Hereditary Neuropathy Unmasked by Levofloxacin

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Clinical Pharmacist Intervention for Patients with Left Ventricular Assist Devices

TO THE EDITOR: The prognosis for patients with heart failure remains very poor, with a 5-year survival rate of approximately 50%.[1] Left ventricular assist devices (LVADs) have been shown to increase significantly both survival and the quality of life of patients with advanced heart failure.[2] Unfortunately, these devices expose patients to many serious complications, including bleeding, thromboembolism, and infection. Consequently, patients with LVADs are usually prescribed antiplatelet agents, anticoagulants, antimicrobials, and heart failure pharmacotherapy.[3] This complex regimen exposes patients with LVADs to potential drug-therapy problems.

Recent guidelines advocate pharmacist involvement with the interdisciplinary LVAD team.[4] We describe clinical pharmacist involvement in the multidisciplinary care of patients with LVADs.

Methods. This review was conducted with institutional review board approval at a large, urban, tertiary care center. In July 2009, the heart failure clinical pharmacy program was expanded to include management of inpatients with LVADs. All patients subsequently admitted to the Cardiothoracic Surgery (CTS) service who received an LVAD from July 1, 2009, to June 30, 2010, were eligible for inclusion in this project. Ambulatory patients with LVADs who were readmitted to the Advanced Heart Failure (AHF) service were also included. Data collection included demographics, medical history, and medications. The primary endpoint was the number of interventions by the rounding clinical pharmacist. During the study period, interventions by operational pharmacists were not included. Clinical pharmacist interventions were also categorized according to drug class (eg, antibiotic, anticoagulant) and type (eg, dose correction, discontinuation of unneeded therapy). Data were analyzed with descriptive statistics.

Results. During the data collection period, 30 patients were admitted to the CTS service and 32 were admitted to the AHF service (71% male, 58% white). Because some of the ambulatory patients with LVADs were readmitted more than once, the total number of encounters in the AHF service was 75. The clinical pharmacist documented 400 interventions in patients with LVADs (262 interventions on the CTS service, average 8.7 interventions per patient encounter; 138 interventions on the AHF service, average 1.8 interventions per patient encounter). Overall, the most common type of pharmacist intervention was change in dose/route/frequency (33%), followed by starting therapy (31%), discontinuing therapy (18%), ordering a laboratory test (12%), and changing therapy (6%). The most common reason for pharmacist intervention was treatment of a disease or condition that was not controlled on present therapy (36%), followed by dose correction (17%), improved monitoring of drug therapy (13%), and adverse drug reaction/drug-drug interaction (11%). Antimicrobial agents was the most frequent medication class involved in pharmacist intervention (Table 1).

Discussion. Patients with chronic heart failure are susceptible to negative clinical outcomes secondary to drug-related problems.[5] Studies have demonstrated that inclusion of a pharmacist in the multidisciplinary care of patients with chronic heart failure can reduce mortality and hospitalization rates.[6] To our knowledge, our study is the first to assess the potential value of a pharmacist in the care of patients with heart failure after LVAD implantation. It demonstrates that a clinical pharmacist on the team has significant opportunity for drug-therapy intervention. The majority of the interventions were with antimicrobial agents, while only 12% of the interventions related to heart failure medications. This is to be expected, as infection is one of the most common complications of device therapy. Furthermore, studies in patients with heart failure who do not have LVADs have suggested that the majority of drug-related adverse outcomes are associated with non–heart failure medications.[5]

Our project was limited by the small sample size, which precludes a cost-savings analysis or an assessment of the impact of the pharmacist on clinical outcomes (ie, readmission, mortality). Larger studies in these areas that include outpatient LVAD clinic settings may lend further support for establishing LVAD clinical pharmacy services. Institutions with LVAD programs should strongly consider allocation of resources toward training and deployment of dedicated pharmacy personnel to assist with the care of these patients.

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Table 1. Pharmacist Intervention by Drug Class			
Drug Class	**CTS, %**	**AHF Service, %**	**Total, %**
Antimicrobial	32.4	63.7	43
Heart failure[a]	12.2	12.3	12
Other cardiovascular[b]	13.7	3.6	10
Antiplatelet or anticoagulant	3.4	4.3	4
Gastrointestinal	8.4	1.4	6
Endocrine	3.4	1.4	3
Pain/central nervous system	6.1	3.6	5
Pulmonary	2	1.4	2
Gout	2	4	2
Fluids, electrolytes	11.8	4.3	9
Other	3.8	0.7	3

AHF = advanced heart failure; CTS = cardiothoracic surgery.
[a]Includes diuretics, β-blockers, angiotensin converting enzyme inhibitors, digoxin, spironolactone, hydralazine, and oral nitrates.
[b]Includes antiarrhythmic and cholesterol-lowering medications.

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Hereditary Neuropathy Unmasked by Levofloxacin

TO THE EDITOR: Levofloxacin, a fluoroquinolone antibiotic with usefulness in a broad range of bacterial infections, is associated with a number of adverse events.[1] Involvement of the peripheral nervous system is considered infrequent and variable.[2] Reports on the effect of the drug in patients with hereditary neuropathy seem to be lacking in the medical literature. We describe a case in which the relationship between levofloxacin and the onset of polyneuropathy seems possible.

Case Report. A 56-year-old man (weight 92 kg) received levofloxacin 500 mg once daily for prostatitis. On the third day of treatment, the patient gradually developed difficulty in walking, diffuse numbness, and burning pain and weakness of the limbs that was more prominent in his legs. The administration of levofloxacin was stopped on the tenth day of treatment, and no other therapy was administered. The patient had no history of medical problems, use of medications, contact with neurotoxic substances, or prior exposure to fluoroquinolone antibiotics. He had never complained of muscle weakness or sensory disturbances, and he had continued to work and exercise until the onset of the prostatitis.

On examination, the patient showed pes cavus; bilateral foot drop; absent tendon reflexes; mild reduction of pain, temperature, vibration, and position sense over the distal portions of the extremities; as well as distal muscle weakness that was more prominent in the lower extremities. The plantar responses were not evaluated. The cranial nerves were intact, and there was no bladder or bowel dysfunction or other dysautonomia. The electromyographic examination revealed findings of a mixed demyelinating and axonal motor and sensory polyneuropathy (Table 1). Results of the examination of the cerebrospinal fluid were normal. The systematic investigation of other causes of polyneuropathy or concurrent illness was negative.

The electromyographic examination of the patient's father and only brother revealed findings compatible with a mild subclinical mixed demyelinating and axonal polyneuropathy. The molecular genetic analysis revealed the existence of the most common type of hereditary motor and sensory neuropathy or Charcot-Marie-Tooth disease.

On reexamination 6 and 12 months later, the patient's clinical picture was unchanged. The patient's father and brother remained asymptomatic.

Discussion. Our patient was diagnosed as having an asymptomatic hereditary polyneuropathy. The onset of the symptomatology could be explained as the initial manifestation of the hereditary polyneuropathy. However, the lack of neuropathy symptoms in the patient's history, as well as the acute onset and rapid evolution of symptoms from the peripheral nervous system in temporal sequence to the initiation of therapy, was consistent with drug-related neuropathy. Moreover, the Naranjo adverse drug reaction probability scale[3] suggested that levofloxacin was a possible cause of the appearance of the polyneuropathy.

Charcot-Marie-Tooth disease is a clinically and genetically heterogeneous group of hereditary peripheral neuropathies. Toxic or idiosyncratic reactions to drugs may uncover a preexisting asymptomatic polyneuropathy.[4] Fluoroquinolones, including levofloxacin, have rarely been associated with sensory and motor polyneuropathy,[2] perhaps because of the fact that physicians sometimes have difficulty in associating this adverse reaction with fluoroquinolone therapy.

In conclusion, the relationship between levofloxacin and the onset of the apparent polyneuropathy seems to be plausible. Prescribers and users of levofloxacin should be aware of this possibility. Levofloxacin should be considered as a cause in cases of rapidly progressive polyneuropathy.

Table 1. Electrophysiologic Data of the Patient and Family Members

Electrophysiologic Tests		Patient[a]		Father	Brother
		First Examination	Second Examination		
Motor nerve conduction					
Median	Ampl (mV)	13.4	11.7	12.5	13.0
	DL (msec)	11.2	13.2	8.5	8.8
	CV (m/sec)	46.5	40.0	46.7	50.0
Peroneal	Ampl (mV)	1.8	0.5	1.2	1.9
	DL (msec)	24.5	26.7	16.5	14.0
	CV (m/sec)	20.2	18.7	35.2	38.6
Sensory nerve conduction					
Sural	Ampl (μV)	3.9	2.8	8.4	7.2
	DL (msec)	3.7	4.2	3.5	3.2
	CV (m/sec)	35.7	29.2	36.4	37.5

Ampl = amplitude; CV = conduction velocity; DL = distal latency.
[a]The first examination of the patient was carried out 14 days after the beginning of symptoms, while the second examination was carried out 12 months later.

In cases with suspected polyneuropathy, fluoroquinolone antibiotics must be administered with extreme caution.

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Comment: Outcomes Associated with AUC_{24}/MIC Nomogram Dosing of Vancomycin

TO THE EDITOR: We have read with interest the recent letter of Michalets et al. describing outcomes associated with the ratio of the area under the 24-hour serum concentration-versus-time curve from zero to 24 hours to the minimum inhibitory concentration (AUC_{24}/MIC) nomogram dosing of vancomycin.[1] In therapeutic guidelines, Rybak et al. recommended that an AUC_{24}/MIC ratio ≥400 is necessary to obtain adequate vancomycin efficacy.[2] If the MIC is ≤1 mg/L, an AUC ≥400 mg•h/L would be sufficient. Therefore, a nomogram was proposed for AUC calculation by Michalets et al.[1,3]

The nomogram is based on the equation AUC_{24} (mg•h/L) = vancomycin total daily dose (mg/24 hours)/[(CrCl(mL/min) × 0.79) + 15.4] × 0.06. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation.

To test the accuracy of this nomogram, we compared steady-state AUC_{24} values obtained using the nomogram above to those obtained using a Bayesian estimation in a sample of patients admitted to the Maastricht University Medical Center.

Methods. We calculated the AUC values of 12 patients recently admitted to our hospital, using 2 different methods. The first method was nomogram dosing of vancomycin using the equation above. The other method was maximum a posteriori Bayesian estimation (MW/PHARM 3.60, Mediware, the Netherlands)[4] using both peak and trough and sometimes in-between (middle) vancomycin concentrations. These concentrations were measured during routine patient care. For calculation of individual pharmacokinetic parameters, at least 1 peak and 1 trough vancomycin plasma concentration should be available.[5] A 2-compartment open population model was used. Bayesian priors from the population, established and routinely used in our institute, were applied: V_1 0.21 ± 0.04 L/kg, k_{elm} 0.0143 ± 0.0029 h^{-1}, k_{slope} ($k_{elr} = k_{slope} \times$ CrCl (mL/min)), 0.00327 ± 0.00109 h^{-1}/mL/min, k_{12} 1.12 ± 0.28 h^{-1}, and k_{21} 0.48 ± 0.12 h^{-1}, where V_1 is volume of distribution central compartment; k_{elm}, metabolic elimination rate constant; k_{slope}, renal elimination rate constant; k_{elr}, renal elimination rate constant; k_{12}, rate constant from the 1st to the 2nd compartment; and k_{21}, vice versa.

Results. The individual results and calculated steady-state trough and peak concentrations are shown in Table 1. According to routine automated susceptibility testing (BD Phoenix, Becton Dickinson Co., Pont-de-Claix, France) of strains (*Staphylococcus aureus* or coagulase-negative staphylococci) isolated from cultures on blood samples collected from our patients, MIC values of ≤1 mg/L were found.

As can be seen, there is a large difference in the AUCs obtained using these 2 methods. The AUC measured with the Bayesian method was >400 mg•h/L for all patients. However, the AUC determined with the nomogram method was much lower (mean 61.7% of Bayesian AUC) for most patients. There was no significant correlation between the AUCs calculated with the 2 methods. The steady-state trough concentrations were in the conventional range and lower than the range advised by the therapeutic guidelines (15-20 mg/L).[2]

Discussion. According to our measurements, the nomogram for vancomycin dosing does not produce adequate results. We believe that this is because of the many presumptions in the equation. Moreover, CrCl calculated from plasma concentrations only approximates CrCl and the glomerular filtration rate. Vancomycin clearance does not correspond with the CrCl, since there is significant variability in the nonrenal clearance component. This is particularly evident in patients with impaired renal function. Furthermore, the variability in the volume of distribution is large, as can be seen in Table 1. Data obtained with use of the nomogram are in concordance with previous findings.[6,7]

In our opinion, an AUC should be calculated with the help of maximum a posteriori Bayesian estimation, and at least 1 peak and 1 trough plasma concentration of vancomycin should be included in the calculations of the individual pharmacokinetic parameters and, with that information, the AUC.

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Table 1. Pharmacokinetic Characteristics of Vancomycin-Exposed Patients

Patient	Age, y	Dose/24 h, mg	CrCl, mL/min	Vancomycin Clearance, mL/min	V_d, L	AUC Bayesian, mg·h/L	AUC Nomogram, mg·h/L	C_{min}, mg/L	C_{max}, mg/L	Peak/Middle/Trough Concentration, n
1	60	1100	69	40	43	458	262	12.5	39.9	2/1/4
2	53	750	83	27	89	460	154	12.9	45.6	9/10/9
3	56	1400	73	50	57	462	321	12.1	44.4	3/0/2
4	78	1000	67	35	109	473	244	12.3	60.5	3/1/3
5	64	450	40	18	118	427	160	15.8	26.6	1/4/0
6	68	2000	87	76	52	438	395	9.5	46.4	2/0/3
7	48	1000	85	34	35	488	202	8.9	63.5	1/0/2
8	71	1100	59	44	27	421	297	8.8	40.7	2/0/2
9	57	1500	74	51	47	493	340	12.5	47.3	2/0/3
10	86	1000	31	38	67	444	419	12.2	39.6	2/0/2
11	29	700	44	27	39	427	231	10.2	41.1	2/0/2
12	52	1800	95	66	94	452	331	13.9	34.4	1/0/1
Mean (± SD)	60 (15)	1150 (453)	67 (20)	42 (17)	65 (30)	454 (23)	280 (86)	11.8 (2.1)	44.2 (10.1)	

AUC = area under the curve; C_{max} = maximum concentration; C_{min} = minimum concentration; CrCl = creatinine clearance; V_d = volume of distribution.

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AUTHORS' REPLY: We appreciate the interest and response regarding our vancomycin nomogram as expressed by Croes et al. Investigators and clinicians should continue to evaluate methods of AUC₂₄/MIC calculations and more importantly, clinical outcomes of AUC₂₄/MIC goal-directed dosing. Croes et al. reported vancomycin dosages and MIC values in 12 patients with bacteremia; however, information was not provided on patient weights, stability of renal function, weight-adjusted volumes of distribution, vancomycin dosing regimens, or whether there was a systematic way in which vancomycin doses were derived.

Measurement of multiple peak and middle concentrations is not part of routine clinical practice in most US institutions as reported by Croes et al. Their routine practice included obtaining a mean of 2.5 peak concentrations per patient in each of 12 patients; 1 patient had 9 peak concentrations obtained. Four of the patients had middle concentrations obtained, and all but 1 of the patients had a mean of 2.7 trough concentrations per patient obtained. The vancomycin dosing reported by Croes et al. for their patients resulted in a mean trough concentration of 11.8 (2.1) μg/mL compared with 20.7 (10.8) μg/mL in our 67 nomogram dosed patients. Their concentrations were used to calculate AUC₂₄ using an a posteriori Bayesian estimation equation. The Bayesian-derived AUC₂₄ was compared to the AUC₂₄ calculation developed by Moise-Broder[1] and not to our prospective dosing nomogram.

Our dosing nomogram was based on achieving an AUC₂₄/MIC of at least 400 using the Moise-Broder equation.[1] The original equation for AUC₂₄/MIC calculation was developed and validated by Moise-Broder et al. by evaluating a subset of 31 patients with *S. aureus* and diagnostic evidence of lower respiratory tract infection. Measured AUCs using a minimum of at least 4 serum concentrations per patient were compared to calculated AUCs during the initial software validation. Comparison of measured and calculated AUC₂₄ values demonstrated precision (r^2 = 0.935) with a median –5.2% error. Furthermore, 21 of the patients had a predicted AUC₂₄/MIC within 15% of the measured AUC₂₄/MIC and 27 had a predicted AUC₂₄/MIC within 25% of the measured AUC₂₄/MIC. Both clinical and microbiologic superiority was demonstrated in the patients who achieved an AUC₂₄/MIC of at least 400 using the validated AUC₂₄ calculation.

The intent of our study was not to validate the Moise-Broder AUC₂₄ calculation but rather to evaluate a new dosing nomogram. We evaluated 67 patients for achievement of goal-calculated AUC₂₄/MIC and trough concentrations of at least 15 μg/mL and for nephrotoxicity compared to a traditional dosing method of 15 mg/kg/dose in 66 patients. Croes et al. did not derive prospective doses using our nomogram but rather have compared their a posteriori Bayesian AUC₂₄ estimations to the Moise-Broder et al. validated AUC₂₄ equation. Importantly, our prospective dosing nomogram achieved desirable outcomes, with only 10.3% of patients achieving a trough concentration less than 10 μg/mL, considered a marker for poor outcomes. Their analysis found that the Moise-Broder calculation appeared to underestimate the AUC₂₄/MIC when compared to their Bayesian methods. Of note, underestimation of AUC₂₄/MIC would lead to higher doses and a higher likelihood to achieve adequate tissue concentrations. Our dosing methods did not indicate increased

toxicity with the higher nomogram doses when compared to traditional dosing.

Limitations in the Croes et al. data include a small number of patients along with the inherent crucial dependence of Bayesian estimations on a priori population pharmacokinetic components. The a priori pharmacokinetic components were previously derived in Croes et al.'s institution, but no information is provided on how many patients were used to derive the a priori population or upon standardization of sampling strategy during this determination. Although clinically useful, Bayesian estimations are not without bias. We continue to evaluate clinical outcomes in our institution that are related to dosing vancomycin using the nomogram.

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