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A Survey of Linezolid Prescription Before and After Protocol Implementation in a Teaching Hospital

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ABSTRACT

Background: Linezolid has been recognized as a safe and effective medicine against a wide variety of Gram-positive pathogens. The primary objective of this study was to assess utilization appropriateness of linezolid and explore the efficiency of protocol intervention to proceed to rational drug usage.
Methods: The project was conducted in a referral teaching hospital from September 2015 to January 2017 in two phases. In the first step, a six-month survey was performed to evaluate the prescribing appropriateness of linezolid. Patients receiving linezolid were identified using hospital information system and the medical charts were analyzed based on accurate indications and duration of linezolid prescription. Subsequently, a restrictive protocol was developed and communicated after a consensus by Drug and Therapeutics Committee in May 2016. After introduction of the protocol, an active daily surveillance of patients was done by hospital pharmacists. The appropriateness of linezolid utilization and infectious consultations according to UpToDate and Sanford Guide to Antimicrobial Therapy were compared before and after protocol implementation.
Results: In the first phase of the study, the indication of linezolid was appropriate in 52.9% of cases (27 out of 51 patients) and improved considerably to 72.9% (35 out of 48 patients) after protocol enforcement (P: 0.04). Furthermore the duration of the linezolid consumption was correct in 66.6% of patients (18 out of 27), increasing to 88.5% (31 of 35) after protocol introduction (P: 0.07). In the first step, 56.9% of linezolid prescriptions were based on infectious disease consultation which enhanced remarkably to 87.5% in the second step (P: 0.001), while, 65.5% and 73.8% of these consultations were appropriate in the study surveys respectively.
Conclusion: The protocol intervention could improve appropriate prescribing of linezolid in the hospital setting. However, ongoing audit studies are recommended to maintain the rational prescription of linezolid.

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Introduction

Rationalizing the use of antibiotics especially those which are considered as the golden resource has been always the top priority of antibiotic stewardship programs all over the world (1). Irrational use of antibiotics both in community and hospital setting has been recognized as a global concern especially in developing countries (1, 2).

Rational use includes the prescription of the appropriate medication with correct dose, for an adequate period of time, and at the lowest cost according to the World Health Organization (WHO) definition. Criteria for appropriate use include evidence-based treatment guidelines, therapeutic benefits, safety, and cost-effectiveness (3).

Drug utilization methods may lower the rate of irrational prescription of the medicines. A number of these methods have been successfully applied in various countries (4, 5). Drug Utilization Evaluation (DUE) is one of the study methods which can be used to measure the appropriate prescription of medicines and can improve the therapeutic outcomes (5).

Linezolid belongs to a novel class of antibiotics called oxazolidinones and represents anti-microbial activity spectrums which covers a wide variety of Gram-positive pathogens especially those resistant to methicillin and vancomycin (6, 7). Linezolid possesses 100% bioavailability after oral and intravenous administration and is available in both dosage forms (6, 8).

However, resistance to linezolid has been observed recently, particularly among enterococci and coagulase-negative staphylococci species (9). Therefore, drug utilization studies should be applied to understand how linezolid has been prescribed and used in hospitals. The ultimate aim of DUE studies is to achieve optimal use of drugs. The quality assessment of these studies determines and enables interventions to overcome the identified problems (10).This study aimed to characterize the rate of linezolid appropriate use, and evaluate the impact of the new restriction policy on rational prescription of linezolid in the hospital.

Methods

The present study was conducted in Imam Khomeini Hospital Complex, a multi-specialty tertiary care hospital from September 2015 to January 2017. This survey did not need Ethics Committee approval as the patient information was not included in the study.

Prescription of Linezolid was the only inclusion criteria for patients during the study. In this context, patients received linezolid were identified in two different time periods including pre-intervention (September 2015 to March 2016) and protocol implementation (May 2016 to January 2017) surveys.

A data collection form was designed by pharmaceutical care department and filled by a pharmacist on a daily schedule. The following data were extracted from patients' medical documents: demographic information; culture and sensitivity results; vancomycin contraindications; previous antibiotic use for the same infection; data on linezolid prescription (indication and duration of prescription).

Following the analysis of the results obtained from the first survey, a restrictive protocol was communicated after a consensus by Drug and Therapeutics Committee in May 2016. Then, linezolid was introduced as an antibiotic that could only be prescribed for approved indications and was subject to ongoing surveillance by the hospital pharmacists. The main justification for prescribing linezolid was considered as the presence of positive blood culture indicating Vancomycin-Resistant Entrococcus (VRE) or infectious consultation identifying vancomycin treatment failure (after 5 days of administration), or vancomycin contraindications. The vancomycin contraindication was defined as a history of vancomycin intolerance including nephrotoxicity following vancomycin administration (two successive tests indicating an absolute increase in serum creatinine levels by 0.5 mg/dl or a relative rise in serum creatinine by 50% from the baseline) and vancomycin hypersensitivity reactions (11).

According to the protocol, the hospital pharmacists verifying the physician order were responsible for reviewing whether the prescription meets the mentioned criteria and should contact the prescriber if there was a discrepancy.

Using the information derived from the patients' files, we rated the appropriateness of linezolid use based on recommendations provided by UpToDate 20.2 and Sanford Guide to Antimicrobial Therapy (12, 13).

Data were analyzed using SPSS. 22 and a p-value lower than 0.05 was considered as statistically significant. Chi-squared and t-test were used to analyze possible associations between variables.

Results

A total of 99 patients receiving linezolid were included in two study surveys (51 and 48 patients, respectively). Demographic characterization of patients including gender, age, death during hospitalization, and the length of stay were similar between the study groups (P> 0.05) (Table 1).

In the first six-month survey, the main sources of linezolid consumption were the intensive care unit (ICU) (29 patients, 56.8%), Liver Transplant (5 patients), and Hematology (4 patients, 7%) departments. Similarly in the second survey, the ICU accounted for the highest amount of linezolid prescription (18 patients, 37.5%) followed by Liver Transplant (10 patients, 20.8%), and Internal sectors (7 patients, 14.5%).

In both phases of the study, the majority of patients received some form of antibiotic before initiating linezolid treatment. In these patients, vancomycin,

Table 1. Demographic information of the study patients.

Parameter	Pre-intervention survey	Post-intervention survey
Patients (n)	51	48
Male (n)	24	23
Age range (year)	0-86	0-80
Ward (n)	15	16
Death during hospitalization (n)	23	17
Length of stay (day)	43.5±1.5	46.2±0.9

meropenem, and ciprofloxacin were the most common agents respectively. Linezolid was used concomitantly (more than a two-day overlap) with meropenem in 61% of patients. Amikacin was the second common antibiotic prescribed concomitantly with linezolid (27%).

Table 2 demonstrates the prescription appropriateness of linezolid during the study surveys. In pre-intervention survey, the indication of linezolid prescription was assumed appropriate in 52.9% of patients, increasing significantly following the introduction of protocol (P=0.04). The appropriate duration was measured for patients who received linezolid for correct indications. The correct duration of linezolid consumption was improved after the intervention, and the difference was marginally significant (P=0.07). Moreover, as outlined by the protocol, the initiation of linezolid most be justified by positive VRE evidenced in blood culture or infectious consultation. Accordingly, the number of infectious consultation increased remarkably after protocol implementation (P< 0.05).

Considering the pathogen sensitivity pattern, infection in 19 and 21 patients of the study surveys were due to VRE and majority of the cases were in ICU departments (8 patients in each group).

In 23.5% of pre-intervention (12 out of 51 patients) and 35.4% (17 out of 48 patients) of post-intervention surveys, concurrent infectious consultation and positive blood culture were the main reasons for prescription of linezolid.

With regards to the distribution of linezolid prescription in hospital wards, the majority (16 cases out of 18) of inappropriate case of linezolid usage were detected in ICU before intervention which corrected after protocol enforcement (no inappropriate indication was observed in the ICU).

In pre-intervention survey, two patients received linezolid due to adverse drug reactions to vancomycin (hypersensitivity reaction and nephrotoxicity). However, in the second survey, the nephrotoxicity led to substitution of vancomycin with linezolid in three patients, and hypersensitivity reaction to vancomycin was reported in one patient.

Table 3 indicates the appropriateness of infectious consultations based on culture, vancomycin treatment failure, and vancomycin contraindications. It has been illustrated that 65.5% and 73.8% consultations in both study surveys were appropriate according to agreed criteria and the comparison of the study groups showed no significant difference (P= 0.45).

Table 2. The prescription appropriateness of linezolid during the study period.

Linezolid usage overview	Pre-intervention N: 51	Post-interventionN: 48	P value
Correct indication (n/%)	27 (52.9 %)	35 (72.9 %)	0.04
Positive blood vancomycin-resistant Enterococci[1] (n)	19	21	0.65
Vancomycin treatment failure (n)	6	10	0.22
Vancomycin contraindications (n)	2	4	0.35
Correct duration (n/%)	18 (66.6 %)	31 (88.5 %)	0.07
Infectious consultation (n/%)	29 (56.9%)	42 (87.5%)	0.001

[1] VRE: Vancomycin-resistant Enterococci

Table 3. The appropriateness of infectious consultation based on the agreed criteria.

Consultation criteria	Pre-interventionN: 29	Post-interventionN: 42	P-value
Appropriate	19 (65.5%)	31 (73.8%)	0.45
• VRE	12	17	
• Vancomycin contraindication	2	4	
• Vancomycin treatment failure	5	10	

VRE: Vancomycin-resistant Enterococci

Discussion

The present study provides a comprehension of linezolid usage in a tertiary care teaching hospital in Iran. In the initial survey on prescription of linezolid, excessive inappropriate utilization was detected. Due to complications of inappropriate prescription of antibiotics, reformative intervention was required.

Excessive and inappropriate antibiotic consumption could promote to development of bacterial resistance and enhance the financial burden of healthcare and adverse effect of drugs. So the appropriateness of linezolid prescription and the emergence of linezolid-resistant strains could be correlated (14, 15).

Irrational prescription of antibiotics has been a universal concern, particularly in the developing countries. (16) An accumulative number of studies have proved the inappropriateness rate of about 41-91% for prescription of all antibiotic in teaching hospitals (17).

Several strategies have been suggested to monitor and manage antibiotic consumption, including formulary replacement or restriction, order form development, education, feedback, and approval requirement from an infectious disease specialist for prescription of antibiotics (1, 4, 14, 18).

According to our protocol, linezolid could be used only for the Gram-positive infections due to vancomycin-resistant Enterococci or subject to prior approval by an infection specialist. In this study, after the restriction policy enforcement, the rate of optimal prescription increased considerably. This data and the findings of other studies performed in developed countries highlight the effective role of antibiotic surveillance programs to rationalize the prescription of antibiotics (11, 19, 20).

In a review by Tunger et al., a considerable rate of antibiotic prescribing was reported in general medical wards. Similarly other studies demonstrated a great proportion of antibiotic prescription in general departments (2, 3, 20). But in our study both before and after initiation of the linezolid-restriction policy, the most frequent wards for linezolid consumption were intensive care units. This finding confirms the higher incidence of vancomycin-resistant Enterococci in intensive care units of our hospital.

The mean duration of hospitalization in this study was 44.8 days which was consistent with another study conducted in selected provinces of Canada reporting 40.6 days as the average length of hospitalization in patients treated with linezolid (11).

In the pre-intervention survey, the majority of inappropriate indications were detected in intensive care units. However, other studies represented the higher rates of inappropriate antibiotic prescription in surgical wards possibly due to obstacles in the diagnosis of surgical infections (21).

In a previously discussed study in Canadian provinces, linezolid was prescribed appropriately in 50% of patients, and was consumed commonly in skin and soft tissue infections (32%) (11). However, our study in a teaching hospital in Tehran revealed a relatively better rate of optimal prescription of linezolid even before intervention (52.9%).

In a DUE study of carbapenems, linezolid, and teicoplanin in another teaching hospital in Tehran province, linezolid had the least usage (n=13, 9.55%) and the least inappropriateness (30.8%) among the four studied antibiotics (22). However, we detected high rate of linezolid prescription and inappropriate indications in our teaching hospital (47.1%).

Our results highlighted that infections due to VRE were limited primarily to the intensive care units. Nevertheless, the distribution of positive VRE in other departments is alarming. This data is in parallel to the findings of Ziglam et al., in the UK but they demonstrated sporadic distribution of resistant strains in renal unit (19).

In our study, the VRE infections were observed in about 40% of the study cases. However, in an antimicrobial susceptibility investigation among Enterococcus species during 2013-2014 in a hospital in Tehran, 90.9% of Enterococcocus Faecium was resistant to vancomycin. According to these findings, the pattern of antibiotic resistance has been changed; and vancomycin-resistant enterococci are emerging problem. Though, none of the isolated samples were resistant to the linezolid (23).

In addition to the restriction policy, other interventions such as educating programs, development of local treatment guidelines, and the constitution of an antibiotic

monitoring team compromising a pharmacist, clinical microbiologist and infectious disease specialist could be beneficial in order to rationalize antibiotic utilization in the future (20).

The restriction policy offered by this study was effective to decrease the linezolid inappropriate prescription. Ongoing audit studies are recommended to achieve and maintain the rational prescription of antibiotics.

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