

## EXTRACTO

**OBJETIVO:** Reportar un caso de dificultad respiratoria con rinoresaca severa en un recién nacido expuesto, prenatalmente, al hidrocloreto de flufenazina.

**RESUMEN DEL CASO:** La seguridad del uso de las fenotiazinas durante el embarazo y el efecto en el feto y recién nacidos no son bien conocidos. Los autores describen una bebé recién nacida que experimentó rinoresaca severa, vómitos y dificultad respiratoria después de ser expuesta, en el útero, al hidrocloreto de flufenazina. Sepsis, atresia coana, y sífilis congénita fueron excluidos como factores causantes de la rinoresaca. La rinoresaca y obstrucción de los pasajes respiratorios superiores respondieron a tratamiento con pseudoefedrina.

**CONCLUSIONES:** La rinoresaca severa, vómito, y dificultad respiratoria que ocurrieron en esta infante no han sido reportados previamente después de exposición prenatal a hidrocloreto de flufenazina. El conocimiento sobre este problema podrá ser beneficioso a los practicantes y se debe considerar en el diagnóstico diferencial de rinoresaca en recién nacidos.

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## RÉSUMÉ

**OBJECTIF:** Il s'agit de rapporter le cas d'un nouveau-né ayant subi une détresse respiratoire suite à une exposition pré-natale au chlorhydrate de fluphénazine.

**RÉSUMÉ DU CAS:** L'innocuité des phénothiazines durant la grossesse et leurs effets sur le fœtus et sur le nouveau-né ne sont pas bien documentés. Nous faisons la description d'un nouveau-né avec une rhinorrhée sévère, des vomissements, et une détresse respiratoire suite à une exposition in utero de chlorhydrate de fluphénazine. La septicémie, l'atrésie choanale, et la syphilis congénitale furent exclues comme causes possibles de la rhinorrhée. Cette rhinorrhée et l'obstruction des voies aériennes supérieures ont bien répondu à l'utilisation de pseudoéphédrine.

**CONCLUSIONS:** Les symptômes décrits chez cet enfant (rhinorrhée sévère, vomissements, et détresse respiratoire) n'avaient jamais été rapportés précédemment suite à une exposition in utero de chlorhydrate de fluphénazine. Cette nouvelle information sera certainement utile aux cliniciens dans leur diagnostic différentiel de la rhinorrhée du nouveau-né.

PIERRE DION

## ANAPHYLACTIC SHOCK FOLLOWING POVIDONE

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**OBJECTIVE:** To report a patient with an anaphylactic reaction related to povidone administration.

**CASE SUMMARY:** A 37-year-old man with a history of allergic rhinitis presented with urticaria, dyspnea, wheezing, rhinorrhea, and dysphonia 20 minutes after the intraarticular administration of mepivacaine hydrochloride and paramethasone acetate in his right knee. Two months after this episode, he was admitted for controlled provocation tests. Tests on mepivacaine were negative. The preparation of paramethasone contained the excipients benzalkonium chloride, polysorbate 80, and povidone. In vitro tests and provocation were negative with polysorbate 80 and benzalkonium chloride, but positive with povidone.

**DISCUSSION:** Povidone, a mixture of synthetic polymers, is commonly used as an excipient in pharmaceutical products, an additive in food products, and a dispersant and stabilizer in hairsprays. Although it is well tolerated when used topically or parenterally, local and systemic effects have been reported. Furthermore, multiorgan involvement resulting from accumulation of the drug in the reticuloendothelial system has been described. The immunologic properties of povidone have not been explored in

humans, but have been in animals. In fact, the capacity of povidone to release histamine and its immunogenicity are proportional to its molecular weight. An immunoglobulin (Ig) E-mediated hypersensitivity reaction in asthma has been reported. In our case, povidone was responsible for the syndrome. However, we cannot determine the exact mechanism. An unspecific histamine release and/or an IgE-mediated hypersensitivity could be involved.

**CONCLUSIONS:** Povidone was responsible for a severe anaphylactic reaction in our patient. The possibility of an iatrogenic adverse effect caused by the excipient but not by the active ingredient should be considered in patients exhibiting similar symptoms. We believe that the excipients used in the preparation of all medicines should be disclosed.

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POVIDONE IS A MIXTURE of synthetic polymers with a molecular weight (MW) ranging from 10 000 to 700 000 Da.<sup>1,2</sup> It is commonly used as an excipient in topical, oral, and parenteral pharmaceutical products.<sup>2,3</sup> It also is used as an additive in food products and as a dispersant and stabilizer in hairsprays.<sup>4,6</sup>

Povidone is chemically inert, nontoxic, lacks antigenic capacity, and does not interfere with antibody formation. Although it is well tolerated by the upper respiratory tract when used topically or parenterally, local adverse effects have been reported. These effects can become systemic when it is used (via the same routes) chronically.<sup>2,3,6-8</sup>

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## CASE REPORT

A 37-year-old man with a history of allergic rhinitis from sensitization to dust mites experienced urticaria, dyspnea, wheezing, rhinorrhea, and dysphonia 20 minutes after intraarticular administration of mepivacaine hydrochloride and paramethasone acetate in his right knee. He was admitted and treated with parenteral corticosteroids, antihistamines, and oxygen therapy. Symptoms resolved uneventfully over the next 24 hours. One month before this episode he had tolerated administration of both drugs without problems. The indication for receiving the injection was the same in both cases: acute inflammation of the right knee after trauma.

Two months after being discharged, the patient was seen in the allergy department. Because of suspected anaphylactic shock and with the written permission of the patient, he was admitted for controlled provocation tests. One drug was used each day. Mepivacaine was tested first because the patient reported undergoing a dental procedure 2 weeks previously in which the drug had been used without problems. Results of the controlled provocation tests with this preparation were negative (Table 1).<sup>9</sup>

The preparation of paramethasone acetate included the excipients benzalkonium chloride, polysorbate 80, and povidone (MW 40 000 Da). Prior in vitro studies with these substances (histamine release test, basophil degranulation test, and lymphoblast transformation test) were negative. These tests were performed in the department of immunology. The respective provocation tests were made with benzalkonium chloride, polysorbate 80, and povidone ordered from the manufacturer of the preparation (Table 2).<sup>10</sup> The declaration of these excipients as product ingredients is not compulsory in Spain or the European Union.<sup>11</sup> Results of provocation testing with polysorbate 80 and benzalkonium chloride were negative, but positive with povidone. The patient refused the final paramethasone test. The reaction to povidone appeared 5 minutes after intramuscular administration of the pure preparation (1 mL), and included aqueous rhinorrhea, conjunctival reddening, dysphagia, dyspnea, rash on the back, and discrete edema of the uvula and anterior pillars. Neither rhonchus nor wheezing was detected. Heart rate was 130 beats/min and blood pressure remained at 120/80 mm Hg. Immediate treatment with subcutaneous epinephrine and intravenous methylprednisolone and dexamethasone resulted in a noticeable improvement after 20 minutes. Intravenous methylprednisolone and dexamethasone were continued for 48 hours. The patient then was discharged. Oral antihistamine was prescribed for some persistent isolated rash, which cleared 2 days later.

## Discussion

Local adverse effects have been reported after the parenteral administration of povidone, including inflammation, granulomatosis, panniculitis, and erythematous and papular lesions.<sup>2,6,7,12</sup> In some patients, after prolonged treatment with povidone, reactions have been observed far from the injection site (brownish induration of papules, nodules, and plaques), especially on the face and chest wall, and occasionally on the back.<sup>2,6,7,12-15</sup> Multiorgan involvement, caused by accumulation of the drug in the reticuloendothelial system, may give rise to asymptomatic hepatosplenomegaly and lymphadenopathy; more serious is the appearance of pulmonary and synovial symptoms from the reduced exchange of gases in the alveolocapillary membrane and from progressive infiltration of the synovia, respectively.<sup>2,16-19</sup> Renal involvement may be manifested as chronic renal insufficiency, with minimal proteinuria and arterial hypertension.<sup>18</sup>

Other adverse reactions reported include pulmonary involvement after the use of hairsprays,<sup>20,21</sup> ocular reactions with the implantation of intraocular lenses,<sup>7</sup> and contact

**Table 1. Results of Controlled Provocation Testing with Mepivacaine<sup>9</sup>**

| DOSE NO. <sup>a</sup> | ROUTE        | VOLUME (mL) | DILUTION  | RESPONSE |
|-----------------------|--------------|-------------|-----------|----------|
| 1                     | prick        |             | 1/100     | negative |
| 2                     | prick        |             | undiluted | negative |
| 3                     | intradermal  | 0.02        | 1/100     | negative |
| 4                     | subcutaneous | 0.1         | 1/10      | negative |
| 5                     | subcutaneous | 0.1         | 1/10      | negative |
| 6                     | subcutaneous | 0.1         | undiluted | negative |
| 7                     | subcutaneous | 0.5         | undiluted | negative |

<sup>a</sup>Interval between doses: 15–20 min.

dermatitis.<sup>22</sup> A patient with asthma experienced an attack 2 hours after administration of an iodine contrast agent with povidone for hysterosalpingography. The attack was followed by asthmatic dyspnea, which persisted more than 1 month despite treatment. The participation of povidone was demonstrated objectively by skin tests, basophil degranulation test, and histamine release test, suggesting the intervention of immunoglobulin (Ig) E. Nevertheless, the reporting authors emphasized that the patient was predisposed to histamine release.<sup>23,24</sup> The capacity of povidone to release histamine is demonstrated clearly in experimental animals. In humans, however, oral administration of the substance has not been associated with this type of effect.<sup>7</sup> The immunologic properties of povidone have not been explored in humans, but have been in experimental animals (their antigenic capacity is proportional to the MW). The degree of immune response that the different-size povidone molecules generate is related to the relative ability of a given molecular size to activate suppressor T-cells versus the ability to activate B-cells. The low-MW preparation, povidone<sub>10</sub> (MW 10 000 Da), is apparently nonimmunogenic, whereas povidone<sub>40</sub> (MW 40 000 Da) and povidone<sub>360</sub> (MW 360 000 Da) induce significant antibody responses. Povidone<sub>10</sub> has been shown to be a potent activator of suppressor T-cells, whereas povidone<sub>40</sub> and povidone<sub>360</sub> have activated B-cells.<sup>6,25</sup> Clinically, the participation of an immunologic mechanism has been suggested in panniculitis (of multiple subcutaneous nodules with fever and general indisposition) in a patient who had received intramuscular injections of povidone for 7 years.<sup>6</sup>

In our case, the clinical reaction with povidone suggested an IgE-mediated hypersensitivity type reaction, but the

**Table 2. Results of Controlled Provocation Testing with Povidone, Polysorbate 80, and Benzalkonium Chloride<sup>10</sup>**

| DOSE NO. <sup>a</sup> | ROUTE         | VOLUME (mL) | DILUTION  | RESPONSE              |
|-----------------------|---------------|-------------|-----------|-----------------------|
| 1                     | prick         |             | 1/10      | negative              |
| 2                     | prick         |             | undiluted | negative              |
| 3                     | intradermal   | 0.1         | 1/10 000  | negative              |
| 4                     | intradermal   | 0.1         | 1/1000    | negative              |
| 5                     | intradermal   | 0.1         | 1/100     | negative              |
| 6                     | intradermal   | 0.1         | 1/10      | negative              |
| 7                     | subcutaneous  | 0.2         | 1/10      | negative              |
| 8                     | intramuscular | 1           | 1/10      | negative              |
| 9                     | intramuscular | 1           | undiluted | negative <sup>b</sup> |

<sup>a</sup>Interval between doses: 15–20 min.

<sup>b</sup>Negative with polysorbate 80 and benzalkonium chloride; positive with povidone.

results of in vitro tests were discordant. We therefore decided to repeat these tests. We supplied the department of immunology with povidone 40 000 Da and in vitro tests were repeated with this product. All test results were now positive. The difference can be explained by having used a povidone of lower MW (10 000 Da) the first time. The hypothesis of the release of histamine by an IgE-mediated mechanism with cellular participation (prick and intradermal) was discordant both with the negative skin tests in the patient and controls and with the need to use the highest dose to provoke the reaction (a mechanism more like the unspecific release of histamine). As in the case of asthma following administration of povidone<sup>24</sup> compared with controls, our patient presented large papules with pseudopods and considerable erythema from the intradermal reaction of histamine. The cutaneous responses obtained in successive intradermal tests with povidone were greater in the patient, hardly exceeding those produced by the negative control but smaller than those produced by histamine. It was not possible to determine the specific IgE for povidone.

It is clear that povidone was responsible for the syndrome in our patient. A definitive diagnosis can be established from the algorithm of Karch and Lasagna<sup>26</sup>: the chronology was compatible, the pattern of reaction was known, there was no other existing process for an alternative explanation of the syndrome, the syndrome disappeared on discontinuation of the compound responsible and reappeared on reexposure, and the patient recovered uneventfully.

Establishing the relationship between a xenobiotic agent and an adverse effect—which is always difficult to demonstrate—is further complicated if the agent is the excipient rather than the active drug. The coexistence of various excipients and the fact that their disclosure is not compulsory in the information provided to the user or the physician increase the problem even more.

Before the episode described, the patient had received injections in the same knee and with the same drugs, without any abnormal response. Later, various drugs were taken orally for other reasons (erythromycin, trimethoprim/sulfamethoxazole, acetaminophen, antihistamines, and antacids), also without provoking adverse effects. Paradoxically, some of them contained povidone. Povidone is absorbed slightly by the intestinal mucosa, which could explain why our patient did not have an attack after taking oral povidone. We do not know what would happen if the mucosa was in an altered state. For obvious reasons, the patient has been advised to avoid any preparation containing povidone.

Finally, based on the described case, two recommendations can be made: the first is to bear in mind the possibility of an iatrogenic adverse effect that is not caused by the active ingredient, but by the excipient; the second is the need to disclose the excipients used in the preparation of a medicine. =

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## EXTRACTO

OBJETIVO: Comunicar el caso de una reacción anafiláctica relacionada con la administración de povidona.

**RESUMEN DEL CASO:** Un hombre de 37 años, con historia previa de rinitis alérgica, presentó urticaria, disnea, sibilancias, rinorrea, y disfonía a los 20 minutos de la administración intraarticular de clorhidrato de mepivacaina y acetato de parametasona en la rodilla derecha. Dos meses después de este episodio fue ingresado en el hospital para realizar pruebas de provocación controlada. Las pruebas con clorhidrato de mepivacaina fueron negativas. La preparación de acetato de parametasona incluía los excipientes polysorbate 80, cloruro de benzalconio, y povidona. Los tests *in vitro* y las pruebas de provocación con povidona fueron positivos, mientras que con polysorbate #80 y cloruro de benzalconio fueron negativos.

**DISCUSION:** La povidona es una mezcla de polímeros sintéticos, usada comúnmente como excipiente en preparaciones farmacéuticas, como aditivo en productos alimenticios y como dispersante y estabilizador en sprays para el cabello. Aunque es bien tolerada cuando se usa por vía tópica o parenteral, se han comunicado algunos casos de reacciones locales o sistémicas. Además se ha descrito que la acumulación de povidona en el sistema retículoendotelial podría producir una afectación multiorgánica. Las propiedades inmunológicas de povidona no han sido exploradas en el hombre, pero sí en animales de experimentación. Así, se ha observado que la capacidad de povidona para liberar histamina y su inmunogenicidad son proporcionales a su peso molecular. Se ha sugerido que un mecanismo de hipersensibilidad IgE-dependiente podría explicar un caso de asma atribuido a povidona. En nuestro caso, la responsabilidad de povidona en el cuadro clínico presentado por el paciente es evidente. Sin embargo, no podemos establecer el mecanismo de esta reacción. Quizás la liberación inespecífica de histamina y/o la hipersensibilidad IgE-mediada podrían estar implicados.

**CONCLUSIONES:** La povidona ha sido responsable de una reacción anafiláctica severa. Hay que tener en cuenta que una reacción adversa puede ser debida al excipiente y no al principio activo. Por este motivo, creemos que los excipientes incluidos en la composición de un medicamento deben ser declarados en todos los casos.

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## RÉSUMÉ

**OBJECTIF:** Présenter le cas d'une réaction anaphylactique imputée à l'administration de povidone.

**RÉSUMÉ DU CAS:** Un homme de 37 ans ayant des antécédents de rhinite allergique a présenté de l'urticaire, de la dyspnée, des sibilants, de la rhinorrhée, et de la dysphonie 20 minutes après l'administration intraarticulaire au genou droit de chlorhydrate de mepivacaine et d'acétate de paraméthasone. Deux mois après cet événement, il a été admis à l'hôpital pour des tests de provocation sous supervision médicale. Le test avec mepivacaine s'est avéré négatif. La préparation de paraméthasone contient de la paraméthasone et comme excipients du chlorure de benzalkonium, du polysorbate 80, et du povidone. Les tests *in vitro* et la provocation au povidone ont été positifs alors que ceux réalisés avec le polysorbate 80 et le chlorure de benzalkonium furent négatifs.

**DISCUSSION:** Le povidone est un mélange de polymères synthétiques utilisés de façon courante comme excipient dans la composition des produits pharmaceutiques, comme additif dans la préparation des aliments, et comme agent de dispersion et stabilisateur dans les vaporisateurs pour les cheveux. Bien qu'il est généralement bien toléré lors de l'application topique ou l'administration parentérale, des réactions locales et systémiques ont été rapportées. On a aussi décrit une atteinte multiorganique suite à l'accumulation de ce produit au niveau du système réticuloendothélial. Les propriétés immunologiques du povidone n'ont pas été investiguées chez l'homme mais seulement chez l'animal. En fait, la capacité du povidone à provoquer la libération d'histamine et son immunogénicité sont proportionnels à son poids moléculaire. Une réaction d'hypersensibilité médiée par immunoglobuline E a été suggérée pour expliquer une réaction asthmatiforme causée par le povidone. Dans ce cas, il est évident que le povidone est responsable de la réaction du patient. Cependant, il est impossible de déterminer le mécanisme responsable. Une libération non spécifique d'histamine et/ou une hypersensibilité médiée par immunoglobuline E pourraient être impliquées.

**CONCLUSIONS:** Le povidone est responsable d'une réaction anaphylactique sévère. La possibilité d'une réaction iatrogénique causée par les excipients d'un médicament doit être gardée en mémoire. Nous croyons que les excipients utilisés dans la préparation des médicaments devraient être dévoilés par les manufacturiers dans tous les cas.

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