Risk of Seizures Associated with the Use of Antibiotics from the Cephalosporin Group

Riesgo de convulsiones asociado al uso de antibióticos del grupo de las cefalosporinas

Alejandro E. Svarch
Head of the Federal Commission for Protection against Sanitary Risks (COFEPRIS)
asvarch@cofepris.gob.mx

Miriam Jackeline Loera Rosales
Commissioner for Evidence and Risk Management at COFEPRIS
mjloera@cofepris.gob.mx

Diana Edith Sánchez Arceo
Executive Director of Pharmacopoeia and Pharmacovigilance at COFEPRIS
dearceo@cofepris.gob.mx

Rogelio Ríos Quintana
Evidence and Risk Management Commission at COFEPRIS
rrios@cofepris.gob.mx

Mayte Guadalupe Cervantes Badillo
Researcher for Mexico at CONAHCYT
mayte.cervantes@conahcyt.mx

Abstract
Mexico is a member of the "International Program for Monitoring Adverse Drug Reactions" of the World Health Organization and, through the National Pharmacovigilance Center, it promotes actions regarding drug safety that contribute to the well-being of patients and their rational use. The evaluation of the safety profile of cephalosporins marketed in Mexico allowed us to identify that the risk of seizures and predisposing factors were not described in the prescribing information of some of them, so COFEPRIS implemented a series of measures to minimize this risk.

Resumen
México es miembro del "Programa Internacional de Monitoreo de Reacciones Adversas a Medicamentos" de la Organización Mundial de la Salud y, a través del Centro Nacional de Farmacovigilancia, promueve acciones en materia de seguridad de medicamentos que contribuyen al bienestar de los pacientes y su uso racional. La evaluación del perfil de seguridad de las cefalosporinas comercializadas en México permitió identificar que el riesgo de convulsiones y los factores de predisposición no estaban descritos en la información para prescribir de algunas de ellas, por lo que la COFEPRIS puso en marcha una serie de medidas para minimizar el riesgo.

Keywords
Pharmacovigilance, risk minimization, adverse drug reaction, cephalosporins, seizures

Palabras clave
Farmacovigilancia, minimización de riesgos, reacción adversa a medicamentos, cefalosporinas, convulsiones

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Background of drug safety regulation

Health and increased life span have been achieved thanks to the development of medicines and vaccines. However, all drugs have an intrinsic risk and only those considered safe, that is, with a favorable risk-benefit ratio, are put on sale.

Drug safety regulation began in the United States in the 1930s in response to the poisoning of several patients with "Elixir Sulfanilamide," a cough syrup containing diethylene glycol, a substance that causes kidney damage and claimed the lives of 105 people (the majority of them children). As a result of this disaster, the U.S. Congress passed the Federal Food, Drug and Cosmetic Act in 1938, thereby creating the regulatory agency responsible for evaluating medicines. Its creation meant that preclinical toxicity tests and clinical studies were required to prove the safety of new drugs.[1]

Years later, in October 1957, the drug thalidomide began to be sold in Germany, for the relief of nausea in the first months of pregnancy. Because it had no adverse effects at high doses, it was made available over

[1] Raquel Herrera Comoglio, "Algunos casos en la historia de la Farmacovigilancia," in R. Herrera Comoglio and Luis Alesso (eds.), *Farmacovigilancia, hacia una mayor seguridad en el uso de los medicamentos*, Cordoba, Uppsala Monitoring Centre, 2012, pp. 90-93.

the counter in more than 40 countries, including United Kingdom, Switzerland, Canada, Japan, Argentina and Brazil. However, the studies only focused on the drug's toxicity, but not on its teratogenic effects (*i.e.*, whether it can cause malformations during gestation of the fetus).

The ingestion of thalidomide, by either the father or the mother, could cause congenital malformations in the baby's limbs, known as phocomelia, in which the fetus does not develop its upper and/or lower limbs correctly. This was a very rare condition, and although in 1959 there were dozens of children with phocomelia, by 1961 there were thousands, so that same year thalidomide began to be withdrawn from the market. This fateful event, which went down in history as the "thalidomide disaster," was the trigger that led the world community to demand more exhaustive studies on the toxicity of new drugs in animals, clinical trials to demonstrate their safety and efficacy, and the adoption of measures to prevent and avoid such events.[2]

In 1963, the World Health Organization (WHO) issued a resolution in which it ratified the need to implement measures for the rapid dissemination of information on adverse drug reactions (ADRs), which are harmful and unwanted effects of drugs. This is how the pilot project for international drug monitoring, the Programme for International Drug Monitoring, began in 1968. Furthermore, the WHO ADR reporting database, VigiBase, has been developed and maintained by its Collaborating Centre, the Uppsala Monitoring Centre (UMC) in Sweden, since 1978.[3]

The "thalidomide disaster" led to the emergence of pharmacovigilance as we know it today. Its definition, according to WHO, is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem,"[4] in order to make rational use of them.

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[2] *Ibid.*, pp. 101-106.

[3] WHO, *The Importance of Pharmacovigilance. Safety Monitoring of Medicinal Products*, Geneva, WHO/Uppsala Monitoring Centre, 2002, pp. 5-8, at *https://www.who.int/publications/i/item/10665-42493* (date of access: April 7, 2024).

[4] *Ibid.*, p. 7.

These activities allow for the identification of increases in known and unknown ADRs, both in the general population and in special populations (pregnant women, children and the elderly). This is mainly the case for new drugs whose complete safety profile is unknown. Drug risk management includes activities such as risk minimization measures and risk communication.

Overview of drug surveillance in Mexico

In Mexico, the reporting of ADRs began in 1989 with the creation of Drug Information Centers. Subsequently, in 1995, pharmacovigilance was instituted within the reforms of the General Health Law 1995-2000. Likewise, in 1995, the National Pharmacovigilance Center (CNFV) was created through the Directorate General of Health Supplies, initiating the Permanent Pharmacovigilance Program. Meanwhile, the country joined the WHO International Drug Monitoring Program in 1999 and, in January 2005, NOM-220-SSA1-2002 "Implementation and Operation of Pharmacovigilance" came into force,[5] which establishes guidelines for the implementation and operation of pharmacovigilance in the country[6] and whose current version is the amendment to NOM-220-SSA1-2016.[7]

The Mexican State's commitment to align with international standards in health regulation was reflected in November 2021, when it became the first Spanish-speaking country to join Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the highest regulatory forum for pharmaceutical products. As a

[5] Silvia Guadalupe Salas Rojas y Alberto Fabián Soto Calderón, "Evolución de la farmacovigilancia a través de los años," in Lucía Isabel Castro Pastrana and S. G. Salas Rojas (eds.), *Farmacovigilancia: la seguridad de los medicamentos en el siglo XXI*, Cholula, Universidad de las Américas Puebla, 2015, pp. 38-40.

[6] Ministry of Health, "Norma Oficial Mexicana NOM-220-SSA1-2016, Instalación y operación de la farmacovigilancia," in DOF, July 19, 2017.

[7] Ministry of Health, "Modificación a la Norma Oficial Mexicana NOM-220-SSA1-2016, Instalación y operación de la farmacovigilancia," *Diario Oficial de la Federación*, September 30, 2020, pp. 141-145.

result, COFEPRIS positioned itself as a regulatory authority in accordance with the highest WHO standards.[8]

Since 2001, the CNFV has been part of the Executive Directorate of Pharmacopoeia and Pharmacovigilance (DEFFV), one of the departments of the Commission of Evidence and Risk Management (CEMAR) of COFEPRIS. The DEFFV manages the ADR database for the entire nation, which constitutes the foundation of pharmacovigilance through which the risks associated with the use of medicines can be detected, evaluated and understood, in order to take timely actions for their prevention and minimization, and to reduce health risks.[9] COFEPRIS's pharmacovigilance activities allow the safety of medicines sold in Mexico to be monitored, in order to ensure their rational use.

In Mexico, according to CNFV data, 726 638 ADR notifications were received in the period from 1995 to 2023, of which 96 721 correspond to 2023 (see Graph). The majority of ADRs reported in the Mexican population correspond to general disorders and alterations at the administration site, nervous system disorders, and gastrointestinal disorders.

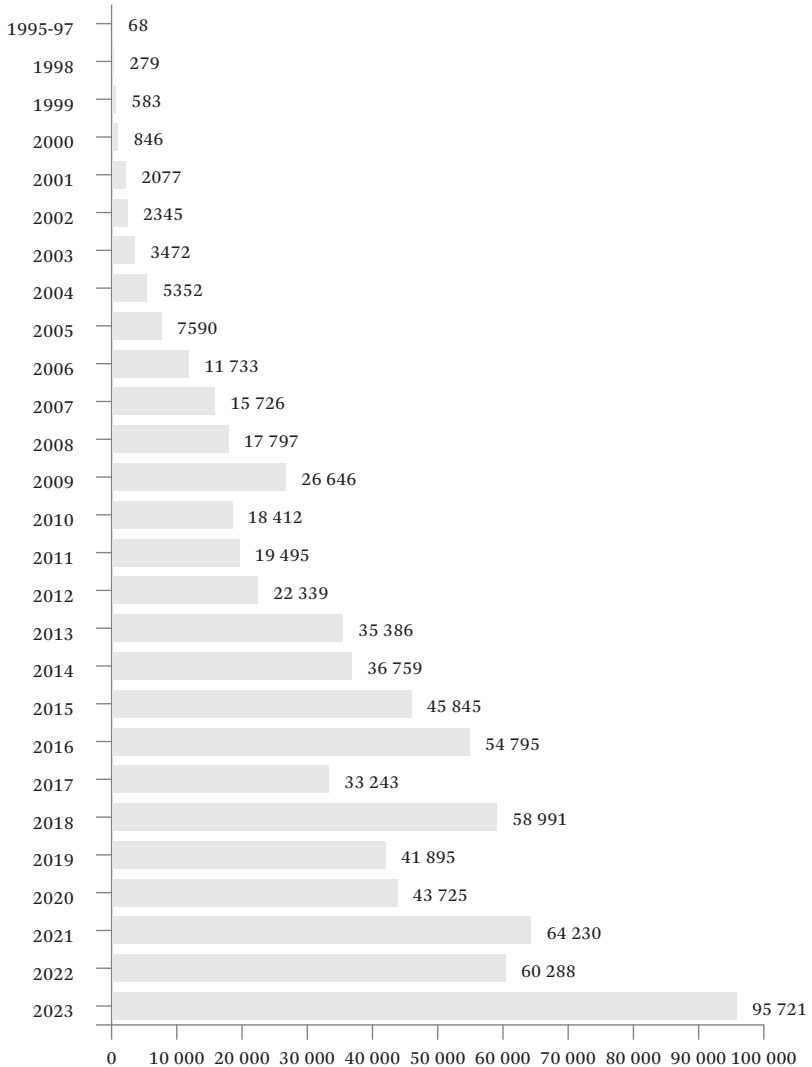
ADRs not only impact the health of patients who suffer them, but also the economic stability of health systems due to the possibility of requiring additional medication, medical care, diagnostic tests and hospital stays or their prolongation. According to data estimated by the WHO, the cost of ADR care fluctuates at around 6% of the health budget in developed countries, while for developing countries it can reach up to 45%.[10] For example, the estimated cost for ADR care in the United States amounted to USD 30.1 bil-

[8] COFEPRIS, "México, primer país hispanohablante miembro de ICH, máximo foro regulatorio de productos farmacéuticos," press release no. 35/2021, November 17, 2021, at *https://www.gob.mx/cofepris/es/articulos/mexico-primer-pais-hispanohablante-miembro-de-ich-maximo-foro-regulatorio-de-productos-farmaceuticos* (date of access: April 5, 2024).

[9] See Regulations of the Federal Commission for Protection against Sanitary Risks, art. 12, section I, and "Executive Directorate of Pharmacopoeia and Pharmacovigilance," in COFEPRIS, Detailed Organization Manual of the Federal Commission for the protection against Sanitary Risks, December 2016, pp. 105-106, at *https://transparencia.cofepris.gob.mx/images/documentos/manuales/MOE-COFEPRIS-2016.pdf* (date of access: April 10, 2024).

[10] WHO, *The Safety of Medicines in Public Health Programmes: Pharmacovigilance, an Essential Tool*, Geneva, WHO, 2006, p. 10, at *https://www.who.int/publications/i/item/9241593911* (date of access: April 10, 2024).

Graph. Notifications received by the CNFV



Source: CNFV-COFEPRIS database, 2023.Importance of pharmacovigilance in health systems.

lion per year,[11] while for Germany it represented a cost of EUR 816 million,[12] both during the past decade.

According to a study carried out in Cuba, it is more cost-effective to invest in a pharmacovigilance program that allows for the timely identification of ADRs and the implementation of risk minimization actions, than to cover the costs that arise from them,[13] although the costs of ADR care vary greatly, depending on whether they cause mild discomfort or a threat to life. A systematic review highlighted the drugs subject to the most ADR reports in hospital units, which include antibiotics, antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, opioids, cardiovascular, antineoplastic, antihypertensive, antithrombotic, antipsychotic, antiepileptic and neurological drugs.[14]

COFEPRIS pharmacovigilance actions to address seizures associated with the use of cephalosporins

The CNFV evaluates the safety profile of medicines and vaccines, such as cephalosporins, a group of antibiotics used to treat bacterial infections. Cephalosporins are classified into five generations, according to their an-

[11] Janet Sultana, Paola Cutroneo and Gianluca Trifirò, "Clinical and Economic Burden of Adverse Drug Reactions," in *Journal of Pharmacology and Pharmacotherapeutics*, vol. 4, supp. 1, December 2013, pp. s73-s77, at *https://doi.org/10.4103/0976-500X.120957* (date of access: April 10, 2024).

[12] Renee G. Stark, Jürgen John and Reiner Leidl, "Health Care Use and Costs of Adverse Drug Events Emerging from Outpatient Treatment in Germany: A Modelling Approach," in *BMC Health Services Research*, vol. 11, article 9, January 13, 2011, at *https://doi.org/10.1186/1472-6963-11-9* (date of access: April 10, 2024).

[13] Giset Jiménez López, Ana María Gálvez González and Anai García Fariñas, "Costo del tratamiento farmacológico de las reacciones adversas graves por medicamentos en Cuba (2003-2013)," in *Revista Cubana de Salud Pública*, vol. 44, no. 4, October-December 2018, pp. 112-124, at *https://www.scielosp.org/j/rcsp/i/2018.v44n4/* (date of access: April 10, 2024).

[14] Antonio Vallano Ferraz, Antonia Agustí Escasany, Consuelo Pedrós Xolvi and Josep Ma. Arnau de Bolós, "Revisión sistemática de los estudios de evaluación del coste de las reacciones adversas a medicamentos," in *Gaceta Sanitaria*, vol. 26, no. 3, May-June 2012, pp. 277-283, at *https://doi.org/10.1192/bjpo.bp.115.001321* (date of access: April 10, 2024).

timicrobial activity characteristics. Adverse reactions described for this group of drugs include: hypersensitivity, coagulation abnormalities, gastrointestinal disorders, hepatotoxicity, and central nervous system (CNS) disorders.[15]

CNS alterations manifest as dizziness, confusion, headaches, among others. In particular, neurotoxicity of cephalosporins is characterized by encephalopathy, myoclonus, seizures and/or nonconvulsive epileptic states. The risk factors associated with seizures from its use are mainly patients with renal failure or a history of neurological disorders. For this reason, a comprehensive evaluation of the patient is recommended to adjust the dose, accompanied by medical supervision when required.[16]

Patient recovery varies depending on age and dose administered, ranging from six hours to one month after drug withdrawal, mostly without side-effects. Similarly, medical interventions for seizure management may include administration of benzodiazepines, monitoring of brain activity with electroencephalograms (EEG) if the patient has neurological complications, and, if necessary, renal replacement therapy or hemodialysis of the patient.[17]

According to information from the CNFV RAM databases, some patients presented convulsive symptoms associated with the use of cephalosporins in Mexico.[18] In addition, a series of reviews of national and international scientific literature and safety communications issued by other regulatory agencies were conducted, in which the association between the use of cephalosporins and the presence of seizures was confirmed.

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[15] Brian J. Werth, "Overview of Antibiotics," in MSD Manual. Consumer Manual, May 2022, at *https://www.msdmanuals.com/home/infections/antibiotics/overview-of-antibiotics* (date of access: February 27, 2024).

[16] See Raoul Sutter, Stephan Rüegg, and Sarah Tschudin-Sutter, "Seizures as Adverse Events of Antibiotic Drugs. A Systematic Review," in *Neurology*, vol. 85, no. 15, October 13, 2016, pp. 1332-1341, at *https://doi.org/10.1212/WNL.0000000000002023* (date of access: April 10, 2024), and Samuel Deshayes, Antoine Coquerel, and Renaud Verdon, "Neurological Adverse Effects Attributable to β-Lactam Antibiotics: A Literature Review," in *Drug Safety*, vol. 40, no. 12, December 2017, pp. 1171-2007, at *https://doi.org/10.1007/s40264-017-0578-2* (date of access: April 10, 2024).

[17] *Ibid*., pp. 1190-1191.

[18] Date of access: June 28, 2023

When reviewing a representative sample of the comprehensive prescribing information (IPPA) for cephalosporins authorized by COFEPRIS, it was found that some of these did not indicate dose adjustment in patients with kidney damage. Similarly, none of them considered the importance of the patient having a history of neurological disorders, nor did they include seizures as possible adverse reactions in some patients.

For this reason, COFEPRIS has implemented several actions to minimize this risk. The first consists of requesting the holders of the health registration (TRS) to update the IPPA with the following information: i) Warnings and precautions: include text on the possibility of convulsions, principally in patients with a history of renal failure or with preexisting CNS disorders; ii) Adverse reactions: add the term *convulsions*; iii) Dose: adjust the dose in case of renal failure.[19] An alert was also issued to the public and health professionals regarding the use of cephalosporins.[20]

Other regulatory agencies have implemented similar actions, as summarized in Table below. It should be noted that, in some cases, the actions implemented focused only on the type of cephalosporin giving rise to the highest number of reports in their population. For example, the FDA focused its actions solely on cefepime[21] and the National Pharmaceutical Regulatory Agency (NPRA) of Malaysia on ceftriaxone.[22] Since in Mexico there are reports of all generations of cephalosporins, the risk minimization

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19 COFEPRIS, "COFEPRIS alerta sobre prescripción de medicamentos con cefalosporinas," press release, 106/2023, October 3, 2023, at *https://www.gob.mx/cofepris/articulos/cofepris-alerta-sobre-prescripcion-de-medicamentos-con-cefalosporinas* (date of access: April 7, 2024).

20 Ministry of Health and COFEPRIS, "Aviso de riesgo sobre el uso de Cefalosporinas," September 7, 2023, at *https://www.gob.mx/cms/uploads/attachment/file/855086/Avisos_de_riesgo_Cefalosporinas_07092023.pdf* (date of access: April 7, 2024).

21 U.S. Food and Drug Administration, "FDA Drug Safety Communication: Cefepime and Risk of Seizure in Patients Not Receiving Dosage Adjustments for Kidney Impairment," January 19, 2016, at *https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-cefepime-and-risk-seizure-patients-not-receiving-dosage-adjustments* (date of access: April 7, 2024).

22 National Pharmaceutical Regulatory Agency-Ministry of Health Malaysia, "Ceftriaxone: Disturbed Consciousness, Seizures or Involuntary Movements," January 31, 2019, at *https://www.npra.gov.my/index.php/en/health-professionals/recent-updates/414-english/safety-alerts-main/safety-alerts-2019/2051-ceftriaxone-disturbed-consciousness-seizures-or-involuntary-movements.html (*date of access: April 7, 2024).

and risk communication actions were extended to the entire group of antibiotics, as did the corresponding agencies for New Zealand,[23] Canada[24] and Panama.[25]

Table. Actions taken by national regulatory agencies to minimize the risk of using cephalosporins

Agency	Period	Cases	Drug	Shares
Food and Drug Administration (United States)	1996-2012	59	Cefepime	Adjust the dose in patients with renal insufficiency.
National Pharmaceutical Regulatory Agency (Malaysia)	2000-2018	11	Ceftriaxone	IPPA updated with TRS.
New Zealand Medicines and Medical Devices Safety Authority	October 31, 2022	26	Cephalosporins (1st-4th generation)	Recommendation to review neurotoxicity in the population with renal failure and, if necessary, withdraw treatment.
Health Canada	Report beginning of 2023	84 (7 Canada and 77 international)	Cephalosporins	Include the risk of seizures in the monograph for all cephalosporins.
Ministry of Health of Panama	Report beginning of 2023	None	Cephalosporins	Sent information from Canada.

Source: Compiled by the authors based on communications from regulatory agencies.

[23] New Zealand Medicines and Medical Devices Safety Authority, "Risk of Neurotoxicity with Cephalosporins," March 2, 2023, at *https://www.medsafe.govt.nz/profs/PUArticles/March2023/Risk-of-neurotoxicity-with-cephalosporins.html* (date of access: April 7, 2024).

[24] Health Canada, "Cephalosporins," in *Health Product InfoWatch*, February 2023, p. 3, at *https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/medeffect-canada/health-product-infowatch/february-2023/health-product-infowatch-february-2023.pdf* (date of access: April 7, 2024).

[25] Ministry of Health-Republic of Panama, "Evaluación del potencial riesgo de convulsiones asociado al uso de cefalosporinas," Drug Safety Note, February 23, 2023, at *https://www.minsa.gob.pa/sites/default/files/alertas/nota_de_seguro_004-23.pdf* (date of access: April 7, 2024).

Final thoughts

One of the objectives of pharmacovigilance is to make better use of medicines for the treatment or prevention of diseases, since all of them carry an intrinsic risk. Good practices in this field, both in the hospital setting and in the pharmaceutical industry, allow us to identify risks and risk factors, especially in recently released drugs, and thus implement measures to avoid or minimize damage. Timely communication of the safety profile of medicines will allow optimal treatment for each patient, promoting confidence and effectiveness of public health programs.[26]

In Mexico, chronic kidney disease is a public health problem. In 2017, the prevalence was estimated at 12.2% and 51.4 deaths per 100 000 inhabitants.[27] In addition to epidemiological data,[28] in Mexico bacterial infections are one of the main causes of morbidity, with cephalosporins being the most commonly prescribed drugs for their treatment.

It is important to take actions to minimize the risk of seizures associated with the use of this group of medications. Therefore, the measures implemented by COFEPRIS, such as updating the IPPA and risk communication, allow health professionals to keep up to date on the safety profile of this group of antibiotics, enabling them to carry out a comprehensive assessment of the patient and provide a higher quality prescription. This permits a rational use of medications, ensuring that the Mexican population receives the most effective and safest treatment possible.

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[26] WHO, *The Safety of Medicines*..., pp. 21-22.

[27] CENIDSP Editorial, "La enfermedad renal crónica en México," in Instituto Nacional de Salud Pública, August 26, 2020, at *https://www.insp.mx/avisos/5296-enfermedad-renal-cronica-mexico.html#sup2* (date of access: April 7, 2024).

[28] Dirección General de Epidemiología-Secretaría de Salud, "Anuarios de Morbilidad 1984 a 2022," at *https://www.gob.mx/salud/acciones-y-programas/anuarios-de-moribilidad-1984-a-2022* (date of access: April 7, 2024).