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Hospital pharmacovigilance's role in managing Stevens-Johnson syndrome: a case report

Alan Maicon DE OLIVEIRA[1], **Fabiana Rossi VARALLO**[1]

[1]School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.

Corresponding author: de Oliveira AM, alanoliveira@usp.br

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Abstract

Stevens-Johnson syndrome is a condition that is considered rare but of severe intensity, potentially induced by medications, with antimicrobials being highlighted as the main culprits. We present a case of an older individual who developed the syndrome, overlapping with Toxic Epidermal Necrolysis, likely due to the use of the drug ciprofloxacin. During hospitalization, the case was managed by the pharmacovigilance sector (I. Systematization of scientific evidence in health; II. Conducting an in-depth investigation of the experienced case, comparing data with scientific information; III. Studying the causality of the adverse reaction; IV. Developing a protocol of practices to be followed, team training, and monitoring of the steps; V. Organizing notification and referral to responsible regulatory agencies) and a multidisciplinary team. Treatment was based on health evidence; however, there was refractoriness to clinical measures, and the patient progressed with worsening skin shedding, infection, cardiac arrest, and death after the resuscitation protocol. In addition to the factors mentioned above, other aspects contributed to the severity of the episode: presence of multimorbidity, advanced age, late seeking of healthcare assistance, and continued use of the drug that induced the reaction, even after the initial symptoms. ANVISA categorized the event as severe and reportable to the Uppsala Monitoring Centre. The hospital pharmacovigilance service collaborated with the multidisciplinary team, contributing to the prompt and appropriate management of the event, risk management, and health education. This study provides content for multiprofessional learning, strategies for safety, and person-centered care.

Keywords: Stevens-Johnson syndrome, anti-infective agents, pharmacovigilance, patient safety, hospital.

Atuação da farmacovigilância hospitalar no manejo da síndrome de Stevens-Johnson: um relato de caso

Resumo

A síndrome de Stevens-Johnson é uma condição que pode ser considerada rara, porém de gravidade severa, podendo ser induzida por medicamentos, sendo os antimicrobianos destacados como principais causadores. Apresentamos um caso de uma pessoa idosa que desenvolveu a síndrome, com sobreposição para Necrólise Epidérmica Tóxica, provavelmente devido ao uso do fármaco ciprofloxacino. Durante sua hospitalização, o caso foi gerenciado pelo setor de farmacovigilância (I. Sistematização de evidências científicas em saúde; II. Realização de investigação aprofundada do caso vivenciado, confrontando os dados com as informações científicas; III. Estudo da causalidade da reação adversa; IV. Desenvolvimento de um protocolo de práticas a serem seguidas, capacitação da equipe e acompanhamento das etapas; V. Organização da notificação e encaminhamento para as agências reguladoras responsáveis) e por equipe multidisciplinar. Foi realizado tratamento com base em evidências de saúde, no entanto, houve refratariedade às medidas clínicas, e a paciente progrediu com agravamento da descamação, infecção, parada cardíaca e óbito após o protocolo de ressuscitação. Além dos fatores mencionados anteriormente, adicionam-se outros aspectos que contribuíram para a gravidade do episódio: presença de multimorbidade, idade avançada, busca tardia por assistência à saúde e continuação do uso do medicamento que induziu a reação, mesmo após os sintomas iniciais. A ANVISA categorizou o evento como grave e reportável para o *Uppsala Monitoring Centre*. O serviço de farmacovigilância hospitalar atuou em conjunto com a equipe multidisciplinar, contribuiu para o pronto e adequado manejo do evento, gerenciamento de risco e educação em saúde. Este estudo oferece conteúdo para aprendizado multiprofissional, estratégias para a segurança e cuidado centrado na pessoa.

Palavras-chave: síndrome de Stevens-Johnson, anti-infecciosos, farmacovigilância, segurança do paciente, hospital.

Introduction

Adverse drug reactions (ADRs) are characterized as recurrent adverse events in the population, even when these people are receiving care in a hospital environment. It is estimated that up to 16% of hospitalizations can result in clinically significant ADR events, thus representing a public health problem[1]. In addition, the management of each episode related to these events can cost the health system[2] up to 12,000 dollars. This evidence underscores the importance of disseminating information on this subject, so that cases of ADRs are identified at an early stage and to prevent them from progressing to serious conditions, which can culminate in death. It is worth noting that ADRs can be considered risk factors for increased length of stay and morbidity and mortality[3]. Therefore, in addition to the economic cost, it has negative effects on clinical and humanistic factors.

Serious ADR diagnoses include Stevens-Johnson syndrome, a dermatological condition that affects the skin and mucous membranes. This syndrome can also affect multiple systems and often results from an adverse hypersensitivity reaction, with antimicrobials being the most common drugs to induce this syndrome[4,5]. It has been observed that Stevens-Johnson syndrome can overlap with Toxic Epidermal Necrolysis, resulting in a mortality prevalence rate of between 10% and 50%[6].

Taking this context into account, pharmacovigilance[7] is understood as one of the clinical services that make up pharmaceutical care[8] and is aimed at practicing actions to promote the identification, evaluation, resolution, and prevention of adverse drug-related events (Figure 1). In addition, through pharmacovigilance, studies are carried out to gain a better understanding of ADRs, as well as reporting these cases to each country's surveillance system, which is also known as phase IV of medication development or post-marketing surveillance[7]. In Brazil, around 12,000 notifications are made every year by national risk management services involving the practice of pharmacovigilance[9]. This therefore certifies pharmacovigilance as a pillar of safety in healthcare.

The aim of this case report is to describe the contribution of a hospital pharmacovigilance service in the care of a patient with probable Stevens-Johnson syndrome, overlapping with Toxic Epidermal Necrolysis, induced by the use of the medication ciprofloxacin. The purpose is also to present the management recommendations drawn up on the basis of the case. This study was reported in accordance with the consensus-based clinical case report guideline (CARE guidelines, 2013) and was approved by the research ethics committee of the University of São Paulo (CAAE: 48459415.2.0000.5477).

Figure 1. Definitions and concepts.

Figure 2. Suggested informative material with recommendations for the management of episodes of drug-induced Stevens-Johnson syndrome in the hospital where the reported case occurred.

Recommendations and Management of Stevens-Johnson Syndrome induced by adverse drug reactions:

1. Discontinuation of the suspected medication causing the reaction;
2. Patient management: Intensive Care Unit / Burn Centers (isolation, aseptic handling, bronchoaspiration, physiotherapy);
3. Assessment of underlying diseases and secondary infections;
4. Control of environmental temperature (30-32°C, as it reduces heat loss through the skin);
5. Maintenance of peripheral venous access away from affected areas (no central line whenever possible) / Catheters changed periodically;
6. Supportive and symptomatic treatment (pain, anxiety, fluid replacement, electrolyte correction (during the first 24 hours));
7. Early and continuous enteral nutrition (reduces the risk of stress ulcers - proteins promote lesion healing) / antacids (gastric bleeding);
8. Treatment of skin lesions (topical anesthetics / antiseptics - body and mouth) / Bare skin covered with saline solution compresses (surgical debridement) / Treatment of oral and ocular lesions;
9. Tetanus prophylaxis;
10. Prophylactic anticoagulation (heparin during hospitalization);
11. Prophylactic antibiotics are not recommended (resistance) / Bacterial sampling (skin - first day and every 48 hours);
12. Systemic corticosteroids (use is controversial as it may cause immunosuppression and dissemination of the infectious process). High doses are recommended at the onset of the illness (48h) / Methylprednisolone;
13. Evaluate the context and possible indication for the use of immunosuppressants (Cyclosporine);
14. Assess the need for immunoglobulin use (reduces the production of autoantibodies);
15. Constant monitoring of pharmacotherapy and health status.

Figure 3. Use of the WHO-UCM decision algorithm for causality analysis of the reported case, with the necessary justifications.

Causality Classification	Evaluation Criteria	✓/✗	Case Observation
Defined	→ Clinical event, potentially including abnormalities in laboratory tests, with a plausible temporal relationship to the administration of the medication.	✓	*"Given the severity of the case, it was not possible to reintroduce the medication to confirm the adverse reaction."*
	→ Cannot be explained by concomitant illnesses or other medications.	✓	
	→ Response to withdrawal is plausible (pharmacologically, pathologically).	✓	
	→ The event is definitively pharmacologically or phenomenologically determined (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon).	✓	
	→ Reintroduction is acceptable, if necessary.	✗	
Probable	→ Clinical event, possibly including abnormalities in laboratory tests, with a reasonable temporal relationship to the administration of the medication.	✓	
	→ Unlikely to be attributed to concomitant diseases or other medications.	✓	
	→ Clinically reasonable response to withdrawal.	✓	
	→ No reintroduction necessary.	✓	
Possible	→ Clinical event, which may include abnormalities in laboratory tests, with a reasonable temporal relationship to the administration of the medication.	✓	*" The episode could not be related to concomitant diseases or other medications, considering evidence-based health. Information about the discontinuation of the medication was available.*
	→ Can also be explained by concomitant diseases or other medications.	✗	
	→ Information about the withdrawal of the medication may be absent or unclear.	✗	
Improbable	→ Clinical event, which may include abnormalities in laboratory tests, with a time interval to the administration of the medication that makes a causal relationship improbable (but not impossible).	✗	*"There was a reasonable temporal relationship between the use of the medication and the development of the adverse reaction. Given that the scientific literature indicates that the medication causing Stevens-Johnson syndrome is generally started between one week and one month before the onset of symptoms. The episode could not be related to concomitant diseases or other medications, considering evidence-based health."*
	→ Concomitant diseases or other medications offer plausible explanations.	✗	
Conditional / Not Classified	→ Clinical event, which may include abnormalities in laboratory tests.	✓	*"The clinical data and diagnosis, as well as the information related to the context of the ADR episode, were available and evaluated."*
	→ More data are required for proper evaluation, or;	✗	
	→ Additional data are under evaluation.	✗	
Not Assessable / Not Classified	→ Report suggesting an adverse reaction.	✓	*"The clinical data and diagnosis, as well as the information related to the context of the ADR episode, were available and assessed. Furthermore, scientific evidence supported the case, as exemplified by Hällgren et al. (2003) in the article 'Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug'."*
	→ Cannot be evaluated due to lack of information or contradictions.	✗	
	→ Data cannot be supplemented or verified.	✗	

The pharmacovigilance service of a teaching hospital in the countryside of the state of São Paulo, run by a clinical pharmacist since 2014, identified, assessed and monitored a case of ADR in a patient (biological sex: female; age: 86 years; color/race: brown; weight: 60 kg) who started using the drug ciprofloxacin according to a medical prescription for primary health care in the municipality where she lived.

The patient had multimorbidities and the use of the drug ciprofloxacin was proposed due to the diagnosis of bacterial infection and the dosage regimen adopted was 500 mg every 12 hours.

According to family members, during the pharmacotherapy, the patient complained of gastric discomfort and prostration, but continued with the treatment, nonetheless. She took the medication for seven days. Then, approximately in the last few days of taking the drug, the patient began to show clinical manifestations of facial edema (lips and eyelids) and also had difficulty eating, so she sought care at a health service and went on to be admitted to hospital at a first establishment (hospital stay at this first institution: three days).

The patient's clinical condition worsened, and she was transferred to the second hospital (where the pharmacovigilance service was based) for further treatment by infectious disease doctors. The patient was admitted with hyperemic and scaly lesions all over her body, including the oral cavity. During the first two days of her hospitalization, she developed increased scaling of the skin, with greater intensity in the dorsal region, and reported pain, as well as keeping her eyes closed, with secretion, without being able to open them spontaneously or with maneuvers. An ophthalmologist was asked to give his opinion on the ophthalmologic demands, and he recommended treatment for the needs identified.

The patient was diagnosed with possible Stevens-Johnson syndrome and potential overlap with Toxic Epidermal Necrolysis. Treatment was conducted using evidence-based healthcare. Figure 2 shows the management protocol drawn up by the pharmacovigilance service, with only items 11, 13 and 14 not being adopted in the case reported, due to a medical decision and clinical assessment. Therefore, bacterial skin sampling was not carried out, nor was the use of cyclosporine or immunoglobulins. However, there was refractoriness to the clinical measures and the patient progressed, during the last four days of this hospitalization, with worsening desquamation (blood lesions), infection, cardiac arrest, and death after the resuscitation protocol (hospital stay in this second institution: six days).

It was established in the medical records that the entire episode was initially caused by an adverse reaction to the drug ciprofloxacin and, according to the causality analysis, the reaction was classified as "probable" (the tool that addresses the ADR causality categories established by the World Health Organization and Uppsala Monitoring Centre (WHO-UMC) was used). Figure 3 shows how the tool was used for the causality analysis of the episode, including all the justification related to the case, resulting in the classification as "probable".

The case was notified to Brazil's National Health Surveillance Agency, which categorized the event as serious and reportable to the Uppsala Monitoring Centre.

In addition, the hospital's pharmacovigilance service developed health education activities for the staff, and information material was produced on the management of medication-induced Stevens-Johnson syndrome episodes (Figure 2).

To summarize and correlate, the pharmacovigilance service acted throughout the case through the following topics:

I. Scientific evidence systematization in health;

II. Carrying out an in-depth investigation of the case (connecting current information to the history obtained through contact with family members, as well as other institutions and health professionals previously visited by the patient), comparing the data with scientific information;

III. Causality study of the adverse reaction associated with the medication (Figure 3);

IV. Developing a protocol of practices to be followed (Figure 2), training the team and monitoring the stages;

V. Organizing notification and forwarding it to the responsible regulatory agencies.

Discussion

The pathogenesis of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis is attributed to specific cell-mediated cytotoxic reactions that lead directly and indirectly to keratinocyte apoptosis through mediators[10]. This is a rare event, despite antimicrobials being one of the most common pharmacological classes to occur[10].

It is estimated that the annual incidence of fluoroquinolone-induced Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis in Sweden is 0.045/100,000 treated patients[5]. The presence of comorbidities and advanced age are risk factors for mortality[11]. Its development is associated with increased costs for healthcare establishments, which justifies the need for a risk/benefit analysis of these health technologies[12].

In Brazil, reports of serious skin reactions are rare[13], which can make it difficult to estimate the frequency, determine risk factors and establish risk mitigation actions. A study conducted in a highly complex hospital in São Paulo found that antimicrobials and antiepileptics were the medications most frequently associated with the occurrence of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis[14]. The authors found that 16.7% of patients with ADR died and 12.2% had long-term complications, with ophthalmic complications being the most common[14].

Currently, there is no treatment considered the gold standard for care[10]. According to UK guidelines[15], discontinuation of the suspected medication and multidisciplinary supportive care are recommended, which should be prioritized over systemic treatment, due to the scarcity of evidence on the efficacy of immunomodulatory therapies, corticosteroids, cyclosporines, as well as the off-label use of the following combinations: immunoglobulin and corticosteroid; immunoglobulins and cyclosporine; cyclosporine in monotherapy[16].

One of the limitations of the proper management of Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis comes from the nonspecificity of the prodromal signs, which resemble flu-like syndrome[17]. Delay in diagnosis or in seeking professional assistance makes it difficult to make the most important clinical decision for management, which is to discontinue the suspected medication[18], which can result in worsening of the case, clinical deterioration and even death.

The latency period between the use of the drug and the development of Stevens-Johnson syndrome/Toxic Epidermal Necrolysis is another diagnostic challenge. Medeiros et al.[14] observed that the average latency time that patients were exposed to suspect medications before developing the first signs of ADR was 13 days. This fact can make it difficult to establish the temporality required for the causal association, especially for polymedicated individuals[19].

In this context, the pharmacovigilance sector performs functions that assist the multi-professional team in investigating the case, with a view to identifying the causes early on, attributing the causal link to the ADR, seeking scientific evidence for evidence-based and personalized pharmacotherapeutic decision-making[20], as well as carrying out health education[21] for professionals, caregivers and patients, with a view to preventing future occurrences, notifying the case to the competent authorities, providing measures to improve patient safety, as well as communicating risks to pharmaceutical market regulation.

Despite the clinical presentation being compatible with Stevens-Johnson syndrome and overlapping with Toxic Epidermal Necrolysis, no histopathological tests were carried out to confirm the diagnosis, which is a limitation of the case reported. However, the systematic evaluation carried out during the follow-up of the episode, including causality analysis using the decision algorithm indicated in the scientific literature[22], reinforces the association of the reaction with the medication used by the patient.

Conclusion

A case was presented of an individual who developed severe cutaneous ADR probably associated with the use of quinolones. Although the pharmacological management of the event was in accordance with the recommendations of guidelines and protocols, the delay in recognizing the signs and symptoms of Stevens-Johnson syndrome and its overlap with Toxic Epidermal Necrolysis may have contributed to the death. The institutional pharmacovigilance service collaborated in the person-centered care offered by the multi-professional team, through the search for evidence for ADRs, health education for the care team and communication of risks to the health agency.

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Collaborators

Conceptualization: AMO; Methodology: AMO, FRV; Investigation: AMO; Formal Analysis: AMO, FRV; Writing – Original Draft: AMO; Writing – Review & Editing :AMO, FRV.

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Conflict of interest statement

The authors declare that there are no conflicts of interest in relation to this article.

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