# Comparison of DOS and Windows version of the MwPharm – a pharmacokinetic software for PK/PD monitoring of digoxin

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**Background and objectives:** Digoxin is the oldest drug indicated for the treatment of systolic heart failure (HF). It is also useful in controlling excessive ventricular rate in the presence of atrial arrhythmias. Therapeutic drug monitoring (TDM) has become an integral part of its prescription, allowing to optimize therapy and to reduce the incidence of toxicity. Since 1991, the MwPharm software package (Mediware, Groningen, The Netherlands / Prague, Czech Republic) has been used for pharmacokinetic and pharmacodynamic (PK/PD) modelling in TDM, including digoxin. First Windows version with a broader spectrum was released in 2014, as a reaction of worse support of the DOS background on later versions of Windows. After its release, the company had decided to not develop DOS versions anymore, even though they are globally used with success. The aim of this study was to compare the usefulness of DOS and Windows version (WIN) of the MwPharm, and their prediction quality in TDM of digoxin.
**Materials and methods:** 29 patients (23 with multidrug treated systolic HF, 4 with atrial fibrillation, 1 pregnant woman treated due to fetus tachycardia, 1 infant with Tetralogy of Fallot) who were treated for > 1 month with digoxin were eligible for inclusion. Patients received digoxin (Digoxin Léčiva®, Zentiva, Prague, Czech Republic) in a median dose 0.125 mg (range 0.063–0.250 mg) once daily. The therapeutic range for digoxin was established at 0.5–2.0 µg/l, according to manufacturer requirements. Both MwPharm versions (DOS version – MwPharm 3.30, Windows version – MwPharm++ 1.3.5) were used to parameterize the population PK model. Serum digoxin concentrations (SDC) were repeatedly examined and the differences between measured and calculated values predicted by both versions, including the percentage prediction error (%PE), were compared.
**Results:** SDC were obtained from 29 patients (mean age 67±20 years, body weight 72±27 kg). WIN, compared to DOS, used lower constants for absorption rate constant (ka) (0.61 vs 2.5), absolute bioavailability (F) (0.65 vs 0.7), total plasma clearance (CL) (6.11 vs 6.45 L/h), and extrarenal fraction (fe) (0.771 vs 0.783). Individual parameters calculated by WIN were consequently also lower – volume of distribution (V) (317 vs 354 l), renal fraction (fr) (0.62 vs 0.88), extrarenal fraction (fe) (0.55 vs 0.63), and elimination half-life ($t_{1/2}$) (59.4 vs 62.7 h). All values predicted by WIN were slightly lower but not significant. There was a close correlation between predicted and measured concentrations (Pearson's correlation coefficient: 0.008 vs 0.314, both $P < 0.0001$), and between SDCs predicted by both models (0.013, $P < 0.0001$). Their %PE was comparable (-0.43), too.
**Conclusions:** Actually used Windows version of the MwPharm software can be used for TDM interchangeably with popular, long-term used, but in these times unsupported DOS version.

**Key words:** MwPharm, therapeutic drug monitoring, digoxin, software.

## Porovnání DOS a Windows verze MwPharm – farmakokinetického softvéru pro PK/PD monitoring digoxinu

**Úvod a cíl práce:** Digoxin je nejstarší lék užívaný v léčbě systolického srdečního selhání. Je rovněž účinný v kontrole nadměrného komorového rytmu v přítomnosti předsíňových arytmií. Terapeutické monitorování hladin léčiv (TDM) se stalo integrální součástí jeho preskripce, umožňující optimalizovat terapii a redukovat incidenci toxicity. Od roku 1991 se MwPharm (Mediware,

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Groningen, Nizozemsko / Praha, Česká republika) používá pro farmakokinetické a farmakodynamické (PK/PD) modelování v rámci TDM, digoxin nevyjímaje. První verze pro Windows se širším spektrem modelů byla vydána v roku 2014 jako reakce na horší podporu DOS verze na novějších verzích operačního systému Windows. Po jeho vydání se společnost rozhodla dále DOS verze nevyvíjet, přestože je celosvětově s úspěchem používaná. Cílem této studie bylo porovnat použitelnost DOS a Windows verze (WIN) MwPharm a kvalitu jejich predikce v rámci TDM digoxinu.

**Metodika:** Do studie bylo zahrnuto 29 pacientů (23 se srdečním selháním léčeným kombinací více léčiv, 4 s fibrilací síní, 1 těhotná žena léčená pro tachykardii plodu, 1 dítě s Fallotovou tetralogií), kteří byly digoxinem léčení po dobu alespoň 1 měsíce. Všichni pacienti užívali digoxin (Digoxin Léčiva®, Zentiva, Praha, Česká republika) jednou denně ve střední dávce 0,125 mg (rozpětí 0,063–0,250 mg). Terapeutické rozmezí digoxinu bylo stanoveno v rozmezí 0,5–2,0 µg/l dle požadavků výrobce. Obě verze MwPharm (DOS verze – MwPharm 3.30, Windows verze – MwPharm++ 1.3.5) byly použity pro parametrizaci populačního PK modelu. Sérové koncentrace digoxinu (SDC) byly opakovaně vyšetřeny, a taky byly srovnány rozdíly mezi změřenými a vypočtenými hodnotami predikovanými oběma modely, včetně predikční chyby (%PE).

**Výsledky**: SDC byly stanoveny u 29 pacientů (67±20 let, 72±27 kg). WIN, ve srovnání s DOS, užívalo nižší konstantu rychlosti absorpce (ka) (0,61 vs. 2,5), absolutní biologickou dostupnost (F) (0,65 vs 0,7), celkovou plazmatickou clearance (CL) (6,11 vs. 6,45 L/h) a extrarenální frakci (fe) (0,771 vs. 0,783). Individuální parametry vypočteny WIN byly také nižší – distribuční objem (V) (317 vs. 354 l), renální frakce (fr) (0,62 vs. 0,88), extrarenální frakce (fe) (0,55 vs. 0,63) a eliminační poločas ($t_{1/2}$) (59,4 vs. 62,7 h). Všechny hodnoty predikovány WIN byly mírně nižší, ale nesignifikantní. Byla pozorovaná úzká korelace mezi predikovanými a změřenými koncentracemi (Pearsonův korelační koeficient: 0,008 vs. 0,314, oba P<0,0001) a mezi SDC predikovanými oběma modely (0,013, P<0,0001). Jejich % PE byla rovněž srovnatelná (-0,43).

**Závěr:** Současná verze softvéru MwPharm určená pro operační systém Windows může být využívána stejně s populární, dlouhodobě používanou, ale v současnosti nepodporovanou verzi pro DOS.

**Klíčová slova:** MwPharm, terapeutické monitorování hladin léčiv, digoxin, software.

## Abbreviations

$C_{max}$ – maximal concentration; $C_{min}$ – minimal concentration; CL – total plasma clearance; $Cl_m$ – metabolic clearance; F – absolute bioavailability; fe – extrarenal fraction; fr – renal fraction; fu – unbound fraction; HF – heart failure; ka – absorption rate constant; $t_{1/2}$ – elimination half-life; TDM - therapeutic drug monitoring; V – volume of distribution; $V_1$ – volume of distribution related to lean body mass

## Introduction

Therapeutic drug monitoring (TDM) is a strategy to individualize drug treatment by monitoring serum or blood drug concentration. TDM enables the assessment of the efficacy and safety of a particular medication in a variety of clinical settings. The goal of this process is to individualize therapeutic regimens for optimal patient benefit, e.g. maximizing the therapeutic effect while minimizing adverse drug reactions.

TDM is commonly used for these drug groups – antibiotics (aminoglycosides, vancomycin), bronchodilators (theophylline), antiepileptics, cytostatics (methotrexate), antiarrhythmics (digoxin, amiodarone), immunosuppressants, psychotropic drugs, etc. [1]. Having been used for over 200 years, digoxin is the oldest, as well as the cheapest, drug indicated for the treatment of systolic heart failure (HF). Its cardioselective parasympathomimetic activity also makes it useful in controlling excessive ventricular rate in the presence of atrial arrhythmias. Since the development of analytical methods, TDM has become an integral part of digoxin prescription, allowing medical practitioners to optimize therapy and to reduce the incidence of toxicity [2].

MwPharm (Mediware, Groningen, The Netherlands / Prague, Czech Republic) is a pharmacokinetic software representing one of the clinical interactive software packages used for TDM. It is used primarily to establish dosing regimens based on population pharmacokinetics of the particular drug for different groups of patients (adults, neonate, patients with specific diagnosis, etc.) and individual physiological parameters. The included curve-fitting facilities allow estimation of pharmacokinetic parameters on the basis of medication history, taking into account a varying status of the patient with respect to body weight and kidney function, optionally using a Bayesan procedure [3]. Thanks to this modelling, it is not necessary to wait until steady state, which is reached within 1–2 weeks at least, and can avoid patient's intoxication or underdosing.

**Tab. 1.** *Baseline characteristics*

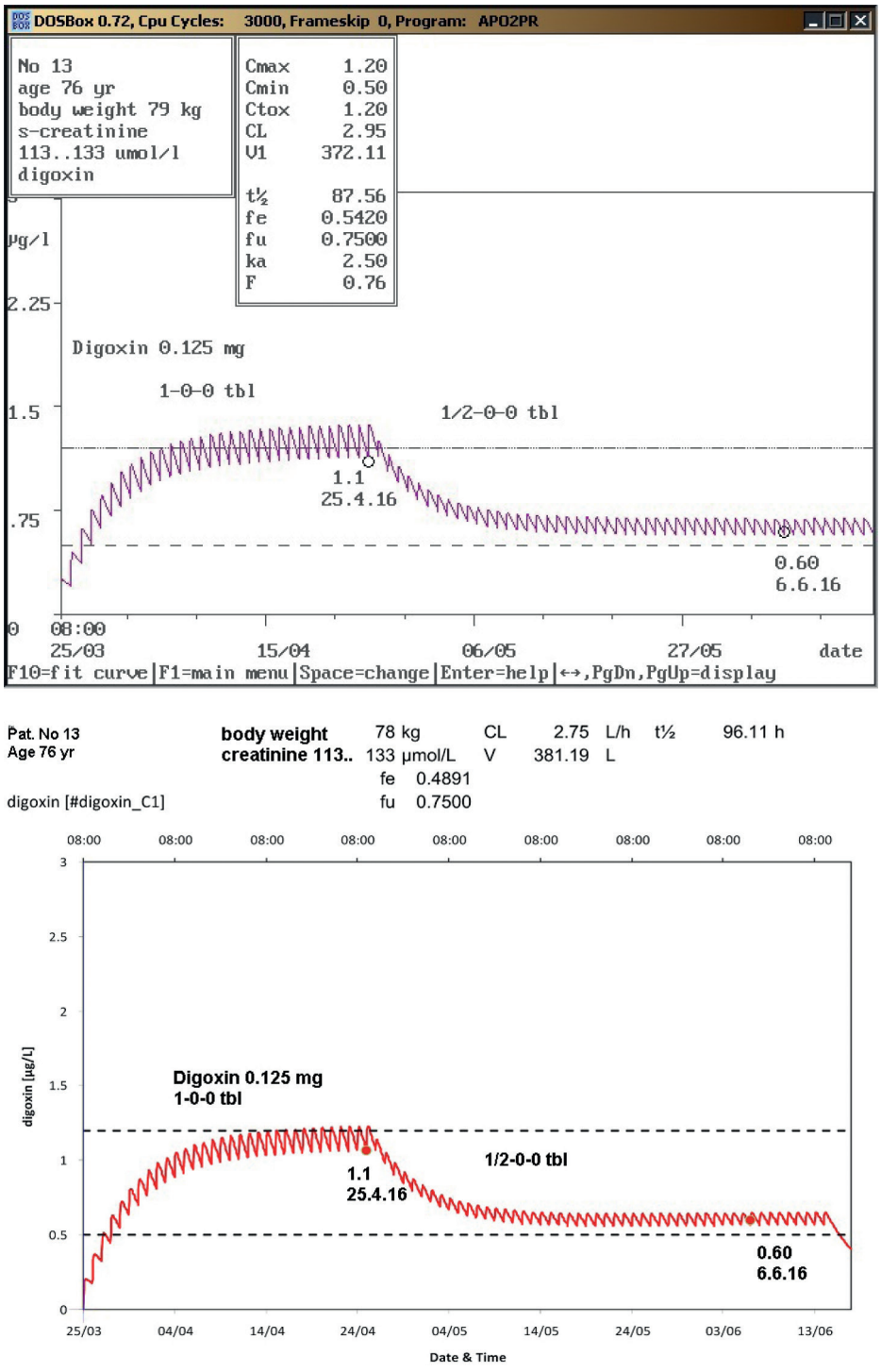
| Parameter | |
|---|---|
| Patients, N | 29 (17 male) |
| Age (years) | 67 ± 20 |
| Height (cm) | 177.1 ± 5.6 |
| Weight (kg) | 72 ± 27 |
| BMI (kg/m2) | 28.7 ± 4.5 |
| Diagnosis | |
| 1. Systolic HF, n (%) | 23 (0.79) |
| 2. Atrial fibrillation, n (%) | 4 (0.14) |
| 3. Fetus tachycardia, n (%) | 2 (0.07) |
| CL (mL/min) | 127 ± 9.4 |

*Data are shown as the mean ± standard deviation.*
*BMI: body mass index; CL: total plasma clearance; HF: heart failure*

MwPharm was originally developed in 1991 and a year later the first fully functional version for DOS platform (MwPharm) was released. The program is developed further in order to implement the latest developments in the field of pharmacokinetics. It consists of a database with over 180 drugs. Pharmacokinetic (PK) models include up to 3 compartment systems combined with injection, infusion, oral and intramuscular inputs. Dosage regimen selection is implemented in a unique interactive fashion. Its qualities were honored as the best in a comparative benchmark study [4]. MwPharm++ is the Windows successor of the well-known DOS software, with a broader spectrum of models, available since 2014 as a reaction to the worse support of the DOS system on the later versions of Windows. After its release, the company had decided to not develop DOS versions anymore, even though they have been world widely used with success. Department of clinical pharmacology at University hospital Ostrava has been using DOS version since 1997 (version 2.0), upgraded to version 3.30 since 1999. It is still used as a referential because there is long-term experience with it. The Windows version was implemented into the department's internal service shortly after its first release and is periodically updated in accordance to available releases.

The hypothesis underlying the current study was that actually used Windows version of the MwPharm software can be used for TDM interchangeably with popular, long-term used, but in these times unsupported DOS version.

**Fig. 1.** *Pharmacokinetic profile of digoxin in a) DOS model, b) Windows model. $C_{max}$, maximal concentration; $C_{min}$, minimal concentration; $C_{tox}$, toxic concentration; CL, total plasma clearance; $V_1$, volume of distribution; $t_{1/2}$, elimination half-life; fe, extrarenal fraction; fu, free fraction of a drug (digoxin) in a plasma; ka, absorption rate constant; F, absolute bioavailability*




## Materials and methods

### Study population

Routine clinical pharmacokinetic data were retrospectively collected from patients at University hospital Ostrava and its departments. 45 patients were screened for eligibility, of whom 16 were excluded from the study group. Finally, 29 subjects (26 hospitalized, 3 outpatient) were included and all of them supervised by medical and nursing staff in 2016. 23 patients with multidrug treated systolic HF were 65–92 years old, 4 patients with atrial fibrillation were 55–64 years old, 1 pregnant woman treated due to fetus tachycardia was 27 years old and 1 infant with Tetralogy of Fallot was 11 months old. The study was performed according to the Declaration of Helsinki, and the hospital ethics review board approved the protocol. Exclusion criteria were as follows: (1) unavailable data of dosage of digoxin, (2) only one measurement.

Treatment of systolic HF was based on the European Society of Cardiology (ESC) guidelines for treatment acute and chronic HF [5]. All patients received digoxin (Digoxin Léčiva®, Zentiva, Prague, Czech Republic) as a part of their treatment at a median dose of 0.125 mg (range 0.063

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*

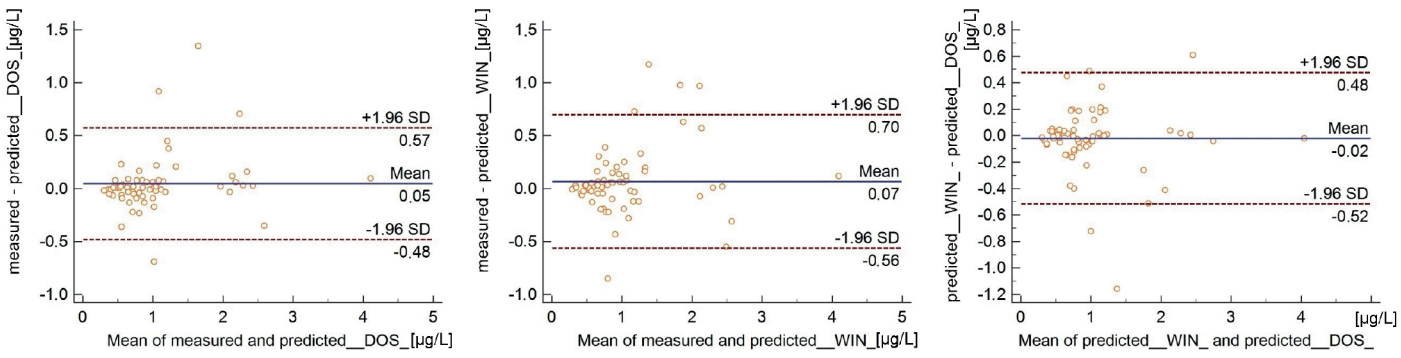
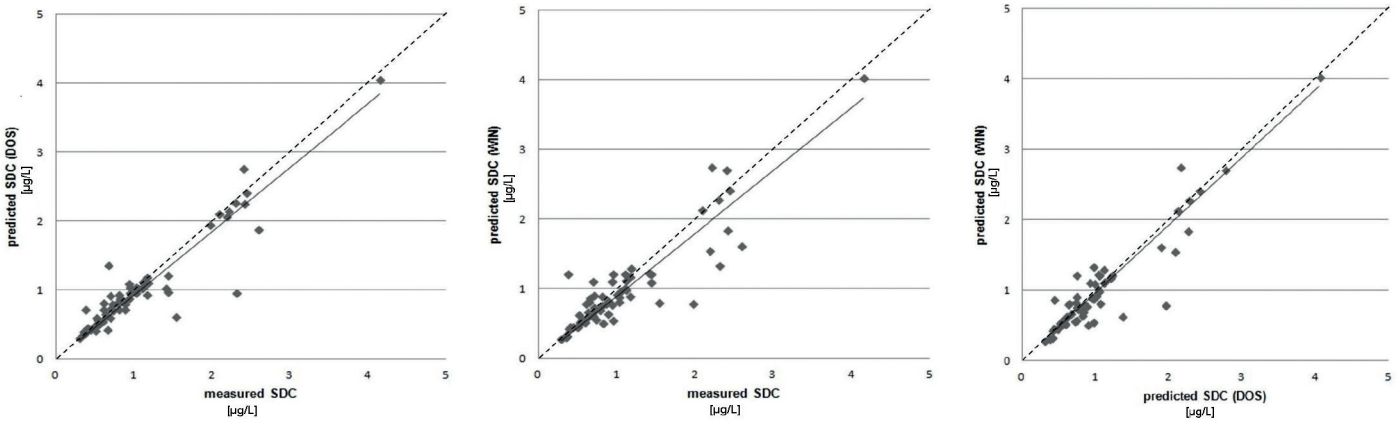


**Fig. 3.** *Comparison of measured and predicted SDC values in DOS modela, in Windows modelb, in WIN and DOS modelc. The full line represents linear regression, while the dashed line is the line of identity (y=x)*




evaluation. Pearson's coefficient of rank correlation was calculated. %PE was calculated as the difference between predicted and the measured value (formula 1) and as the difference between both models (formula 2). RMSE was calculated according to formula 3.

%PE = (1) %PE = (2) RMSE = (3)

**Tab. 3.** *Plasma levels (SDC) of digoxin*

| Parameter | measured | predicted (DOS) | predicted (WIN) |
|---|---|---|---|
| SDC (µg/L) | 0.86 (0.60–1.16) | 0.88 (0.60–1.05) | 0.83 (0.57–1.19) |
| %PE (1) (%) | | -1.3 (-6.4 –7.1) | -3.2 (-11.8–7.2) |
| %PE (2) (%) | | | -0.4 (-10.2–8.6) |
| RMSE (%) | | 1.2 (0.2–1.3) | 2 (0.6–2.9) |

*%PE was calculated as a difference between predicted and measured values (1), and as a difference between both models (2). Individualized data are presented as a median (interquartile range).*
*%PE: percentage prediction error; RMSE: root mean square error; SDC: serum digoxin concentration;*

## Statistical analysis

Statistical analysis of all data was performed using Prism 8.3.0 (GraphPad Software, San Diego, CA, USA) and MedCalc 18.2.1. (MedCalc Software, Ostend, Belgium). All values are presented as median (interquartile range). For comparison of repeated measurements of SDC's the Wilcoxon signed-rank test was used.

To make the point that methods used to measure chosen parameters had good correlation when a set of samples had been chosen, the Bland and Altman plot was used. Correlations between calculated SDC's in both models were evaluated by Pearson's correlation as appropriate. All data were analyzed on an intention-to-treat basis and for each test, a P value <0.05 was considered statistically significant.

## Results

The baseline demographic, clinical characteristics laboratory findings of the study cohort are listed in Table 1. The final analysis included 29 patients.

All pharmacokinetic parameters of digoxin - populational and individualized data are summarized in Table 2. WIN uses lower absorption rate constant ($k_a$) (0.61 vs 2.5), and absolute bioavailability (F) (0.65 vs 0.7), compared to DOS. Further differences were observed between total plasma clearance (CL) (6.11 vs 6.45 L/h) and extrarenal fraction ($f_e$) (0.771 vs 0.783). Changes in $k_a$ and F manifested in minor differences between minimal ($C_{min}$) and maximal ($C_{max}$) concentration - narrowing of the curve, as evident from the graphic output of both models - for DOS (Fig 1a) and for Windows (Fig 1b). It was obvious that WIN predicted lower values of pharmacokinetic parameters than DOS, but there were no significant differences between measured and predicted values by both versions (Table 3).

The distribution of error on Bland-Altman analysis of measured and predicted SDC is given in Fig 2a (for DOS) and Fig 2b (for Windows). The distribution of errors of predicted SDC in both models is given in Fig 2c. As it is shown, most points lie inside the limits which indicates that there is agreement between the models.

Comparison of measured and predicted values of SDC is given in Fig 3a (for DOS) and Fig 3b (for WIN). Comparison of predicted values of SDC in both models is given in Fig 3c. There was a close correlation between predicted and measured SDCs (the Pearson's coefficient of correlation was 0.008 for DOS vs 0.314 for WIN model, both P<0.0001) and between SDCs predicted by both models (0.013, P<0.0001).

## Discussion

To our knowledge, this study is the first one evaluating quality of the long-term prediction of serum drug levels achieved by two different versions of the same TDM software package. We demonstrated that formerly popular, long-term used, but in these times unsupported DOS version of the MwPharm software can be used for TDM of digoxin interchangeably with actually used Windows version - dosing advice will not be affected regardless of the chosen version.

TDM of digoxin has been used for more than 50 years [10]. Based on the published studies, it is considered appropriate to target a SDC in the therapeutic range of 0.5 to 2 µg/l, but there is a large interindividual variability [15]. The risk of digitalis intoxication (ADRs) increases at serum concentrations of ≥2.0 µg/l [10]. The purpose of blood concentration monitoring of digoxin is the prevention of ADRs, especially extracardiac ADRs, and digoxin should be administered at minimum effective concentrations. SDC at 0.5–0.9 µg/l reduces mortality and hospitalizations in all HF

patients > 65 years, including those with preserved systolic function and at higher serum digoxin concentration, digoxin reduces HF hospitalization but has no effect on mortality or all-cause hospitalizations [16].

Due to the fact that during routine TDM we focus prioritally on a safety (avoiding overdose, revealing non-compliance), the one-compartment (pharmacokinetic) model, used by MwPharm, is thus sufficient for these purposes, even though pharmacokinetics of digoxin is better described by the two-compartment (PK/PD) model [5, 17].

In the context of our finding, a major limitation of this study should be acknowledged. A small sample size in a subgroup of infants and pregnant women (one infant or pregnant woman) which is a common problem of studies in diseases with low incidence. Although there is a PK/PD target for digoxin, a comparison of two different versions of the same software package is still lacking [18]. This makes it difficult to analyze the results with respect to efficacy. Diversion of data (especially, difference in the PK of digoxin and its high concentrations in children and pregnant women) taken into account by a model is necessary.

## Conclusions

The digoxin model in the Windows version of the MwPharm software suite was validated. Based on available evidence and our study results, we conclude that there is no significant difference between quality of prediction of plasma levels of digoxin by both TDM software packages, their %PE were comparable. DOS and WIN versions of the s/w suite can be used for TDM of digoxin interchangeably.

In general, variations in results occurred with the same immunoassay processed on different analysers, as well as using different TDM software packages. In case when blood samples from the same patient are every time analyzed in different laboratories, it may increase an amount of the possible laboratory-based errors. These apparent and marked differences in SDC may have significant implications for patient care. Clearly, there is considerable potential for confusion or dosing error. Accurate TDM remains essential to ensure appropriate concentrations are maintained.

Consequently, it should be considered if routinely using updated versions of the same TDM software always brings benefits to patients – not only in case of MwPharm, but also other packages. As a result, future research is needed to gain a better understanding of this thema.

## Author contributions

TP: manuscript writing and literature search; BK: manuscript writing and literature search; MG: study design; IK: study design

## Conflict od interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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