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Health economics assessment study of teicoplanin *versus* vancomycin in Gram-positive infections

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SUMMARY

The objective of this study, conducted at Hospital Clínico San Carlos, Madrid, Spain, was to compare the cost of treatment of Gram-positive infections with teicoplanin and vancomycin under normal conditions. Using a prospective observational study design for drug utilization and economic assessment, we evaluated the comparability of the sample, adverse events, features of treatment with teicoplanin/vancomycin and factors influencing the consumption of resources until the end of glycopeptide treatment or discharge (whichever occurred later) using Health System perspective. Costs were assigned using the hospital's evaluation at the time of the study. Analyses made: multivariate, sensitivity (by modifying staff or acquisition costs) and simulation of reduction of stay by early discharge in the teicoplanin group. Study participants included 201 patients who had been using teicoplanin (n = 100) or vancomycin (n = 101) for at least four days. Data collected daily outside morning work timetable. Costs of acquisition, administration and monitoring by course of treatment (mean ± SD, in euros) were lower in the vancomycin group (teicoplanin €647.62 ± €572.75 vs. *vancomycin €378.11 ± €225.90); when total costs (including hospital stay) were considered, no differences were found (teicoplanin €4,432.04 ± €3,383.46* vs. *vancomycin €4,364.44 ± €2,734.24). Conditions of use and results were similar for both antibiotics. The economic results of acquisition, administration and monitoring were advantageous for vancomycin; when global costs of care were taken into account, these differences were not evident. Tolerability was significantly advantageous in the teicoplanin group (with regard to phlebitis and elevation of creatininemia), without differences in clinical or economic outcomes. The formulation of teicoplanin did not take advantage of its potential benefits of administration.*

Key words: Teicoplanin - Vancomycin - Glycopeptides - Pharmacoeconomics - Observational study - Economic assessment

Evaluación de costes sanitarios relacionados con el tratamiento con teicoplanina frente a vancomicina en las infecciones por grampositivos

RESUMEN

El objetivo de este estudio, realizado en el Hospital Clínico San Carlos de Madrid, en España, fue comparar el coste del tratamiento de las infecciones por grampositivos con teicoplanina y vancomicina en la práctica clínica habitual. Mediante un diseño prospectivo observacional orientado al análisis de la utilización del fármaco y la valoración económica, se evaluó el grado de comparabilidad de la muestra, los efectos adversos, las características del tratamiento con teicoplanina/vancomicina y los factores que influyeron sobre la utilización de los recursos sanitarios hasta el final del tratamiento con el glucopéptido o el alta hospitalaria (tomando como referencia siempre lo que ocurriese más tarde) desde la perspectiva de los Servicios de Salud. Los costes se calcularon según la evaluación hospitalaria durante el periodo del estudio. Se realizó un análisis multivariado, de sensibilidad (modificando los costes de adquisición o relativos al personal sanitario) y de simulación de la reducción de la estancia hospitalaria por la anticipación del alta en el grupo tratado con teicoplanina. En el estudio participaron 201 pacientes tratados con teicoplanina (n=100) o vancomicina (n=101) durante al menos cuatro días. Toda la información relativa a los pacientes del estudio se recogió diariamente. Los costes de adquisición y administración del fármaco y de control de los pacientes durante el tratamiento (media ± DE, en euros) fueron menores en el grupo tratado con vancomicina (647,62 ± 572,75 para la teicoplanina frente a 378,11 ± 225,90 para la vancomicina); cuando se consideraron los costes globales, incluyendo la estancia hospitalaria, no se hallaron diferencias entre ambos grupos (4432,04 ± 3383,46 para la teicoplanina y 4364,44 ± 2734,24 para la vancomicina). Las condiciones de uso y los resultados obtenidos fueron similares con ambos antibióticos. El coste económico de la adquisición y administración del fármaco y del control de los pacientes fue menor en el grupo tratado con vancomicina, pero cuando se consideraron los costes globales incluyendo la estancia hospitalaria, fueron similares en ambos grupos. La tolerabilidad fue significativamente mejor en el grupo tratado con teicoplanina (con relación a la aparición de flebitis y elevaciones de la creatininemia), sin que existiesen diferencias en la eficacia clínica ni el coste económico. La formulación de teicoplanina no mostró ningún posible beneficio en cuanto a la administración.

Palabras clave: Teicoplanina - Vancomicina - Glucopéptidos - Farmacoeconomía - Estudio observacional - Evaluación económica

INTRODUCTION

Within the group of glycopeptides there are only two currently available alternatives: vancomycin and teicoplanin. In recent years Gram-positive bacteria have developed resistance, and this has led to widespread use of these antimicrobials over the last decade (1, 2). Their similar features, mainly in terms of spectrum and efficacy, mean that they are often confused. However, there are fundamental differences in route of administration, dosage, toxicity and cost, and these differences may determine the selection of one or the other in specific situations.

The varied information in the literature leads us to conclude that vancomycin is less likely to cause resistance and has lower acquisition costs. However, it entails greater renal toxicity, and higher administration and monitoring costs. On the other hand, teicoplanin is more easily administered and used in outpatient treatment. Its lower toxicity means that it does not need monitoring, although in cases of possible resistance it is not as reliable and is more expensive. Nevertheless, the sources of this information are incomplete and different (clinical trials or observational studies) (3-6).

Some publications have tried to solve the problem of the cost-effectiveness of vancomycin or teicoplanin, although almost all have used theoretical models based on data from different sources, some of which cannot be extrapolated in the usual way (7-9). A more recent study considers information from real patients but examines clinical records retrospectively in a setting (intensive care unit) that makes it difficult to observe the best features of teicoplanin, namely, the possibility of intramuscular use and thus early discharge (3). Therefore, these studies do not take into account aspects such as incidence of vancomycin-induced renal toxicity in normal practice; cost of real doses used and frequency of monitoring; influence on the duration of hospital stay and the frequency of continued outpatient treatment.

In order to address these issues, we designed a prospective cohort study, which allowed us to assess the differences between courses of treatment in normal circumstances in the patients admitted to any of the hospital services and patients treated for Gram-positive infection. We assess the conditions of use of the drugs, with the possibility of observing continuation of outpatient treatment and of evaluating the consumption of resources.

PATIENTS AND METHODS

Patients

Using medication request information in the pharmacy service, we located patients receiving vancomycin (i.v.) or teicoplanin (i.v. or i.m.). Eligible participants were all patients in the Hospital Clínico San Carlos, in any service or with any illness, with suspected or reported Gram-positive infection and who had received vancomycin or teicoplanin for a minimum of four days. Owing to the higher frequency of vancomycin prescription, and in order to avoid differences due to the period of data collection, patients in the vancomycin group were selected at random using a computer-generated table of random numbers from those patients who had been prescribed this antibiotic daily. At this time, we had no knowledge whatsoever of the characteristics of the patient or treatment.

Data was collected by a collaborating investigator from the Clinical Pharmacology Service who collected the data on each patient on a daily basis outside the normal morning work schedule. Data were collected from 1996 to 1997.

The necessary data were registered to: 1) evaluate patient characteristics that could influence the result and check the comparability of the sample (sex, age, weight, expected hospital stay based on Diagnostic Related Groups [DRG]), serum creatinine before treatment, previous hemodialysis, risk factors for renal toxicity (see Table 1), reason for discharge (improvement, death, voluntary, transfer to another hospital), McCabe classification (rapidly fatal, ultimately fatal, non-fatal) (10), Winston clinical situation (critical, poor, regular, stable) (11), empiric initiation of glycopeptide therapy, request for microbiologic cultures, positive result of cultures, presence of glycopeptide-sensitive bacteria, presence of glycopeptide-resistant bacteria, reason for end of treatment (improvement, ineffectiveness, intolerance, death), continued treatment with antibiotics after finishing glycopeptide course, number of concomitant infusions through the same vein, service (medical, oncology, intensive care), reason for admission (infection, endocrine, immunology, hematology, circulatory, respiratory, digestive, genitourinary, dermatology, motor system, badly defined, poisoning/injury), site of infection (lung, motor system, bone prosthesis, heart, heart prosthesis, vessels, urine, nervous system, central nervous system prosthesis, skin, blood, unknown, others); 2) evaluate results on safety attributable to glycopeptides (possible appearance of adverse events was evaluated daily, in particular possible nephrotoxicity, defined as an increase in serum creatinine of $\geq$0.5 if basal value is $\leq$3, or an increase of $\geq$1 if base value is >3 mg/dl, as well as the appearance of phlebitis, diarrhea or "red man" syndrome); and 3) evaluate the characterstics of glycopeptide therapy and the influence on consumption of resources of the following: duration of glycopeptide therapy,

Table 1. Demographic and clinical characteristics of the sample.

	Teicoplanin (n = 100)	Vancomycin (n = 101)	Statistical significance
Sex (M/F)	50/50	40/61	0.14 NS
Mean age ± SD (years)	64.17 ± 17.98	61.03 ± 17.46	0.21 NS
Mean weight ± SD (kg)	67.05 ± 11.36	69.37 ± 13.03	0.18 NS
Expected stay for DRG (days) (mean ± SD)	13.98 ± 4.94	13.33 ± 3.54	0.29 NS
Serum creatinine prior to treatment (mean ± SE)	1.50 ± 1.37	1.62 ± 1.64	0.58 NS
Patients in a previous hemodialysis program	1	3	0.30 NS
Risk factors for renal toxicity:			
Previous renal insufficiency	26	23	0.59 NS
Previous glycopeptides		5	0.00*
Previous aminoglycosides	19	18	0.83 NS
Previous cephalosporins	56	41	0.03*
Previous penicillins	7	17	0.03*
Previous other antibiotics (0/1/2)	6831/1	59/41/1	0.36 NS
Previous other nephrotoxic drugs	1	2	0.56 NS
Previous chemotherapy	13	12	0.81 NS
Previous contrasts	15	3	0.00*
Previous diuretics	27	27	0.96 NS
Previous amphotericin B	0	2	0.10 NS
Previous cyclosporin	1	0	0.23 NS
Previous shock	3	2	0.64 NS
Reason for discharge:			
Improvement/death/voluntary + hospital transfer	67/27/6	71/23/9	0.60 NS
McCabe classification:			
1: rapidly fatal/2: ultimately fatal/3: non-fatal	10/57/33	4/55/42	0.15 NS
Winston clinical situation scale:			
Critical/poor/regular/stable	8/47/36/9	5/37/55/4	0.051 NS

DRG: Diagnostic Related Groups. *p <0.05.

number of doses administered, number of vials of glycopeptide consumed, number of doses administered after discharge, number of changes of i.v. route, frequency of monitoring of serum levels of vancomycin, number of hemodialysis procedures (excluding patients already in hemodialysis), duration of follow-up (from the beginning of treatment until discharge) and total duration of admission to hospital.

Statistical method

First, variables were explored using descriptive techniques. Comparative contrasts of means were made (Student's *t*-test), as well as a comparison of proportions (Mantel-Haenszel 2 for discrete quantitative and ordinal variables). The number of patients presenting nephrotoxicity was analyzed using a logistic regression model which included all the variables that could have an effect on the increase in creatinine: glycopeptide antibiotic; McCabe classification, Winston clinical situation and duration of antibiotic therapy; previous risk factors for renal toxicity: renal disease, renal insufficiency, administration of nephrotoxic drugs, aminoglycosides, glycopeptides, chemotherapy, contrasts, amphotericin B and situation of shock prior to treatment; presence of risk factors for renal toxicity: concomitant treatment with aminoglycosides, amphotericin B, chemotherapy, contrasts, cyclosporin and concomitant shock; number of drugs administered through the same i.v. route; and number of concomitant factors per patient. Those factors which showed no significant effect were gradually withdrawn (backward procedure), placing value during the withdrawal on the possible existence of confusion (modification of the coefficient greater than 10–15%), in which case they were maintained.

The duration of follow-up was analyzed using a multiple regression model which included all those variables that could influence the duration of follow-up: age, sex, service, Winston clinical situation, increase in creatinine, prior administration of vancomycin/teicoplanin, reason for discharge, reason for admission, empiric initiation of glycopeptide therapy, request for cultures, positive result of cultures, presence of glycopeptide-sensitive bacteria, presence of glycopeptide-resistant bacteria, site of infection, prior renal insufficiency, number of concomitant nephrotoxicity factors, expected hospital stay based on DRG, reason for end of treatment, site of infection and McCabe classification. Those factors which showed no significant effect were gradually withdrawn (backward procedure), placing value during the withdrawal sequence on the possible existence of confusion (modification of the coefficient greater than 10–15%) in which case they were maintained. Follow-up durations of more than six months were excluded as they were considered exceptional and as having no medical cause. It was shown that this does not influence the relationship between groups.

The statistical analysis was made using the program SPSS-PC (5.0). *P* values lower than 0.05 were considered significant. Ordinal and qualitative variables were treated as dummy variables.

This study received the approval of the hospital's Clinical Research Ethics Committee.

Economic analysis

The direct cost of treatment was determined by: drug (number of vials and cost per unit), number of doses administered (time and personnel costs), number of monitoring procedures (cost of personnel for extraction and analysis, material and reactants), cost of consultations in outpatient administration; adverse events: changes in i.v. route (personnel, material), number of hemodialysis procedures; and prolongation of hospital follow-up time (from initiation of antibiotic). The assignation of costs was made from the real costs of acquisition for the hospital (glycopeptide and materials), the value that procedures had for the hospital (administration, change of routes, monitoring, hemodialysis) and length of hospital stay in days. Indirect costs (from loss of productivity during cure) were not taken into consideration as no significant differences were found in the application of treatment (duration of admission and follow-up).

The calculation of imputable costs took into account values available in the hospital with regard to procedures of administration, changes of route, hemodialysis and average cost of stay per day, as well as costs of acquisition of materials and medication (glycopeptides). This information can be seen in Table 2.

Table 2. Economic valuations used in the calculation of costs (in euros).

	Reference	Scenario 1	Scenario 2
Vial vancomycin 500 mg	6.92		
Vial teicoplanin 200 mg	19.45		15.03
Change of i.v. route	2.89	5.66	
I.m. administration	1.31	3.65	
I.v. administration	2.07	3.99	
Monitoring	16.05	19.04	
Hemodialysis	90.15	103.37	
Cost/day of hospital stay	269.67		
Nursing personnel/hour	12.80		
Medical personnel/hour	18.25		

Notes: The columns for Scenarios 1 and 2 show the changes with respect to the reference situation. In the simulation of change of admission time, reference values have been used.

In order to evaluate the consistency of the results, a sensitivity analysis was made, taking into account the possibility of change to higher personnel costs (Scenario 1) and of acquisition of teicoplanin at an arbitrary level of €15.03/vial (Scenario 2), and the influence of these possibilities on the results. The applied costs of these scenarios are found in Table 1. To place a value on the effect of an improvement in the conditions of teicoplanin use (considering the possibility of bringing forward discharge and continuing intramuscular outpatient administration), a simulation was made on the model obtained in the study: a lower admission time was applied to the patients who could reduce their admission time (those who finished glycopeptide therapy the day before discharge or later) and the influence on the results was checked.

RESULTS

Data from 201 patients were recorded (teicoplanin: n = 100; vancomycin: n = 101) (the difference was due to the fact that the number participating in the study was assigned after selection).

Description of the characteristics of the sample

The patients included in both of the groups can be considered homogenous in those clinical characteristics that

Table 3. Characteristics of antibiotic therapy with teicoplanin/vancomycin.

	Teicoplanin	Vancomycin	Significance
Empiric initiation	47	52	0.52 NS
Request for cultures	99	96	0.09 NS
Positive culture result	69	70	0.95 NS
Presence of sensitive bacteria	59	59	0.93 NS
Presence of resistant bacteria	10	12	0.67 NS
Reason for end of treatment: Improvement/inefficacy + intolerance/death	63/13/19	77/16/5	0.007
Continued antibiotic treatment after glycopeptide	30	33	0.68 NS
Number of concomitant drugs administered through the same i.v. route			
Mean ± SD	8.14 ± 5.92	7.52 ± 6.52	0.48 NS
Median (Q1, Q3)	7 (3, 12)	5 (3, 12)	–

Table 4. Results on safety.

	Teicoplanin	Vancomycin	Significance
No. of ADR: 0/1/2/3	93/3/4/0	81/17/2/1	0.062 (MH)
Difference in basal creatinine (mg/dl)			
Mean ± SD	–0.08 ± 0.09	0.23 ± 0.23	0.21 NS
Median (Q1, Q3)	0 (–0.3, 0.1)	0 (–0.2, 0.3)	–
No. of patients with analytic criterion of nephrotoxicity*	7	14	–

ADR: adverse drug reactions. MH: Mantel-Haenszel. *Increase in creatinine ≥0.5 if base value ≤3, or increase ≥1 if base value >3 mg/dl.

could influence the result, as well as the characteristics included in Table 1. The distribution of underlying diseases by system, reason for admission by system and site of infection were also analyzed, and no differences were found among them. Significant differences were found among some of the variables included within the risk factors for renal toxicity, in the reason for end of treatment and an almost significant difference in the Winston clinical situation scale.

Similarly, the characteristics associated with antibiotic therapy were analyzed and all aspects evaluated were homogenous (Table 3).

Evaluation of safety results

Thirty-five suspected adverse reactions were recorded (teicoplanin 11; vancomycin 24; $p = 0.061$), and all were cases of phlebitis. The evaluation of causality was as follows: 4 possible, 7 probable in the case of teicoplanin; and 10 possible, 13 probable and 1 definitely related in the case of vancomycin. All were evaluated as slight. In two cases (teicoplanin one, vancomycin one) treatment was suspended.

With regard to renal toxicity, the assessment of change in base creatinine does not show significant differences between the groups (Table 4). The number of patients who fulfill the analytical criteria for nephrotoxicity was analyzed using a logistic regression model. The final model (Table 5) shows a significant effect of the glycopeptide antibiotic ($p = 0.022$, OR= 4.01), which indicates that in the vancomycin group the number of patients who fulfill this criterion is higher.

No cases of diarrhea or "red man" syndrome were recorded.

Table 5. Analysis of creatinine increase using a logistic regression model.

Variable	Significance	OR	CI 95 OR
Glycopeptide (vancomycin/teicoplanin)	0.022	4.01	1.22–13.19
Duration glycopeptide treatment	0.031	0.92	0.86–0.99
Previous renal disease	0.012	6.73	1.52–29.70
Previous nephrotoxicity	0.031	38.91	1.39–1,091.47
Previous chemotherapy	0.831	1.17	0.28–4.92
Concomitant aminoglycosides	0.003	6.61	1.92–22.79
Number of concomitant drugs same i.v. route	0.19	1.13	1.0–1.25
Constant	0.000		

Model χ^2: χ^2: 29.197; DF: 7; significance: 0.0001; vancomycin = 1, teicoplanin = 0; OR: odds ratio.

Table 6. Characteristics of glycopeptide treatment.

	Teicoplanin	Vancomycin	Significance
Duration glycopeptide treatment			
Mean ± SD	13.94 ± 10.82	14.72 ± 9.52	0.58 NS
Median (Q1, Q3)	11.00 (7, 16)	12.00 (8, 19)	
Number of doses administered per patient			
Mean ± SD	20.13 ± 16.67	22.44 ± 13.61	0.28 NS
Median (Q1, Q3)	14 (9, 24)	18 (12, 29)	–
Number of vials consumed per patient (vancomycin 500 mg; teicoplanin 200 mg)			
Mean ± SD	30.8 ± 27.69	42.28 ± 27.59	–
Median (Q1, Q3)	22 (14, 36)	34 (24, 51)	–
Number of doses outside the hospital	3	2	–
Changes of i.v. route during glycopeptide therapy			
Mean ± SD	2.32 ± 1.71	2.34 ± 1.62	0.91 NS
Median (Q1, Q3)	2 (1, 3)	2 (1, 3)	–
Frequency of monitoring of serum levels			
Mean ± SD	–	2.01 ± 0.21	–
Median (Q1, Q3)	–	2 (0, 3)	–
Hemodialysis procedures (excluding patients in previous programs)			
Mean ± SD	0.28 ± 1.58	0.18 ± 1.44	0.65 NS
Median (Q1, Q3)	5 (2, 9)	2 (2, 14)	0.65 NS

Table 7. Total admission time (days) and follow-up characteristics.

	Teicoplanin	Vancomycin	Significance
Duration follow-up			
Mean ± SD	31.80 ± 33.98	34.87 ± 41.92	0.57 NS
Median (Q1, Q3)	21 (10, 41)	22 (13, 35)	–
Duration follow-up (>180 excluded)			
Mean ± SD	30.05 ± 29.29	32.48 ± 33.28	0.86 NS
Median (Q1, Q3)	19 (10, 39)	22 (12, 34)	–
N	98	100	–
Duration hospital admission			
Mean ± SD	50.27 ± 44.63	62.67 ± 98.99	0.26 NS
Median (Q1, Q3)	40 (23, 61)	36 (22, 56)	–
Duration hospital admission (>180 excluded)			
Mean ± SD	47.97 ± 38.49	5.55 ± 37.67	0.66 NS
Median (Q1, Q3)	39 (23, 58)	34 (22, 51)	–
N	98	97	–

Characteristics of treatment and assessment of costs

Characteristics of treatment

Only one patient in the teicoplanin group received i.m. dosing and in two more, the i.m. route replaced i.v. The remaining doses and patients were administered by i.v. The number of doses administered after discharge was very low (teicoplanin: three doses, one patient; vancomycin: two doses, one patient).

No differences were found in the duration of treatment or in the number of doses administered. The mean number

Table 8. Analysis of influence of glycopeptide on duration of follow-up (time from beginning of treatment until discharge), using a multiple regression model.

Variable	B ± SE	Significance	CI 95
Reason for end of treatment (with regard to death):			
Inefficacy	27.39 ± 7.67	0.000	12.37–42.46
Improvement	15.42 ± 5.8	0.009	3.96–26.7
Intolerance	7.84 ± 28.99	0.787	–49.38–65.04
Neurological admission	17.60 ± 6.30	0.006	5.17–30.02
Vascular catheter infection	22.97 ± 10.99	0.038	1.29–44.64
McCabe classification (with respect to 1):			
Class 3	18.84 ± 8.54	0.029	1.99–35.69
Class 2	13.78 ± 8.17	0.093	–2.33–29.90
Glycopeptide (vancomycin = 1/teicoplanin = 0)	–3.5 ± 4.17	0.357	–12.09–4.38
(Constant)	0.18 ± 8.21	0.982	–

R Square = 0.172
Adjusted R Square = 0.137
F = 4.837; Signif F = 0.0000
Vancomycin = 1; teicoplanin = 0
McCabe 3: non-fatal disease
McCabe 2: ultimately fatal disease
McCabe 1: rapidly fatal disease
Duration of follow-up (> 180 excluded)
B: Regression coefficient
CI 95: Confidence interval at 95% of regression coefficient

of monitorings of serum levels of vancomycin by course of treatment was two.

In spite of the different incidence of phlebitis, no differences were found between groups with respect to the number of changes of i.v. route during the antibiotic treatment period or in the number of drugs infused concomitantly in the same vein (Table 6).

No differences were found between groups with regard to the number of hemodialysis procedures or the number of patients who underwent this procedure. The same was true even when patients already in hemodialysis programs were excluded (Table 6).

Duration of stay and follow-up

No differences were found in any of the time intervals assessed (total admission, duration of treatment or follow-up from the beginning of treatment until discharge) in bivariate analyses (Table 7).

The duration of follow-up (time from the beginning of glycopeptide treatment until discharge) was analyzed using a multiple regression model which included all those factors considered as having influence. As can be seen in Table 8, the antibiotic chosen did not have a significant influence on the duration of follow-up. A significant influence was observed, however, in the sense that follow-up was extended by the following factors: end of treatment because of intolerance, improvement or inefficacy (with regard to death), neurological admission, infection of vascular catheter, and the less severe degrees of illness according to the McCabe classification (with regard to the most severe).

The total duration of admission was also analyzed using a multiple regression model, and no difference owing to antibiotic therapy was found.

Evaluation of costs

As can be seen in Table 9, the cost of acquisition of vancomycin is lower than that of teicoplanin. This situation does not change after adding expenses stemming from administration, change of route and monitoring. However, no differences were found after adding hospitalization costs during follow-up.

In the sensitivity analysis, two alternative scenarios were considered (the costs in each case are shown in Table 2; the results in Table 9).

In Scenario 1 the cost of personnel is higher than that of the study. This option is considered relevant because of the possibility of different health-care areas in which these situations could arise. In this case, we found a notable in-

Table 9. Estimated costs (in euros) in the reference situation and analysis of sensitivity in two oppositing scenarios.

	Reference			Scenario 1			Scenario 2		
	Teicoplanin	Vancomycin	*p*	Teicoplanin	Vancomycin	*p*	Teicoplanin	Vancomycin	*p*
A. Antibiotic cost per treatment	599.40 ± 538.73	292.52 ± 190.86	0.000	599.40 ± 538.73	292.52 ± 190.86	0.000	462.93 ± 416.07	292.52 ± 190.86	0.000
B1. Cost of administration	41.51 ± 34.56	46.54 ± 28.21		146.60 ± 121.37	163.36 ± 99.02		41.51 ± 34.56	46.54 ± 28.21	
B2. Cost of change of route	6.70 ± 4.96	6.78 ± 4.70		21.32 ± 15.77	21.56 ± 14.95		6.70 ± 4.96	6.78 ± 4.70	
B3. Cost of monitoring drug	0	32.26 ± 35.15		0	73.97 ± 80.55		0	32.26 ± 35.15	
B. Sum B1+B2+B3	48.22 ± 37.93	85.58 ± 49.31	0.000	167.92 ± 131.97	258.90 ± 140.17	0.000	48.22 ± 37.93	85.58 ± 49.31	0.000
C. Cost of drug and administration: A+B	647.62 ± 572.75	378.11 ± 225.90	0.000	767.32 ± 658.93	551.43 ± 309.09	0.004	511.15 ± 450.16	378.11 ± 225.90	0.009
D. Cost of dialysis	25.24 ± 142.15	16.07 ± 127.75		28.94 ± 163.00	18.42 ± 146.48		25.24 ± 142.15	16.07 ± 127.75	
E. Cost of admission during treatment	3,759.17 ± 2,918.24	3,970.26 ± 2,567.69		3,759.17 ± 2,918.24	3,970.26 ± 2,567.69		3,759.17 ± 2,918.24	3,970.26 ± 2,567.69	
F. Admission + dialysis: D+E	3,784.41 ± 2,920.75	3,986.33 ± 2,588.87	0.605	3,788.11 ± 2,921.70	3,988.68 ± 2,592.48	0.607	3,784.41 ± 2,920.75	3,986.33 ± 2,588.87	0.605
G. Total direct costs: C+F	4,432.04 ± 3,383.46	4,364.44 ± 2,734.24	0.876	4,555.44 ± 3,468.34	4,540.11 ± 2,813.42	0.973	4,295.57 ± 3,282.69	4,364.44 ± 2,734.24	0.872
Total cost (C+F)/day of treatment	320.28 ± 27.14	298.90 ± 11.86		329.58 ± 30.33	311.76 ± 15.29		310.07 ± 22.78	298.90 ± 11.86	

Scenario 1: High personnel costs; Scenario 2: Reduction in cost of vial of teicoplanin; Note: The economic valuations used are found in Table 2.

crease in the costs connected with administration of the glycopeptide, specifically change of route and monitoring, which penalized the vancomycin group. With regard to total costs, the mean values are almost identical.

In Scenario 2 the cost of acquisition of teicoplanin was modified to an arbitrary level of €15.03/vial. This scenario has been included because of the possible strategy of modification of the price of teicoplanin with respect to vancomycin. This scenario reduces the differences in the costs of acquisition, which are still different. In the total cost, the mean value of teicoplanin is slightly lower than that of vancomycin but the difference is not significant.

With regard to the simulation of the model obtained in the study, a reduction in admission time was applied to the most likely teicoplanin patients (those who finished glycopeptide therapy the day before discharge), and the effect on the results was checked. In theory, the number of patients likely to improve their stay was 39 in the teicoplanin group. For the mean values of the total cost to be identical, it would be sufficient to reduce the stay by 0.64 days, on average, in the likely patients.

DISCUSSION

The results of our study show that the costs of therapy derived from glycopeptide acquisition, administration and monitoring by course of treatment (mean ± SD, in euros) are significantly lower in the vancomycin group (teicoplanin €647.62 ± €572.75; vancomycin €378.11 ± €225.90). Using this model, it would be necessary to reduce the cost of acquisition of teicoplanin to €15.03/vial, for the difference to no longer be significant. The differences indicated are reduced notably when the total costs are taken into consideration (those derived from treatment plus those from stay during follow-up) (teicoplanin €4,432.04 ± €3,383.46; vancomycin €4,364.44 ± €2,734.24), and they lose their statistical significance.

Although not experimental, an observational study offers a vision that is closer to reality in the evaluation of costs in normal circumstances. This study has verified the comparability of the samples over a large number of variables (base demographic characteristics, disease characteristics and those that predict outcome) which are very similar among the samples of both antibiotics, with the exception of some risk factors, renal toxicity and reason for end of glycopeptide treatment, which could be random owing to the high number of variables evaluated. Nevertheless, multivariate analysis allows us to control the effect of those factors that, presumably, can influence the response.

With regard to statistical power, the sample size in the study is sufficient for the detection of differences in the analysis of adverse reactions as well as acquisition, monitoring and administration costs of glycopeptides. When considering the global calculated cost of care, we must assume limitations in power due to the enormous variability. In this sense, however, we must point out that ours is a prospective study with a wider consideration of economic variables than previous studies on vancomycin and teicoplanin. Furthermore, the means found for this variable have been close enough for the demonstration of differences to be of interest.

Patients were selected from those who had already begun treatment, and data was collected outside the work timetable so as not to interfere with the normal treatment process. Therefore, we can guarantee that there was no influence on the prescription of both glycopeptides (carried out according to the normal criteria of the prescribing physician). Given that the number of vancomycin prescriptions was higher than that of teicoplanin, and in order to avoid temporary gaps in the recruitment of both groups, the selection of the vancomycin group was made from among those available each day, using random assignation from a computer-generated list.

The design of the study is particularly suitable in that it accesses the real clinical results of the application of treatment, whereas almost all publications part from theoretical models with heterogeneous information, leading to very different estimations. Only one of the studies examined, by Calbo *et al.* (3), uses data from real patients. In comparison with this study, ours has the following advantages: 1) it is prospective; 2) the sample used is greater; 3) in the Calbo study the patients were in the intensive care unit, which leads to selective characteristics and does not allow one of the advantages of teicoplanin (early discharge because of continued hospital treatment) to be shown and 4) in the aforementioned study, a cost-minimization study, clinical results are not considered with regard to length of stay as it imputes to cost, which would prevent us from detecting differences related to varying effectiveness or tolerability. Nevertheless, the valuations taken for the economic assignation of costs is similar to those used in our study.

The results obtained in our study for costs directly stemming from the acquisition, administration and monitoring of glycopeptides are significantly lower for vancomycin, with figures that are quite similar to those evaluated by Calbo *et al.* (3).

Monitoring of vancomycin introduces an increase in direct cost, which has been considered in the study. Nevertheless, we must not underestimate the fact that, in agreement with McCormack *et al.* (12), the monitoring of vancomycin plasma levels leads to a reduction in the doses used, a reduction in incorrect dosage and less severe adverse effects. This may have favorable influence on the measurable direct cost of the drug.

Given that length of hospital stay was the factor that most significantly modified the total cost of treatment (13), this was controlled by all the factors which could be connected to the patient and modify the result, such as type of admission service, reason for admission, expected hospital stay based on DRG, clinical situation and illness of the patient (McCabe and Winston scales), age, etc. In this sense, we think that all the confusion factors are sufficiently controlled to guarantee the result.

The circumstances of use of both glycopeptides are similar. In both cases, they are mainly administered intravenously and in the hospital. Intramuscular administration of teicoplanin is not used, nor is early discharge as a result of this route of administration. Therefore, a simulation has been made on the model obtained in the study, since it is thought that better use of the different formulations of teicoplanin could improve the results.

More suspected adverse reactions were found in the vancomycin group (24 *vs.* 11), and this agrees with the results reported by Wood (5). In all cases these involved phlebitis. The number of drugs administered simultaneously by the same route was similar, so we can conclude that administration of vancomycin is connected with a greater incidence of phlebitis. However, we can also state that this fact does not have a significant influence on the number of changes of i.v. route within the global care process, and so does not affect the cost of treatment. The evaluation of causality could lead to the existence of other concomitant causes, which limits the possibility of finding differences in a global indicator. There were no cases of diarrhea or "red man" syndrome; this is related to the improvement in purification of vancomycin and normal infusion over one to two hours.

Although no significant differences were detected with regard to changes in base creatininemia, the number of patients fulfilling the analytical criterion of renal toxicity was significantly higher in the vancomycin group. The logistic regression model controls sufficient factors to guarantee that there is no confusion, but a real effect ($p = 0.02$). This finding is consistent with the results of other studies, although they report fewer significant differences in the vancomycin group. The fact that serum levels are monitored and doses are adjusted accordingly undoubtedly influences this situation. In spite of these differences with respect to the effect on creatininemia, no change was detected in the number of hemodialysis procedures (teicoplanin 0.28 ± 1.58; vancomycin 0.18 ± 1.44; $p = 0.65$), or in the duration of follow-up (teicoplanin 31.80 ± 33.98; vancomycin 34.87 ± 41.92; $p = 0.57$), regardless of whether the latter was considered in bivariate or multivariate analysis. Therefore, we can say that this effect does not affect the total cost of treatment.

With regard to cost, the most significant factor is hospital stay. By controlling all those relevant factors affecting length of stay (disease, severity, age, service, continued antibiotic therapy after suspension of the drug studied [an indicator of whether the patient is kept in hospital because of infection]) this factor can be used to compare the cost of treatments, which can in part be attributed to the differences in adverse reactions or efficacy of the treatments under study. Only the cost of added hemodialysis (if it took place) would be underestimated in this evaluation, and therefore it is included as another factor. Phlebitis in itself is not important enough to be considered with respect to cost, except insofar as it influences the change in i.v. route. As it is a very small value, which disappears in the cost of stay, it is included in the section for costs related to the use of treatment (under change of i.v. route).

As far as the sensitivity analysis is concerned, in Scenario 1 the increase in staff costs reduces the differences in total costs until they are almost equal, at the expense of leaving the vancomycin group more affected by administration and, especially, monitoring costs. In Scenario 2, the reduction in the acquisition of teicoplanin reduces the acquisition costs of this group. This places the total average cost only slightly lower, although this is not significant. Both of these suppositions contribute to the study's consistency, since with some values or others, the results are not notably changed. Thus, differences exist in the acquisition and use of the drugs, but not in total cost. We did not consider a scenario with reduction of vancomycin acquisition costs since it would not contribute differential elements as the costs of therapy would be lower.

The fundamental problem in the use of teicoplanin, which is revealed in this study, is that it is almost never used after discharge. This could be due to a lack of awareness among physicians about the cost of resources, to the infrequent use of this route in the hospital environment, or to the use in patients who are not going to be discharged early anyway. This can be compared with studies such as

that by Davey *et al.* (7) who found that 28.4% of treatment with teicoplanin took place after discharge. The simulation on the model obtained in the study allows us to evaluate the possibility of improvement in the results if the potential advantages of teicoplanin are exploited. Thus, it is interesting to note that by simply reducing by 0.64 days the length of stay in patients who are able to reduce their stay, total average costs between teicoplanin and vancomycin would be identical.

Thus it would be expected that, in the forms of care that keep the patient out of the hospital (hospital care, day hospitals, etc.) and all the situations in which it is foreseeable that patients may be discharged rapidly once they recover from the procedure for which the glycopeptide is being prescribed, the use of teicoplanin would have a very favorable cost-effectiveness relationship.

CONCLUSIONS

In conclusion, the sample studied shows conditions of use and results (clinical and stay) that are very similar for both these antibiotics. The economic results of acquisition, administration and monitoring are significantly advantageous for vancomycin, although when the global costs of care are taken into consideration, these differences become very small and extremely variable. Tolerability is significantly advantageous in the teicoplanin group (with regard to phlebitis and increase in creatininemia), without differences in clinical or economic outcomes. It has been found that the formulation teicoplanin does not exploit its potential advantages of administration.

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REFERENCES

1. Ena, J., Dick, R.W., Jones, R.N. et al. *The epidemiology of intravenous vancomycin usage in a University Hospital.* JAMA 1993; 269: 598-602.
2. Janknegt, R. *The treatment of staphylococcal infections with special reference to pharmacokinetic, pharmacodynamic and pharmacoeconomic considerations.* Pharm World Sci 1997; 19: 133-141.
3. Calbo, F., Abad, F., Rodríguez, F. et al. *Estudio farmacoeconómico comparativo de vancomicina y teicoplanina en pacientes de cuidados intensivos.* Farmacoterapia 1998; 15: 20-26.
4. Cobo, J. *Vancomicina y teicoplanina: Aspectos diferenciales.* Enferm Infecc Microbiol Clín 1995; 13: 600-610.
5. Wood, M.J. *The comparative efficacy and safety of teicoplanin and vancomycin.* J Antimicrob Chemother 1996; 37: 209-222.
6. Zeckel, M.L. *A closer look at vancomycin, teicoplanin, and antimicrobial resistance.* J Chemother 1997; 9: 311-335.
7. Davey, P.G., South, R., Malek, M. *Impact of glycopeptide therapy after hospital discharge on inpatient costs: A comparison of teicoplanin and vancomicin.* J Antimicrob Chemother 1996; 37: 623-633.
8. Spencer, C.M., Bryson, H.M. *Teicoplanin, a pharmacoeconomic evaluation of its use in the treatment of Gram-positive infections.* Pharmacoeconomics 1995; 7: 357-374.
9. Honorato, J., López de Ocáriz, A., Díaz, M. *Farmacoeconomía y antibióticos.* Actualidades en la infección por grampositivos (publicación de la Fundación para el Estudio de la Infección) 1995; 5: 1-6.
10. McCabe, W.R., Jackson, G.G. *Gram-negative bacteremia. I: Etiology and ecology.* Arch Intern Med 1962; 110: 847-855.
11. Winston, D.J., Murphy, W., Young, L.S. et al. *Piperacillin therapy for serious bacterial infections.* Am J Med 1980; 69: 255-261.
12. McCormack, J.P., Lynd, L.D., Pfeifer, N.M. *Vancomycin cost containment through a therapeutic and pharmacokinetic drug monitoring service.* Can J Hosp Pharm 1989; 42: 3-9.
13. Eisenberg, J.M., Koffer, H., Glick, H.A. et al. *What is the cost of nephrotoxicity associated with aminoglycosides?* Ann Intern Med 1987; 107: 900-909.