Case Report

Successful Diflunisal Desensitization in a Transthyretin Amyloidosis Patient With Ibuprofen Allergy: A Case Report

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ABSTRACT

Background: Amyloid diseases are hereditary and include transthyretin (TTR) amyloidosis where subunit protein mutations may occur in genes for TTR, leading to the deposition of fibrils (low molecular weight subunits (5 to 25 KD of proteins) in extracellular tissues. By reducing the formation of TTR amyloid, diflunisal, a nonsteroidal anti-inflammatory drug, can preserve the quality of life and significantly reduce disease progression. We present a case of a 61-year-old male patient with a history of ibuprofen allergy, diagnosed with TTR amyloidosis, complicated with peripheral neuropathy, cardiac, and liver amyloid. He developed bilateral mild eye swelling from the ibuprofen oral provocation test. With a similar structural backbone of carboxylic acid, he could develop pseudoallergy to diflunisal with an unknown likelihood of developing an allergic reaction.

Objectives: This study aims to design successful diflunisal desensitization in a patient with TTR amyloidosis.

Methods: The patient underwent a 14-step diflunisal desensitization procedure using 2 tablets of diflunisal 500 mg that was dissolved in 40 mL of sodium bicarbonate 8.4% injection to create serial 10-fold dilutions. Oral desensitization was administered in the escalation of the doses at 30-min intervals, with a starting dose of 0.1 mg until a final dose of 250 mg was reached.

Results: The patient tolerated diflunisal desensitization and was continued on diflunisal treatment without any evidence of an allergic reaction.

Conclusion: Diflunisal desensitization can be considered in patients with a history of ibuprofen allergy if there are no available alternative treatments. To the best of our knowledge, this is the first article describing a patient with angioedema to ibuprofen who could tolerate oral diflunisal after desensitization.

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Introduction

Amyloid diseases are hereditary and include transthyretin (TTR) amyloidosis where subunit protein mutations may occur in genes for TTR leading to the deposition of fibrils (low molecular weight subunits (5 to 25 K_D of proteins) in extracellular tissues [1]. The presentation of TTR amyloidosis includes peripheral and or autonomic neuropathy, infiltrative cardiomyopathy, and vitreous amyloid or leptomeningeal disease [2].

The treatment of TTR amyloidosis, where mutant amyloid precursor TTR proteins are produced by the liver, includes reduction of TTR synthesis, stabilization of TTR tetramers, antibodies, biologic agents, and hepatorenal or hepato-cardiac transplantation for advanced end-organ damages [3]. By reducing the formation of TTR amyloid, diflunisal, a nonsteroidal anti-inflammatory drug (NSAID), aids to stabilize TTR tetramers and prevent the release of amyloidogenic monomers. In a randomized trial involving 130 patients, diflunisal was compared to placebo and has shown to preserve the quality of life and significantly reduce the progression of neurologic impairment in patients with familial amyloid polyneuropathy [4]. In this article, we report a case of a patient with a known drug allergy to ibuprofen who was successfully desensitized with diflunisal for TTR amyloidosis.

Case Description

Introduction

A 61-year-old Chinese male with known drug allergies to ampicillin and ibuprofen, and periorbital edema with both drugs, was diagnosed with TTR amyloidosis, complicated with peripheral neuropathy, cardiac, and liver amyloid. He underwent an ibuprofen oral provocation test with ibuprofen 320 mg and developed bilateral mild eye swelling. There were no systemic symptoms and he was discharged well with the following anti-histamines: PO loratadine 10 mg OM PRN itch for 5 days and PO chlorpheniramine 4 mg ON PRN itch for 5 days. Since then, the patient has yet to try aspirin or other NSAIDs. However, he was noted to have taken etoricoxib, a selective cyclooxygenase-2 inhibitor, with no issues.

Given the patient's TTR amyloidosis, the stabilization of TTR tetramers is required. Both diflunisal and tafamidis are known to stabilize TTR tetramers. However, because of the high treatment costs associated with tafamidis and its unavailability in our country, a desensitization procedure with diflunisal was considered. There is currently no validated desensitization protocol with diflunisal, so we sought to design one.

Materials and Methods

The desensitization procedure was performed with the absence of premedication in an intermediate care area under the close supervision of physicians and nurses with resuscitation equipment on standby. The patient has also refrained from the administration of any anti-histamines and corticosteroids 24 h before the procedure which could mask any possible allergy reactions to diflunisal.

Two tablets of diflunisal 500 mg (AA Pharma Inc., Ontario, Canada) were dissolved in 40 mL of sodium bicarbonate 8.4% injection to create serial 10-fold dilutions (the lowest concentration was 0.1 mg/mL). Oral desensitization was administered in the escalation of doses at 30-min intervals, with a starting dose of 0.1 mg until a final dose of 250 mg was reached. The whole desensitization procedure took 7 h to complete (Table 1). The starting dose and dose escalation intervals are extrapolated from published aspirin desensitization protocols [5, 6].

Results

The patient tolerated the procedure uneventfully. The use of oral diflunisal, 250 mg twice daily, was then started. The patient was continued on diflunisal treatment without any evidence of allergic reaction.

Discussion

Hypersensitivity reactions to NSAIDs can be categorized as pseudoallergic or allergic reactions. Pseudoallergic reactions are non-immunologic in nature, resulting from COX-1 inhibiting the properties of the drug. Patients who present with pseudoallergic reactions may react to most cyclooxygenase-1 (COX-1) inhibitors, including aspirin. On the other hand, allergic reactions are presumed to be immunoglobulin E (IgE)-mediated, specific to the chemical structure of the drugs [7]. Hence, drug desensitization protocols were developed to safely reintroduce drugs in patients who develop IgE or non-IgE mediated hypersensitivity reactions [8]. In this case, the patient developed bilateral eye swelling with ibuprofen oral provocation test at 320 mg but tolerated etoricoxib (COX-2 selective inhibitor). There was no other NSAIDs exposure other than the two mentioned.

Comparing diflunisal (Figure 1), a non-selective NSAID and ibuprofen (Figure 2), both NSAIDs are

Table 1. Diflunisal desensitization protocol

Step	Route	Diflunisal Suspension (mg/ml)	Amount (mL)	Dose (mg)	Cumulative Dose (mg)
1	PO	0.1 mg/mL (suspension C)	1.0	0.1	0.1
2	PO	0.1 mg/mL (suspension C)	2.0	0.2	0.3
3	PO	0.1 mg/mL (suspension C)	4.0	0.4	0.7
4	PO	1 mg/mL (suspension B)	1.0	1.0	1.7
5	PO	1 mg/mL (suspension B)	2.0	2.0	3.7
6	PO	1 mg/mL (suspension B)	4.0	4.0	7.7
7	PO	25 mg/mL (suspension A)	0.4	10.0	17.7
8	PO	25 mg/mL (suspension A)	0.8	20.0	37.7
9	PO	25 mg/mL (suspension A)	1.6	40.0	77.7
10	PO	25 mg/mL (suspension A)	3.2	80.0	157.7
11	PO	25 mg/mL (suspension A)	4.0	100.0	257.7
12	PO	25 mg/mL (suspension A)	6.0	150.0	407.7
13	PO	25 mg/mL (suspension A)	8.0	200.0	607.7
14	PO	500 mg tablet	0.5 tablet	250.0	857.7

†The interval between doses (Step 1-14) is 30 min.

known as carboxylic acids with minor structural differences at the side chains where diflunisal is salicylic acid and ibuprofen is propionic acid. Hence, with a similar structural backbone of carboxylic acid, the patient could develop pseudoallergy to diflunisal, with an unknown likelihood of developing an allergic reaction. With caution, diflunisal desensitization was proposed. Rapid aspirin desensitization was proven to be effective but there are only a few NSAIDs desensitization protocols published [6]. Besides, no data was available on extemporaneous preparation of diflunisal suspensions.

Diflunisal is an organic acid that dissolves readily in a dilute alkali solution to give a stable solution at room temperature [9]. Based on PubChem, the solubility of diflunisal is 14.5 mg/L at neutral or acidic pH, which is impractical to be formulated into a solution for oral desensitization. One study has shown that buffering gastric pH toward neutral using sodium bicarbonate has enhanced the absorption of diflunisal in addition to its bioavailability [10]. Hence, it was extrapolated that the solubility of diflunisal may be improved with the use

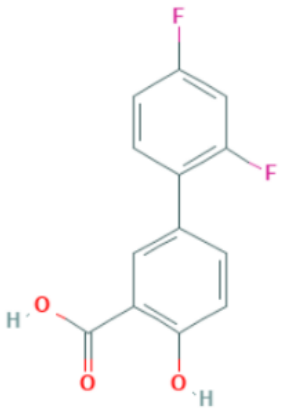

Figure 1. Structure of diflunisal

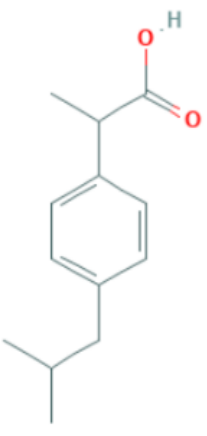

Figure 2. Structure of ibuprofen

of sodium bicarbonate as the solvent. At a 25 mg/mL concentration, diflunisal formed a uniform suspension in sodium bicarbonate injectable solution. The total dose of sodium bicarbonate that the patient received by the end of this desensitization procedure was approximately 3.2 g. As this is an acceptable daily dose to be administered to the patient, the preparation of diflunisal solution at a higher concentration was not explored. A successful oral desensitization using omeprazole granules dissolving in bicarbonate solution has been reported [11], despite the paucity of data on the tolerability of such solution.

Conclusion

To our knowledge, this is the first article describing a patient with angioedema to ibuprofen who could tolerate oral diflunisal after desensitization. When indicated, this newly designed desensitization protocol may be useful in patients with ibuprofen or diflunisal-induced allergy. The brief desensitization protocol offers an effective method for inducing tolerance when no alternative treatments are available.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Bellotti V, Nuvolone M, Giorgetti S, Obici L, Palladini G, Russo P, et al. The workings of the amyloid diseases. Ann Med. 2007; 39(3):200-7. [PMID]

[2] Bhogal S, Ladia V, Sitwala P, Cook E, Bajaj K, Ramu V, et al. Cardiac amyloidosis: An updated review with emphasis on diagnosis and future directions. Curr Probl Cardiol. 2018; 43(1):10-34. [DOI:10.1016/j.cpcardiol.2017.04.003] [PMID]

[3] Kolstoe SE, Wood SP. Drug targets for amyloidosis. Biochem Soc Trans. 2010; 38(2):466-70. [PMID]

[4] Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, et al. Repurposing diflunisal for familial amyloid polyneuropathy: A randomized clinical trial. JAMA. 2013; 310(24):2658-67. [DOI:10.1001/jama.2013.283815] [PMID] [PMCID]

[5] Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. Am J Cardiol. 2005; 95(4):509-10. [DOI:10.1016/j.amjcard.2004.10.022] [PMID]

[6] Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. J Allergy Clin Immunol. 2000; 105(5):997-1001. [PMID]

[7] Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma Immunol. 2001; 87(3):177-80. [DOI:10.1016/S1081-1206(10)62221-1]

[8] Vultaggio A, Matucci A, Nencini F, Bormioli S, Vivarelli E, Maggi E. Mechanisms of drug desensitization: Not only mast cells. Front Pharmacol. 2020; 11:590991. [PMID] [PMCID]

[9] Diflunisal. Diflunisal tablets USP. Vaughan, Ontario: AA Pharma Inc; 2014. https://www.aapharma.ca/downloads/en/PIL/2016/Diflunisal-PM.pdf

[10] Nuernberg B, Brune K. Bufferring the stomach content enhances the absorption of diflunisal in man. Biopharm Drug Dispos. 1989; 10(4):377-87. [DOI:10.1002/bdd.2510100405] [PMID]

[11] Otani IM, Banerji A. Immediate and delayed hypersensitivity reactions to proton pump inhibitors: Evaluation and management. Curr Allergy Asthma Rep. 2016; 16(3):17. [DOI:10.1007/s11882-016-0595-8] [PMID]