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Pharmacokinetic software for therapeutic drug monitoring: A scoping review protocol

Software de contenido farmacocinético para la monitorización terapéutica de fármacos: Protocolo de revisión exploratoria

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Abstract

Objective: Nomograms, equations and pharmacokinetic software are considered the main tools available for therapeutic drug monitoring. Due to its great applicability to various groups of drugs, the use of software is widely extended in clinical practice. The main goals of the studies using this type of software do not normally include the description of its features, therefore, the information about its characteristic is scarce. Moreover, no review of the literature has been published that brings together all the information available about these software. The present study aimed to synthesize the available evidence regarding software applied to therapeutic drug monitoring to facilitate its identification, evaluation and selection by users.

Method: This article describe a scoping review protocol, developed following the PRISMA-P and PRISMA-ScR guidelines. An electronic literature search was performed in MEDLINE, EMBASE, OpenAire and BASE (Bielefeld Academic Search Engine) databases. Only those software for which the following information was available were included: name of the software, developer/marketer, type of pharmacokinetic analysis allowed, and drugs included in the analysis.

Results: In this study we will synthesized the most relevant characteristics for the clinical practice of the pharmacokinetic software available. A critical appraisal of the sources if information will be included. Also, if it is possible, a comparison of the available tools will be carried out

KEYWORDS
Therapeutic drug monitoring; Software; Pharmacokinetics; Drug dosage calculations; Computer assisted drug therapy.

Resumen

Objetivo: Los nomogramas, ecuaciones y *software* de contenido farmacocinético se consideran las principales herramientas disponibles para la monitorización farmacocinética clínica. Debido a su gran aplicabilidad en numerosos grupos de fármacos, el empleo de *software* se encuentra ampliamente extendido en la práctica clínica. Generalmente, el objetivo principal de los estudios que incluyen el uso de estos *software* no es la descripción de los mismos, por lo que la información disponible es escasa y, además, no se dispone de una revisión que aúne toda la información disponible referente a este tipo de *software* El objetivo de este estudio será sintetizar la evidencia disponible sobre los distintos *software* de aplicación en la monitorización farmacocinética para facilitar a los usuarios su identificación, evaluación y selección.

Método: Se realizará una revisión exploratoria de la literatura cuyo protocolo se describe en este artículo, de acuerdo con las recomendaciones PRISMA para la elaboración de revisiones exploratorias y publicación de protocolos. Se realizará una búsqueda bibliográfica en las bases de datos Medline, Embase, OpenAire y Bielefeld Academic Search Engine. Se incluirán en el estudio aquellos *software* detectados de los que se disponga de la siguiente información: nombre del *software*, desarrollador/comercializador, tipo de análisis farmacocinético y fármacos incluidos.

Resultados: En este estudio se espera realizar una síntesis de las características más relevantes en la práctica clínica de los *software* de contenido farmacocinético disponibles en el mercado. Se realizará una

PALABRAS CLAVE
Monitorización terapéutica de fármacos; Software; Farmacocinética; Cálculo de dosis de medicamentos; Farmacoterapia asistida por ordenador.

in order to facilitate the evaluation and selection of pharmacokinetic software.
Conclusions: Pharmacokinetic software has become a relevant tool for therapeutic drugs monitoring. Currently available evidence on such tools is scarce, which precludes a rapid and effective comparative analysis between the different options available. An analysis of the main characteristics and a comparison between different pharmacokinetic software will be useful to the users, leading to a greater integration of these tools in healthcare practice.

síntesis narrativa crítica de las fuentes de información utilizadas. Además, se llevará a cabo, si es posible, una comparación de los mismos para facilitar la evaluación y selección por parte de los usuarios.
Conclusiones: Los *software* de contenido farmacocinético se han convertido en un recurso fundamental en la práctica de la monitorización terapéutica de fármacos. La evidencia disponible en la actualidad es escasa y no permite a los usuarios realizar de forma rápida y eficiente un análisis comparativo entre los distintos *software* disponibles. El análisis sobre las características principales y comparación entre los distintos *software* de aplicación farmacocinética será de gran utilidad a sus usuarios para una mayor integración de estas herramientas en la práctica asistencial.

Introduction

Since the decade of the 1970s, pharmacokinetics has been used as a tool to optimize dosing regimens of certain drugs with a view to maximizing their effectiveness and avoiding undesired side effects. To address the issue, the demographical, genetic, biological and clinical parameters that may influence inter- or intraindividual variability in blood concentrations of drugs susceptible of pharmacokinetic monitoring must be considered. For drugs with a good correlation between blood levels and pharmacological effects, therapeutic drug monitoring (TDM) is applied in clinical practice to manage high inter- or intraindividual variability, limited therapeutic range, target concentration levels difficult to reach or high toxicity beyond the therapeutic range[1,2]. TDM applications frequently include drugs such as anticonvulsants, antimicrobials and immunosuppressants, among others. TDM of these drugs has allowed clinicians to reach the desired therapeutic effects quickly and safely, providing clear benefits in terms of outcomes and health[3].

Some strategies currently employed to optimize drug dosing involve the use of nomograms, mathematical equations and TDM based on software-assisted population pharmacokinetic (popPK) models. Nomograms are charts that establish a relation between the recommended dose of a drug and other patient characteristics such as kidney function, body weight or drug concentration in the blood[4]. These charts, based on pharmacokinetic studies or statistical analyses of the relevant population, are an accessible, easy-to-use tool for dose adjustment. The use of mathematical equations allows for static estimation of pharmacokinetic parameters at the time of determining the blood levels of the drug. This approach furnishes objective data at specific moments in time, but does not allow for adjustments to be made in the event of significant changes in the clinical status of patients. Finally, the use of software-implemented popPK models makes it possible to combine patient data with popPK models in order to estimate pharmacokinetic parameters. The software, generally based on Bayes' theorem, allows for drug concentration predictions and dose recommendations that consider the patient's deviations from the popPK models[5-8].

The use of pharmacokinetic software is on the rise thanks to the profuse development of popPK models and the large number of drugs which dosing regimens could be optimized using TDM, making it a highly valued tool in standard clinical practice[9]. An extensive use is conditioned by the lack of information regarding the software, its limited accessibility and, sometimes, the technical difficulties its use involves for non-specialized operators. In addition, some authors have pointed out that most pharmacokinetic software will require further development to improve its ease of use and its data storage and report generating capacities[6].

An increase in the development and supply of pharmacokinetic software has occurred in recent years. The information available on each of these applications is scarce and varies greatly, making it difficult for health professionals to select a tool of choice. There is also a lack of detailed descriptions and technical data regarding the software, since most of the published studies are aimed at highlighting clinical interventions performed with the aid of the application rather than describing or assessing the latter.

The goal of the current review is to identify the most common software available for TDM and dose individualization and to describe their main characteristics, in an attempt to facilitate and promote their use by healthcare professionals in clinical practice.

Methods

Design of the study

The protocol was developed following PRISMA-P[10] recommendations for the publication of systematic review and meta-analysis protocols using methodology described in the Joanna Briggs Institute Reviewer's Manual[11]. Required modifications were introduced to adapt these recommendations to an exploratory review.

The review was designed in accordance with PRISMA-ScR[12] recommendations and has been entered into the Open Science Framework international registry (ID: 10.17605/OSF.IO/M53NF).

Participation of patients and the public

The performance of the present protocol involves no patients or members of the general public.

Eligibility criteria

Studies are to be selected on the basis of the following criteria:

- Inclusion criteria: Studies identifying pharmacokinetic software that is useful for TDM in adult and pediatric populations. No restrictions will apply regarding the design of the studies or the groups of drugs included therein.
- Exclusion criteria: Studies in languages other than English or Spanish or not available in full-text form will be excluded.

Sources of information

A search of the literature will be performed in two biomedical databases: MEDLINE, through the PubMed search engine, and EMBASE. At the same time, searches will be carried out on the OpenAIRE and BASE electronic databases to seek out information published as grey literature. Articles that are of interest to the study and are detected through citations, but do not come up among the results of the search strategy described below, will also be included, manually.

Search strategy

The strategy applied to searches of the MEDLINE and EMBASE biomedical databases will consist in a combination of indexed terms and free terms, adapted to each of the databases. The strategy is described in detail in table 1.

In searching the OpenAIRE database the terms "therapeutic drug monitoring" and "software" will be used; search of BASE will include the terms "therapeutic drug monitoring", "drug therapy software", "drug dosage software" and "pharmacokinetic software".

In addition, searches will be updated before the end of the data collection process, to identify those studies that might have been published between the end of the search and the completion of the data extraction process.

All available references and full texts that are identified in the search of the literature will be exported to the Mendeley® reference management tool for subsequent classification of studies as duplicated, included or excluded.

Table 1. Search strategy applied to searches of the different biomedical databases

Biomedical database	Search strategy
PubMed	("therapeutic drug monitoring" OR "Drug Dosage Calculations") AND ("software" OR "Drug Therapy, Computer-Assisted" [MeSH Terms] OR "Population pharmacokinetics")
EMBASE	('therapeutic drug monitoring' OR 'drug dosage calculations') AND ('software'/exp OR 'computer assisted drug therapy'/exp OR 'population pharmacokinetics'/exp)

Recording of the studies

Selection process

— *Study selection*

Articles will be selected by two independent reviewers. After removing duplicated papers, a preliminary series of articles will be selected by analyzing study titles and abstracts. Articles selected in this initial phase will be subject to an in-depth assessment that includes perusing the full text and choosing those papers that meet eligibility criteria. Discrepancies in the selection process will be resolved through discussion; in the event that no agreement is reached, the decision will rest in the hands of a third reviewer. The reasons for exclusion of discarded studies will be recorded. None of the reviewers will be blinded to the names or affiliation details of publications or authors.

— *Selection of software*

All software named or described in the selected studies will be identified. An additional search will be carried out on digital platforms when the information provided by the studies is not adequate for the correct selection, and whenever possible the software development and support team will be contacted to request information and guarantee that it complies with the characteristics described in the studio.

When the available information on software is not enough to collect and subsequently assess the relevant variables, the software will be described in a supplement or a table so that the data may help users to identify it. The minimum information required will be: name of the software, name of its developer or distributor, type of pharmacokinetic analysis it performs and what drugs it includes.

Data management

The data will be collected in an ad hoc table using Excel® spreadsheets to compile and classify the information according to the different variables.

— *Data selection and extraction process*

The variables will be previously defined and extracted from each study for the identification and analysis of the software. The data will be extracted from the selected studies by two reviewers working independently in pairs. Any discrepancies that may arise will be resolved by each pair through discussion and consensus. In the case that no agreement is reached, a third researcher will be included in the discussion and ultimately, a vote will be carried out.

Study variables

The following data will be collected for each of the identified software systems:

- Identification.
- Developer/distributor.
- Year and country of creation.
- General description of purpose.
- Drugs included.
- Target population.
- Type of pharmacokinetic analysis available.
- Capacity for generating reports, creating charts and integrating into other systems.
- Potential for inclusion of new drugs, by the user or by request to the developer.
- Inclusion by default of population data.
- Potential for inclusion of new populations by the user or by request to the developer.
- Potential for software trial for users training.
- Software access routes: online, by e-mail or through the developer's telephone contact.
- Languages in which the software is available.
- Latest update.
- Subscription: pay for use or open access.
- Experience of use: in clinical practice, in research or unknown.
- Number of publications in which it is cited.

Critical assessment of sources

The articles selected for software detection will be analyzed individually. In order to synthesize their characteristics, the following variables will be collected: identification, aim of the study, detected software applications, software description (yes/no), year of publication.

Furthermore, if an additional search on digital platforms and/or contacting the software development and support team to request further information is necessary, the information source and the collected data will be grouped together and synthesized.

Results

Search of the literature

Firstly, the results obtained from the search of the literature will be displayed on a PRISMA flowchart that will include the studies that have been selected and those that have been ruled out based on their title or abstract or because they were duplicated or met some other exclusion criteria, the reason for their rejection being stated. The characteristics of the selected articles will be described on a table.

Sources of information

A narrative synthesis of the sources of information used in the present study will be drawn up. In addition, the characteristics of the selected articles and the information obtained by searching digital platforms or contacting the software development and support team will be summarized on tables or charts.

Software

A descriptive table of the detected software, including the selected variables (described under section "Study variables"), will be drawn up. This will present the main characteristics of the chosen software, allowing for analysis and selection on the part of users. A second table or attachment will be added, including tools regarding which it was not possible to obtain minimal information (this is described under section "Selection process").

The software shall be classified in accordance with the drugs that are covered by each one of them. They will be grouped together on the basis of the ATC classification and this information will be presented in the form of charts or tables that allow the user to identify the available software depending on their pharmacotherapeutic area of interest.

Based on the obtained results, if it is considered necessary, a comparative analysis of the detected software will be carried out. To this end, a scale or scoring or classification system will be produced to assess the quality of the software. The kind of tool employed for this, and the process of assessment, will be described in detail.

Synthesis of results

We do not expect to find enough data to allow for quantitative synthesis. All the information will be categorized, and a narrative and qualitative synthesis of the evidence will be drawn up. Tables and figures will be used to offer an overview of the evidence that is found.

Risk of bias in individual studies

Quality and risk of bias evaluations are optional in exploratory reviews[12] and are frequently not included. If we finally decide to include them, the methods employed will be described and the basis for our decisions and our choice of relevant evaluation tools will be provided.

Discussion

Pharmacokinetic software are currently a fundamental tool for TDM and have become an essential resource in clinical practice. The results of the present study will allow users to directly and efficiently identify their software of choice based on functionality and usability needs. In the discussion section the authors will also include a quality classification of the software tools, based on their characteristics, in order to further assist users in making their selection.

The present study's protocol was developed following two of the PRISMA guides: the protocol design guide[10] and the exploratory review design guide[12], in addition to the methodology described in the Joanna Briggs Institute Reviewer's Manual[11]. The decision to perform an exploratory review stems from the need to have a general overview of the existing evidence on pharmacokinetic software after identifying a vacuum in this regard in the current scientific literature. Mapping of the relevant literature in this area will allow us to synthesize available knowledge and identify present gaps in research.

One of the study's limitations is the fact that it only includes articles published in English and Spanish, which could entail a loss of relevant information that might have been published in other languages. However, it is our hope that the studies we have included from the grey literature confer this review an advantage, since this kind of search brings up a wealth of software and it is quite likely that many of these have not been the subject of scientific papers but may be identified through the sources we will supply. Furthermore, no restrictions will be applied regarding the year of publication of the chosen studies.

The strongest point of our study is that to our knowledge this will be the first descriptive and comparative analysis of all pharmacokinetic software for TDM that are available on the market. Another strength of the study lies in the fact that it is to be carried out following internationally recognized methodological standards that will support the quality of our results. Both the preliminary screening of the articles and the extraction of data will be performed by two independent researchers with experience of the methodology in order to minimize the likelihood of personal bias.

In summary, the paper will represent an advance in the knowledge and selection of pharmacokinetic software for clinical use, allowing users to make individualized choices that are based on their needs and requirements.

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Conflict of interest

No conflict of interests.

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