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. Involvement of the peripheral nervous system is considered infrequent and variable. 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 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.

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 |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Patienta          | First Examination | Second Examination | Father            | Brother           |
|                   |                   |                   |                   |                   |                   |
| 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.

aThe 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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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). Using both methods, peak and trough 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. A 2-compartment open population model was used. Bayesian priors from the population, established and routinely used in our institute, were applied: $V_i = 0.21 \pm 0.04 L/kg$, $k_{\text{tin}} = 0.0143 \pm 0.0029 h^{-1}$, $k_{\text{srp}} = k_{\text{srp}} \times \text{CrCl} (\text{ml/min})$, $0.00327 \pm 0.00109 h^{-1} \text{ml/min}$, $k_{\text{dr}} = 1.12 \pm 0.28 h^{-1}$, and $k_{\text{elr}} = 0.48 \pm 0.12 h^{-1}$, where $V_i$ is volume of distribution central compartment; $k_{\text{tin}}$: metabolic elimination rate constant; $k_{\text{srp}}$: renal elimination rate constant; $k_{\text{dr}}$: renal elimination rate constant; $k_{\text{elr}}$: renal clearance.

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 $\leq 1$ mg/L were found.

As can be seen, there is a large difference in the AUCs obtained using these 2 methods. The AUC calculated 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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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 $\leq 1$ mg/L, an AUC $>400$ mg*h/L would be sufficient. Therefore, a nomogram was proposed for AUC calculation by Michalets et al.3

The nomogram is based on the equation AUC$_{24}$ (mg*h/L) = vancomycin total daily dose (mg/24 hours)/[(CrCl(ml/min) $\times 0.79$) + $15.4$] $\times 0.06$. 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.