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Selective anaphylaxis to paracetamol in a child

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Summary

Paracetamol anaphylaxis is a very rare event, with only a few cases described in literature and even less reported in children. We report the case of a 15-year-old boy, referred to Immunoallergy Department due to four reproducible episodes of anaphylaxis after paracetamol administration, since the age of 8 years. The most severe episode occurred at 12 years, characterized by glottis edema with respiratory distress, hypotension, generalized urticaria and facial edema, immediately after intravenous administration of paracetamol during a post-operatory recovery. He had always and still tolerates ibuprofen; an oral challenge test with meloxicam was negative. Skin prick and intradermal tests with paracetamol were negative. Serum-specific IgE and CAST to paracetamol were also negative. This report provides an alert to health-care professionals regarding the potential severity of reactions occurring within the therapeutic range of this widely used drug.

Introduction

Paracetamol (acetaminophen) is an analgesic and antipyretic drug widely prescribed throughout the world, and is available without prescription in many countries. In Portugal, since 2003, paracetamol has been consecutively, year after year, the most sold drug (1). While overdose paracetamol hepatotoxicity is well known and described, adverse reactions after its administration within its therapeutic range are rarely reported, with anaphylaxis being considered a very uncommon event. Because of its rarity, these hypersensitivity reactions are possibly misdiagnosed.
We report herein a case of reproducible episodes of anaphylaxis due to paracetamol administration in a child, in which the absence of diagnosis resulted in further episodes of increased severity.

Case description

A 15-year-old boy came to Immunoallergy Department due to four reproducible episodes of anaphylaxis after paracetamol administration. He reported a previous history of recurrent wheezing until the age of 4 years and allergic rhinoconjunctivitis since the age of 13 years. He has a family history of atopy: her sister has allergic rhinoconjunctivitis and her mother has cold urticaria. He had previously ingested paracetamol without reaction. His first anaphylactic episode was at the age of 8 years and occurred 10 minutes after oral intake of paracetamol 500 mg; the symptoms included generalized urticaria, wheezing and ocular, lips and ears angioedema. The second episode was similar, at 9 years of age. In both, emergency room assistance was required. The third episode was the most severe

and occurred at the age of 12, characterized by glottis edema with respiratory distress, hypotension with prostration, generalized urticaria and facial edema, immediately after administration of intravenous paracetamol 1g during a post-operatory recovery; he was treated with adrenaline, corticosteroid and anti-histamine with improvement. The last episode occurred when he was 14 year-old, after oral intake of paracetamol 1g for headache, and was similar to the first one. He had always tolerated ibuprofen, since the first years of life, until the present. He has not taken any other nonsteroidal anti-inflammatory drugs (NSAIDs).

The diagnostic work-up study included skin prick test (concentration 10 mg/mL) and intradermal tests (1/1000, 1/100 and 1/10 concentrations) to paracetamol, which were all negative. The child also underwent skin prick tests to common aeroallergens, which were positive to grass pollens. Serum-specific IgE measurement to paracetamol (UniCAP®, Phadia, Uppsala, Sweden) was negative, and so was the cellular allergen stimulation test (CAST®, Bühlmann, Schönenbuch, Switzerland). An oral drug challenge test with meloxicam was performed, to provide him a safe therapeutic option, available if necessary for intravenous administration; a cumulative dose of 15mg was reached and no adverse reactions occurred. The patient was advised to strictly avoid paracetamol and to use, as needed, ibuprofen and meloxicam as NSAIDs.

Discussion

A safety evaluation of non-narcotic analgesics in therapeutic doses ranked paracetamol as among the safest ones (2). This allowed it to become widely used, and a freely available over-the-counter preparation, in many countries.

While overdose paracetamol hepatotoxicity is well known, hypersensitivity reactions to paracetamol, on the contrary, are uncommonly identified in the medical literature (Table 1) (3-26), particularly at pediatric age. Anaphylaxis to this drug is considered a very rare event, with only six cases previously reported in children (4,10,18,21,24).

After administration at therapeutic doses, 70–90% of the drug is conjugated to form glucuronide and sulphate and 5–10% oxidized by P-450 enzymes to form a toxic metabolite that is conjugated with glutathione and excreted. In overdose, the conjugation pathway becomes saturated and glutathione stores are depleted resulting in accumulation of the hepatotoxic metabolite, N-acetyl-p-benzoquinone imine. In contrast, pathogenesis of hypersensitivity and anaphylactic reactions remains uncertain. Paracetamol is a weak inhibitor of cyclo-oxygenase, and so the inhibition of prostaglandins synthesis could be a mechanism to explain also paracetamol hypersensitivity, similar to acetylsalicylic acid (ASA) and NSAIDs hypersensitivity mechanism (27). However, it would result, as proposed by some authors, in aspirin-induced urticaria/anaphylactic reactions representing a relevant risk factor for paracetamol hypersensitivity (22,24,28). Nevertheless, paracetamol is generally safe for use in about 94% of patients intolerant to ASA and other NSAIDs (27,29); also, some patients with anaphylaxis to paracetamol, included the one reported here, tolerate these anti-inflammatory drugs (4,6,8,12,16,21,25). Therefore, in these cases, there is probably another underlying mechanism, not related to cyclo-oxygenase inhibition, which could be immunoglobulin E (IgE) mediated (27, 30).

The absence of serum specific IgE in vitro assays for routine clinical use difficult diagnosis and identification of patients with an IgE-mediated reaction to paracetamol; also, some authors reported negative serum specific IgE in patients with a proved IgE-mediated mechanism (26), which indicates that it has very low sensitivity. In addition, skin tests are of limited value for low molecular weight compounds such as paracetamol, although six cases were reported with positive skin tests (8,13,15,20,26), but none of them at pediatric age. Therefore, diagnosis of paracetamol hypersensitivity relies most of the times in oral challenge or reproducible complains after accidental re-exposure.

In our patient, we failed to prove an IgE mediated mechanism underlying anaphylaxis, since both serum specific IgE and skin tests with paracetamol were negative. Due to the severity of the third episode reported, and keeping in mind the reproducible complains about accidental re-exposure, in this case an oral challenge was not indicated. Even though, the drug challenge would not elucidate the underlying pathophysiological mechanism. Therefore, and regarding the acute onset and the type of clinical manifestations (anaphylaxis) as highly suggestive of an IgE involvement (27, 30), we decided to perform CAST, which was negative. We couldn't, however, affirm that no detection of specific IgE does means that it is a non-IgE mediated mechanism. As stated before, diagnosis is difficult, some of these techniques lack validation and the process of diagnosis has been very heterogeneous, as we can see from Table 1. Still, we should refer that, among the literature reviews regarding paracetamol hypersensitivity, an IgE mediated mechanism was never reported in children.

Several studies suggested that the intensity of reactions to paracetamol could be dose related (5,31), but in this particu-

Table 1 - Reported hypersensitivity adverse reactions to paracetamol [3-26].

Reference	Sex	Age	Dosage	Symptoms / Signs	Skin tests	Oral challenge or accidental re-exposure
Stricker BH et al, 1985 [3]	M	36	500 mg	Bronchospasm, urticaria, hypotension, tachycardia	NS	ND
	M	26	1 g	Collapse, urticaria	NS	ND
	F	54	500 mg	Urticaria, bronchospasm	NS	ND
	F	67	500 mg	Urticaria, Quincke's oedema	NS	ND
	F	43	500 mg	Severe bronchospasm	NS	ND
Ellis M et al, 1989 [4]	F	C	32 mg	Pruritic throat, nasal congestion, cough, wheezing	ND	Positive
	M	C	32 mg	Nasal congestion, pruritus, cough, wheezing	ND	Positive
Van Diem L et al, 1990 [5]	F	46	500 mg	Rash, vomiting, diarrhea, respiratory distress	ND	Positive
Leung R et al, 1992 [6]	NS	NS	500 mg/1 g	Pruritus, urticaria / Angioedema, bronchospasm	ND	Positive
	NS	NS	500 mg	Urticaria, angioedema	ND	ND
	NS	NS	500 mg/1 g	Urticaria, angioedema / Angioedema, hypotension	ND	ND
	NS	NS	500 mg	Erythema, bronchospasm	ND	Positive
	NS	NS	500 mg	Urticaria, hypotension	ND	ND
Doan T et al, 1993 [7]	F	47	1 g	Syncope, hypotension, flushing, dyspnea	ND	Positive
Martín JA et al, 1993 [8]	F	A	75 mg	Generalized urticaria, angioedema	Positive	Positive
Brown G, 1996 [9]	M	21	NS	Hypotension	ND	ND
	F	53	NS	Hypotension, respiratory failure	ND	ND
Schwarz N et al, 1996 [10]	F	13	650 mg	Angioedema, respiratory distress	ND	Positive
Morais-Almeida M et al, 1997 [11]	M	7	500 mg	Generalized urticaria, angioedema of face, hands and feet	ND	Positive
Vidal C et al, 1997 [12]	F	40	500 mg	Palmar pruritus, generalized urticaria, dyspnea, chest tightness, loss of consciousness	NS	Positive
Sabbah A et al, 1997 [13]	F	39	1000 mg	Urticaria	Positive	Positive
	M	A	NS	Urticaria	ND	Positive
	M	60	500 mg	Generalized urticaria	Negative	ND
Ownby DR, 1997 [14]	F	8	160 mg	Generalized itching, urticaria	ND	Positive
Galindo PA et al, 1998 [15]	F	20	500 mg	Generalized urticaria, respiratory distress, wheezing	Positive	ND
Mendizabal SL et al, 1998 [16]	F	27	NS	Facial angioedema, tongue edema, dyspnea	Negative	ND
	F	48	650 mg	Itching erythematous plaque on right mammary areola	NS	Positive
	F	48	650 mg	Generalized urticaria	NS	Positive
	F	27	650 mg	Generalized urticaria	NS	Positive
	F	24	NS	Generalized urticaria	Negative	Positive
Spitz E, 1999 [17]	M	29	250 mg	Urticaria, hypotension	NS	Positive
Kumar RK et al, 1999 [18]	F	15	NS	Urticaria, tachycardia, severe hypotension, hypokalemia	ND	Positive
Ayonrinde OT et al, 2000 [19]	F	65	1 g	Respiratory distress, hypotension	ND	ND
Paramo B et al, 2000 [20]	F	21	650 mg	Generalized urticaria, angioedema	Positive	Positive
	F	24	650 mg	Angioedema, hypotension	Positive	Positive
	F	54	650 mg	Generalized urticaria, angioedema	Negative	Positive
	F	65	650 mg	Facial urticaria	Negative	Positive
Liao CM et al, 2002 [21]	F	9	120 mg	Generalized urticaria, hypotension	Negative	Positive
Bachmeyer C et al, 2002 [22]	F	28	NS	Generalized urticaria, chest tightness, loss of consciousness, hypotension	Negative	Positive
Gowrinath K et al, 2004 [23]	F	58	500 mg	Rash, angioedema, respiratory distress, hypotension	ND	ND
Boussetta K et al, 2005 [24]	NS	C	NS	Facial angioedema, conjunctivitis, dyspnea with wheezing	ND	Positive
Ho MH et al, 2008 [25]	M	17	500 mg	Rash, hypotension	ND	Positive
Spínola Santos A et al, 2010 [26]	F	30	250 mg/1 g	Generalized urticaria	Positive	ND
Case report	M	15	500 mg/1 g	Generalized urticaria, angioedema, wheezing / Glottis edema, respiratory distress, hypotension, generalized urticaria, facial angioedema	Negative	Positive

A: adult (the real age is not stated); C: children (the real age is not stated); ND: not done; NS: not stated in the article

lar case it also seems to be dependent on the route of the administration; the most severe reaction occurred after intravenous administration, while the same dosage later taken by oral administration did not provoke such a severe reaction.
Paracetamol hypersensitivity is rare, and this report provides an alert to health-care professionals regarding the potential severity of reactions occurring within the therapeutic range of this widely used drug. After reproducible complains, the lack of diagnosis in this boy leaded to a severe anaphylactic episode after intravenous administration of paracetamol. All cases should be reported to National Drug Surveillance Authorities and publication of these case reports is required in order to better evaluate the incidence of these reactions.

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