to 0.250 mg) taken orally once a day. Blood samples of digoxin (4 ml, EDTA anticoagulant) were obtained by venipuncture during steady state before the morning dose. Serum digoxin concentration (SDC) was determined by Microparticle Enzyme Immunoassay (MEIA) method on AxSYM immunology analyzer (Abbott Laboratories, Abbott Park, IL, USA) using original manufacturer's reagents and procedures.

Therapeutic intervals for digoxin used in University hospital Ostrava are as follows: for children 0.8–2.0 µg/l [6], for adults 0.5–1.2 µg/l (especially, >65 years)[7], and for pregnant women 2.0–2.5 µg/l [8]. Inaccuracy was determined using three concentration levels of the commercial control samples. Each sample was analyzed three times. Average result was compared to manufacturers declared value and the bias was calculated (Table 1). Acceptance criteria for each analyte were established according to the CLIA Proficiency Testing Criteria [9]. Precision was determined as described in National Committee for Clinical Laboratory Standards (NCCLS) protocol EP5-T2 (including an additional estimate of between day precision) using human serum with 0.9, 1.9, and 3.2 µg/l of digoxin added [10].

Demographic and medical data such as age, weight, concomitant medications, and renal function (serum creatinine concentration) were collected from the TDM request forms.

Pharmacokinetics

PK calculations were performed using two versions of MwPharm software – MwPharm 3.30 (DOS version, 1997) and MwPharm++ 1.3.5 (Windows version, 2016). The KinPop module of MwPharm was used to build a one compartment model, whereas previous studies applied a non-compartmental analysis [11, 12]. The KinPop module uses a two-stage, Bayesian PK analysis procedure [13].

A visual inspection of each PK plasma concentration time curve in MwPharm was performed before inclusion of these data for the parametrization of the PK model. Non-compartmental parameters were also calculated using MwPharm.

Parametrization of the population pharmacokinetic models

We evaluated two PK models („digoxin" /DOS model/ and „digoxin_C1" / WIN model/) to predict the pharmacokinetics of digoxin as follows: first, we fitted all PK parameters (k_a, F, V, Cl_m, f_u, f_e, f_r, $t_{1/2}$) and evaluated their statistics. Second, one by one, each of the parameters was set to Bayesian and the outcomes were statistically evaluated.

Validation of the pharmacokinetic models

From this study, measured concentrations of individual patients assigned to digoxin were compared mutually, and to calculated concentrations of these individual patients at the same times with our PK models in MwPharm using their age, serum creatinine, height, and weight. Differences of <20% between calculated and measured concentrations were allowed [14].

Evaluation of the pharmacokinetic models

Percentage prediction error (%PE), Root Mean Square Error (RMSE) and Bland-Altman plot were used for prediction of precision

Tab. 2 *Pharmacokinetic parameters of digoxin*

Parameter	DOS	WIN	%PE
POPULATIONAL DATA			
F	0.7	0.65	
t1/2 (h)	45.14	47.61	
CL (L/h)	6.45	6.11	
CLm (L/h/1.85 m²)	1.4	1.4	
V (L/h)	420	420	
V1 (L/kg/LBM)	6	6	
fu	0.75	0.75	
fe	0.7829	0.771	
fr	0.88	0.88	
INDIVIDUALIZED DATA			
V (L)	354 (326; 572)	317 (232;573)	-0.8 (-9.4; 7.3)
V1 (L/kg/LBM)	6 (5.8; 8.0)	5.6 (4.3; 299.5)	-2.4 (-11.4; 8.1)
fr	0.88 (0.82; 1.05)	0.62 (0.32; 2.08)	-1.4 (-8.9; 6.7)
fe	0.63 (0.56; 0.87)	0.55 (0.37; 0.87)	-0.7 (-5.3; 4.1)
t1/2 (h)	62.7 (43; 135.7)	59.4 (38.9; 141.2)	-1.8 (-5.2; 3.4)

Individualized data are presented as a median (interquartile range).
CL: total plasma clearance; CLm: metabolical clearance; F: bioavailability; fe: extrarenal fraction; fr: renal fraction; fu: unbound fraction; ka: absorption rate constant; V: volume of distribution; V1: volume of distribution related to lean body mass

Fig. 2. *Bland-Altman analysis of measured and predicted SDC values of digoxin by DOS versiona, by Windows versionb, by Windows and DOSc. SD, Standard Deviation*