

Original article

Hypersensitivity reactions to paracetamol in children: a study of 25 cases

Background: Allergic-like reactions to paracetamol (acetaminophen) are rare. Paracetamol allergic and nonallergic hypersensitivity (HS) has been diagnosed in a few patients with skin and/or respiratory symptoms, immediate and accelerated urticaria, and angioedema especially. Most patients with HS to paracetamol were also hypersensitive to anti-inflammatory drugs (i.e. acetylsalicylic acid, ASA), suggesting that their reactions resulted from a nonallergic HS. However, anaphylactic reactions, and potentially harmful toxidermias, such as acute generalized exanthematic pustulosis and toxic epidermal necrolysis, have been related to specific paracetamol allergic HS, with tolerance to anti-inflammatory drugs.

Patients and methods: We report the results of a study performed in 25 children with suspected paracetamol HS. Diagnosis of paracetamol HS was based on a suggestive clinical history and a positive response in an oral challenge (OC) test.

Results: Paracetamol HS was diagnosed in only one child (4%). In this child, a positive response to an OC with ASA diagnosed HS to anti-inflammatory drugs.

Conclusions: Our results in children agree with those of the literature, showing that paracetamol HS is rare, and is associated with HS to anti-inflammatory drugs in most patients.

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Key words: acetaminophen; child; drug hypersensitivity; nonsteroidal anti-inflammatory drugs; paracetamol.

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Accepted for publication 15 February 2005

Hypersensitivity (HS) reactions to drugs are thought to be involved in 6–10% of all types of adverse drug reactions (1). They may result from specific interactions between the drugs and antibodies or lymphocytes (allergic HS) or from nonspecific (i.e. pharmacologic) mechanisms (nonallergic HS) (2).

Although paracetamol (acetaminophen) is widely used, HS-like reactions to this drug are rare, especially in children (3, 4). However, immediate and accelerated urticaria and/or angioedema, dyspnea and rhinitis (3–8), and rare allergic and nonallergic anaphylactic reactions (3, 9–12), have been reported in children and adults. Most reactions to paracetamol occur in patients with a nonallergic HS to nonsteroidal anti-inflammatory drugs (NSAIDs) (13, 14). However, in a few patients, reactions result from an allergic HS, with tolerance to acetylsalicylic acid (ASA) and other NSAIDs (5, 15–17).

We report the results of a study performed in 25 children with suspected paracetamol HS.

Patients and methods

Patients

We studied 25 children (14 male + 11 female), mean age 6 years, 4 months (range: 8 months–15 years), reporting 26 reactions attributed to paracetamol. In 12 children, paracetamol was associated with other drugs or biologic agents such as ASA ($n = 4$), josamycin ($n = 1$), amoxycillin combined with clavulanic acid ($n = 1$), DTP Pol.HI vaccine ($n = 1$), and miscellaneous drugs ($n = 3$).

Clinical characteristics of the reactions are indicated in Table 1. Most reactions reported were urticaria and/or angioedema ($n = 20$, 80%). The reactions were immediate (≤ 2 h after the beginning of treatment) or accelerated (2–48 h) in 18 children (72%). Personal or familial history of atopy was reported in 36% and 48% of the children respectively.

Three children also reported reactions to ASA ($n = 1$), ibuprofen ($n = 1$), or both drugs ($n = 1$).

Methods

Diagnosis of paracetamol HS was based on the clinical history or an oral challenge (OC) test. The OC with ASA was performed in

Table 1. Clinical characteristics of 25 children with suspected paracetamol hypersensitivity

Reaction (chronology and type)	Immediate (≤ 2 h)	Accelerated (≤ 48 h)	Delayed (> 48 h)	Unknown	Total
Urticaria and/or AO	4	10	1	5	20
MPR	1				1
Unknown	1	1		1	3
Conjunctivitis and dyspnea		1			1
FHM disease				1	1
Total	6	12	1	7	26

AO, angioedema; MPR, maculopapular rash; FHM, foot, hand and mouth.

children with a history highly suggestive of paracetamol HS or in children with positive OC to paracetamol, except for children with a history suggestive of ASA HS. The OC tests were performed in the hospital, under strict supervision. Children received a first dose of 1 mg of the drug. The dose was increased gradually, with a 20 min interval between each dose, until the appropriate cumulative dose per day for age and weight was reached.

Results

Paracetamol HS was diagnosed in only one child, based on a highly suggestive clinical history. This child reported two accelerated reactions (facial angioedema, conjunctivitis, and dyspnea with wheezing), a few months apart, 8–10 h after an isolated intake of paracetamol. In this child, OC with ASA-induced accelerated urticaria and angioedema.

The OC with paracetamol were tolerated in the 24 other children, including the three children reporting reactions to NSAIDs. Those children were diagnosed hypersensitive to NSAIDs based on a suggestive clinical history (recurrent immediate or accelerated urticarias and angioedemas, $n = 2$) or on a positive response in OC ($n = 1$).

Discussion

A few studies have been performed in patients with suspected HS to paracetamol. In our study, paracetamol HS was diagnosed in only one child. Our results confirm that HS reactions to paracetamol are rare (3, 4).

Reactions to paracetamol are dominated by cutaneous symptoms, urticaria and/or angioedema especially (3, 5, 7, 15). Systemic reactions, with cutaneous, nasal, and bronchial symptoms (8, 18), and a few cases of allergic and nonallergic anaphylactic reactions (3, 9–12), have also been reported. In our study, all the children reported cutaneous symptoms (urticaria and/or angioedema especially), except for one child with recurrent angioedema, conjunctivitis and wheezing dyspnea. None of the children reported a generalized reaction with cardiovascular involvement.

Only a few patients with suspected HS reactions to paracetamol report a highly suggestive clinical history. In

the study by Kvedariene et al. (3), paracetamol HS was diagnosed in 13 (15.5%) of 84 children and adult patients. Diagnosis was based on a convincing clinical history (severe anaphylaxis) in only two patients. In our study, only one child reported recurrent accelerated reactions associated with an isolated intake of paracetamol.

Diagnostic workup of paracetamol HS may include skin tests and *in vitro* tests. Diagnostic and predictive values of immediate-reading skin tests (pricks and intradermal) and *in vitro* tests [serum-specific immunoglobulin E (IgE) determination, histamine and cysteinyl-leukotriene release tests (CAST), flow cytometry] with paracetamol are controversial (4, 6, 10, 15, 19, 20). Immediate responses in skin tests have been reported in a few patients (11, 21). However, immediate responses in skin tests were negative in most patients with immediate reactions to paracetamol (4, 6, 10, 16). Thus, the diagnosis of paracetamol and/or NSAID HS relies mainly on OC tests (3, 22).

Reactions associated with paracetamol intake may result from allergic or nonallergic HS to other drugs, such as antimicrobials and NSAIDs, or from the infectious disease for which the drugs have been prescribed. In four children in our study, the reaction occurred during treatment with paracetamol and NSAIDs. Based on OC, all these children were diagnosed as having no paracetamol HS. However, ASA HS was diagnosed in three of them on the basis of a suggestive clinical history ($n = 2$) or of a positive response in OC ($n = 1$).

Most reactions to paracetamol occur in patients with a nonallergic HS to NSAIDs. Asero studied 261 patients reporting urticarial reactions to NSAIDs, of which 36% were diagnosed hypersensitive to one or several NSAIDs and/or paracetamol (13). Nettis et al. (14) diagnosed paracetamol HS in 9.6% of the patients with a well-documented HS to NSAIDs. Risk of paracetamol HS was increased in atopic patients, in patients with allergic-like reactions to antimicrobial drugs, and in patients with immediate and/or anaphylactic reactions to paracetamol (14, 23, 24). In our study, only one child was diagnosed hypersensitive to paracetamol. In this child, OC diagnosed also ASA HS. This child had a personal history of atopy (atopic dermatitis with cow's milk allergy).

However, selective reactions to paracetamol, with tolerance of NSAIDs, such as ASA (6, 11, 13, 15) or ibuprofen (16, 17), have been reported in a few patients. Several pathophysiologic mechanisms may be involved:

- 1 Pharmacologic mechanisms, distinct from those involved in nonallergic HS to NSAIDs. Paracetamol has a low inhibitory activity on cyclo-oxygenase (Cox)-1, < 5% of the NSAID-hypersensitive patients react with paracetamol, and a few patients with paracetamol HS are tolerant to ASA and other NSAIDs (6, 13, 15–17, 20). Paracetamol may preferentially inhibit Cox-3, an other isoenzyme of Cox (25–27).

- 2 An allergic HS to paracetamol, suggested by studies showing immediate responses in skin tests with this drug (11, 21), and detectable serum-specific IgE (11) in patients with paracetamol-induced urticaria, angioedema, and anaphylaxis. Moreover, nonimmediate HS reactions with positive responses in patch-tests with paracetamol have been reported in a few patients (5).

Conclusion

The results of our study in 25 children with suspected paracetamol HS confirm that paracetamol HS is a rare condition. In most patients, paracetamol HS is associated with a nonspecific HS to ASA and other NSAIDs.

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Diagnosis of paracetamol HS is based on clinical history of the patients. When the clinical history is not suggestive, diagnosis is based on OC tests. At present, immediate reading skin tests and *in vitro* tests for immediate HS (specific IgE determination, cellular activation tests) are not commonly available and are not validated.

Finally, in asthmatic patients, paracetamol is the drug of choice (25), although cross-reactivity with NSAIDs exists, and although frequent exposure to paracetamol may increase the risk of wheezing or asthma (28–30).

Acknowledgment

The authors wish to thank Ms Claire Feeney for editorial assistance.

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