Disclosure of Interest: None declared.

PP205—COMPARISON OF PHARMACODYNAMIC EFFECT OF TWO DIFFERENT MODIFIED-RELEASE ORAL DILTIAZEM FORMULATIONS
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Introduction: Different pharmaceutical formulations of the cardiovascular drug, calcium antagonist, diltiazem may reflect in its different bioavailability, that may subsequently influence the pharmacological effects. The primary purpose of the study was to compare the cardiovascular activities of 2 different modified-release formulations of diltiazem: gelatine capsules with micropellets and film-coated tablets. Secondary, we would like to consider if the pharmacodynamic data may be useful in concluding the therapeutic equivalence of different diltiazem formulations.

Patients (or Materials) and Methods: The study was conducted on a group of healthy, male subjects that participated in a randomized, 2-way cross-over bioavailability trial of 2 diltiazem MR formulation after single and multiple doses of 120 mg. During the course of the study standard bioavailability parameters (AUCt, AUCinf, Cmax, Cmin) for both formulations were calculated. Bioequivalence testing was based on Shuirmann’s procedure. Pharmacological effects were evaluated after single- and multiple-dose administration. Blood pressure, ECG parameters (QTc, PQ) and heart rate variability (HRV) were measured continuously (ECG Holter monitoring) up to 24 hours after administration and analyzed at the same time points as pharmacokinetic samples to plot the effect-time profile. Classical HRV analysis in time and frequency domains was conducted and several components of HRV estimated (RR, RMS, SDNN, PNN, LF, HF and LF/HF). Mean values at each time point and calculated effect parameters (AUEC, Emax, Tmax) were compared statistically between formulations (t-test, p < 0.05). Pharmacological data were correlated with pharmacokinetic parameters.

Results: Bioavailability analysis concluded inequivalence (CI for Cmax:single: 0.78–0.95). In pharmacodynamic analysis the only statistically significant difference was observed after multiple doses of diltiazem for the extend of PQ effect (AUECO-8 [ms*h]; P = 0.0289). Differences for the other calculated BP, ECG and HRV parameters were statistically insignificant (p ≥ 0.05), although distinct diversity has been observed. Bioequivalence couldn’t be concluded in the basis of PD data. High variability of values was observed (CV% > 50%–60%).

Conclusion: Differences in the most of tested pharmacodynamic parameters were found between 2 diltiazem formulations. Although most of them were statistically insignificant they may indicate the diversity of 2 tested modified-release oral diltiazem formulations in respect of bioavailability and pharmacodynamics. Because of their high variability cardiovascular parameters can be used in the estimation of therapeutic equivalence only in limited range.

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PP207—PHARMACOKINETICS OF SUGAMMADEX 16 MG/KG IN CHINESE SUBJECTS
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Introduction: The objectives of this study were to determine the pharmacokinetics (PK) and safety of single-dose sugammadex (16 mg/kg) in healthy Chinese adult volunteers. The 16-mg/kg dose was chosen because this is the highest recommended dose for use in clinical practice, for immediate reversal of NMB.

Patients (or Materials) and Methods: In this open-label study, healthy Chinese subjects received intravenous (IV) sugammadex (16 mg/kg) as a 10-second bolus infusion. Blood samples were collected pre-sugammadex and at regular intervals up to 24 hours post-sugammadex for PK assessment. Safety was also evaluated, via adverse events (AEs), vital signs, ECG, and laboratory parameters.

Results: Twelve subjects were included (6 male; 6 female). Geometric mean (CV%) weight was 58.3 (3.7%) kg and 53.6 (9.8%) kg for males and females, respectively. The main pharmacokinetic parameters are shown in the Table. After the 16-mg/kg sugammadex dose, plasma sugammadex concentrations showed a polyexponential decline over time, indicating 2 to 3 compartments, with an overall geometric mean (CV%) terminal half-life (t1/2) of 145 (17.9%) minutes (139 [17.7%] minutes for males; 152 [18.6%] minutes for females). No influence of gender on the PK of sugammadex was observed. Three subjects experienced an AE (dysgeusia of mild intensity in all cases), which was considered possibly or probably related to sugammadex. Dysgeusia is a known adverse drug reaction in healthy conscious subjects. There were no clinically significant changes in vital signs, ECG, or laboratory parameters.

| Table. Geometric mean (CV %) pharmacokinetic parameters for sugammadex 16 mg/kg in Chinese subjects. |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Male (n = 6) | Female (n = 6) | Total (n = 12) |
| Tmax, min | > 2.0 (2.0–3.0) | > 2.0 (2.0–3.0) | > 2.0 (2.0–3.0) |
| Cmax, µg/mL | 214 (27.7%) | 182 (10.6%) | 197 (21.7%) |
| CL, mL/min | 104 (12.3%) | 95.8 (12.4%) | 99.7 (12.6%) |
| Vss, L | 10.7 (10.7%) | 10.3 (7.4%) | 10.3 (9.0%) |

Values given as median (range). Tmax = time to maximum observed concentration; Cmax = maximum observed concentration; CL = clearance; Vss = volume of distribution at equilibrium.

Conclusion: After a single IV bolus infusion dose of sugammadex 16 mg/kg in healthy Chinese subjects, peak sugammadex concentration was 197 µg/mL, clearance was 99.7 µL/min, and volume of distribution was 10.5 L. No influence of gender on the PK of sugammadex was observed. Overall between-subject variability on clearance and volume of distribution was ~10%. Sugammadex was generally well tolerated in Chinese volunteers.