boletim de FARMACOVIGILÂNCIA

VOLUME 27
NUMBER 9 AND 10
SEPTEMBER/OCTOBER
2023

ISO IDMP (Identification of Medicinal Products) guidelines, pharmacovigilance and electronic clinical records

Pharmacovigilance aims to identify, evaluate, understand, and prevent adverse effects of medications. To achieve this goal of protecting public health, it's essential to detect, record, monitor, and analyze data on the safety of medications during the post-market authorization phase. In Portugal, the registration of notifications of suspected adverse drug reactions (ADRs) is done using the ADR reporting database, the **Portal RAM**, which communicates with **EudraVigilance,** the European database supporting all pharmacovigilance activities in the European system.

In 2021, Portal RAM contained around 99,000 reports of suspected ADRs while EudraVigilance contained around 22.3 million notifications. If we consider that up to 40% of patients experience some type of ADR in the community and that 6.7% of hospitalized patients suffer serious ADRs, we can conclude that there is still a lot work to be carried out to promote the reporting of suspected ADRs to pharmacovigilance systems.

We need to reflect on the reasons why suspected ADRs do not get to be reported to pharmacovigilance systems. Among several possible reasons, one of those that arouses the most interest is the **inefficiency of the reporting process**. ADRs are often recorded in information systems used in clinical practice without being communicated to the National Pharmacovigilance System, or they are registered in duplicate in both systems. To mitigate this challenge, INFARMED has been developing web services between the Portal RAM and the information systems used in healthcare organizations.. However, current information systems are quite heterogeneous, as they vary from one health organization to another, and are developed by a range of different companies. All this makes integration and access to data between different areas of intervention complicated.

On the other hand, records made in different scenarios comply with **varying coding standards or conventions**. For example, clinical terms recorded in electronic clinical records (ECRs) are coded using the SNOMED-CT standard, while in regulatory science the MedDRA standard is used. This implies that, when transmitting information across systems, data has to be recoded per the respective standard.

In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) has been using the mappings obtained from SNOMED to MedDRA and vice versa, with the aim of facilitating the transmission of information between ECRs and regulatory databases. Indeed, according to the work from the MedDRA Users Group Meeting, which took place in Berlin in April 2023, reporting of ADRs to the Yellow Card scheme (equivalent to INFARMED's Portal RAM), is available for at least 93% of primary care information systems. In 2022, the Yellow Card scheme received 65,000 suspected ADR cases, of which 9,000 (about 14%) corresponded to SNOMED/MedDRA.

INDEX CARD

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Advisory Board: Conselho Diretivo do INFARMED, I.P.
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Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

In the field of drug information, the International Organization for Standardization (ISO) has developed the **ISO IDMP** (Identification of Medicinal Products) standard. This aims to standardize the coding of information relating to medicines, which will in turn facilitate intra- and intersector transmission by allowing for **easier interoperability** between different information systems.

Through the characterization and standardized communication of drug information between different stakeholders, it will be possible to **preserve the transmitted data and improve its quality**. For pharmacovigilance, this is particularly relevant - on the Portal RAM, for example, data analyzed since 2017 shows that around 32% of ADR notifications do not have information regarding the trademark name of the suspected medicine. With the implementation of ISO IDMP this indicator can be improved through the systematic collection of more information on the medicines involved in each case.

Several **national medicines authorities**, including INFARMED in collaboration with the European Medicines Agency (EMA), are **harmonizing the data** in their databases in accordance with the **ISO IDMP** standard. The implementation of this standard by national authorities is being undertaken through the European **UNICOM** (Up-scaling the global univocal identification of medicines) project.

The development of standards such as ISO IDMP and the mapping of standards used in various contexts, as is the case with SNOMED and MedDRA, is essential to ensure the transmission of information between **clinical practice** and pharmacovigilance, with notable gains in both directions. In clinical practice, access to data from the pharmacovigilance system will support decisions with a focus on ensuring patient safety, through a more effective identification and management of ADRs. For pharmacovigilance, this integration will improve the quality and number of suspected ADR reports, an essential tool for evidence-based regulatory decision making.

Rui Vilar, Luís Vítor Silva

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials Online publication date
Golimumab *Simponi*	**Physicians:** internal medicine, rheumatology, gastroenterology **Pharmacists:** hospital	Important changes to administration instructions for the SmartJect pre-filled pen 09-08-2023
Methylprednisolone + Lidocaine *Depo-Medrol Com Lidocaína*	**Physicians:** clinic and hospital rheumatology, physiarthry and orthopaedics dpt directors **Pharmacists:** hospital services	Introduction of contraindication: intramuscular route 17-07-2023

Compiled by Patrícia Catalão

Next: More posters from the scientific programme of the event commemorating the 30th anniversary of INFARMED - ***Pharmacovigilance: Involving the Citizen***. In this Issue: interchange between brand and generic medicines, adverse reactions to common antibiotics, isotretinoin and radiopharmaceuticals.

Brand-to-Generic and other Product Substitution Issues: Characterization of Spontaneous Reports received by a Portuguese Pharmacovigilance Unit

SISTEMA NACIONAL Farmacovigilância Infarmed

Farmacovigilância: Envolver o Cidadão

30 de maio de 2023 | 09:00 - 18:00
Centro de Cultura e Congressos da Secção Regional do Norte da Ordem dos Médicos, Porto

Inês Tavares[1,2], Joana Abrantes[1,2], Rita Gaspar[3], Liseta Lemos[1,2,3]

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www.aibili.pt

Introduction

Generic drugs constitute a less expensive alternative to brand drugs, presenting similar clinical benefits and safety profile. However, there is a significant proportion of healthcare professionals and consumers who hold negative perceptions of these drugs [1]. Furthermore, there have been several reports of Adverse Drug Reactions (ADRs) associated with product substitution.

Aim

This study aims to characterize the Spontaneous Reports (SRs) received by the Pharmacovigilance Unit of Coimbra (UFC) containing ADRs associated with the substitution of drugs from brand to generic and other appropriate substitutions.

Methods

SRs were identified through a search on the National Pharmacovigilance System's database from 2013 (1st SR containing a product substitution issue) until 2022 using Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms (PT) concerning Product Substitution Issues, including brand to brand, brand to generic, generic to brand, generic to generic, reference biologic to biosimilar and biosimilar to reference biologic. The cases were characterized according to reported ADRs (PT), substitution and reporter type, patient demography, seriousness according to WHO criteria [2], and suspected drug Anatomical Therapeutic Chemical (ATC) Classification System code.

Results

The UFC received 58 SRs during the study period containing at least one ADR associated with product substitution, representing a percentage of 0.96% of all SRs received. Product substitution issues were most frequently reported for female patients (n=37; 63.79%), and adults (aged between 18 and 64 years old) (n=33;56.90%). Over half of the SRs were reported by Pharmacists (n=31; 53.45%). ADRs were most frequently associated with the substitution of brand-to-generic (n=27;46.55%) and generic-to-generic (n=18; 31.03%). Half of the SRs were considered Serious, with "Clinically important" (n=17; 29.31%) and "Disability" (n=11; 18.97%) being the most frequent seriousness criteria. The suspected drugs most frequently reported are represented in Figure 1 and belong to ATC L – Antineoplastic and immunomodulating agents (n=20; 33.90%), followed by C – Cardiovascular system (n=15; 25.42%) and N – Nervous system (n=14; 23.73%), with the remaining 16.95% pertaining to other ATC classes. The 58 SRs identified contained 136 ADRs. The most frequently reported ADRs (Figure 2) were "drug ineffective" (n=12; 8.82%), "diarrhoea" (n=6; 4.41%) and "nausea" and "dizziness" (n=4; 2.94%).

Figure 1: Most frequently reported drugs associated with Product Substitution Issues

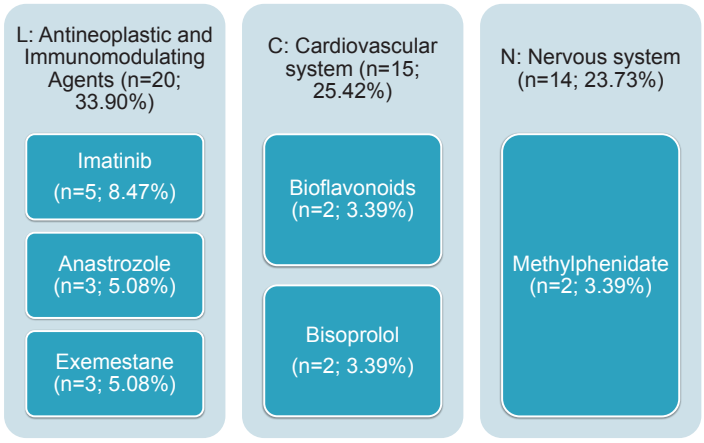
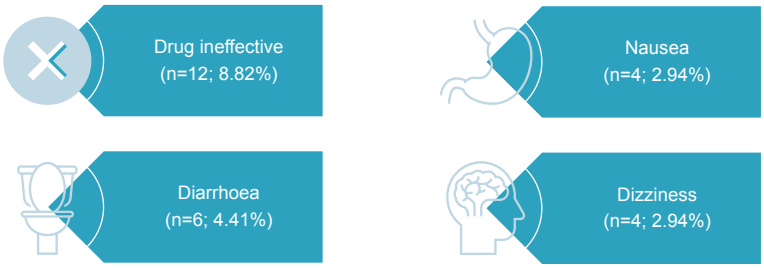


Figure 2: Most frequently reported ADRs associated with Product Substitution Issues



Conclusions

Although product substitution issues are relatively infrequent when compared to the total of SRs, these reports should be encouraged among healthcare professionals and consumers. Further studies should be conducted to determine whether these ADRs can be ruled as psychogenic reactions, and to assess safety and effectiveness of generic drugs in the real world.

[1] Colgan S, Faasse K, Martin LR, et al. Perceptions of generic medication in the general population, doctors and pharmacists: a systematic review. BMJ Open 2015;5:e008915. doi:10.1136/bmjopen-2015-008915; [2] WHO-UMC (2010) World Health Organization criteria for serious adverse event or reaction.

Funding

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Nefrite Intersticial Aguda induzida pela Flucloxacilina

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Farmacovigilância: Envolver o cidadão

Ordem dos Médicos Secção Regional do Norte - Centro de Cultura e Congressos

Porto | 30 de maio de 2023

INTRODUÇÃO

A nefrite intersticial aguda (NIA) constitui uma lesão renal que pode ser originada por diversos fatores como, por exemplo, fármacos, infeções e doenças sistémicas [1,2]. A exposição a medicamentos é das causas mais comuns em todas as faixas etárias. Na ocorrência desta reação adversa a medicamentos (RAM), destacam se os antibióticos, anti-inflamatórios não esteroides, antiepiléticos, diuréticos e inibidores da bomba de protões [3,4].

OBJETIVO

Averiguar se a NIA induzida pela flucloxacilina (isoxazolilpenicilina) é, de facto, uma RAM "muito rara", conforme consta no resumo das características do medicamento (RCM).

MÉTODOS

Realizou-se uma análise retrospetiva de todas as notificações de RAM reportadas nas bases de dados nacional (Portal RAM), europeia (EudraVigilance) e mundial (VigiBase) relacionadas com a *system organ class* (SOC) *renal and urinary disorders* associada à denominação comum internacional (DCI) flucloxacilina.

No Portal RAM, a pesquisa foi realizada por DCI e SOC; e no Eudravigilance a análise foi executada apenas por DCI. Através dos dados obtidos até **24-04-2023**, determinou-se o número de casos reportados com os *preferred terms* (PT) *tubulointerstitial nephritis* (TN) e *acute kidney injury* (AKI).

Na VigiBase, efetuou-se uma análise qualitativa dos casos por SOC e DCI até **31-03-2023**, determinando-se os PT mais notificados, a prevalência, a distribuição por faixa etária e os PT mais co-reportados. Adicionalmente, procedeu-se a uma análise quantitativa dos casos observados versus casos esperados.

RESULTADOS E DISCUSSÃO

Portal RAM – Notificação de Reações Adversas a Medicamentos | Infarmed – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

De acordo com os dados obtidos do Portal RAM (**Figura 1** e **Figura 2**), em Portugal, foram notificados dois casos de PT TN e dois casos de PT AKI (n=4).

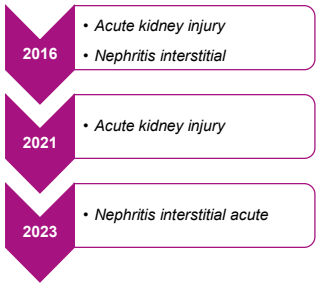

Figura 1. Distribuição temporal das notificações de suspeitas de RAM notificadas com os PT TN e AKI no Portal RAM.

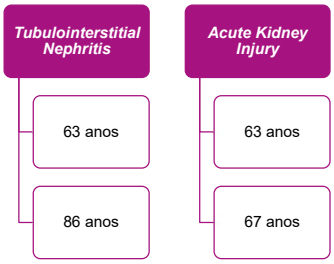

Figura 2. Idade dos doentes dos casos reportados no Portal RAM com os PT TN e AKI.

EudraVigilance | European Medicines Agency – Science Medicines Health

A SOC em estudo posicionou-se em 7.º lugar (n=435; 7%) entre as mais submetidas, com uma taxa de notificação do PT TN de 26% (n=113) e do PT AKI de 32% (n=138) (**Figura 3**). Com o PT TN, o maior número de casos observou-se no grupo dos 65 aos 85 anos (**Figura 4**).

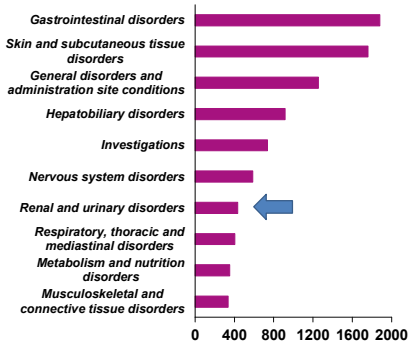

Figura 3. Distribuição das notificações de suspeitas de RAM por SOC (n=435) da DCI flucloxacilina no EudraVigilance.

Figura 4. Distribuição etária das notificações de suspeitas de RAM reportadas com o PT TN. Adaptado do EudraVigilance.

VigiBase | World Health Organization | Uppsala Monitoring Centre

A SOC *renal and urinary disorders* assumiu, também, o 7.º lugar na lista das mais notificadas (n=789; 6%) (**Figura 5**). Os PT mais reportados foram o PT TN (n=222; 28%) e o PT AKI (n=263; 33%). Dos PT mais co-reportados, evidenciaram-se as RAM náuseas, prurido, *rash* e pirexia, sendo que estas manifestações clínicas podem estar associadas à NIA.

Relativamente ao PT TN, 85% (n=189) dos casos corresponderam a RAM notificadas com os *lowest level terms* (LLT) *nephritis interstitial*, *nephritis interstitial acute*, *acute nephritis interstitial* e *interstitial nephritis acute*. Ademais, verificou-se que houve um predomínio de casos reportados do PT TN na faixa etária acima dos 65 anos. (**Figura 6**).

No que diz respeito à análise quantitativa (**Figura 7**), os dados indicaram que os casos observados de PT TN superaram em elevado número os casos esperados ($N_{esperado}$ = 7; $N_{observado}$ = 222; e IC_{025} = 4,7).

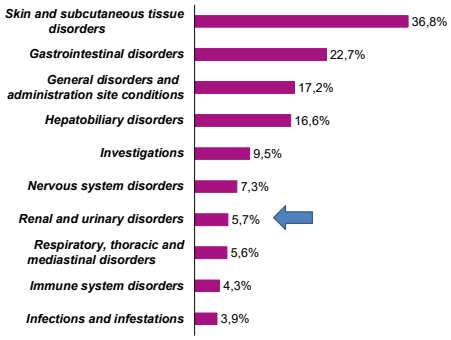

Figura 5. Distribuição das notificações de suspeitas de RAM por SOC da DCI flucloxacilina na VigiBase (n=789).

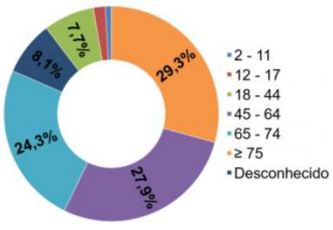

Figura 6. Distribuição etária (em anos) das notificações de suspeitas de RAM (DCI flucloxacilina e PT TN).

DCI Flucloxacilina PT TN	
Portugal	**Mundial**
$N_{observado}$ = 1 $N_{esperado}$ = 0 IC_{025} = -2,8	$N_{observado}$ = 222 $N_{esperado}$ = 7 **IC_{025} = 4,7**

Figura 7. Relação entre o n.º de casos esperados versus o n.º de casos observados do PT TN, em Portugal e a nível global.

Nota: Os dados extraídos a partir da VigiBase são provenientes de uma variedade de fontes e a probabilidade de relação entre um medicamento suspeito e a RAM não é igual em todos os casos. Ainda, é de salientar que este estudo não representa a opinião do Uppsala Monitoring Centre ou da Organização Mundial da Saúde.

CONCLUSÃO

A NIA induzida pela flucloxacilina é uma condição clínica difícil de identificar e, por conseguinte, poderá existir uma subnotificação de casos ou a notificação poderá ser efetuada pela utilização de diferentes LLT. Concluiu-se que, a nível mundial, a ocorrência desta RAM está a superar o número de casos esperados, o que leva a suspeitar que poderá não se tratar de uma RAM "muito rara" conforme consta no RCM. Como perspetivas futuras, salienta-se a importância do desenvolvimento de uma campanha informativa, de forma a sensibilizar os profissionais de saúde e as Unidades Regionais de Farmacovigilância para este risco, e a conhecer melhor o perfil de segurança da flucloxacilina.

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AGRADECIMENTOS

A Unidade de Farmacovigilância do Algarve e Baixo Alentejo (UFALBA) agradece a todos os Notificadores, Profissionais de Saúde e Utentes pela colaboração com o Sistema Nacional de Farmacovigilância.

Um agradecimento especial a todos os colaboradores e antigos colaboradores da UFALBA, bem como a toda a equipa da Direção de Gestão do Risco de Medicamentos (DGRM) da Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED) e às congéneres Unidades Regionais de Farmacovigilância.

Isotretinoin-induced Adverse Drug Reactions: National reporting and contributions to PRAC Assessment Report on Isotretinoin PSUR(s)

SISTEMA NACIONAL Farmacovigilância Infarmed

Farmacovigilância: Envolver o Cidadão

30 de maio de 2023 | 09:00 - 18:00
Centro de Cultura e Congressos da Secção Regional do Norte da Ordem dos Médicos, Porto

Joana Abrantes[1,2], Inês Tavares[1,2], Rita Gaspar[3], Liseta Lemos[1,2,3]

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Introduction

Isotretinoin, a systemic retinoid medication used for severe acne treatment, has been associated with various adverse drug reactions (ADRs) such as dry skin, arthralgia, conjunctivitis, and depression. Recent safety concerns about isotretinoin led to the need for pharmacovigilance (PhV) studies to assess its safety and effectiveness, in real-world. [1]

Aim

This study aimed to investigate suspected ADRs associated with isotretinoin reported to the Portuguese Pharmacovigilance System (PPS), which also contributed to the Pharmacovigilance Risk Assessment Committee (PRAC) scientific conclusions in the Assessment Report on the Periodic Safety Update Reports (PSURs) for isotretinoin (oral formulations) in late 2021.

Methods

A retrospective analysis of all Spontaneous Reports (SRs) of suspected ADRs associated with oral isotretinoin use reported to the PPS between January 2012 and March 2023 was conducted. Patient demographics, suspected ADRs, and the indication for isotretinoin use were collected. SRs were also identified according to the WHO seriousness criteria, and on their standardised causality assessment. ADRs were characterized according to their MedDRA® Preferred Term [PT] and System Organ Classification [SOC]. The December 2021 PSUR(s) for isotretinoin concluded that the product information of products containing isotretinoin should be amended to include “dry eye”, “sacroiliitis” and “urethritis”. A search query of these ADRs was performed on the SRs.

Results

The study analysed 44 SRs of suspected ADRs associated with isotretinoin use.

Of these, 39 cases were related to isotretinoin use for acne treatment, while the remaining cases involved the use of isotretinoin for Pityriasis rubra pilaris (PRP), Darier's disease, and overlapping Psoriasis and Dermatitis.

The figure 1 displayed below is a histogram illustrating the gender demographics within the SRs population. This graphical representation provides a visual depiction of the distribution of two gender categories.

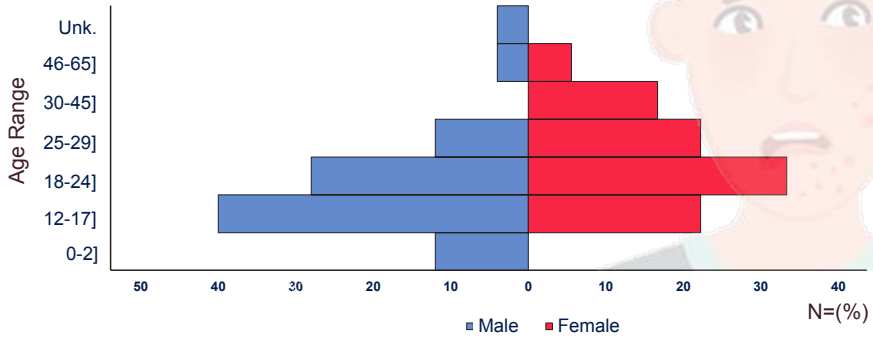

Figure 1. Percentage of male and female individuals in spontaneous reports received.

The most frequently reported ADRs are comprised in SOCs “Skin and subcutaneous tissue disorders” and “Psychiatric disorders”.

Regarding ADRs concomitantly present on the PSURs for isotretinoin (oral formulations) and SRs analysed, a search query was performed. Three cases containing at least one ADR related to the PT “dry eyes” were reported, and three cases containing the PT term "joint pain" were also reported, and while it is not specifically related to sacroiliitis, joint pain can be a symptom of sacroiliitis and other joint-related conditions. However, the term "urethritis" does not appear in the search query. In all of these cases, whenever a causality assessment was conducted, it was deemed as "Probable/Likely".

Concerning seriousness assessment, 18 (41%) SRs were clinically important, 4 (9%) SRs resulted in hospitalization, 1 (2%) SR was life-threatening, 2 (5%) SRs resulted in incapacity, and 3 (7%) SRs were congenital anomalies. The remaining cases were not serious.

Conclusions

This results suggest that isotretinoin is associated with a wide range of suspected ADRs, including life-threatening events. These findings are consistent with the conclusions drawn by the European Medicines Agency's PRAC on the relationship between isotretinoin and persistent dry eye, that considers a causal relationship to be at least reasonably possible. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) agreed with the PRAC's scientific conclusions and recommended changes to the product information. The SNF contribution to this conclusion highlights the importance of PhV in optimizing the benefit-risk balance of medications containing isotretinoin.

References:

Funding

FITEC Fundo de Inovação, Transferência de Tecnologia e Economia Circular | PI PROGRAMA INTERFACE | Programa Nacional de Reformas | REPÚBLICA PORTUGUESA

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ADVERSE REACTIONS MEDIATED BY ^{99m}Tc-TETROFOSMIN

A Systematic Review of the Literature

Sara Martins[1]*; Sara Costa[2]; Ângelo Jesus[2]; Ana Martín Suárez[1]

INTRODUCTION

Radiopharmaceuticals can be used for diagnostic or therapeutic purposes, within the scope of nuclear medicine (Laroche et al., 2015; Pérez-Iruela et al., 2021; Schreuder et al., 2019, 2021). Radiopharmaceuticals labelled with ^{99m}Tc are used in about 85% of diagnostic exams, with ^{99m}Tc-Tetrofosmin being one of the main options when studying cardiac function (D'Arceuil, 2010; Manabe et al., 2018). The incidence of adverse reactions associated with radiopharmaceuticals appears to be low (Laroche et al., 2015; Schreuder et al., 2019, 2021). The use of low doses, the severity of reactions or the lack of notifications may contribute to this phenomenon not being adequately studied (Hesslewood & Keeling, 1997; Pérez-Iruela et al., 2021; Schreuder et al., 2021; Silberstein et al., 1996). Therefore, a global and updated review of adverse reactions related to radiopharmaceuticals is essential, to allow the detection, understanding and management of these adverse reactions by healthcare professionals and patients.

OBJECTIVE

Perform a systematic review regarding the reactions associated with the radiopharmaceutical ^{99m}Tc-Tetrofosmin.

METHODS

A systematic search for information was carried out using the MEDLINE database (PubMed). The research strategy followed the *Preferred Reporting Items for Systematic Reviews* (PRISMA) *guidelines* and the Population, Intervention, Controls, Outcome (PICO) method (Figure 1) to answer the research question, define the keywords, define the inclusion and exclusion criteria and develop the research equation (Page, McKenzie, et al., 2021; Page, Moher, et al., 2021). Two researchers developed the search key. Clinical trials, cohort studies, case studies or case series and case-control studies were included, in English, Spanish and Portuguese. To identify and select relevant studies to include in the systematic review, the following research equation was defined:

"Radiopharmaceuticals"[nm] AND "Radiopharmaceuticals/adverse effects[MAJR]".

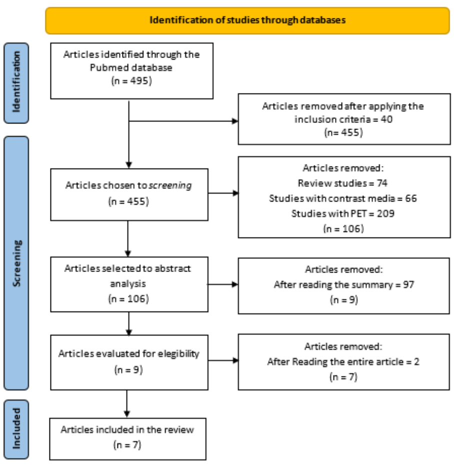

Figure 1 – Selection of the articles according to the PRISMA *guidelines*
.

RESULTS

As a result of the search, 495 potentially relevant articles were obtained.

After applying the inclusion criteria, 40 articles were removed as they did not fit. Sixty six articles that referred to contrast media, 209 articles that focused on radiopharmaceuticals used in positron emission tomography (PET) and 74 review articles were also removed. Of the remaining 106 articles, the *abstract* was read and 97 were excluded. Of the remaining 9 articles, 2 were eliminated because they did not qualitatively characterize the ADRs associated with ^{99m}Tc-Tetrofosmin. In the end, 7 articles were considered eligible for analysis (table 1).

Table 1 – Summary of information from the selected articles.

	Study	Total Notifications	Total ADRs *vs* ADRs associated with ^{99m}Tc-Tetrofosmine
1	(EANM, 1995)	146	73 were considered ADRs; 3 associated with ^{99m}Tc-Tetrofosmin.
2	(Hesslewood, 1996)	145	64 were considered ADRs; 5 associated with ^{99m}Tc-Tetrofosmin.
3	(Hesslewood, 2002)	131	62 were considered ADRs; 2 associated with ^{99m}Tc-Tetrofosmin.
4	(Hesslewood, 2003)	112	61 were considered ADRs to radiopharmaceuticals (35 considered probable or possible); 2 associated with ^{99m}Tc-Tetrofosmin.
5	(Silberstein, 2014)	21	5 classified as unlikely; 2 associated with ^{99m}Tc-Tetrofosmin.
6	(Kennedy-Dixon et al., 2017)	204	13 considered invalid; 34 associated with ^{99m}Tc-Tetrofosmin.
7	(Schreuder et al., 2021)	379	223 associated with ^{99m}Tc-Tetrofosmin, 72 unrelated, 16 unlikely, 114 possible, 13 probable and 8 ADRs.

There was a prevalence of between 2.7% and 7.81% of adverse drug reactions (ADRs) associated with the radiopharmaceutical ^{99m}Tc-Tetrofosmin. No major medical events were reported, and most reports were resolved quickly and without the need for treatment. The majority of reported reactions belong to the SOC "diseases of the skin and cutaneous tissue", "general disorders and administration site conditions", "diseases of the nervous system" and "gastrointestinal problems".

DISCUSSION

There is a lower frequency of notifications attributed to radiopharmaceuticals, than other drugs (Schreuder et al., 2019). This phenomenon can be explained considering several factors, such as: low administration dose; absence of pharmacological effect and low frequency of administration (in most cases only once). Another relevant reason may be related to the voluntary identification and reporting of adverse reactions (Schreuder et al., 2019).

There are also other aspects that may influence the reporting of adverse effects:

1) simultaneous use of non-radioactive drugs as part of the study such as stress agent in myocardial perfusion scintigraphy or diuretics in renal scintigraphy. Some adverse reactions may be caused by the use of these non-radioactive drugs and be inadvertently associated with the radiopharmaceutical, and some reactions may be omitted because health professionals may assume that they are due to the procedure itself, like dyspnea during myocardial perfusion scintigraphy;

2) not all institutions keep good records of their adverse effects;

3) health professionals may not report adverse reactions that they consider minor or that are already reported in the literature;

4) the level of awareness about the importance of reporting adverse reactions may not be consistent between institutions due to different perceptions on the topic;

5) the Nuclear Medicine department may never be informed of the occurrence of adverse reactions because the patient normally does not return to the service (Schreuder et al., 2019).

CONCLUSION

The use of radiopharmaceuticals is growing exponentially, making it important that both healthcare professionals and patients are aware of the possible adverse reactions associated with them.

It is also important to know about other drugs that can be used in the procedure, or that the patient may be taking simultaneously, in order to assess causality. Pharmacovigilance studies on radiopharmaceuticals are scarce, but extremely relevant and relevant given the growing use of radiopharmaceuticals.

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	Patients	Patient/caregiver guide Patient guide
		10-07-2023
Eculizumab *Soliris*		**Physician's guide concerning patients with:**
	Physicians: haematology	Nocturnal paroxysmal haemoglobinuria (NPH)
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	Patients	Patient card 13-07-2023
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Compiled by Patrícia Catalão