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REVIEW ARTICLE

Benchmarking Therapeutic Drug Monitoring Software: A Review of Available Computer Tools

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Abstract Therapeutic drug monitoring (TDM) aims to optimize treatments by individualizing dosage regimens based on the measurement of blood concentrations. Dosage individualization to maintain concentrations within a target range requires pharmacokinetic and clinical capabilities. Bayesian calculations currently represent the gold standard TDM approach but require computation assistance. In recent decades computer programs have been developed to assist clinicians in this assignment. The aim of this survey was to assess and compare computer tools designed to support TDM clinical activities. The literature and the Internet were searched to identify software. All programs were tested on personal computers. Each program was scored against a standardized grid covering pharmacokinetic relevance, user friendliness, computing aspects, interfacing and storage. A weighting factor was applied to each criterion of the grid to account for its relative importance. To assess the robustness of the software, six representative clinical vignettes were processed through each of them. Altogether, 12 software tools were identified, tested and ranked, representing a comprehensive review of the available software. Numbers of drugs handled by the software vary widely (from two to 180), and eight programs offer users the possibility of adding new drug models based on population pharmacokinetic analyses. Bayesian computation to predict dosage adaptation from blood concentration (a posteriori adjustment) is performed by ten tools, while nine are also able to propose a priori dosage regimens, based only on individual patient covariates such as age, sex and bodyweight. Among those applying Bayesian calculation, MM-USC*PACK© uses the non-parametric approach. The top two programs emerging from this benchmark were MwPharm© and TCIWorks. Most other programs evaluated had good potential while being less sophisticated or less user friendly. Programs vary in complexity and might not fit all healthcare settings. Each software tool must therefore be regarded with respect to the individual needs of hospitals or clinicians. Programs should be easy and fast for routine activities, including for non-experienced users. Computer-assisted TDM is gaining growing interest and should further improve, especially in terms of information system interfacing, user friendliness, data storage capability and report generation.

1 Introduction

The monitoring of drug therapy aims to forecast treatment success, failure or toxicity, and to adjust prescriptions as a consequence. Circulating drug concentration is a traditional pharmacokinetic surrogate used for this purpose, in what is called therapeutic drug monitoring (TDM) [1]. TDM

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assumes that circulating drug concentrations better predict the effect of pharmaceutical agents and clinical outcome than doses. Practically, TDM approaches attempt to optimize individual dosage regimens through the maintenance of concentrations within a given therapeutic range [2]. Dosage individualization consists either of a priori adjustment (without blood drug concentration measurement) based on demographic, biological, pharmacogenetic and clinical covariates, or of a posteriori adjustment based on drug concentration determination [3]. TDM-guided dosage individualization is currently applied to a number of drugs such as antibacterials, anticonvulsants, digoxin and immunosuppressants [4]. Major benefits for patients reside in optimizing the drug concentration exposure, leading to more rapid and sustained therapeutic control and to improved safety, which might even reduce the duration of hospitalization [1, 5].

Maintaining optimal drug concentrations is, however, a complex and demanding task. It requires solid knowledge of evidence-based clinical guidelines, clinical pharmacology and pharmacokinetics, as well as definite mathematical skills for dosage calculation [5]. It therefore represents a time-consuming activity for healthcare professionals and often requires the intervention of a specialist [1]. In such circumstances, computer-assisted decision making [6] is advantageous, as algorithms implemented enable the automated calculation of doses, while integrating patients' individual factors such as age, bodyweight, sex, kidney function, disease and drug interactions along with drug concentration results [7, 8].

Whereas most industries have experienced an information technology revolution since the 1980s, healthcare systems are generally moving rather slowly in that direction [9]. The main healthcare domain currently undergoing profound transformation is the field of electronic medical records and of networks to share these medical data [9, 10]. Dispensation and dosing of drugs also represent a field of interest in which intelligent technologies could be useful [10]. In parallel, technological efforts towards the miniaturization of monitoring tests (e.g. TDM determinations) are necessary [11], along with the development of robust and user-friendly computer tools to provide seamless monitoring services in clinics [1].

Indeed, in recent decades, several programs have been designed to assist clinicians in interpreting blood drug concentrations and to improve the appropriateness of drug dosing in routine clinical practice [12–19]. Recently, computer-assisted decision tools for monitoring gained renewed attention, holding further potential for TDM-guided dosing optimization. In 1993, Buffington et al. [12] published a review of computer programs designed for TDM-guided dosage optimization available in the USA. Since then, however, few evaluations on this type of software have been presented, and no further review has ever been published to our knowledge.

The aim of this survey is to provide an updated comparative evaluation of all software designed for routine TDM-guided dosage adjustment that are widely available throughout the world.

2 Search Strategy and Selection Criteria

A literature search for clinical pharmacokinetic software programs was performed through MEDLINE (1966 to October 2012) and Google using the following keywords: therapeutic drug monitoring, software, program, computerized, clinical pharmacokinetics, computer assisted decision-making, dosing, drug dosage. The web portal of David Bourne's pharmPK forum [20] was also used as a resource for program identification.

As programs widely differ in their features, their expected characteristics had to be assessed along multiple axes. This led to the design of a comprehensive evaluation grid to standardize the comparison of software. Criteria were defined based on the authors' experience in routine TDM practice. General characteristics addressed were as follows: user interface, visual aspect, user friendliness; possibility of interfacing with other hospital software (e.g. laboratory software or patient's medical records); possibility to store patient's or user's information; the quality of report generated for physicians; the cost; and computational aspects such as import and export functions. To take into account the variety of fee schemes, prices were calculated for a 5-year annual subscription. Pharmacokinetic aspects addressed were as follows: drugs and type of population covered by the programs; type of models, calculation approaches, simulation capabilities; modularity; quality of pharmacokinetic plots generated; and further utilities such as creatinine clearance calculation. The full grid of criteria is available in Tables SI and SII of the Online Resource.

The evaluation of all software programs was performed on a standard personal computer by one pharmacist user, backed up by two clinical pharmacologists experienced in computing and the clinical practice of TDM. A score was assigned to each criterion, ranging from 1 (for the lowest performance) to 5 (for the highest performance). For binary items (yes/no), a score of either 2 or 4 was allocated and for ternary criteria a score of 1, 3 or 5 was allocated to balance the marks attributed. Scoring definitions are detailed in the Online Resource (Table SI). The scoring approach had to be balanced, since criteria obviously differ in their importance. In that endeavour, five physicians, five pharmacists and five computer engineers were asked to attribute a weight from 1 to 3 to each criterion (1 for low importance, 2 for useful but not essential and 3 for essential). A final weighting factor for each criterion was then calculated by arithmetic average. Finally, a ranking of the software programs could be established by summing the weighted scores to obtain a global score for each program. Scores by category were also calculated in order to appraise more finely the various facets of the programs.

When characteristics of programs were unclear, contact with the authors or developers was sought to clarify relevant points. Validation by the author or by the software developing company was proposed and the grid was distributed to those willing to participate. They were asked to fill it in using the explanatory table sent along with the grid (Table SI). This allowed a double-control and confirmation of missing information.

To improve the robustness of our evaluation, six clinical vignettes, inspired by real clinical TDM cases encountered in our routine activity, were also tested. These cases aided the evaluation of the software based on systematic testing of real-life situations. They also provided an insight of a priori and a posteriori predictions offered, and of the type of specific cases that could typically be handled by the programs.

3 Therapeutic Drug Monitoring Software

3.1 History and Evolution

USC*PACK© was the first available software dedicated to monitoring and dosage adjustment. Developed by the Laboratory of Applied Pharmacokinetics at the University of Southern California (Los Angeles, CA, USA) and launched in 1973 [21], it is still in use and evolving. It represents a comprehensive software that includes MM-USC*PACK© (now called RightDose™) and is designed for clinical practice and dosage adjustment. Later, in 1982, the Department of Pharmacology and Pharmacotherapy at the University of Groninigen (Groningen, The Netherlands) developed MwPharm©. MediWare (Charles University, Prague, Czech Republic), now hosting the program, was established in 1987. Abbott Laboratories also developed a software package in the early 1990s called Abbottbase Pharmacokinetic Systems or PKS [18]. It was widely used, at least in the USA, during the 1990s [12]. The program distribution has, however, been discontinued for some years. Similarly, there are other programs that existed in the 1990s but are no longer available (e.g. SeBA-GEN [22], ATM [13], Simkin [23]). Either they are not marketed any more, or their development was merged with other software. For example, Kinetidex® has been Thomson Reuters' software since 2001, resulting from a merge between Simkin and Micromedex®. In the meantime, other initiatives have appeared, mostly from the academic field. A pharmacist from Creighton University (Omaha, NB, USA) developed multiple programs dedicated to assisting hospital pharmacy practice under the global name RxKinetics Software. Among them, three programs are intended for dosage adjustment, with the first one, Kinetics©, launched in 1986. More recently, programs have been developed in Asia. JPKD® for desktop and TDM for R (which is a variant of JPKD® developed as a plug-in for the R statistical program) were both developed by Kaoshiung Medical University (Kaoshiung, Taiwan) and released in 2006. New initiatives are still emerging, the latest of which comes from the University of Otago (Dunedin, New Zealand) and the University of Queensland (Brisbane, QLD, Australia), which released the first version of TCIWorks in 2011.

3.2 Widely Available Software Packages

Twelve clinical pharmacokinetic programs were identified: MM-USC*PACK©, MwPharm©, TCIWorks, JPKD®, TDM for R, Antibiotic Kinetics©, APK©, Kinetics©, Kinetidex®, T.D.M.S. 2000™, DataKinetics™, RADKinetics. Antibiotic Kinetics©, APK© and Kinetics© belong to the RxKinetics© programs. Specific versions reviewed are indicated in Table 1. Moreover, major features are described for each software in Tables 2 and 3.

All criteria considered are presented in the detailed evaluation grid accessible in the Online Resource (Table SII), with their associated weight. A summary of the results, scored by category and ranked, is shown in Table 4.

We were able to contact authors or the developing company for 11 of the 12 programs (only developers from RADKinetics could not be reached because of broken links on their website and unavailability of contact information). Some developers declined participation, considering either that it was difficult to self-rate items or that our demand included requests for information viewed as proprietary. Eventually, five developers provided feedback for MM-USC*PACK©, MwPharm©, Antibiotic Kinetics©, APK©, Kinetics©, JPKD®, TDM for R, and T.D.M.S. 2000™.

Among these 12 programs, DataKinetics™ is no longer marketed. A website still exists for RADKinetics and the program can be downloaded, but there is apparently neither support nor updates anymore. There has been no update for JPKD® since 2007, but support is still available.

3.3 Software Requirements and Individual Characteristics

3.3.1 General Characteristics

Nowadays, all of the recent program versions run on the Windows® operating system (Microsoft Corp., Redmond,

Table 1 Descriptive characteristics of the program

Characteristic	MwPharm©	MM-USC*PACK©	TCIWorks	RxKinetics programs©			JPKD®	TDM for R	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RADKinetics
				Antibiotic Kinetics©	APK©	Kinetics©						
Author(s)	D.K.F. Meijer, et al.	R.W. Jelliffe, M. Neely, A. Bustad	S. Dufull, L. Van Den Berg, C. Kirkpatrick	R. Tharp and certified developer	R. Tharp and certified developer	R. Tharp and certified developer	Y. Lee, J.M. Lai, Y.H. Lu et al.	M. Chen, Y. Lee	R.K. Klasco (and authors of SimKin Program)	P.O. Anderson, A. Gupta	NA	R. Rademacker
Company/ institution	University of Groningen (developer), Faculty of Medicine of Charles University, Prague and Mediware (marketer)	Laboratory of Applied Pharmacokinetics, School of Medicine, USC	School of Pharmacy, University of Otago/School of Pharmacy, University of Queensland	School of Pharmacy and Health Profession, Creighton University	School of Pharmacy and Health Profession, Creighton University	School of Pharmacy and Health Profession, Creighton University	Graduate College of Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung	Graduate College of Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung	Thomson Reuters Corp.	Healthware Inc.	MDK Inc. (developer), ASHP (marketer)	NA
Location of company/ institution	The Netherlands/ Czech Republic	USA	New Zealand/ Australia	USA	USA	USA	Taiwan	Taiwan	USA	USA	USA	USA
Date of the first version	1991	1973	2010	1999	1999	1986	2006	2006	NA	1986	NA	NA
Version reviewed	4.0	15.2	1.0	2.3.9	3.5.3	2.2.5	3.0	2.2.1	11.0	11.02	5.0.15	2.0.1
Computer language of the source program	C#	C++/Matlab	Java	Pascal	Pascal	Visual Basic	Java	R	NA	C++	NA	NA
Still marketed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Website	mediware.cz	lapk.org/ software.php	tciworks.info	rxkinetics.com	rxkinetics.com	rxkinetics.com	pkpd.kmu.edu.tw/ jpkd/	pkpd.kmu.edu.tw/ tdm/	truvenhealth.com/ products/	tdms2000.com		showcase.netins. net/web/ radman/

NA not available

Table 2 Features of the programs: general characteristics

Characteristic	MM-USC*Pack©	MwPharm©	TCIWorks	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	T.D.M.S. 2000™	DataKinetics™	RADKinetics
User interface												
Platform	Windows®	Windows®	Windows®/ Mac®/Linux	Windows®/mobile device (no iOS®)/Mac®/ Linux	Windows®/ Mac®/ Linux	Windows®/ mobile device	Windows®/ mobile device	Windows®	Windows® (no international version)	Windows®	Windows®/ mobile device (no iOS®)	Windows® (old version)
User friendliness	Need practice	Need practice	Need practice	Very easy	Not user friendly	Very easy	Very easy	Very easy	Easy	Need practice	Easy	Easy
Clinical manual	No	No	Limited	No	No	Yes	Yes	Yes	Yes	Limited	Limited	No
Interfacing	No	Yes, with Mirth™ Connect technology	No	No	No	Yes, only to collect some patient data	Yes, only to collect some patient data	Yes, only to collect patient data	No	No	No	No
Storage												
Patient records/ database	Yes, on local files (no real database)	Yes	Yes	No	No	No	Consultations only	Yes	Yes	Yes	Consultations only	Consultations only
Report generation	Yes	Yes, customizable	Yes, customizable	Yes	No	Yes	Yes, customizable	Yes, customizable	Yes, customizable	Yes, customizable	Yes, customizable	Yes
Cost[a]	Donation US$595	US$1,530	Free	Free	Free	US$125	US$150	US$250	US$1,520 annually	US$600 annually	US$900	US$100
Computational aspect												
GUI	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data import/ export	Yes	Yes	No	Yes	No	No	Administrative data only export	Administrative data only export	No	No	No	No
Technical manual	Sparse	Yes	Getting started guide	Yes	No	Yes	Yes	Yes	Yes	Getting started guide	Yes	No

GUI graphical user interface

[a] Cost indicated for a single seat license

Table 3 Features of the programs: pharmacokinetics

Feature	MM-USC*Pack©	MwPharm©	TCIWorks	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
Population and drugs												
Add drug model interface	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No
Models												
A priori regimen proposal	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Bayesian analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
First dose handled	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No
Non-steady-state situation handled	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Modularity												
Possibility of user-defined parameters	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
User-defined boundaries value target	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plot												
PK plot generation	Yes	Yes	Yes	Not for all drugs	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Percentiles	Yes	No	No	No	No	No	No	No	No	No	No	No
Various												
Creatinine clearance calculation	Jelliffe	Cockroft & Gault	Cockroft & Gault	None	None	Cockroft & Gault/Schwartz/Jelliffe	Cockroft & Gault/MDRD/Schwartz/Jelliffe/Salazar & Corcoran	Cockroft & Gault/MDRD/Jelliffe/Salazar & Corcoran	Cockroft & Gault/Schwartz	Cockroft & Gault/Schwartz	Cockroft & Gault/Schwartz/Jelliffe	Cockroft & Gault

MDRD Modification of Diet in Renal Disease, *PK* pharmacokinetic

Table 4 Weighted scores for each category and overall category rounded to unit and ranking

Category	MM-USC* Pack©	MwPharm©	TCIworks	JPKD®	TDM for R	Antibiotic Kinetics©	APK	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
General characteristics												
User interface	79 (10)	95 (4)	89 (7)	90 (6)	73 (11)	105 (3)	111 (1)	106 (2)	92 (5)	80 (9)	83 (8)	61 (12)
Interfacing	13 (5)	26 (1)	13 (5)	13 (5)	13 (5)	18 (2)	18 (2)	18 (2)	13 (5)	13 (5)	13 (5)	13 (5)
Storage	34 (7)	46 (1)	30 (8)	16 (10)	16 (10)	16 (10)	46 (2)	46 (2)	36 (5)	34 (6)	37 (4)	29 (9)
Report	16 (10)	58 (1)	45 (7)	36 (8)	13 (12)	34 (9)	56 (2)	56 (2)	50 (6)	50 (6)	53 (4)	16 (10)
Cost	26 (4)	19 (8)	28 (3)	23 (6)	23 (6)	23 (5)	28 (1)	28 (1)	12 (12)	19 (8)	16 (10)	16 (11)
Computational aspects	60 (3)	59 (4)	78 (1)	66 (2)	53 (10)	58 (5)	58 (5)	58 (5)	51 (11)	55 (9)	58 (5)	41 (12)
Total	228 (10)	304 (3)	284 (4)	244 (9)	191 (11)	253 (7)	317 (1)	311 (2)	253 (6)	251 (8)	259 (5)	176 (12)
Pharmacokinetic aspects												
Population and drug	59 (7)	76 (1)	60 (6)	70 (2)	40 (11)	53 (9)	65 (3)	56 (8)	62 (5)	63 (4)	49 (10)	33 (12)
Models	191 (1)	179 (3)	184 (2)	120 (9)	117 (10)	139 (8)	148 (7)	153 (6)	174 (4)	174 (5)	117 (11)	98 (12)
Modularity	48 (7)	43 (8)	53 (1)	53 (1)	33 (11)	48 (4)	48 (4)	48 (4)	49 (3)	39 (9)	33 (11)	38 (10)
Plot	42 (1)	34 (3)	37 (2)	26 (10)	15 (11)	32 (6)	32 (6)	32 (6)	34 (3)	34 (3)	32 (6)	15 (11)
Various	22 (9)	34 (2)	25 (7)	19 (11)	19 (11)	25 (5)	25 (5)	23 (8)	31 (4)	33 (3)	35 (1)	20 (11)
Total	363 (2)	366 (1)	358 (3)	288 (9)	225 (11)	297 (8)	317 (6)	311 (7)	350 (4)	342 (5)	266 (10)	204 (12)
Authors												
Expertise of authors	51 (1)	51 (1)	49 (3)	32 (9)	32 (9)	37 (6)	37 (6)	37 (6)	23 (12)	42 (5)	42 (4)	32 (9)
Global score	641 (5)	720 (1)	692 (2)	564 (10)	448 (11)	587 (8)	671 (3)	659 (4)	627 (7)	636 (6)	567 (9)	412 (12)

All data given as weighted score (rank). Rankings were given from 1 for the best classified to 12 for the worst classified

WA, USA). Kinetidex® runs only on US-English Windows®. Kinetics© is sold only in the USA, Canada and the UK (as it uses a dot to separate decimals instead of a comma as in other countries). As users of personal digital assistants, smartphones and Mac® computers (Apple, Cupertino, CA, USA) dramatically increased over the last few years, this should also be taken into consideration. At present, JPKD®, APK© and Kinetics© have developed an application for mobile devices. TCIWorks, JPKD® and TDM for R can be run on Mac OS X® environment (Apple). The Internet is the most rapid and convenient media for presentation and distribution of software. All of the software packages are hosted on websites, ranging from a simple advertisement for Kinetidex® to a comprehensive source of information with technical information, including teaching topics and/or screenshots, for JPKD® or MM-USC*PACK©. Most programs are easy to download through the internet, at least as demonstration versions. The importance of support documentation should not be underestimated and a user manual should be part of the software bundle. Technical and sometimes clinical manuals are included with most software packages. However, there is a large discrepancy between software, ranging from a 'getting started' guide for T.D.M.S. 2000™, MwPharm© or TCIWorks, to a comprehensive manual directly integrated into the software with word search capability for the RxKinetics©, DataKinetics™ and Kinetidex® programs. In addition to documentation, JPKD® and TDM for R publish video demonstrations on their respective websites. Kinetidex® and DataKinetics™ also provide sample cases that are included in their documentation. Only a few of the programs include information on drugs' pharmacokinetics, or even sometimes TDM itself (e.g. the RxKinetics© programs and DataKinetics™). In addition, convenient contact details for support is important. The RxKinetics© programs and the new version of MM-USC*PACK© (now known as RightDose™) also offer access to a users' forum for questions and discussions.

Another requirement for TDM software is the ability to interface with laboratory information management systems, especially for collecting blood drug concentrations, receiving administrative and clinical patient data, and sending reports to patient's electronic records. Although interfacing with hospital information systems may be challenging, since they differ worldwide, initiatives such as Health Level Seven International (HL7; http://www.hl7.org/) aim to standardize electronic health data transfer. Additionally, interfaces have been developed in recent years for applications that do not support HL7 standard and thus allow interoperability. MwPharm© is the only program that can be relatively easily interfaced with hospital information systems through the Mirth^{TM} Connect technology (Mirth Corp., Irvine, CA, USA). For administrative and some demographic data, the software designers behind RxKinetics© have developed a basic interface to allow a health information system to dump such data into the software.

Users may ideally wish to record their patients' administrative and clinical data, as well as concentration measurements and predictions issued. MwPharm©, TCIWorks, Kinetics©, Kinetidex® and T.D.M.S. 2000^{TM} have full patient databases that store patients' administrative data, as well as dosages and drug concentration results that were entered for dosage individualization. USC*PACK© does not have a fully integrated database but can save patients' data on a local file on the user's personal computer. Some other programs only have an administrative database that records patients' basic data. Another issue is the confidentiality of data: APK©, Kinetics© and MwPharm© use an encrypted database.

Software must be able to generate reports that can be transmitted to physicians and have the ability to save the possible associated advice consultation into the patient's medical records. Quality and readability of the report generated vary widely between programs, from TDM reports that are not transmissible to physicians to clear, printable reports with a highly structured core (it should be noted that TDM for R does not generate any kind of report). Essential information comprises patient administrative and clinical data, history of drug dosages and concentration measurements, and a clearly readable pharmacokinetic interpretation. In addition, some reports can include a free text field that can be filled in by the consultant. Reports ideally need to be customizable to better meet each institution's visual identity guidelines.

Another important issue that users face during the choice of software is its cost. Surprisingly, costs are not consistently weighted with regards to software capabilities. Some are free (TCIWorks, JPKD®, TDM for R), others are subject to a one-off donation (MM-USC*PACK©), while others require a first-year subscription fee followed by a license charge for subsequent years, which basically includes provision for updates.

Graphical user interface (GUI) is a must-have nowadays. Each program has a unique graphical design that makes it more or less user-friendly but definitely facilitates navigation across windows, files or menus. Only TDM for R is based on a command-line interface.

For research purposes, import/export capabilities could represent a valuable feature. Few programs offer this facility: JPKD® allows for exporting data in comma-separated variables (CSV) format; MwPharm© offers import and export possibilities in structured text (TXT) format; extraction of administrative data is possible from APK©, in CSV format, but as it concerned only administrative data, it was not considered as data exportation for the purpose of this evaluation.

APK© was noted to have the best result in the 'general characteristics' category, closely followed by MwPharm© (Table 4). APK© offers a simple solution and is remarkably flexible, particularly for non-experienced users, while having a favourable cost–quality ratio. MwPharm© and TCIWorks also offer many interesting features but represent more sophisticated tools.

3.3.2 Pharmacokinetic Aspects

The number of drugs covered by each program varies from two for RADKinetics to more than 180 for MwPharm© (Table 5). The drug of interest can be chosen in the library offered by the program. For some programs, even definitions of specific populations for drug use are available (e.g. neonates). Few programs take into account drug and/or disease interactions: T.D.M.S. 2000^{TM}, MwPharm©, JPKD® and Kinetidex®. Moreover, in the last decade, important progress has been achieved in the field of pharmacogenetics, which can be used for a priori dosage regimen adaptation in some clinical situations [24]. Integrating a TDM and pharmacogenetics approach therefore appears more and more suitable for optimization of pharmacotherapy in the context of personalized medicine [25, 26]. Additionally, some food–drug interactions are progressively being discovered, which involve various mechanisms such as an increase or decrease of bioavailability or an induction or inhibition of metabolism [27, 28]. The most famous examples are probably those involving grapefruit or alcohol [29]. When sufficiently described and quantified, pharmacogenetic features and these interactions should certainly be included in TDM programs in the near future.

A fundamental pharmacokinetic aspect of programs concerns the possibility for the user to add their own drug models. In eight programs (MwPharm©, MM-USC*PACK©, TCIWorks, Antibiotic Kinetics©, APK©, Kinetics©, JPKD®, T.D.M.S. 2000^{TM}), a new model for a drug or a population can be defined within an 'add drug model interface' provided, by entering model parameters either from a single population pharmacokinetic study or from a systematic pharmacokinetic review of studies. For example, APK© offers pre-defined parameter fields using a one-compartment model where the values have to be entered, whereas some other programs can handle multi-compartmental models or different types of administration. USC*PACK© employs a non-parametric adaptive grid (NPAG) program [30], which makes it more complicated for non-experienced users but has the great advantage of

Table 5 Drugs supported by the programs

Drug	MM-USC*PACK©	MwPharm©	TCIworks	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
Cardiovascular system												
Digoxin		✓		✓	✓			✓	✓	✓	✓	
Quinidine		✓								✓		
Procainamide		✓										
Others		42										
General anti-infectives for systemic use												
Ceftazidime		✓										
Aminoglycoside				✓	✓						✓	
Streptomycin		✓										
Tobramycin	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	
Gentamicin		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Amikacin	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	
Netilmicin		✓				✓	✓	✓			✓	
Vancomycin	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Kanamycin		✓										
Indinavir				✓	✓							
Ritonavir				✓	✓							
Zidovudine		✓										
Enfuvirtide				✓	✓							
Others		36								3		
Antineoplastic and immunomodulating agents												
Imatinib				✓	✓							
Ciclosporin		✓		✓	✓							
Tacrolimus				✓	✓							
Everolimus				✓	✓							
Sirolimus				✓								
Others		10										
Nervous system												
Acetylsalicylic acid (aspirin)		✓										
Paracetamol		✓										
Phenobarbital		✓								✓		
Phenytoin		✓		✓	✓					✓	✓	
Carbamazepine	✓	✓		✓	✓							
Valproic acid	✓	✓		✓	✓				✓			
Lithium		✓		✓	✓					✓		

Table 5 continued

Drug	MM-USC*PACK©	MwPharm©	TCIworks	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
Others		42										
Respiratory system												
Theophylline		✓		✓	✓				✓	✓	✓	
Aminophylline					✓			✓				
Oxtriphylline					✓							
Others		2										
Miscellaneous		30					1	2				
Other one-compartment drugs							✓			✓	✓	

Drug classification according to WHO Anatomical Therapeutic Chemical classification

✓ Drug handled by the software

accommodating any kind of model of up to three compartments. Conversely, TCIWorks offers a very simple and intuitive tool for the user to add his/her own model of up to two compartments. Moreover, it offers the possibility to freely import and export drug models plugged in as extensible markup language (XML) data format and thus easily share drugs models.

APK©, Antibiotic Kinetics© and RADKinetics account only for intravenous administration owing to the fact that drugs handled by these programs are only given through this route of administration. Only the more sophisticated packages (i.e. MM-USC*PACK©, TCIWorks, MwPharm©, Kinetidex®, T.D.M.S. 2000™) are able to handle data for drugs administered by continuous intravenous infusions. Those same programs are also able to deal with non-steady-state and irregular regimens, which represents a substantial feature. In fact, they offer a convenient interface to enter concentrations with detailed information on dosage history. It is worth noting that APK© and Kinetics© can deal with non-steady-state situations, but require three concentration–time data points. APK© is also able to deal with a first dose, but requires at least two concentration–time data points to perform calculations, and would not use a Bayesian analysis in that case, but rather a simple regression approach.

It is crucial that programs document the prediction and individualization methods employed to ensure accuracy and appropriateness. Equations are, however, detailed in only a minority of support sources, namely in T.D.M.S. 2000™, DataKinetics™, MwPharm© or RxKinetics©. Whereas in the 1990s only half of the programs offered Bayesian prediction [12], nowadays such approaches are widely implemented; ten of 12 programs offer such techniques. This is particularly convenient for routine practice because of the limited number of samples required and the flexibility of sampling times. It is worth noting that only MM-USC*PACK© uses a non-parametric approach, which provides the advantage of assuming no distribution and of allowing subpopulation clusters [31], which is not easily achievable with normal or log-normal distribution assumptions [32]. Nine of the computer tools are able to compute an a priori regimen and, among those, seven are also able to estimate a loading dose.

For users who would not know concentration targets, default therapeutic range targets are often provided by the software. To be easily used according to up-to-date institution recommendations or specific patient cases, therapeutic targets should be readily modifiable, which is the case in most software packages.

Pharmacokinetic curve plotting is offered by all software except JPKD® (which proposes it only for aminoglycosides), RADKinetics and TDM for R. Only MM-USC*PACK© offers the option to include the population variability through adding percentiles to plots.

From a clinical point of view, it is essential that clinicians be aware of the creatinine clearance of certain drugs. Many programs, in addition to Cockroft-Gault, suggest other creatinine clearance calculations such as Schwartz, Cockroft-Gault adjusted to bodyweight, MDRD or Jelliffe's equations. TDM for R and JPKD® do not provide this parameter.

Regarding this 'pharmacokinetic aspects' category, the most sophisticated programs had the highest scores: MwPharm©, MM-USC*PACK© and TCIWorks (Table 4).

3.3.3 *Authors*

All programs have been developed by pharmacists and/or medical doctors, usually supported by skilled computer specialists. They were all developed in an academic environment (except perhaps for Kinetidex®, for which no information could be obtained). TCIWorks received grant support from a pharmaceutical company (Pfizer) among other academic sponsors. Only two programs have been described in the literature in the past (USC*PACK© [21] and MwPharm© [19]), but the publications concern old versions. Literature regarding the use of the programs is also quite poor. However, among the literature that does exist, USC*PACK© is the best furnished, particularly regarding its use in clinical practice [33–36]. TCIWorks has also recently started to be documented as well [37, 38].

3.4 Clinical Vignettes

Clinical vignettes were tested in each program whenever possible (see Table SIII in the Online Resource), in order to gain insight into dose adjustments and predicted concentrations. These results are only presented for descriptive purposes. As much as possible, vignettes were entered into each program in the same manner. However, difficulties were encountered, such as (1) introduction of a first dose or interruption of treatment, especially when a dosing interval or a delay before restarting treatment was indicated; (2) drug administered in neonates and low bodyweight patients; and (3) administration by continuous intravenous infusions.

Nevertheless, when vignettes were able to be processed, most of them roughly converged to a similar prediction, except for phenytoin (a drug characterized by non-linear kinetics), where extrapolated concentrations were aberrant in some programs.

3.5 Overall Classification

From a global benchmarking point of view, MwPharm© and TCIWorks turned out to be the best ranked TDM programs. Because they represent sophisticated tools, they fulfil many of the criteria considered: both are complete software offering calculation of patient parameters, a priori and a posteriori dose suggestions, a structured patient database and good quality reports. However, such tools can be rather complex to use, which is especially true for MwPharm©, whereas TCIWorks is more intuitive. MwPharm© benefits from a large drug library, but, unfortunately, no description of the drug models is available, which means that not all drugs are easily usable. TCIWorks does not have a drug library yet. USC*PACK© should also be considered as a comprehensive software; however, despite its large number of users worldwide, it lacks user friendliness and flexibility compared with other programs and provides no structured database or report transmissible to practitioners. The success of the software definitely lies in its good pharmacokinetic capabilities and its long experience.

The three RxKinetics© programs, Antibiotic Kinetics©, APK© (the third best classified program) and Kinetics©, offer simpler but very flexible solutions, particularly for non-experienced users, with a good cost/capabilities ratio. Antibiotic Kinetics© is the least sophisticated of the three, and is unable to save any patient or consultation data. APK© and Kinetics© provide patient records and reports of good quality. These computer tools aim to deal with daily clinical practice. T.D.M.S. 2000™ and Kinetidex® also offer nice features with Bayesian analysis, a database, and the ability to detail complete patient dose administration and concentration measurements. However, these programs are expensive. User friendliness could be improved for most software, especially T.D.M.S. 2000™. JPKD® and TDM for R allow a simple adaptation from a single measurement at steady state. JPKD® is a simple, intuitive, convenient and free tool. Conversely, TDM for R requires the user to already be an experienced R user.

4 Discussion

Overall, for many years now, lots of effort has been put into the development of computer tools throughout the world to facilitate the practice of TDM and to provide reliable dosing optimization advice with convenient and complete software. This article presents a comprehensive review of the characteristics of the available software. From simple, efficient and low-cost programs (JPKD®, APK©) to comprehensive packages (MwPharm©, TCIWorks, USC*PACK©), the panel of available tools is fairly variable.

Each software tool must be regarded with respect to the individual needs of hospitals or clinicians. Major limitations to achieve this benchmark probably reside in the uniqueness associated with each of these programs. Depending on the intended users, specific TDM practice, whether it is to be used in clinical research or not, etc., a certain tool would better fit one institution than another. In this article, we followed a general and consensual strategy, and our grid focuses on all aspects that we considered, as clinical pharmacologists, as being required by an 'ideal' TDM software tool for a large population of potential users. The weight assigned, by three different types of professionals (physicians, pharmacists, computer engineers), attempts to balance these aspects of the tools. This should, however, not prevent individual users from defining their own weighting factors (even 0) for Table SII in the Online Resource and to obtain a global score that would better reflect their own needs. Our grid, used to rank the software, is a complete and detailed list describing characteristics of the programs assessed; however, it only focuses on dosage optimization in the context of TDM. Thus, it may possibly have missed some features that make each program unique.

MwPharm© and TCIWorks were found to provide optimal characteristics for TDM but to represent sophisticated tools that offer detail beyond the traditional needs for drug adjustment. For simple adaptation based on one concentration, simpler tools such as JPKD® or APK© may be sufficient for many clinicians.

TCIWorks is in an early stage of its development and looks promising. It has more flexibility and is more intuitive for users than most other programs presented in this review. Its developers aimed to implement target concentration intervention (TCI) rather than TDM. TCI is an evolving concept that proposes targeting of a concentration associated with a desired effect rather than a traditional therapeutic range [39]. Moreover, future versions of TCIWorks should include the possibility to add a pharmacodynamic block to models.

Although MM-USC*PACK© was not among the best ranked programs, it is used worldwide and is still often considered as a reference for precision and prediction (MwPharm© [40] or Abbottbase PKS [41] were previously compared to it). Moreover, in addition to the clinical interface for dosage adjustment, USC*PACK© offers a full modelling tool employing the NPAG algorithm. Customized pharmacokinetic/pharmacodynamic models can be built up through a graphical approach by placing boxes on the screen and connecting them with arrows (USC*PACK BOXES). Additionally, USC*PACK© also offers programs for infectious disease and cardiology. Finally, new features are under development (interfacing, database search function, and drug and disease interactions).

It is also worth noting that other types of tools than stand-alone TDM programs do exist. A good example is the ISBA (ImmunoSuppressant Bayesian dose Adjustment) web portal from Limoges University Hospital in France (https://pharmaco.chu-limoges.fr/), which proposes TDM adaptation for ciclosporin, tacrolimus, mycophenolate mofetil and, coming soon, for aminoglycosides and glycopeptides, methotrexate and anticancer agents. When dosage adjustment for one of these drugs is desired, the user fills in a data entry sheet on the portal to give information about patient clinical evolution, the context of the request, drug intake and blood drug concentration. Adaptation is then proposed based on Bayesian estimation and validated by a pharmacologist. It is then sent to the applicant via an electronic standardized report, normally in 24 h. A similar portal exists for fluorouracil dosage optimization, called ODPM (Onco Drug Personalized Medicine), which has been developed by the Cancerology Institute of the West Paul Papin and University of Angers, France (http://www.odpm.fr/). Web portals could therefore represent an alternative to autonomous software despite their requirement of remote human third-party intervention.

Bayesian dosing optimization is widely applied now, being considered the gold standard. For instance, the pharmacokinetic Bayesian method is recommended in the "Australian Therapeutic Guidelines: Antibiotics" [42, 43]. The use of this approach allows computation of a priori dosage regimens based on the individual's characteristics, the use of random time sampling, performance of clinical interpretation in non-steady-state situations, and more accurate predictions [44]. However, such complex mathematical calculations would not be possible without computer tools, and this is why all currently marketed TDM programs now integrate it.

To date, the usefulness of TDM remains controversial, with studies showing positive, negative or no significant impact on patient outcomes [45]. Despite the heterogeneity of the data, TDM services have been used since the 1970s in clinical practice, after some early trials with lithium and digoxin in the 1960s [1, 45]. This has been encouraged by the introduction of computerization, especially in Europe (notably in The Netherlands [46]), Australia [47] and the USA [48, 49]. Computer-assisted advice should indeed be part of a global multidisciplinary TDM strategy, as foreseen some decades ago [50]. Even though it was reported that unassisted clinicians tend to use suboptimal loading, maintenance and total doses than when computer support is available [5, 51], dosage optimization programs do not replace clinicians with pharmacokinetic skills. Physicians and other specialists involved in patient care should be aware of the potential of TDM and increasingly take advantage of these powerful computer tools. In the late 1990s, Bates emphasised the importance of educational approaches to change physicians' opinions and interventions, in addition to the efficiency of computer tools [52].

Despite the growing availability of dosage adjustment tools, there is still room for improvement. Programs should ensure user friendliness through smart design and flexibility, enabling easy and quick use in routine activities, including by non-experienced users. Expected pharmacokinetic variability should be displayed, e.g. via visual representation of percentiles. More importantly, to be used in hospitals, the program should interface with other applications, in particular with laboratory information management systems, patient administrative databases and electronic medical records. Moreover, the ability to export data should enable further research. Accurate Bayesian approaches should be routinely preferred for optimal dosing regimen prediction. Comprehensive but clear and pedagogical printed reports, customizable for institutions, should be produced. Support should ideally be provided both by the developers and by a community users group, with access to clinical and technical documentation. Finally, TDM applications should become easily portable to ubiquitous and user-friendly mobile devices, in order to be used directly at the point of care, at the patient's bedside [53] or even by the patients themselves.

5 Conclusion

While the 12 presently available TDM programs reviewed here reveal an encouraging evolution, none of them yet fulfils all of the requirements of an ideal tool [8]. The major challenge currently is to develop programs with comprehensive clinical and research capabilities, while still showing simplicity, flexibility and user friendliness that would make these tools easy to run by all types of users.

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