Drug information center: challenges of the research process to answer enquiries in hospital pharmaceutical practices

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ABSTRACT

Objective To characterise information requests (IRs) from hospitals received by a drug information center (DIC-RS) according to the resolution of the inquiries.

Method The sample consisted of all requestors and their respective IRs registered in the DIC-RS database from January 2012 to December 2016. Request without information in the consulted literature (RWI) were categorised according to the institution of origin. IRs from hospitals were classified by the information source, topic and subtopic of the questions, and the number of drugs and the pharmacological or therapeutic group.

Results A total of 2,500 IRs were analysed. Of those, 25% did not exhibit conclusive information in the consulted sources. RWI from hospitals represented 51% of all RWI, followed by those from community pharmacies (13%) and health centres (9%). Tertiary literature was the most commonly used source (73%) for IRs from hospitals. The greatest difficulties in finding information were related to off-label drug administration and indication issues (52% of RWI). The most common type of off-label use was related to changes in the original pharmaceutical form of the drug. Furthermore, 61% of RWI were directed at a specific drug, mostly systemic anti-infectives.

Conclusion We found that a quarter of the answers did not exhibit conclusive information in the consulted sources. Answers to IRs from the hospital environment exhibited the greatest extent of limited information, and off-label use was responsible for most cases.

INTRODUCTION

According to the WHO, rational drug usage is when 'patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community'. The WHO determined 12 essential interventions to promote rational use of medicines, including offering independent information on drugs.¹ Ideally, drug information should 'provide impartial, well-referenced and critically evaluated information about any aspect of pharmaceutical practice'.²

One of the main current challenges in choosing the most rational therapy for patients is the amount of existing information. Overwhelming numbers of scientific articles are published on a daily basis, which directly conflicts with the reduced

time available to healthcare professionals to read and remain up-to-date on current research. The limited time to research information on specific doubts related to the treatment of a given patient can preclude consultations of databases, such as MEDLINE,³ Up to Date⁴ and Clinical Evidence;⁵ original articles; and systematic reviews. Thus, matching clinical practice with the best scientific evidence becomes a challenge.⁶

Drug information centres (DICs) originated from the need to align the large amount of available information on drugs with the application of this knowledge in clinical practice. The DICs must supply individualised, impartial, updated and appropriate information based on the best scientific evidence and aim to promote secure and efficient therapeutic practices at the best cost-benefit to society.²

One of the fundamental functions of DICs is to receive and answer medicine-related questions from healthcare professionals, i.e., to provide passive information.⁷ Passive information is that offered in response to an applicant's question. The pharmacist expects the interested party to ask the question. It differs from the active information, which is that produced by the DIC for all health professionals.² Müllerová and Vlcek⁸ have evaluated the activity of 84 DICs from 16 European countries and found that all exhibited passive information as their main activity.

The passive information provided by the DIC-RS is carried out by a pharmacist with professional experience in the area and assisted by fellows (undergraduate pharmacy students). The work systematics follows Flow Chart 1 (online supplementary annex 2). The identification of the theme makes it possible to select the sources of information that will be initially used to search for the information, prioritising the consultation in tertiary sources. Online supplementary annex 1 lists the main sources used. The previous consultation to the database of the Centre provides the location of answers already elaborated on the question, in which case the response will be reviewed and updated. In cases of consultation in secondary and primary sources, the response contains the search strategy in the databases to ensure the reproducibility of the search, the number of documents retrieved and the articles selected.

In this context, several studies addressed the services of DICs and have characterised indicators of assistance on the performed activities according

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to the number of information requests (IRs), user profiles, IR topics, response time and user satisfaction.^{9,10} Studies from 2016 and 2017 investigated the quality of responses produced by DICs in Scandinavia.^{11,12} However, no study has characterised the identification of information by the context of the question. The objective of the present study was to classify RWI in the consulted sources according to the most prevalent institution of origin.

METHODS

Data were collected from the database of the DIC from Rio Grande do Sul State (DIC-RS, Brazilian Portuguese abbreviation: CIM-RS), which is one of the oldest still functioning centres in Brazil and a national reference in this area. The DIC-RS addresses drug-related questions from high-level healthcare professionals acting in several fields, such as community pharmacies, health centres, hospitals and universities, among others. The DIC-RS is located at the School of Pharmaceutical Sciences of the Federal University of Rio Grande do Sul (UFRGS) and has its own bibliographic collection and access to several electronic databases and other sources of electronic information provided by the UFRGS. Therefore, the DIC-RS has access to the major electronic sources of drug-related information recommended for DICs.^{2,13}

The sample was composed of all requestors and their respective IRs registered in the DIC-RS database from January 2012 to December 2016. The answers sent to requestors were reviewed, stored as pdf files in electronic folders, and organised by year and month. The passive information provided by DIC-RS was performed by a pharmacist with professional experience in the field and assisted by fellows (undergraduate pharmacy students).

The answer to each IR included a search for phrases indicating that no specific information could be found for the resolution of the main question of the requestor, including: 'No specific information on the context of the question was found in the consulted sources.' Questions for which no specific information was found will hereinafter be known as 'Request without information in the consulted literature (RWI).' The research was carried out manually by reading 2,500 IRs. The RWI review was conducted by a pharmacist with a doctorate in Pharmaceutical Sciences.

Questions regarding adverse drug reaction that were not found in the database were considered RWI. Other situations include indications of the use of medications in neonatal, premature and geriatric populations, as well as the mode of administration by any way other than that established during drug registration.

Information on the institution of origin for each requestor was classified as a hospital, a community pharmacy (drugstore), a health centre, a compounding pharmacy, a university, another DIC, a Department of Health or other. RWI from the most prevalent institution of origin was classified as:

- A. Sources of information used in the references of the response and classified as tertiary, secondary or primary. According to the concept adopted by the DIC-RS, tertiary sources are those that exhibit information documented in a compact format (textbooks, monograph books, review articles and systematic reviews/meta-analyses). Secondary sources comprise primary literature indexing and abstracting services. Medline is one example of a secondary source used by the DIC-RS. Finally, primary sources are scientific articles that report results from original studies (randomised clinical trials, cohort studies and case-control studies, among others).
- B. Researched topics were classified as follows: mode of use/administration, compatibility, conservation, equivalence,

pharmacotherapy, indications of use, drug interactions, legislation, dosage, adverse reactions or other;

1. Topics were subclassified into the following categories: off-label use for indication, route of administration, pharmaceutical form (PF), dosage and age range. Off-label use was considered when the indication of use, route of administration, transformations and derivations of the PF, dosage and age range were not approved by the US Food and Drug Administration (FDA) and the Brazilian National Sanitary Surveillance Agency (ANVISA). This designation was verified by consulting the Drugdex system and the labels of the reference drugs, which were available in the electronic package inserts (<http://portal.anvisa.gov.br/bulario-eletronico1>).

- C. The drug, pharmacological or therapeutic group involved in the question was classified according to the Anatomical Therapeutic Chemical (ATC) classification of the WHO.¹⁴

The classification used in this study has been routinely used by the DIC-RS since its inauguration in 1999, and was based on the criteria established at the First Meeting of the Brazilian Medicine Information Centres in 1996 (Drug Information Centre: Diagnostic Brazil).¹⁵

The data were summarised and are expressed as relative frequencies in graphs and tables using Microsoft Excel for Mac 2011, version 14.1.0.

A Data Use Agreement was completed by all researchers involved in the data extraction to ensure the confidentiality and privacy of the participants during all phases of the research. The requestors' data are anonymized for this research. The present project was approved by the Ethics Committee of the UFRGS (Protocol number 1. 802.754).

RESULTS

During a 5-year period (January 2012 to December 2016), a total of 2,500 IRs received by the DIC-RS were analysed. Of these, 25% (625) exhibited no conclusive information in the consulted sources, i.e., no information was found in tertiary, secondary or primary sources that met the needs expressed by the requestor in the IR. Figure 1 shows that the institutions of origin of the RWI were predominantly hospitals, 51% (n=318), followed by community pharmacies, 13% (n=81), other, 10% (62), health center, 9% (n=56), compounding pharmacies, 7% (n=44), university, 4% (n=25), Department of Health, 3% (n=19) and DIC 3% (n=19).

As for the type of reference source used to answer the RWI, each exhibited an average of 7.5 references, of which 5.5 were tertiary, 1.5 secondary and 0.5 primary sources. Searches in databases, such as Micromedex, represented 49% of all searches, followed by PubMed (10%). A secondary source, such as PubMed/Medline, was used as a guide to find the primary source in 50% of the cases.

In the case of IR with information in the literature, the average number of references consulted was 7.5, of which 7 were tertiary, 0.4 secondary and 0.1 primary sources. It was possible to observe that, in most cases, consultation with tertiary and secondary sources was enough to answer the questions.

Of all RWI from hospitals (n=318), 61% (194) referenced a specific drug, with the highest frequency for anti-infectives for systemic use (26%), followed by drugs that act on the central nervous system (14%), and the alimentary tract and metabolism (13%), as shown in figure 2.

Figure 1 Institution of origin of RWI (n=625).

With respect to IR topics, most were classified as administration/mode of use (53%), followed by indication of use (10%) and adverse reactions (7%), as shown in [figure 3](#).

Regarding topic subclassification, 52% of RWI from hospitals referred to off-label use of the inquired drugs and were distributed as follows: changing the original PF of the drug (45%), route of administration (32%), age (13%), dosage (6%) and indication of use (4%), as shown in [figure 4](#).

DISCUSSION

In this study, we found that a -quarter of all answers provided by the DIC-RS did not exhibit conclusive information in the

Figure 3 Classification of RWI from hospitals according to topic (n=318).

consulted sources and that the majority of RWI were from hospital professionals. This is due to hospital practice issues involving critical, paediatric and pregnant patients, which are not always available in studies. Moreover, hospital assistance has become more sophisticated and complex due to the incorporation of novel healthcare technologies,¹⁶ including new drugs, and novel indications or formulations for existing drugs.¹⁷ Furthermore, an increasingly deeper level of knowledge is required of healthcare professionals.

The RWI include inquiries where the absence of scientific basis of the event under study, in some cases, already answers the enquirers' question.

Figure 2 First-level ATC classification of drugs present in RWI from hospitals (n=318).

Figure 4 Subclassification of topics with respect to off-label use (n=165).

Tertiary sources of information were the most commonly used to answer RWI from hospitals. This is in agreement with the recommendations for DICs, namely that data research obeys the following consultation sequence: tertiary, secondary and primary.¹³ Further, other factors may justify the more frequent use of tertiary sources, such as availability, easy handling, promptness of use, objectivity and variety of information. However, it is important to note that tertiary sources are more prone to contain outdated information. Consulting primary sources in all IRs, on the other hand, is not always possible, due to the type of question and the time limit for the answer.

In the DIC-RS, in the case of IRs involving the specific patient, the time between receiving the question and sending the response must be less than 24 hours. Further, there are questions for which primary sources are less relevant, such as those regarding legislation, the availability of the product in the market and drug interactions. In turn, in IRs that do not involve specific patients, the consultant may extend the deadline to allow for a more detailed search.

Topic analysis of RWI from hospital professionals showed that the most difficult topics to find information on were related to the administration of drugs and indications of use, especially for off-label use, followed by questions related to adverse drug reactions (ADRs). IRs related to ADRs concerned possible causal relations between the use of a particular drug and the occurrence of an adverse event observed in the practice, whether or not it was described in the literature.

The subclassification of the most frequent off-label use was related to the need to change the original PF of the drug (43%). The majority of hospitalised patients (intensive care units) have problems with oral administration or with ingesting solid PFs,¹⁸ as is the case with paediatric¹⁹ and unconscious patients. In this sense, the PF of the drug must be changed for administration via alternative routes, such as enteral or nasogastric tube feeding. For this, knowledge of the technology of the PF, the release system of the active substance, its pharmacokinetic profile (especially the absorption site of the drug) and its stability in the resulting off-label preparation is essential in hospital assistance. In general, the off-label route of administration is not specified by the manufacturers at the time of drug registration, maybe because it is a situation that results from therapeutic practice and those determinants are not controlled in pre-registration clinical trials. Because these situations are very specific and not anticipated in the tests of the manufacturing laboratory, information is often limited to experiments performed in research studies, which are rarely performed under the same conditions and thus hamper the direct application of the information.

The off-label use of PF refers to any change in the pharmaceutical form of the drug. For example, hospitalised patients are often unable to receive oral medications and may receive prescribed oral drug therapy through the enteral catheter. The technique for administering oral medications via enteral catheter basically consists of tablet maceration or capsule opening and dissolution in water for further administration.²⁰ In this sense, changing the administration route through off-label use was responsible for approximately one-third of the cases and was present in questions about use in serious situations, such as hospitalised patients who did not respond to conventional therapy. This change in the administration route can cause changes in pharmacokinetics and bioavailability, and reduce the efficacy of the drug. Though procedures like this must be performed only in exceptional cases, if there are no alternative routes of administration,²¹ these procedures become a necessity in clinical practice. This becomes a problem, given the scarcity

of information found in the literature as well as in the manufacturer's specifications.

As for questions on off-label use related to the age range (such as paediatrics, neonatology, geriatrics), the lack of information is mainly due to the lack of approved therapeutic options and to studies for specific populations.²² In all answers provided to the requestors, information on evidence of increased adverse events and reduced efficacy in the target population was provided. In the case of paediatrics, for example, there are important challenges related to the difficulties of performing tests involving this age group, either for ethical reasons, high cost or even for as long as a paediatric study may require.

Anti-infectives for systemic use were among the most commonly inquired about drugs in RWI from hospitals and are among the most commonly prescribed drugs for off-label use,²³ as are antipsychotics^{24, 25} and antihyperglycemic agents.^{10, 26} Information on the safety, efficacy or pharmacokinetics of such agents in specific populations, such as paediatrics, neonatology and geriatrics, is scarce, so responding to clinical issues about drug management for off-label use in these specific populations in hospitals is quite difficult.

Regarding user satisfaction in the DIC-RS, previous surveys revealed a level of satisfaction related to the quality of information received by the enquirer, provided by DIC-RS, between 69% and 91%. In all surveys, 100% of the enquirers stated that they intended to consult the DIC-RS again.²⁷ A survey conducted in 2012 showed that 88.1% of the enquirers of the DIC-RS stated that they were satisfied with information quality (clarity, objectivity and timeliness of response).²⁷ Data from the last survey (2016) included 112 eligible enquirers, 97 of whom were interviewed, show that 74% of the users stated that they were satisfied with a clear answer, 80% were satisfied with objectivity and 95% claimed that they would return in a future moment to use the service. In general, the service produced a positive evaluation (data not yet published). Other studies also reveal similar levels of user satisfaction (80%) and high levels of positive impact on patient care.¹⁸

Finally, as a perspective of the study is the conduction of a new satisfaction survey for the users of the DIC-RS. The objective will be to assess the relevance to the requestor of an RWI. A limitation of our study is in comparing data with the literature, since our work is innovative. We hope that this study will encourage other DICs to conduct projects in this area. In this sense, it will be possible to map the main limitations of data in

What this paper adds

What is already known on this subject

- The fundamental functions of DICs are to receive and answer medicine-related questions from healthcare professionals, i.e., to provide passive information.
- Studies have characterised indicators of assistance on the performed activities according to the number of information requests, user profiles, IR topics, response time and user satisfaction.

What this study adds

- Characterise information requests from hospitals received by a DIC-RS according to the resolution of the inquiries.
- A quarter of the answers did not exhibit conclusive information in the consulted database.
- The greatest difficulties in finding information were related to off-label drug administration and indication issues.

the literature, and thus impel new research to respond to user needs.

CONCLUSION

The present study identified that a -quarter of the provided responses did not meet the needs of information requested by the users of a given DIC. Half of the RWI were from hospital professionals, and off-label use was responsible for the majority of cases.

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