PHARMACOKINETICS AND PHARMACODYNAMIC DOSAGE ADAPTATION OF CEFACLOR IN SYSTEMIC INFECTIONS

A. Tomas; O. Horvat; M.P. Kusturica; N. Pavlović; B. Milijašević; Z. Tomić; and A. Sabo
Medical faculty, University of Novi Sad, Serbia

Background: Cefaclor was one of the commonly used antimicrobials in Serbia, but due to fast development of resistance, other oral cephalosporins rapidly upstaged cefaclor and cefaclor was removed from the list of the drugs reimbursed by the National Health Insurance Fund. Use of recommended dosing regimen (250-500mg/8-12h) is likely to result in sub-therapeutic concentrations for a wide portion of dosing interval due to short half-life of cefaclor, which may facilitate development of resistance. The aim of this study was to determine adequate dosing interval for cefaclor in treatment of systemic infections using Pharmacokinetic (PK) and pharmacodnamic (PD) parameters with special regard to postantibiotic effect (PAE).

Material and Methods: PK profile of cefaclor in healthy volunteers and PK/PD indices relating to efficacy of cephalosporins were determined, as well as minimum inhibitory concentration (MIC) and PAE of cefaclor on 4 susceptible bacteria.

Results: Cmax of 23.142 ± 5.67 µg/mL was measured after 40-60 minutes. Tmax was 0.72 ± 0.13 hours. Calculated AUC0-6h was 29.148 ± 9.27 µg/mL/h. MICs were in range of 1-2 µg/mL. Cefaclor induced PAE of 1-2h. There was inconsistency between standard dosing regimen and PK/PD parameters. Main PK/PD index relating to efficacy of cephalosporins (%T>MIC) for the 750mg dose was 33.5-42.1%. PK/PD breakpoints for cefaclor were between 0.3-1µg/mL. Even the maximum dose with standard dosing intervals is not appropriate for eradication of susceptible organisms. Short PAE can’t compensate for sub-inhibitory concentrations at the half of the dosing interval.

Conclusions: In reference to PK/PD parameters cefaclor should be administered every 6h for the doses of 500mg and 750mg, and every 4-4.5h for the 250mg dose in order to maximize its therapeutic efficacy and minimize development of resistance.

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NO ACCUMULATION OF A HIGH PROPHYLACTIC NADROPARIN DOSAGE IN PATIENTS WITH MODERATE RENAL INSUFFICIENCY ASSESSED BY PEAK ANTI-XA ACTIVITY

F. Atiq; P.M.L.A. van den Bent; F.W.G. Leebeek; T. van Gelder; and J. Versmissen
Erasmus Medical Center, Rotterdam, The Netherlands

Introduction: Low-molecular weight heparins (LMWHs) have been shown to accumulate in patients with renal insufficiency, especially in therapeutic dosages. However, no appropriate studies have been conducted for prophylactic dosages of nadroparin. As a consequence, dose reduction is often recommended especially in high prophylactic dosages. We assessed accumulation of a high prophylactic dosage of nadroparin in patients with renal insufficiency.

Materials and Methods: We conducted a prospective cohort study and measured peak anti-Xa activity 4 hours after subcutaneous nadroparin injection on day 1, 3, 5 and if possible day 10 in adults with and without renal insufficiency defined as a glomerular filtration rate (GFR) below or above 50 mL/min/1.73 m². Patients with a GFR below 10 mL/min/1.73 m² were excluded.

Results: We included 14 patients in each group. In the group with renal failure 12 patients had a GFR between 30 and 50 mL/min/1.73 m². Peak anti-Xa activity showed a high interindividual variability, but was fairly constant within each patient. There was no rise in peak anti-Xa activity on day 3 and 5 after consecutive administration.

Conclusions: Prophylactic dosages of nadroparin showed no accumulation in patients with a GFR between 30–50 mL/min/1.73 m². Dose reduction in this group could lead to suboptimal thromboprophylaxis. Due to underrepresentation of patients with GFR <30 mL/min/1.73 m² (n = 2) we cannot give recommendations for this group.

POSSIBILITIES OF OPTIMIZATION OF STATIN THERAPY BASED ON GENOTYPING SLC01B1 AND CYP2C9 AT PATIENTS WITH CARDIOVASCULAR DISEASE

A.M. Sirotnikina; A.A. Khokhlov; E.A. Voronina; and D.A. Sychev
1Yaroslavl State Medical University, Yaroslavl, Russia; and 2Russian Medical Academy of Postgraduate Education, Moscow, Russia

Introduction: The individual mode of drugs dispensing on the basis of genotyping can promote more effective and safe therapy. Frequency of detection of gene polymorphism of SLC01B1(TC + CC) in Russia is between 30 and 45%. Identification of carriers pathological C-allele allows personalized approach to drugs selection and the mode of its dispensing. The isoenzyme of cytochrome P450 (CYP2C9) is responsible for a metabolism of many drugs. Genetic variability of CYP2C9*2/*3 in addition to SLC01B1 can affect on pharmacokinetics of drugs. The aim was to determine the frequency of polymorphism of SLC01B1, frequency of polymorphisms of CYP2C9*2/*3 in carriers of C allele of the gene SLC01B1 in group of patients with dyslipidemia, to identify the prevalence of polymorphisms of several genes of one patient.

Material and Methods: DNA of 604 patients at the age of 52.2 ± 11.9 years (353 men, 251 women) with a dyslipidemia were analysed.

Results: Polymorphism of SLC01B1(TC/CC) was detected in DNA of 202 patients (33.4%). TC: 177 (29.3%); CC: 25 (4.1%). Carriers of C allele had SLCO1B1 genotyping of C/T: 177 (29.3%). The structure of polymorphism of CYP2C9*2/*3 in DNA of 15 patients (13.3%). The structure of occurrence of polymorphism of the studied genes was analysed: 1 patient had polymorphisms of SLC01B1(CC) + CYP2C9*2(TT), 2 patient – heterozygote of SLC01B1(TC+CC) and CYP2C9*2/*3 (AC +CT).

Conclusions: In the studied population of patients with dyslipidemia a significant number of polymorphism of SLC01B1 was found, that may interfere a profile of safety of statins. Prevalence of polymorphism of CYP2C9*2/*3 is also important. Early detection of polymorphisms in several genes involved in the biotransformation of drugs in DNA of one patient with polymorbidity pathology can predict the risk of adverse side effects.

DOES POLYPHARMACY IN ELDERLY PATIENTS WITH HEART FAILURE INFLUENCE MORTALITY AND HOSPITALISATION?

M. Eijsink; M. Zeeman; J. van Wijngaarden; E. Badings; and E. van’t Riet
Deventer Hospital, Deventer, The Netherlands

Background: The incidence of heart failure among the elderly is increasing. Ageing is often accompanied with comorbidity and therefore patients often face polypharmacy. Whether polypharmacy is related to any adverse outcome is unknown. We performed a study

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