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Work of a multidisciplinary team in the control of the prescription of ertapenem

BRIEF REPORT

Work of a multidisciplinary team in the control of the prescription of ertapenem☆

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Abstract
Objective: To determine the effectiveness of the intervention of a multidiscipline antimicrobial control group in the correct prescription of Ertapenem.
Method: A 4-month long, prospective study into prescriptions for ertapenem was carried out in a third-level hospital. Assessment into the degree of suitability of each prescription according to the infections commission usage criteria. In the situation where prescriptions were not suitable, recommendations were given and acceptance of this was recorded. The effectiveness of the antimicrobial treatment used was assessed and treatment was considered effective when there was remission of the signs and symptoms of the infection when the treatment was completed. The treatment was considered to have failed when the signs and symptoms of infection persisted or progressed, requiring the addition of another antimicrobial agent, changing antibiotics or the prolongation of the treatment for longer than 2 weeks. Lastly, the differences in the average length of stay and the duration of the antibiotic treatment between groups were analysed.
Results: Forty-eight prescriptions were assessed. The usage criterion was adequate in 48% of cases, with 78% effectiveness in this group. In the cases where the prescription was not adequate, but a change in prescription was accepted, the effectiveness was 92%, with 55.5% of those cases not accepting recommendation for change. The average stay was higher in this last group (P=.07). The duration of the antibiotic treatment in the patients who accepted the change in prescription was significantly less than in those who did not accept it (2 vs 7.4 days, P<.0001).
Conclusions: The control of ertapenem prescriptions by a multidisciplinary group was effective.

Actuación de un equipo multidisplinario en el control de la prescripción de ertapenem

Resumen

Objetivo: Determinar la efectividad de la intervención de un grupo multidisciplinario de control antimicrobiano en la correcta prescripción de ertapenem.

Método: Estudio prospectivo, durante un período de 4 meses, de las prescripciones de ertapenem realizadas en un hospital de tercer nivel. Evaluación del grado de adecuación de cada prescripción a los criterios de utilización de la comisión de infecciones. En las situaciones en las que no se adecuaban, se emitió una recomendación y se registró la aceptación de éstas. Se evaluó la efectividad del tratamiento antimicrobiano utilizado; para ello, se consideró tratamiento efectivo cuando hubo remisión de los signos y los síntomas de la infección al finalizar el tratamiento. Se consideró fracaso del tratamiento cuando los signos y los síntomas de la infección persistieron o progresaron, requiriendo la adición de otro antimicrobiano, la sustitución por otro/s antibiótico/s o la prolongación del tratamiento más allá de 2 semanas. Finalmente, se analizaron las diferencias de estancia media y duración de tratamiento antibiótico entre los grupos.

Resultados: Se evaluaron 48 prescripciones. Se adecuaron a los criterios de uso un 48% de éstas, con una efectividad del 78% en este grupo. En los casos en los que la prescripción no se adecuó, pero se aceptó un cambio de tratamiento, la efectividad fue del 92%, y fue del 55,5% en los casos en los que no se aceptó esta recomendación. La tendencia de la estancia media fue mayor en este último grupo (p = 0,07). La duración del tratamiento antibiótico en los pacientes en los que se aceptó el cambio fue significativamente menor que en los que no se aceptó (2 frente a 7,4 días; p < 0,0001).

Conclusiones: El control de las prescripciones de ertapenem por un equipo multidisciplinario fue efectivo.

Introduction

Resistance to antibiotics is considered to be a significant public health problem.[1-3] Infections with multi-resistant bacteria are associated with higher mortality and morbidity incidence rates, longer hospital stays, and higher costs,[4,5] all of which has to do with the fact that there is less and less marketing of antimicrobial agents with new action mechanisms.[6,7]

The main cause of increased resistance is the improper use of antimicrobial drugs, which occurs in 50% of cases in some studies,[8] and is caused by deficient ongoing training in antibiotic treatment, scant use of microbiology information, and the false sense of security produced by administering these drugs.[9,10]

For these reasons, the leading scientific organisations have issued a general alert, and some, such as the Centres for Disease Control and Prevention, have created an action plan to prevent the incidence rate of resistant microorganisms from continuing to grow.[11] The Infectious Diseases Society of America[12] has also recently published a guide on antibiotics policy which stresses the need for carrying out other types of interventions that are not exclusively restrictive, such as forming multidisciplinary groups containing at least 1 infectious disease specialist and 1 pharmacist. This group must perform a prospective follow-up on prescriptions, measures restricting access to antimicrobial agents, the creation of empirical treatment guides, therapeutic de-escalation and dosage adjustment.[13-15]

Few studies corroborate the use of multidisciplinary groups in daily clinical practice, and fewer still measure the effectiveness of antimicrobial treatment recommended by an multidisciplinary group. Nickman et al[15] evaluated the effectiveness of a multidisciplinary group that analysed the duration of post-operative antibiotic treatment and achieved better use of antibiotics; nevertheless, they did not evaluate clinical effectiveness, which is why the infection rate in both groups may be of interest.[16]

Ertapenem is one of the most interesting drugs for analysing the effectiveness of these groups, due to its having appeared on the market only recently, having a microbiologic spectrum that is different from that of other antibiotics in its class, and its high cost.[17]

The purpose of our study is to determine the effectiveness of a multidisciplinary antimicrobial drug control group intervening to correctly prescribe ertapenem in a general tertiary referral hospital; this hospital has listed ertapenem in its pharmacology guide since mid-2006 for the usage recommendations compiled in Table 1.

Method

Quasi-experimental study four months in length (January-April 2007) in a tertiary referral hospital with a restrictive antibiotic policy approved by the infections committee (IC), which manages antibiotic use prior to administering the drugs by means of a pharmacist's approval in departments with a unitary dose distribution system, and by means of a specific form in departments where there is no such system.

A multidisciplinary group, made up of a hospital pharmacy specialist and a specialist in infectious disease, prospectively

Table 1 Indications approved by the infections committee for treatment with ertapenem

1. Community-acquired pneumonia with suspected macroscopic aspiration

2. Community-acquired intra-abdominal infection, cholecystitis, or pyelonephritis with a risk of Escherichia coli ESBL

   2.A. Severe sepsis or septic shock

   2.B. Treatment with quinolones, aminopenicillins, or cephalosporins in the last 2 months

   2.C. Three of the following criteria: >60 years, DM, recurring UTI, urinary catheter, hospitalisation within the last yeara[a]

DM indicates diabetes mellitus; ESBL, extended spectrum beta-lactamases; UTI, urinary tract infection.
[a]Risk criteria taken from the study by Rodríguez-Baño et al.[22]

identified all daily ertapenem prescriptions in admitted patients. In order to verify compliance with the hospital's restricted usage recommendations (Table 1), each patient's clinical history was consulted, with the collaboration of the microbiology department, in order to have early knowledge of the results concerning isolation and sensitivity.

For those cases in which prescribing the drug did not follow the indications approved by the IC, the prescribing clinic was offered a treatment alternative. In all cases, the patient was in follow-up until resolution of the infection, discharge from the hospital, or death, and re-admitted patients were in follow-up until a month after their discharge.

Treatment was considered to be effective when the patient was clinically recovered, which implied the total remission of signs and symptoms related to the infection at the end of the treatment. Treatment was considered unsuccessful when the signs and symptoms of the infection persisted and progressed, and required the addition of another antimicrobial agent, substitution of the original treatment with another antibiotic or antibiotics, or prolonging the treatment by more than 2 weeks.

The following variables were recorded: age, sex, health care department, prescribing physician, indication requested on the prescription sheet, main diagnosis, suitability of the indication, intervention performed (alternative treatment), acceptance, effectiveness of the antibiotic treatment (ertapenem or accepted alternative treatment), duration of antibiotic treatment and hospital stay. The SPSS program, version 15.0, was used to detail a statistical description of the results and an analysis of the χ^2 (categorical variables) or of the variance (continuous variables) was used to detect differences between the results for different strata or subgroups. The threshold of statistical significance was 95%.

The principal variables that were measured were prescription suitability according to the IC's indications, the degree of acceptance of recommendations made by the multidisciplinary group and the effectiveness of the antimicrobial treatment in use.

Results

We evaluated 48 ertapenem prescriptions, which corresponded to 28 male and 20 female patients. The mean age was 58.7 years (16-84). Table 2 shows the health care departments in which patients had been admitted and the indications for which they requested use of the antibiotic treatment.

The health care departments that issued the most prescriptions for ertapenem were the surgical ones (60%). The indications with the most prescription requests were community-acquired intra-abdominal infection, cholecystitis

Table 2 Distribution of prescriptions by department and indication

	Percentage of prescriptions (n)	Percentage of indicated prescriptions (n)[a]
Department		
Surgery	33.3 (16)	43.7 (7)
Emergency surgery	27.0 (13)	38.4 (5)
Intensive care unit		80 (4)
Observation	6.3 (3)	33.3 (1)
Others	23.0 (11)	54.5 (6)
Indication for treatment		
Aspiration pneumonia	10.4 (5)	60 (3)
Risk of *Escherichia coli* ESBL due to sepsis	25.0 (12)	33.3 (4)
Risk of *Escherichia coli* ESBL due to previous antibiotic treatment	25.0 (12)	50 (6)
Risk of *Escherichia coli* ESBL due to all three risk factors	33.3 (16)	44 (7)
Isolation of *Escherichia coli* ESBL	4.0 (2)	100 (2)
Unknown	2.0 (1)	2.0 (1)

ESBL indicates extended spectrum beta-lactamases.
[a]Prescriptions indicated following evaluation by the multidisciplinary group.

or pyelonephritis with some risk factor for *Escherichia coli* extended-spectrum beta-lactamases (ESBL) (83%).

Forty-eight percent% (n=23) of the ertapenem prescriptions met hospital protocol. The most frequent profiles for unsuitability were a lack of risk factors for *E coli* ESBL; for this situation, the treatment recommended by the IC was amoxicillin/clavulanic acid. In a lower number of prescriptions, patients presented a risk of infection by nosocomial microorganisms, in which case a broader-spectrum antimicrobial treatment was recommended (Table 2). The 3 most common *E coli* ESBL risk factors were as follows: patient older than 65, diabetic, having been hospitalised in the past year.

Unsuitability was related to the health care department and the prescribing doctor, although results were not statistically significant.

In all cases in which prescription was not suitable, an alternative antibiotic treatment was recommended: amoxicillin/clavulanic acid in 40% (n=10), piperacillin/tazobactam in 16% (n=4), imipenem/vancomycin in 12% (n=3), teicoplanin and ceftriaxone in 8% (n=2) and cloaxillin and gentamycin in 4% (n=1). In 61% of cases in which an alternative treatment was recommended, that treatment was accepted (15 prescriptions). The most common reason for not accepting the alternative was that the prescribing doctor suspected *E coli* ESBL, despite the patient not having any risk factors. The acceptance rate was 67%, 40%, 62.5%, and 75% during months 1, 2, 3, and 4, respectively, indicating that the highest percentage was reached in the last month.

There were no statistically significant differences in the mean age for each group.

The effectiveness of the antimicrobial treatment used for clinical resolution of the illness was 78% in the group with a suitable indication for ertapenem, 92% in patients receiving treatment with the proposed alternative, and 69% in those treated with ertapenem despite not meeting the IC's

indications. Differences were not statistically significant (table 3).

We detected a lower tendency of prolonged hospital stays among the group that accepted the alternative treatment compared with the group that did not, although the differences were not statistically significant (P=.07). However, The mean duration of treatment was shorter in the group that accepted the alternative compared to the one that did not and used ertapenem (2 days vs 7.4 days; P<.0001). We only found 25 patients who had undergone a microbiologic culture, and of these patients only 2 presented isolated *E coli* ESBL (8%).

Discussion

In our study, half of the prescriptions were not suitable; these results are similar to those recorded in antibiotic use studies[8,18] and in those similar to our own.[19]

The suggested change in treatment was accepted in more than half of all cases, which is a similar result to that recorded by other authors[20]; nevertheless, acceptance could have been increased if the multidisciplinary group had been formed before the study began. We observe that the best acceptance rate percentage was achieved in the last month of follow-up.

The fact that there were no statistically significant differences in effectiveness results among the 3 groups could be due to the small sample size, given that there was a tendency towards increased effectiveness in the group that accepted the recommended alternative treatment, and the percentage of re-admissions, the mean length of treatment and the mean hospital stay were higher in the group that did not accept the alternatives. This result is consistent with the study carried out by Barenfanger et al,[21] in which the mean hospital stay was reduced by 2.7 days in the intervention group.

Table 3 Effectiveness of the antimicrobial treatment actually used

	Group		
	Group 1 (n=23 patients)	Group 2 (n=12 patients)	Group 3 (n=13 patients)
Mean age, y	57.08	53.38	67
Percent male patients, n	39 (9)	75 (9)	77 (10)
Mean length of antibiotic treatment, d	8	2	7
Mean hospital stay, d	37	20	15.5
Results			
Effective treatment, % (n)	78.2 (18)	91.6 (11)	69.2 (9)
Not effective treatment, % (n)	21.8 (5)	8.4 (1)	30.8 (4)
Reasons for treatment failure			
Change in antibiotics % (n)	80 (4)	100 (1)	25 (1)
Re-admission, % (n)	0 (0)	0 (0)	50 (2)
Death, % (n)	20 (1)	0 (0)	25 (1)

Group 1 indicates patients whose initial indication was suitable for ertapenem according to the infection committee's (IC) criteria; group 2, patients for whom prescribing ertapenem did not meet IC recommendations and for whom the proposed alternative treatment was accepted; group 3, patients treated with ertapenem despite not meeting IC recommendations.

Our study measures the effectiveness of the antimicrobial treatment, unlike most antibiotic policy studies that evaluate results in reducing antibiotic consumption, costs or resistance rates after performing various interventions (restrictive and/or persuasive), but do not measure the effectiveness of the treatment that is actually used. This is the case in the study by García et al,[13] which achieves a reduction in the total consumption of antimicrobial drugs by putting together a multidisciplinary group similar to our own which evaluates all prescriptions of restricted antibiotics in the hospital in one year, and which recommends another treatment for cases in which the IC's conditions are not met.

The most important limitations of our study are, firstly, the prescribing health care departments, since the number of prescriptions was much higher in one than in the rest of the hospital departments; this could be a factor masking unsuitable use of this antibiotic, and therefore, the results cannot be extended to other hospital departments. The second limitation is not having included a measure of the severity of patients' conditions; however, the number of patients admitted to the intensive care unit was quite low, and logically, this population was in a more critical state than the rest.

We can conclude that constituting a multidisciplinary group to follow up on antibiotics is helpful in improving the use of ertapenem.

For future studies, it will be necessary to include a larger number of patients and measure the ecological impact of having a multidisciplinary group in a hospital to monitor antimicrobial treatments.

Acknowledgments

References

1. Alanis AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res. 2005;36:697-705.

2. Infectious Diseases Society of America. Bad bugs, no drugs: as antibiotic discovery stagnates, a public health crisis brews. Alexandria, VA: Infectious Diseases Society of America; 2004. [Accessed January 15, 2008] Available from: http://www.idsociety.org/badbugsnodrugs.html

3. Smolinski MS, Hamburg MA, Lederberg J. Microbial threats to health: emergence, detection, and response. Washington, DC: Institute of Medicine; 2003.

4. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE. Trenes in antimicrobial drug development: implications for the future. Clin Infect Dis. 2004;38:1279-86.

5. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG, et al. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial availability. Task Force of the Infectious Diseases Society of America. Clin Infect Dis. 2006;42:657-68.

6. Gyssens IC, Kullberg BJ. Improving the quality of antimicrobial drug use can result in cost containment. Pharm World Sci. 1995;17:163-7.

7. Holmberg SD, Soloman SL, Blake PA. Health and economic impacts of antimicrobial resistance. Rev Infect Dis. 1987;90:65-78.

8. House of Lords Select Committee on Science and Technology. Resistance to antibiotics. Session 2000-01. 3rd Report. London: The Stationery Office Ltd; 2001.

9. Avorn J, Solomon DH. Cultural and economic factors that (mis) shape antibiotic use: the nonpharmacologic basis of therapeutics. Ann Intern Med. 2000;133:128-35.

10. Interagency Task Force on Antimicrobial Resistance. Action plan to combat antimicrobial resistance; part 1: domestic. 2001. [Accessed February 12, 2008] Available from: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf

11. Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in healthcare settings, 2006. [Accessed January 20, 2008] Available from: http://www.cdc.gov/ncidod/dhqp/index.html

12. Timothy D, Owens R, McGowan J, Gerding D, Weinstein R, Burke J, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159-77.

13. García A, Varela J, Alonso P, López I, Seoane M, Pérez M, et al. Eficacia de la evaluación crítica diaria de las prescripciones de antibióticos restringidos. Farm Hosp. 1998;22:306-12.

14. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: a systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. J Antimicrob Chemother. 2003;52:764-71.

15. Nickman NA, Blissenbach HF, Herrick JD. Medical committee enforcement of policy limiting postsurgical antibiotic use. Am J Hosp Pharm. 1984;41:2053-6.

16. Bouza E, Cosín J; Grupo Cooperativo para el Estudio de la Infección. Estudio de Prevalencia hospitalaria y consumo de antibióticos. Med Clin (Barc). 1986;87:353-8.

17. Rodríguez-Baño J, Navarro MD. Impact of ESBL on empirical therapy and antibiotic policies. Enferm Infecc Microbiol Clin. 2007;25 Suppl 2:54-9.

18. Apisarnthanarak A, Danchaivijitr S, Bailey TC, Fraser VJ. Inappropriate antibiotic use in a tertiary care center in Thailand: an incidence study and review of experience in Thailand. Infect Control Hosp Epidemiol. 2006;27:416-20.

19. Apisarnthanarak A, Danchaivijitr S, Khawcharoenporn T, Limsrivilai J, Warachan B, Bailey TC, et al. Effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand. Clin Infect Dis. 2006;42:768-75.

20. Arnold FW, McDonald LC, Smith RS, Newman D, Ramirez JA. Improving antimicrobial use in the hospital setting by providing usage feedback to prescribing physicians. Infect Control Hosp. Epidemiol. 2006;27:378-82.

21. Barenfanger J, Short MA, Groesch AA. Improved antimicrobial interventions have benefits. J Clin Microbiol. 2001;39:2823-8.

22. Rodriguez-Baño J, Navarro MD, Romero L, Muniain MA, Perea EJ, Pérez-Cano R, et al. Clinical and molecular epidemiology of extended-spectrum beta-lactamase-producing Escherichia coli as a cause of nosocomial infection or colonization: implications for control. Clin Infect Dis. 2006;42:37-45.