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RESEARCH ARTICLE

Flare-Up Phenomenon of Intradermal Test with Anaphylactic Reaction to Paracetamol (Acetaminophen)

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Abstract: ***Background***: Paracetamol is a Non-Steroidal Anti-Inflammatory Drug (NSAID) that can produce hypersensitive reactions mediated by specific immunological mechanisms (IgE or T cell-dependent) or by a non-immunological mechanism (inhibition of cyclooxygenase COX-1).

Objective: An 80-year-old man with a history of allergy to pyrazolones, with good tolerance to other NSAIDs was referred to our allergy department because he presented a generalized urticaria after the administration of Intravenous (IV) paracetamol.

Methods: We performed an Intradermal Test (IDT) with paracetamol (0.02mg/ml) and later a Single Blind Oral Challenge Test (SBOCT) with oral paracetamol.

Results: IDT reading at 15min showed negative result so an SBOCT was performed with oral paracetamol. With an accumulative dose of 250mg, after 20min, he developed discomfort, nausea and dizziness, urticarial, hypotension (BP 80/40) as well as flare-up phenomenon was observed in the site of the IDT with paracetamol. Tryptase levels during the reaction and 2hrs later were increased.

Conclusion: We present an anaphylactic shock due to sensitization to paracetamol because of a type I hypersensitivity mechanism, diagnosed by SBOCT and a positive IDT because of flare-up phenomenon, in a patient with previous pyrazolones allergy and with tolerance to other NSAIDs**.** Some relevant patents are also summarized in this paper.

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1. INTRODUCTION

Paracetamol (acetaminophen) is a Non-Steroidal Anti-Inflammatory Drug (NSAID) with antipyretic and analgesic properties. Although the most frequent reactions occur by the inhibition of cyclooxygenase COX-1, because of non-immunological mechanism, it can also be mediated by IgE (immediate reactions) or T-cell (non-immediate reactions), although they are unusual [1]. Type I hypersensitivity reactions have been reported, such as urticaria, angioedema, and even anaphylaxis [2]

2. MATERIALS AND METHODS

We present an 80-year-old man with a history of chronic ischemic heart disease, bronchial asthma, and urothelial carcinoma with chemotherapy treatment. He was diagnosed by clinical history, two years before allergy to pyrazolones (acute urticaria because of metamizole), with good tolerance to other NSAIDs. In August 2016, he presented a generalized urticaria without other systemic symptoms 30min after the administration of Intravenous (IV) paracetamol. The reaction resolved with Subcutaneous (SC) dexclorfeniramine in several hours with no residual lesions. Afterwards, he has been tolerating daily 100mg of Acetylsalicylic Acid (ASA) with no incidences. He was referred to our allergy service for drug allergy study, because of the need to use paracetamol frequently as pretreatment of chemotherapy.

We performed an Intradermal Test (IDT) with paracetamol (0.02mg/ml) with reading at 15min, based on the fact that the positive control with histamine reaches its maximum reaction at 10-15min, with a negative result. The concentration of IDT was less than standardized test due to individual risk and personal history of the patient. We didn't perform a prick test because of the lower sensitivity than the IDT. After obtaining informed consent from the patient, a Single Blind Oral Challenge Test (SBOCT) was then performed with oral paracetamol.

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3. RESULTS

With an accumulative dose of 185mg (after 60mg and 125mg doses with increases of 1hr interval), he developed 20min after discomfort, nausea and dizziness. No cutaneous lesions initially appeared, but a flare-up phenomenon was observed in the site of the IDT with paracetamol (Fig. **1**).

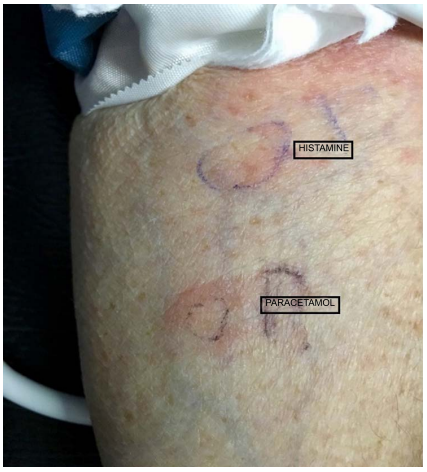

Fig. (1). Flare-up phenomenon was observed in the site of the IDT with paracetamol.

Ten minutes later, he developed pruritus in trunk and erythema with maculopapular lesions, in the lumbosacral region as well as hypotension (BP 80/40) that disappeared with 500ml of physiological saline, 80mg of metilprednisolone, 5mg of dexchlorpheniramine IV and 0.3mg intramuscular epinefrine. Afterwards, the same exanthema extended to the thorax and lower limbs (Fig. **2**). The reaction resolved completely in an hour.

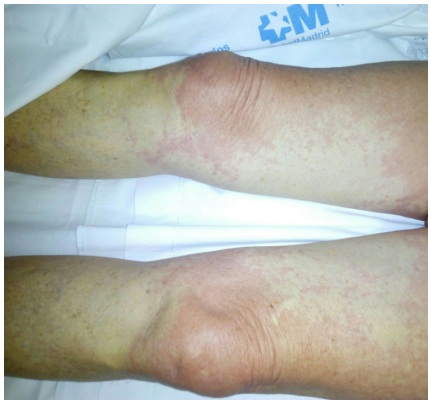

Fig. (2). Exanthema extended to the thorax and lower limbs.

Tryptase levels during the reaction and 2hrs later were increased (34.6 and 39.8µg/L, respectively). Basal tryptase level was 5.7µg/L.

We diagnosed the patient of an anaphylactic shock due to sensitization to paracetamol because of a type I hypersensitivity mechanism. Pyrazolones were previously forbidden, and to refuse NSAID intolerance, we performed SBOCT with ASA up to doses of 650mg, well tolerated. Due to the implication of two different groups of NSAIDs (pyrazolones and paracetamol), he was diagnosed with a double selective sensitization, and the use of other different groups of NSAIDs was allowed.

4. DISCUSSION

We present an anaphylactic shock due to sensitization to paracetamol diagnosed by SBOCT and a flare reaction at previous negative IDT site with the oral challenge because of flare-up phenomenon, in a patient with previous pyrazolones allergy and with tolerance to other NSAIDs.

The IDT with paracetamol confirms IgE mechanism. Patients with type I hypersensitivity reactions due to a selective allergy to paracetamol with tolerance others NSAIDs, such as our patient, have been reported in the literature. Most of these patients have been diagnosed by clinical history or positive SBOCT [2-5]. However, the utility of SPT with paracetamol is yet unknown, although, in the literature, it is uncommonly described positive IDT and much less because of a flare-up phenomenon [6, 7].

Some few cases of skin test with paracetamol are reported in the literature [2, 5-7] but Rojas-Pérez-Ezquerra *et al*. [4] described the largest series published until the date of selective allergy to paracetamol (13 cases) in which no SPT were positive in any of them but with positive SBOCT in all the patients.

In vitro tests are not available in many hospitals and their utility is still questionable. In some cases, high levels of IgE have been detected in these patients, as Paramo *et al*. [2] reported in two patients with selective allergy to paracetamol. In our case, we were not able to perform it, due to lack of *in vitro* test study to confirm specific IgE to the drug in our hospital.

Although paracetamol anaphylaxis is uncommon, there are some cases reported in the literature. In this case, an old patient with the previous allergy to other NSAIDs (pyrazolones), the avoidance of antipyretic drugs was not an option because it was necessary for oncological pretreatment with chemotherapy because it is the only NSAID that can be administrated IV. This limited their therapeutic alternatives, so we considered that SBOCT was indispensable. In this case, SBOCT was a trigger for a positive IDT (flare-up phenomenon) and the anaphylactic shock could not be avoided.

Flare-up phenomenon has been described with different drugs such as beta-lactams antibiotics [8]. González de Olano *et al*. [9] reported a case with ibuprofen but as far as we know, no cases have been reported with paracetamol.

CONCLUSION

We emphasized the importance of having better diagnostic tools for SPT or blood tests to determine specific IgE to confirm the diagnosis without performing SBOCT, with the potential risks for patients. At this moment, the challenge test continues to be the gold standard for drug allergy diagnosis.

RECENT PATENTS REVIEW

Anaphylaxis, anaphylactic shock, angioedema and urticaria, are specific type I hypersensitivity drug reactions.

Anaphylactic shock due to sensitization to paracetamol, as well as other immediate clinical patterns like commented before have been reported with this drug in the literature [2-5].

Anaphylaxis is an acute, potentially life-threatening hypersensitivity reaction, involving the release of mediators from mast cells, basophils and recruited inflammatory cells. Many patents have been filled and granted for the treatment of anaphylaxis shock.

Common anaphylaxis triggers include foods - including nuts, milk, fish, shellfish, eggs and some fruits, drugs: including some antibiotics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin, insect stings (particularly wasp and bee stings), general anesthesic, contrast agents - special dyes used in some medical tests to help certain areas of your body show up better on scans- latex - a type of rubber found in some rubber gloves and condoms. Paracetamol has been described as a possible trigger but not very frequently [4].

Paracetamol is therapeutically cataloged as an analgesic and antipyretic, although at high doses can also exert anti-inflammatory action [10].

Paracetamol is N- (4-hydroxyphenyl) ACETA way. It is a widely available analgesic which is marketed under multiple brands in different pharmaceutical presentations [11]. Also, paracetamol is an active drug likely to be combined with other active ingredients for various applications. Also they exist in the market many pharmaceutical preparations in which the paracetamol occurs associated with other drugs.

Accordingly, it is possible to obtain a solution of stable paracetamol by incorporating in the solution antioxidant substances that can react with p-aminophenolates resulting their O-derivatives or coordination compounds, preferably selected from the group consisting of reducing sugars such as glucose, galactose, fructose; acid forms of the sugars or their salts such as lactobionate, gluconate; glucuronate, glucoheptanoate, galactate, lactobionate or lactones such as gluconolactone [12]; chemical species containing sulfur in an oxidation state less than +6, sodium formaldehyde sulfoxylate, sulfites or thiourea and that these substances can produce derivatives with the phenolate form of paracetamol [13].

The patent WO2016069155 provides a method of producing N-acetyl-p-aminophenol *in vitro*, the method comprising culturing a recombinant prokaryotic host cell as described above, or elsewhere herein, *in vitro* in a culture medium and under conditions that provide for expression of the 4ABH and NhoA, wherein the cell produces *p*-aminobenzoic Acid (PABA), wherein 4ABH catalyzes the conversion of PABA to produce p-aminophenol, and wherein the NhoA catalyzes the conversion of p-aminophenol to produce N-acetyl-p-aminophenol. In some cases, the method comprises purifying the N-acetyl-p-aminophenol produced by the host cell. In some cases, the host cell is *Escherichia coli*. In some cases, the host cell is a yeast cell, e.g., *Saccharomyces cerevisiae*. In some cases, the N-acetyl-p-aminophenol is produced in an amount of at least 50mg/l culture medium [14]. Therefore, it is also very large number of pharmaceutical patents around paracetamol [12-16].

CURRENT AND FUTURE DEVELOPMENTS

In the past years the use of NSAIDs is increasing, because of high number of diseases which needs the chronic use of these drugs. From this group, paracetamol are one of the most subgroups of NSAIDs used in these chronic patients in the general population for mild pains. Because of extensive use, probably sensitization is becoming more frequent in patients. Flare up is a phenomen that happens infrequently but helps diagnosis. Usually if patients have immediate or non-immediate allergy to these subgroup, it is recommended to forbid the whole group. But more frequently in the clinical practice it has been observed that patients develop allergy to only one, and tolerate the others from the same group.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval is not applicable, as this is not a clinical trial.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for experimentation in this research. The tests are the daily clinical practice, and they have been approved and published previously, according to Helsinki declaration.

CONSENT FOR PUBLICATION

The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

CONFLICT OF INTEREST

The authors declare that they have followed the protocols of their work center on the publication of patient data and that all patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

All authors mentioned above have been participated in different forms of the total result of this manuscript.

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