimated theoretical value: $PIF_{best\ case} = 1,25 \times PIF$; $Y_{best\ case} = X + X^2/60$

1. Possible arrival on the Spanish market of: patents of the product (-20%), clinical packaging Navoban® 50 ampoules (-35%), patents of the product in clinical packaking (-50%), validated generic equivalent in clinical packaging (-60%).

Table 3 *Effectiveness, average cost and cost-effectiveness ratio*

RESULTS	*Patients' age*	*Hospital analytic perspective*		*Patients analytic perspective*	
		AR T	*AR CD*	*AR T*	*AR CD*
Effectiveness* (%)	2-12	50	34.70	76	47.80
	13-17	33.30	44.30	57.20	33.30
Average cost ($)	2-12	33.09	24.54	85.20	26.71
	13-17	34.39	22.69	82.92	31.14
Cost- effectiveness ratio ($)	2-12	66.19	70.72	112.10	55.88
	13-17	103.29	51.22	144.96	93.53

* Sum of the probabilities of the positive end-points.

Table 4 *Incremental effectiveness, incremental cost, incremental cost-effectiveness and more cost-effective antiemetic regimen*

Analytic perspective	*Patients' age*	*IE (%)*	*IC ($)*	*ICE ($)*	*Willingness to pay per extra effectiveness unit ($)*	*More cost-effective AR*
Hospital	2-12	15.3	855.78	55.93	106.08	AR T
	13-17	- 11	1170.32	-	-	AR CD
Patients	2-12	28.2	5848.75	207.40	≈ 214	AR T
	13-17	23.9	5177.21	216.62	≈ 407	AR T

Annex 1 Quantification in units (Q), valoration in $/unit (V) and associated costs in $ (QxV) of each identified resourc Hospital's analytic perspective.

a. Stage prior to the preparation-administration of ARs

Costs	*TROP*			*CPM-DEX*		
	Q	*V*	*Q x V*	*Q*	*V*	*Q x V*
Associated with the prescription						
Cost of pediatrician's time necessary to:						
decide if it is possible or not to prescribe the AR evaluate possible pharmacological interactions evaluate the need to adjust the AR dose evaluate the need to adjust the dose of concomitant drugs	5 ± 1.5	0.22	1.10	10 ± 3	0.22	2.2
Cost of pharmacist's time necessary to: evaluate possible physico-chemical interactions	-	-	-	2 ± 0.5	0.21	0.42
Associated with the acquisition of antiemetic regimen drugs	1 amp. Navoban®	25.98	25.98	3 amp. Largactil® 2 amp. Fortecortin®	0.31 0.45	0.93 0.90

Navoban®, 1 amp. of 5 mg/5 ml, Sandoz Pharma SAE. Largactil®, 5 amp. of 25 mg/5 ml, Rhone-Poulenc Rorer SA. Fortecortin®, 100 amp. of 4 mg/ ml, Merck Farma y Química SA.

b. ARs preparation-administration stage

Costs	*TROP*			*CPM-DEX*		
	Q	*V*	*Q x V*	*Q*	*V*	*Q x V*
Associated with the preparation						
Costs of supplies:						
Non sterile rubber gloves	-	-	-	3	0.04	0.12
Alcohol swabs	2	0.07	0.14	6	0.07	0.42
Sterile plastic syringe 5 ml	1	0.04	0.04	3	0.04	0.12
Sterile plastic syringe 2 ml	-	-	-	2	0.04	0.08
Cost of viaflex of 100 ml ClNa 0,9%.	1	1.07	1.07	3	1.07	3.21
Cost of nursing time to prepare the AR dose	2.5±0.5	0.20	0.5	11.5±2.5	0.2	2.3
Associated with the administration *Cost of nursing time to administer AR dose*	3 (2.5-5.6)	0.20	0.6	19.7 (15-25)	0.2	3.94
Associated with the surveillance of the infusion *Cost of nursing time to measure arterial pressure*	-	-	-	4 ± 1.4	0.2	0.8

Annex 1 (Continued) Quantification in units (Q), valoration in $/unit (V) and associated costs in $ (QxV) of each identified resource. Hospital's analytic perspective.

c. Stage following the AR administration

Costs	*TROP*			*CPM-DEX*		
	Q	*V*	*Q x V*	*Q*	*V*	*Q x*
Associated with therapeutic failure						
Laundry costs[1]	1.75	0.41	0.72	2.3	0.41	0.94
Cost of nursing time necessary to:						
change of bed-linen and pyjamas[2]	7	0.20	1.4	9.3	0.20	1.86
comfort the patient[2]	7	0.20	1.4	9.3	0.20	1.86
contact and inform pediatrician	1.5 ± 0.6	0.20	0.30	1.5 ± 0.6	0.20	0.30
Cost of rescue antiemetic therapy[3]						
Prescription costs						
Cost of pediatrician's time necessary to:						
be informed by the nurse, visit and examine the patient, decide whether to stop AR and initiate rescue therapy.	8 ± 6.7	0.22	1.76	8 ± 6.7	0.22	1.76
Cost of pharmacist's time necessary to:						
check the prescription and physico-chemical interactions	3 ± 1	0.21	0.63	3 ± 1	0.21	0.63
Purchase cost of metoclopramide[4]	11.5 amp. Primperan®	0.24	2.76	11.5 amp. Primperan®	0.24	2.76
Costs of metoclopramide preparation[5]						
Cost of supplies:	2	0.07	0.23	2	0.07	0.23
Alcohol swabs	1	0.10	0.16	1	0.10	0.16
Sterile plastic syringe 20 ml	1	0.97	1.56	1	0.97	1.56
Cost of viaflex 50 ml of ClNa 0,9%	4 ± 0.5	0.20	1.26	4 ± 0.5	0.20	1.26
Cost of nursing time to prepare the dose						
Administration costs[5]	3	0.20	0.95	3	0.20	0.95
Cost of nursing time to administer the dose	(2.5 - 5.6)			(2.5 - 5.6)		
Associated with clinical complications						
Costs of diagnostic clinical tests:						
Ionogramme	1	2.38	2.38	1	2.38	2.38
Cost of pediatrician's time necessary to:						
evaluate the patient's situation, hydric balance and ionogramme, and to decide on correction measures	8 ± 4.5	0.22	1.76	8 ± 4.5	0.22	1.76
Cost of treatment of clinical complications[6]	1	3.94	3.94	1	3.94	3.94
Associated with adverse effects						
Cost of nursing time necessary to:						
comfort the patient, contact and inform pediatrician	6 ± 3.6	0.20	1.2	6 ± 3.6	0.20	1.2
Cost of pediatrician's time necessary to:						
Be informed by the nurse, visit the patient, evaluate the adverse effect, evaluate the need for pharmacological treatment and for AR suspension	12 ± 2.5	0.22	2.64	12 ± 2.5	0.22	2.64
Cost of treatment of adverse effects[7]	1	2.13	2.13	1	2.13	2.13

1. One unit per 5 emetic episodes. 2. 4 ± 1 min per 5 emetic episodes.
   Mean number of emetic episodes per day of cycle with failure: 8,75 AR TROP and 11,6 AR CPM-DEX.
3. Patients receive at least one rescue antiemetic dose: metoclopramide 1-2 mg/kg/dose, maximum dose 100 mg; 30 min i.v. infusion (Primperan® amp. 10 mg/2 ml).
4. Mean number of amp. of Primperan used in a 24 hour period: 11.5.
5. To calculate the associated costs in the preparation and administration of the antiemetic rescue therapy the formula QxVxF was used, where F is the mean number of antiemetic rescue doses administered in the 24 hour period of the study. F=1.6.
6. 24 cases of clinical complications in 221 days of chemotherapy studied: 1 hypopotassemia, 4 pirosis, 11 gastralgia and 8 intestinal pain. Mean cost per clinical complication due to poor emetic control $3.94.
7. 12 cases of adverse effects requiring treatment over 111 days of chemotherapy evaluated with AR TROP: 1 hypertensión, 3 intestinal pain, 2 gastralgia, 2 constipation, 2 headache and 1 headache + dizziness. Mean cost per unit of adverse effects treated caused by AR TROP $2.13.
   11 cases of adverse effects requiring treatment over 110 days of chemotherapy evaluated with AR CPM-DEX: 1 gastralgia, 2 somnolence + gastralgia, 1 intestinal pain and 7 headaches. Mean cost per unit of adverse effects treated caused by AR CPM-DEX $2.13.

Annex 2 Quantification in units (Q), valoration in $/unit (V) and associated costs in $ (QxV) of each identified resource. Patient's analytic perspective.

Costs	*TROP*			*CPM-DEX*		
	Q	*V*	*Q x V*	*Q*	*V*	*Q x V*
Associated with the acquisition of antiemetic regimen drugs[1]	2.5 amp. Navoban®	30.47	76.17	7.5 amp. Largactil® 5 amp. Fortecortin®	0.36 0.55	5.45
Associated with the preparation						
Cost viaflex 100 ml of ClNa 0,9%[1]	2.5	1.25	3.12	7.5	1.25	9.37
Associated with therapeutic failure						
Purchase cost of metoclopramide [2]	11.5 amp.	0.28	3.22	11.5 amp.	0.28	3.22
Cost viaflex 50 ml of ClNa 0,9%[3]	1.60	1.14	1.82	1.60	1.14	1.82
Associated with clinical complications						
Cost of dianostic clinical tests: Ionogramme	1	39.55	39.55	1	39.55	39.55
Cost of treatment of clinical complications[4]	1	2.75	2.75	1	2.75	2.75
Associated with adverse effects						
Cost of treatment of adverse effects[5]	1	1.49	1.49	1	1.43	1.43

1. Units of quantification = number of units consumed every 24 hours by mean number of days of the duration of the 87 cycles of chemotherapy analysed (2,5).
2. Mean number of Primperan® amp. used by cycle: 11.5.
3. Mean number of doses of rescue antiemetic administered per cycle: 1.6.
4. 24 cases of clinical complications in 87 cycles of chemotherapy: 1 hypopotassemia, 4 pirosis, 11 gastralgia and 8 intestinal pain. Mean cost per unit of clinical complication treatment $2.75.
5. 12 cases of adverse effects requiring treatment over 43 cycles of chemotherapy evaluated with AR TROP: 1 hypertensión, 3 intestinal pain, 2 gastralgia, 2 constipation, 2 headache and 1 headache + dizziness. Mean cost per unit of adverse effects treated caused by AR TROP $1.49.
   11 cases of adverse effects requiring treatment over 44 cycles of chemotherapy evaluated with AR CPM-DEX: 1 gastralgia, 2 somnolence + gastralgia, 1 intestinal pain and 7 headaches. Mean cost per unit of adverse effects treated caused by AR CPM-DEX $1.43.