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PP012—NOT-IN-TRIAL SIMULATIONS: PREDICTING CARDIOVASCULAR RISK FROM CLINICAL TRIALS TO REAL LIFE CONDITIONS

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Introduction: Safety signals regarding drug effects on cardiac conductivity have been found after the approval of medicines, despite evidence suggesting that they could be deemed safe during development. Such a discrepancy may be caused by the known differences between real-life conditions and the so-called clinical trial population, which represents a subset of the target patient population, as defined by the many inclusion and exclusion criteria in clinical protocols. No formal quantitative method is available to assess the implications of differences betwen experimental conditions and therapeutic use of the drug. This study demonstrates the relevance of pharmacokinetic-pharmacodynamic (PKPD) relationships to characterize drug-induced QTc-interval prolongation and to assess the implications discrepancies between clinical trials and real life conditions.

Patients (or Materials) and Methods: *d,l*-sotalol data from healthy subjects and from the Rotterdam Study cohort were used as paradigm compound to assess treatment response in a Phase I setting and in real-life situation, respectively. Using not-trial-simulation principles and nonlinear mixed effects modeling, drug-induced effects were estimated across populations to discriminate the potential implications of other relevant factors.

Results: Inclusion criteria were shown to restrict the representativeness of the trial population compared with real-life conditions. A significant part of the typical patient population was excluded from trials based on weight and baseline QT-interval measurements. Relative risk was statistically different between sotalol users with and without heart failure, hypertension, diabetes, and myocardial infarction. Although drug-induced effects do cause an increase in relative risk of QT interval prolongation, the presence of diabetes represented an increase in relative risk from 4.0 to 6.5, whereas for myocardial infarction it increased to 15.5 ($P < 0.01$).

Conclusion: Our results show that drug-induced effects on QTc-interval do not fully explain the distribution of QTc values observed in the population. The increased prevalence of high QTc values in a real-life population can be assigned to comorbidities and concomitant medications. This discrepancy substantiates the need to account for these factors when evaluating cardiovascular risk of novel medicinal products. Moreover, the concept of not-in-trial simulations can be used as a tool for risk management, integrating pharmacokinetic-pharmacodynamic relationships as the basis for discriminating drug-specific properties from other relevant factors in noncontrolled settings.

Disclosure of Interest: None declared.

PP014—PHARMACOLOGICAL INTERVENTIONS: A WAY TO IMPROVE THE QUALITY OF ANTIBIOTIC USE

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Introduction: The clinical pharmacist has recently been involved in clinical work as a member of the Infectious Disease Committee (IDC) to optimize the appropriate use of antibiotics. The objective of this study is to evaluate the contribution of the clinical pharmacist in this multidisciplinary team.

Patients (or Materials) and Methods: A 5-month prospective study in a private hospital of 150 beds. The antibiotic treatment of each patient was reviewed by the clinical pharmacist, within the first 24 hours after prescription, to detect/prevent Drug-Related Problems (DRP): adverse drug reactions, irrational drug utilization, and therapeutic failure. Furthermore, a pharmacotherapeutic follow-up was made until hospital discharge. The clinical pharmacist called the physician to make a recommendation when DRP were detected or suspected. Patient medical records and laboratory and microbiological reports were used as sources of information. Creatinine clearance was calculated with the Crockcroft-Gault equation. Patient's demographic data, description of pharmacologic interventions, and their acceptance were registered daily in a specific database.

Results: The study included 112 patients with a mean age of 76.3 (15.1) years (10-99); 57 were women (50.9%). The clinical pharmacist made 163 pharmacologic interventions (range, 1–11 interventions per patient), 42 (25.8%) having previously been agreed on with the other members of the IDC. The description of these interventions was as follows: drug choice and therapeutic de-escalation (n = 20 [12.3%]), excessive duration of antibiotic therapy (n = 22 [13.5%]), sequential therapy (n = 23 [14.1%]), and dose adjustment due to pharmacokinetic/pharmacodynamic parameters (n = 18, 11%), kidney dysfunction (n = 69 [42.3%]) or obesity (n = 11 [6.8%]). These drugs were penicillins (n = 48 [29.4%]), quinolones (n = 46 [28.2%]), carbapenems (n = 16 [9.8%]), cephalosporins (n = 16 [9.8%]), aminoglycosides (n = 7, 4.3%), oxazolidinones (n = 5 [3.1%]), macrolides (n = 4 [2.5%]) and others (n = 21 [12.9%]). Intravenous administration was the main route (n = 142 [87.1%]) while oral administration was used in few cases (n = 21 [12.9%]). Finally, 133 (81.6%) pharmacologic interventions were accepted.

Conclusion: The contribution of the clinical pharmacist in the multidisciplinary team is becoming increasingly valuable and may improve the quality of antibiotic use. The high acceptance of this work seems to show that multidisciplinary teams are needed, with the objective that patients receive the safest and most effective pharmacological treatment as possible.

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PP015—CHRONOTHERAPY WITH DOCETAXEL, CISPLATIN, AND 5-FLUOROURACIL (5-FU) IN PATIENTS WITH ORAL SQUAMOUS CELL CARCINOMA

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