World Allergy Organization Journal 12 (2019) 100002

Contents lists available at ScienceDirect

World Allergy Organization Journal

journal homepage: https://www.sciencedirect.com/journal/wao-journal

Desensitization in patients with hypersensitivity to haem arginate: A case report

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ARTICLE INFO

Keywords:
Porphyria
Hypersensitivity to haem arginate
Hemin arginate

ABSTRACT

Background: Porphyria comprises a group of metabolic disorders caused by the irregular activities of enzymes within the haem biosynthetic pathway. This disease can provoke a large variety of symptoms. Acute porphyria attacks need to be treated urgently to avoid prolonged illness and fatal complications. Haem arginate, a concentrated haem solution stabilized with arginine, is the only preparation available for treatment in Europe and South America. This report describes a safe desensitization protocol for patients who require such treatment and have haem arginate hypersensitivity.

Case presentation: A 25-year-old female patient diagnosed with acute intermittent porphyria, who had an anaphylactic reaction while receiving haem arginate. The patient was treated with a desensitization protocol for patients with hypersensitivity to haem arginate.

Conclusion: Porphyria is a disease that can significantly compromise a patient's quality of life. The desensitization protocol for patients with hypersensitivity to haem arginate is a safe and effective treatment option for patients with a history of haem arginate allergies, to whom it is not possible to administer haematin.

Background

Porphyria is a group of genetic disorders characterized by errors in the metabolism of the haem biosynthesis pathway. The porphyria could be present clinically as acute neurovisceral symptoms, skin lesions or both, produced by the accumulation of porphyrins or its precursors. Fortunately, most patients remain asymptomatic throughout their lives.[1–3] Porphyria can be classified as acute or inducible, and non-acute or chronic cutaneous.[2,4] The prognosis for porphyria cases is positive following an early diagnosis and aggressive treatment.[5,6] The diseases are characterized by episodic acute neurovisceral attacks that can be life-threatening, with symptoms such as severe colicky pain in the lower abdomen, nausea, vomiting, tachycardia, hypertension, arrhythmias, neurological manifestations such as muscle weakness, peripheral motor neuropathy (dysphagia, flaccid paralysis, respiratory insufficiency, urinary retention or incontinence), confusion, delirium, seizures, and in some cases bullous skin lesions and photosensitivity.[7,8] Symptoms in porphyria crisis may be caused by drugs (barbiturates, hydantoins, rifampin, progestins, endogenous steroid hormones, and illegal drugs), alcohol, endocrine factors (menstrual cycle), infection, stress, calorie restriction (fasting or dieting) and are followed by full recovery but recurrent acute attacks.[4,9,10]

Once diagnosed, treatment should start as soon as possible. Intravenous haem arginate and carbohydrate loading are the two current treatments for this disease. Intravenous haem loading is considered the first treatment option for an acute attack. Its administration reduces the haem group oxygen deficit as well as the production of porphyrins through a feedback process that inhibits delta-aminolevulinic synthetase activity. Therefore, heam arginate helps to re-establish normal levels of hemoproteins, preventing the build-up of delta-aminolevulinic acids and porphobilinogen precursors, which trigger the disease. The preparation of haem arginate available for administering in Europe and South America is Normosang®,[5] a concentrated haem solution with a half-life of 10.8 h (250 mg haem per ampule) stabilized as a complex with arginine suspended in a mixture of ethanol and propylene glycol.[11–13]

For the treatment of an acute porphyria attack, the dose of haem arginate is 3 mg/kg (limited to a maximum of 250 mg) once a day for four consecutive days. The administration is recommended using an in-line filter. Haem arginate is a dark solution, which makes it difficult to check for the absence of particles. It should be protected from light

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https://doi.org/10.1016/j.waojou.2018.11.002
Received 19 April 2018; Received in revised form 14 November 2018; Accepted 28 November 2018

during the infusion, diluted with sodium chloride 0.9% in a glass bottle because hemin degrades somewhat more quickly in PVC plastic, and used within 1 h of preparation. Shorter infusion durations of 15–20 min are preferred. After infusion, the vein should be flushed well with 100 mL of sodium chloride 0.9%, initially as three or four 10 mL boluses and then the remaining volume may be infused over 10–15 min.

Among the known side effects of the components of Normosang, some reports of haem arginate producing skin discolouration in cases of extravasation, thrombophlebitis at peripheral vein infusion in less than 1% of cases, and the disappearance of the superficial venous system, as well as an iron overload (250 g dose of haem contains 22.7 mg of iron), in prolonged or repeated treatments.[13]

With regards to ethanol, side effects such as flushing, tachycardia, weakness, fatigue, and other dysphoric symptoms have all been reported. Polyethylene glycol has not produced any known side effects when administered intravenously.

Hypersensitivity reactions to haem arginate have been described as rare; to the best of our knowledge, only one reported case exists.[14] However, in this article, we report another case of hypersensitivity to haem arginate in a young woman, who subsequently underwent a successful desensitization protocol.

Case presentation

A 25-year-old female patient with a 6-year history of acute intermittent porphyria, with 4–5 acute attacks per year, treated on each occasion with 5 doses of haem arginate. No further clinical history of note, except for a known allergy to hyoscine butylbromide. During the last attack, while in the emergency room (ER) department of Fundación Santa de Bogota, Colombia, the patient presented facial and thorax erythema in the second minute of the infusion with haem arginate, as well as urticaria, facial angioedema, dysphagia, dyspnea, and coughing, accompanied by hypertension and tachycardia. When examined, the patient registered the following results: blood pressure 135/90 mmHg, heart rate 165 bpm, breathing rate 23 breaths per minute, 90% oxygen saturation without supplementary oxygen. The symptoms and signs presented by the patient were compared with the adverse effects reported for Normosang; no similarity was found; therefore, it was considered that the patient had an allergic reaction instead of an adverse effect. She was treated with adrenaline dose of 0.5 mg, clemastine (0.05 mg/kg) and methylprednisolone 80 mg, administered intravenously once and her condition improved rapidly.

Because of the lack of other medical treatment available in Colombia, the Allergy Department was consulted. The symptoms suggested that it was a case of anaphylaxis caused by an immunoglobulin E (IgE) mediated reaction. We were unable to measure the serum tryptase owing to the lack of necessary equipment in our clinic. However, we were able to reject the alternative hypotheses that the patient's symptoms were side effects of a different medicine or of haem arginate. The patient informed us that they were not taking any other medicine. Therefore, we decided on treatment by premedication and desensitization.

Because there was no protocol available in the literature for this particular medication, the allergists involved in this case decided to create one based on the model used for antineoplastic drugs described by the Harvard University Workforce lead by Dr. M. Castells.[15–19]

After consent from the patient, she was admitted to the intensive care unit (ICU) and the desensitization protocol for haem arginate was started 12 hours after the allergic reaction. The medication was administered 12 hours after the allergic reaction considering the half-life of the medication and the last dose with the allergic reaction was given.

Protocol

Following the recommendations for the use of heam arginate, a dilution was prepared prior to its administration. The haem arginate dose was diluted in 100 mL of 0.9% NaCl aqueous solution in a glass bottle covered with a UV-protective bag. An infusion set for photosensitive solutions and an in-line filter was used throughout the administration of the medicine. The protocol began with a dose of 1.8 mg of heam arginate diluted in 100 mL, which was increased every 15 min in line with the quantities outlined until the dose reached 180 mg in 100 mL (Table 1).

The patient's notes emphasized the need to suspend the procedure should any allergic reactions arise, and that any such reactions should be treated immediately until they had completely subsided. Once this had been achieved, the desensitization protocol could be resumed at the same dose during which the symptoms appeared.

The desensitization protocol on the patient was completed without any allergic reactions during the progressive administration of each dosage of the medication. The ICU doctors ordered the transfer to a hospitalization ward, a daily dose of 180 mg haem arginate was administered for the following 5 days. The doses were administered without any complications. Premedication with 80 g methylprednisolone/day and 25 mg hydroxyzine/day was administered 30 min prior to the administration of each dose of haem arginate during the 5 days of treatment required by the patient.

Once treatment was begun, the clinical response was excellent and symptoms (severe colicky pain in the abdomen, nausea, and vomiting) were under complete control. Three months after the first desensitization protocol, the patient returned to the emergency department suffering another attack, which required another desensitization protocol and also yielded a positive response with no complications. In total, the patient underwent the protocol six more times after the initial desensitization, with consistently positive results. On the last occasion, the patient successfully underwent the treatment with no adverse effects and without premedication.

Discussion

Acute intermittent porphyria is a rare genetic condition that manifests in acute, life-threatening attacks and usually affects young women, such as the patient in this case report. Specific treatment with intravenous haem infusion has had positive outcomes.[4–6,11] Hypersensitivity reactions have been described as rare. In a letter to the editor, Daimon et al., reported the case of a 29-year-old woman who was admitted to hospital with abdominal pain, vomiting, and constipation. On examination, she was diagnosed with acute intermittent porphyria. She has subsequently prescribed a treatment of haem arginate, but two years

Table 1
Desensitization protocol for haem arginate.

Step	Solution	Rate of infusion (mL/h)	Time (min)	Administered dosage (mg)	Cumulative dosage (mg)
1	A	2	15	0.009	0.009
2	A	5	15	0.0225	0.0315
3	A	10	15	0.045	0.0765
4	A	20	15	0.09	0.1665
5	B	5	15	0.225	0.3915
6	B	10	15	0.45	0.8415
7	B	20	15	0.9	1.7415
8	B	40	15	1.8	3.5415
9	C	10	15	4.5	8.0415
10	C	20	15	9	17.0415
11	C	40	15	18	35.0415
12	C	27	185	149.85	180,0415

Total time: 5.8 h.
Total dose: 180 mg.
Solution A (100 mL): Concentration of the solution of 0.018 mg/mL and dosage in solution of 1.8 mg.
Solution B (100 mL): Concentration of the solution of 0.18 mg/mL and dosage in solution of 18 mg.
Solution C (100 mL): Concentration of the solution of 1.8 mg/mL and dosage in solution of 180 mg.

later, after the 25th dose, she developed symptoms of anaphylaxis (dyspnea, severe urticarial and hypertension). These symptoms reappeared at each attempt to re-administer the medicine; therefore, an alternative treatment was necessary. The next treatment provided was a course of haematin, thanks to which the patient recovered and showed no further signs of allergy. Consequently, the authors concluded that the original allergic reaction could have been triggered by one of the other components in the medicine and not directly by the haem. They surmised that side effects can include immediate anaphylactic shock and that in such cases haematin is an alternative treatment option.[14]

In the case reported in this article, a similar situation was observed in a young woman, who, after 6 years of positive responses to haem arginate, developed an allergic reaction to the medication. In Colombia, the only available medicinal product of haem alginate is Normosang. Therefore, its administration is of vital use in cases of porphyria[15–19]

The case reported was an IgE-mediated response to haem arginate, in which a specific characteristic of this reaction was observed by the appearance of hypersensitivity after multiple doses. Repeated exposure to drug antigens is needed to develop a specific IgE, which explains why several courses of treatment produce the patients' hypersensitivity. The severity of the symptoms depends on each patient, and this can occur even when low doses are administered.[6]

Regarding the options for the diagnosis of allergy to hemin arginate, intradermal skin testing (IDST) and skin-prick testing (SPT) cannot be conducted because haem arginate is an irritant and the infusion is hypertonic. Therefore, it must be exclusively administered intravenously by very slow intravenous perfusion and carefully avoiding contact with the skin to avoid the adverse local effects already described.

The recommendation for diagnosis is the use of serum tryptase as a marker for mast cell activation. Because there are no standardized protocols for other tests, such as BAT for haem ariginate, these protocols cannot be recommended at this time.

The goal of the desensitization protocol was to administer suboptimal doses of antigens, to make the mast cells and basophils unresponsive to antigens either through administering an excess of monomeric antigens that cannot bind to IgE-specific receptors, or through rapid internalization of binding receptors from the cell membrane, without affecting the function of the mastocytes or basophils when faced with other stimuli.[15]

The protocol used for desensitization to antineoplastic drugs described by Castells et al.[15–19] was used as a guideline for the development of the protocol for haem arginate. The choice of the base protocol, as well as the number of steps undertaken, were based on the success and efficiency reported in Dr. Castell's original study, as well as in other tests undertaken globally.[15–20]

To the best of our knowledge, no protocols for this medication have been established. Administration of the drug was performed in 12 steps using dilutions until the total dose of 180 mg was completed, which was required daily by the patient; the total dose was administered in 5.8 h. Four concentrations (A, B and C, Table) were used every 15 min. The amount of drug delivered in each subsequent step was approximate twice the dose of the previous step.

The attending group of physicians must be trained to recognize and manage complications, and one-on-one care should be provided. For this reason, our patient was first treated in the ICU.[16] As a safety precaution, the premedication was continued throughout the protocol for each of the 3 doses required by the patient during the hospitalization. This was in line with other desensitization protocols administered to first-time patients, in which similar precautionary measures were taken.[20] In light of the findings of other researchers, who have recently suggested that premedication is no longer necessary after the first day of desensitization, this protocol has been successfully implemented without any premedication at all.[21]

The patient received a clear explanation that the drug desensitization induces a transient, immunological tolerance lasting a maximum of 48 hours after the last dose is given. It is important to clarify that if there is a need to use the drug at a later date, the procedure must begin again.[15]

Conclusion

A desensitization protocol for the treatment of porphyria was developed because of the vital necessity for medical treatment and the lack of alternative clinical options (such as haematin) in our country. From our experience in this one case, the protocol was safe and efficient. We recommend the use of this protocol in cases with a similar profile. However, more studies are needed to explain the physiopathological mechanisms underlying the hypersensitivity to this drug and the temporary tolerance induced by desensitization.

Consent for publication

This case report does not have any confidential information of patients, images or videos. An informed consent was filled out with each patient for this publication.

Availability of data and materials

There are no digital records of the patients as part of the case reports.

Competing of interest

The authors of this publication declare no conflict of interest.

Funding

Not applicable.

Authors' contributions

All authors of the manuscript were involved in the care of the patients, writing, reviewing and the editing the document.

Acknowledgements

Not applicable.

List of abbreviations

ER	Emergency room
IgE	Immunoglobulin E
ICU	Intensive Care Unit
PVC	Polyvinyl chloride plastic
UV	Ultraviolet

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