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Therapeutic Drug Monitoring of Gentamicin in Patients with Bronchopneumonia: Cost Considerations and Patient Outcomes

Bronkopnömonili Hastaların Gentamisin İlaç Tedavisinin İzlenmesi: Maliyet Mulahazaları ve Hasta Çıktıları

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Abstract

Objective: In Malaysia, therapeutic drug monitoring (TDM) service started in the late 1980s. Serum concentration measurements depend on commercially available drug assays, which are costly. In the present study, we attempted to document the impact of TDM service on cost and patient outcomes.

Materials and Methods: We reviewed the medical records of the patients who were admitted to the hospital over a five-year period, diagnosed with bronchopneumonia and treated with gentamicin. Outcome measures were duration of fever, incidence of nephrotoxicity and length of hospital stay. We calculated the costs of laboratory and clinical investigations, the costs associated with the administration of gentamicin doses, the cost of providing TDM services, the costs associated with medical care by professional staff and the costs of hospital stays during gentamicin treatment.

Results: Sixty-six patients were found to meet the inclusion criteria (10 patients were provided with TDM service and 56 patients were not). There was no significant difference in the duration of fever or the length of hospital stay during gentamicin therapy between the two groups. Although serum creatinine levels were not checked in all of the patients after gentamicin therapy, the data analysis did not show any cases of nephrotoxicity. There was no significant difference in the costs of laboratory investigations, the total cost of gentamicin therapy and the costs associated with professional staff between the two groups. The cost of the hospital stay during gentamicin therapy and the total cost of hospitalization were significantly higher in the TDM group.

Conclusion: Evaluation in patients with bronchopneumonia shows that TDM in our setting was associated with higher cost; however, we did not observe any significant differences in the clinical outcomes.

Key Words: Bronchopneumonia, Cost evaluation, Malaysia, Patient outcome, Therapeutic drug monitoring

Özet

Amaç: Malezyada, terapötik ilaç izleme (TDM) hizmeti 1980'lerin sonlarında başladı. Serum konsantrasyonu ölçümleri piyasada bulunan pahalı ilaç deneylerine bağlıdır. Bu çalışmada, maliyet ve hasta çıktılarına TDM hizmet etkisini incelemeye çalıştık.

Gereç ve Yöntem: Beş yıl içinde hastaneye başvuran bronkopnömoni tanısı ve gentamisin ile tedavi edilen hastaların tıbbi kayıtları incelendi. Araştırmanın çıktılarında nefrotoksisite ve hastanede yatış süresini ateş, sıklığı süresi mevcuttu. Laboratuvar ve klinik araştırmaların maliyeti, gentamisin dozlarda uygulanması ile ilgili maliyetleri, TDM hizmetlerini sağlamanın maliyetinin, profesyonel personel tarafından tıbbi bakım ile ilgili maliyetler ve gentamisin tedavisi sırasında hastane masrafları hesaplanmıştır.

Bulgular: Dahil edilme kriterlerine uygun 66 hasta incelenmiştir (10 hasta TDM hizmeti almmış ve 56 hasta almamıştır). İki grup arasında gentamisin tedavisi sırasında ateş veya hastanede kalış süresini açısından anlamlı fark bulunmamıştır. Gentamisin tedavisi sonrasında hastaların serum kreatinin düzeyleri tümünde kontrol edilmemekle birlikte, veri analizinde nefrotoksisite vakası görülmemiştir. Laboratuvar tetkikleri, gentamisin tedavisi ve iki grup arasında profesyonel kadrosu ile ilişkili maliyetlerin toplam maliyetinin maliyetleri açısından anlamlı bir fark bulunmamıştır. Gentamisin tedavisi sırasında hastanede kalmak maliyeti ve toplam hastane maliyeti TDM grubunda anlamlı derecede yüksek bulunmuştur.

Sonuç: Bu çalışmada bronkopnömoni hastalarının değerlendirilmesinde TDM'in daha yüksek maliyet ile ilişkili olduğu görülmektedir, ancak klinik sonuçlar arasında anlamlı bir farklılık gözlenmemiştir.

Anahtar Kelimeler: Bronkopnömoni, Hasta sonucu, Malezya, Maliyet değerlendirme, Terapötik ilaç izleme

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Introduction

Therapeutic drug monitoring (TDM) service comprises of measuring drug concentration, generating individual patient's pharmacokinetic data, and interpreting such data together with other information about the patient's clinical conditions to optimise his/her drug therapy. Findings from studies that have evaluated the effects of TDM on patient outcomes have shown mixed results [1]. Favorable outcomes associated with TDM service include decreases in adverse effects, mortality rates and length of stay [2, 3]. Nevertheless, changes in these parameters are not always economically favorable. For example, a reduction in the mortality rate in the TDM group may increase the length of stay and morbidity, which would be associated with additional costs [4].

Studies that have evaluated the TDM service of aminoglycosides have shown significant reductions in aminoglycoside doses, incidences of nephrotoxicity, duration of therapy, and length of hospital stay. In addition, studies have demonstrated a faster resolution of infection in patients who received clinical pharmacokinetic service consultations compared with patients who did not. These studies of aminoglycosides also found significant cost savings in the TDM group compared with the control group [5-8].

TDM in Malaysia started in the late 1980s. The first study that evaluated the impact of TDM service showed an increase in the therapeutic concentrations of gentamicin from 38% to 67.6% of cases. In addition, toxic trough concentrations dropped from 30% to 12.8% [9]. To the best of our knowledge, there have not been any outcome studies of TDM in our country. The present study is a retrospective study of the impact of gentamicin TDM on cost and patient outcome in patients with bronchopneumonia.

Materials and Methods

The present study was performed at a public hospital in the northern state of Malaysia. The hospital has a 314-bed capacity with an average annual admission rate of 18,500 patients. A computer-generated list was provided by the medical records office. We reviewed the medical records of patients who were diagnosed with bronchopneumonia and treated with gentamicin from 2001 to 2005. The criteria for review included all adult patients (>18 years old) who were admitted to the medical wards, diagnosed with bronchopneumonia with a proven or suspected gram-negative infection, normal renal function, and treated with gentamicin for at least 72 h. This included all of the patients with and without the gentamicin TDM service. Patients who were first provided with TDM service 72 h after the initiation of gentamicin treatment, patients who received concurrent treatment with known nephrotoxic drugs (e.g., amphotericin B and cyclosporine) or patients with a past history of aminoglycoside toxicity were excluded from the review. Patients who were not provided with the TDM service served as the control group. The study was approved by the Director of Hospital Kulim, Malaysia.

Outcome measures were duration of fever, incidence of nephrotoxicity, and length of hospital stay (LOS). Fever was defined as more than one reading of daily body temperature 38˚C or higher. Nephrotoxicity was defined as a 50% increase in serum creatinine compared with the baseline level. The LOS was calculated as the duration that the patient was hospitalized during gentamicin therapy [10, 11].

We calculated the costs of laboratory and clinical investigations, the costs associated with the administration of gentamicin doses, the costs of providing TDM service, the costs associated with medical care by professional staff and the costs of the hospital stay during gentamicin treatment.

The costs of laboratory and clinical investigations were calculated from hospital charges of each specific test multiplied by the number of tests performed in the patient. The costs of providing the gentamicin TDM service was calculated by adding the fixed costs and the operating costs. Fixed costs included the costs of the physical facility, which were based on the size of the laboratory and the costs of the laboratory equipment. The costs of the laboratory equipment were calculated for the year 2005, assuming a 3% depreciation rate from the cost upon purchase [12]. Gentamicin represented 36% of all assays performed in the year 2005, and both the laboratory and equipment costs were adjusted accordingly. The operating costs were calculated from the costs of reagents, consumables, and professional staff (e.g., pharmacists, nurses, and doctors) salaries. The cost of providing medical care was calculated from the average duration that doctors and nurses spent attending to patients. The cost of the hospital stay during gentamicin therapy was calculated from hospital room charges and the duration of hospitalization during gentamicin therapy.

The data were analyzed using SPSS v. 12.0. Descriptive statistics were used accordingly. A chi-square test was used to identify associations among gender and ethnicity variables between the two groups. A Mann-Whitney test was used to identify the differences between the two groups regarding laboratory results, LOS, total gentamicin doses, the number of antibiotics given, the duration of fever, and the different hospitalization costs. A Kruskal-Wallis test was used to determine the age differences between the groups. In the present study, a p value <0.05 was considered statistically significant.

Results

The medical records listed 2193 patients who were hospitalized for bronchopneumonia over the 5-y period that was

assessed in the present study (2001 to 2005). Interestingly, 1189 patients were found to be hospitalized for at least 72 h. Only 872 medical records were available at the time of the study, and a total of 139 patients were found to be on gentamicin therapy. Seventy-three patients were excluded for various reasons: the duration of gentamicin therapy was too short in 49 patients, five patients had existing renal impairment, we had insufficient data for one patient, and 18 patients were rejected because TDM services were provided four days after the initiation of gentamicin treatment. Table 1 shows the demographic details of the patients in both of the groups. The patients in the control group were treated with a greater number of concurrent antibiotics compared with the patients in the TDM group; however, the difference was not statistically significant (Mann-Whitney test, p=0.115).

The majority of the patients in both of the groups were older than 36 years old. Although there were significant differences in gender between the two groups, there was no significant difference in the ethnicity or the age of the patients between the two groups. In the control group, the most common concomitant diseases were diabetes mellitus and hypertension, whereas ischemic heart disease was the most frequent disease in the TDM group. Interestingly, the patients in the control group had more diseases than the patients in the TDM group; however, there was no significant difference in the number of concomitant diseases between the two groups (Mann-Whitney test, p=0.990).

Table 1. Demographic characteristics of the control group and the TDM group

Demographics	Control group (n=56) N (%)	TDM group (n=10) N (%)	p value
Age* (years)			
18-25	2 (3.6)	1 (10.0)	0.316
26-35	6 (10.7)	0 (0.0)	
36-45	8 (14.3)	1 (10.0)	
46-55	9 (16.1)	4 (40.0)	
>55	31 (55.4)	4 (40.0)	
Total	56 (100.0)	10 (100.0)	
Mean±SD	54.9±15.4	54.0±16.6	
Median	57.5	51.5	
Range	20-84	24-87	
Gender†			
Male	41 (73.2)	3 (30.0)	0.008
Female	15 (26.8)	7 (70.0)	
Total	56 (100)	10 (100)	
Ethnic group†			
Malay	37 (66.1)	8 (80.0)	0.309
Chinese	5 (8.9)	1 (10.0)	
Indian	13 (23.2)	1 (10.0)	
Others	1 (1.8)	0 (0.0)	
Total	56 (100)	10 (100)	

*Kruskal-Wallis test, †chi-square test

In the control group, 41.1% of the patients were febrile before starting gentamicin treatment, whereas only 5.4% were febrile after therapy. In the TDM group, 50% of the patients were febrile during the pretherapy period, whereas no patient was febrile in the posttherapy period. There was no significant difference in the duration of fever or the length of hospital stay during gentamicin therapy between the two groups (Table 2). Serum creatinine data before gentamicin therapy were available for 53 patients in the control group and for all of the patients in the TDM group. However, not all of the patients had their serum creatinine checked after gentamicin therapy. The available data showed that none of the patients had a posttherapy serum creatinine value that had increased more than 50% compared with the baseline value.

The fixed costs and the operating costs were found to be MYR72.68 and RM24.55, respectively. These numbers were calculated by assuming the cost of providing TDM service of one gentamicin assay to be MYR97.23 (1 Euro ≈ MYR4.02). Table 3 shows the cumulative costs in the two groups. There were no significant differences in the costs of the laboratory investigations, the total costs of gentamicin therapy or the costs associated with professional staff between the two groups. The cost of the hospital stay during gentamicin therapy and the total cost of hospitalization were significantly higher in the TDM group (Mann-Whitney test; $p = 0.003$ and $p < 0.001$, respectively).

Discussion

Different studies have reported variations in the outcomes associated with the application of TDM [1]. In the present study, the outcomes of the patients who were provided with the TDM service did not differ from the patients who did not receive the service. However, the number of analyzable data was small despite a five-year data review. In addition, it was difficult to determine the overall incidence of nephrotoxicity because it was not a common practice to monitor serum creatinine after completion of gentamicin therapy. As a result, the number of patients with available posttherapy creatinine values was small, and the data from the available patients show that none of the patients had more than a 50% change in serum creatinine compared with the baseline values.

The patients in the control and TDM groups received an average of one concomitant antibiotic. Commonly used

Table 2. Outcome measures during gentamicin therapy

	Control group (n=56)			TDM group (n=10)			
Vital signs	Mean±SD	Median	Range	Mean±SD	Median	Range	p value
Duration of fever* (days)	2.3±1.9	1.0	1 to 7	4.0±3.7	4.0	1 to 10	0.352
Change in serum creatinine*	(n=6) -6.5%±28.5%	8.9%	-46% to 34%	(n=3) 6.9%±13.0%	6.3%	-6% to 20%	0.548
Length of hospital stay during gentamicin therapy (days)	5.4±2.9	4.0	3.0 to 20.0	6.5±3.1	5.5	3.0 to 13.0	0.133

*Mann-Whitney test

Table 3. Cost distribution among the control and TDM groups

	Control group (n=56)			TDM group (n=10)			
Cost type	Mean±SD (MYR)	Median (MYR)	Range (MYR)	Mean±SD (MYR)	Median (MYR)	Range (MYR)	p value†
Laboratory and clinical investigations*	46.30±44.80	37.00	10.00 to 320.00	36.80±13.30	39.50	10.00 to 57.00	0.727
Gentamicin dose	9.90±5.30	8.50	3.70 to 31.40	10.30±6.20	8.40	4.40 to 23.90	0.865
TDM service	-	-	-	252.79±131.25	194.46	194.46 to 583.38	-
Professional staff	21.50±11.90	16.00	12.00 to 80.20	26.10±12.60	22.10	12.00 to 52.10	0.133
Hospital stay during gentamicin therapy	11.00±22.70	6.00	4.50 to 175.00	36.60±62.40	13.50	6.00 to 210.00	0.003
Total	86.33±72.15	75.82	20.92 to 525.36	362.66±156.56	276.56	260.21 to 706.70	<0.001

*In the control group (n=53). †Mann-Whitney test

concomitant antibiotics were cefuroxime, ceftazidime, and penicillin G. The use of second- and third-generation cephalosporins in the treatment of pneumonia is consistent with the current recommendations [13, 14]. Interestingly, there was no significant difference in the number of antibiotics used between the two groups. The average duration of fever in the TDM group was higher than the control group, but the difference was not clinically significant.

Although the average duration of the hospital stay during gentamicin therapy was longer in the TDM group compared with the control group, the difference was not significant. Because of the nature of the retrospective study, it was difficult to assess the influence of the severity of the disease on the duration of hospital stay. Nevertheless, there was no significant difference between the two groups in the number of concomitant disease states. Destache et al. compared two groups of adult patients (i.e., TDM vs. non-TDM) who were treated with aminoglycosides in a tertiary care facility and did not find any significant difference in the length of hospital stay between the two groups [6]. Although Destache et al. observed a significant difference in the number of concomitant diseases between the control and TDM groups, there was no effect of any one of these diseases on the duration of hospital stay. Bootman et al. [4] reported a longer length of stay in patients who were monitored by TDM service for gentamicin compared with patients who did not have this service. They argued that TDM service might contribute to the increased survival rate of patients, which would result in an increased duration of therapy and a longer hospital stay.

Each patient received the standard laboratory and X-ray investigations when admitted to the medical ward, which might explain why there was no significant difference in the costs of laboratory and clinical investigation tests between the two groups. In our setting, gentamicin doses are given as an intravenous bolus without any additional consumables, which minimizes the total cost. As a result, the cost associated with the administration of each gentamicin dose constituted only 2.9% and 11.4% of the total hospitalization costs in the TDM and control groups, respectively.

The costs associated with the TDM service contributed to approximately 70% of the total hospitalization costs. The costs that were estimated for TDM laboratory space, laboratory equipment, reagents and consumables represented approximately 95% of the total TDM service cost. Because the

TDM laboratory uses commercially available reagent kits purchased from vendors, the cost of these reagent kits increased the total cost of the reagents and consumables. In the present study, a depreciation rate of 3% was applied for the laboratory equipment that was used for the gentamicin monitoring [12,15]. The depreciation rate for the purchased cost of the equipment only resulted in a slight reduction in the total cost.

In our setting, hospital stay charges are based on three different categories: MYR70, MYR20 and MYR3 for the first class, second class and third class, respectively. The category of hospital stay charges depends on each patient's economic and employment status. In the TDM group, approximately 30% of the patients were imposed with the first- and second-class charges. In the control group, all but one of the patients was charged the third-class category. Nevertheless, the costs associated with the hospital stay during gentamicin therapy were not significantly high and only contributed 10.1% and 12.8% to the total hospitalization costs in the TDM and control groups, respectively.

In conclusion the TDM service cost represented more than two-thirds of the total hospitalization costs. Although the cost of the hospital stay during gentamicin therapy and the total cost of hospitalization in the TDM group were significantly higher than the costs in the control group, we did not observe any significant differences in the clinical outcomes.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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