

## The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial

V. Kvedariene\*, A. M. Bencherioua†, D. Messaad†, P. Godard†, J. Bousquet† and P. Demoly†

\*Vilnius University Hospital 'Santariskiu klinikos', Vilnius, Lithuania and †Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier, France

### Summary

**Background** Hypersensitivity to paracetamol (acetaminophen) is rare and very few clinical data are available in the literature.

**Materials and methods** Eighty-four patients (28 males and 56 females, 5–70 years old) with a suspicion of paracetamol hypersensitivity were referred to our drug allergy clinic between May 1996 and May 2000. The reaction had occurred 1–96 months prior to the consultation. Single-blinded placebo-controlled oral challenges were carried out in 82 patients, under strict hospital surveillance.

**Results** Most of the patients experienced skin eruptions 82/84 (97.6%), with 10 cases of anaphylactic shock (11.9%). Twenty-six (30.9%) reactions were immediate (occurring within the first hour after drug intake), 53 (63.1%) non-immediate and five could not remember. Oral provocation tests (OPT) demonstrated drug hypersensitivity in 11 patients only. The two patients not tested (due to a history of life-threatening reaction) were included in the positive group. Thus, 13 (15.5%) patients had paracetamol hypersensitivity and 71 (84.5%) had not. All the 13 positive patients had skin eruptions, five with anaphylactic shock. 9/13 had immediate reactions. Using OPT, 10 out of 11 had the same clinical reaction but more delayed. In both groups, whether hypersensitive to paracetamol or not: atopy was similar (7/13–53.8% and 31/71–43.7%), sex ratio was not different (M/F 0.3 and 0.5), 3/13 (23.1%) and 0/71 (0%) had aspirin/ibuprofen hypersensitivity.

**Conclusion** The clinical history of paracetamol (acetaminophen) hypersensitivity is rarely sufficient to set a firm diagnosis and only OPT can confirm this. Careful OPT reproduces the same symptoms (not more severe in our hands) with the same or slightly more delayed chronology. Atopy and sex are not risk factors.

**Keywords** drug hypersensitivity, acetaminophen, paracetamol

Submitted 18 October 2001; revised 4 March 2002; accepted 15 May 2002

### Introduction

Paracetamol (acetaminophen) is a world-wide-used analgesic and anti-pyretic drug with no anti-inflammatory effect. It is a frequent substitute for aspirin in patients with aspirin hypersensitivity. Hypersensitivity to paracetamol is rare and limited clinical data are available in the literature [1–7]. Isolated cutaneous reactions such as urticaria/angioedema and maculopapular eruption, bronchospasms or anaphylaxis have been described, as well as systemic reactions (anaphylaxis, vasculitis, hepatitis with glomerulonephritis, rhabdomyolysis, and possibly hypersensitivity syndrome, toxic epidermal necrolysis and Stevens Johnson syndrome). In the reported cases of systemic reactions, the patients were taking several medications at the same time. Polymedication is frequent (in particular during the treatment of a respiratory tract infection for example) and, when a clinical reaction apparently allergic in nature occurs, it

is often hard if not impossible to detect the culprit drug by clinical history. A thorough drug allergy work up is therefore needed but there is no large series in the literature to help in this regard. We are reporting our diagnostic strategy in 84 consecutive patients who were referred to our drug allergy clinic with a suspicion of paracetamol hypersensitivity.

### Materials and methods

Eighty-four patients with a suspicion of paracetamol hypersensitivity were referred to our allergy clinic during a 4-year period (from May 1996 to May 2000). There were 28 males and 56 females, 5–70 years old (Table 1). The time elapsed before the reaction and the allergy work up ranged from 1 to 96 months. Reasons for paracetamol intake were mostly ENT infections and fevers (Table 1). Considering that no other reliable tests exist for the clarification of the event and that the drug is of potential necessity for the patient in the future, drug provocation tests do not require the authorization of an ethical committee, but of course requires the patients informed consent.

Correspondence: Pascal Demoly, MD, PhD, Maladies Respiratoires, INSERM U454, Hôpital Arnaud de Villeneuve, CHU de Montpellier, 34295 Montpellier Cedex, France. E-mail: demoly@montp.inserm.fr

**Table 1.** Clinical characteristics of the patients (+) and controls (-)

|                                                          | Paracetamol (+)   | Paracetamol (-)   | Total             |
|----------------------------------------------------------|-------------------|-------------------|-------------------|
| Number                                                   | 13                | 71                | 84                |
| Sex M/F                                                  | 3/10              | 25/46             | 28/56             |
| Age <sup>1</sup><br>(years)                              | 39<br>(30.7–47.5) | 34<br>(18.0–49.0) | 34<br>(18.0–48.7) |
| Reasons for prescription                                 |                   |                   |                   |
| ENT infection                                            | 1                 | 20                | 21                |
| Fever                                                    | 2                 | 7                 | 9                 |
| Headache                                                 | 4                 | 7                 | 11                |
| Other pains                                              | 2                 | 15                | 17                |
| Unknown                                                  | 4                 | 22                | 26                |
| Time elapsed since<br>the reaction <sup>1</sup> (months) | 8<br>(3–30)       | 8<br>(3–39)       | 8<br>(3–36)       |
| Chronology of the reaction <sup>2</sup>                  |                   |                   |                   |
| Immediate                                                | 9                 | 17                | 26                |
| Non-immediate                                            | 4                 | 49                | 53                |
| Unknown                                                  | 0                 | 5                 | 5                 |
| Clinical symptoms                                        |                   |                   |                   |
| Anaphylactic shock                                       | 5                 | 5                 | 10                |
| Skin eruptions <sup>3</sup>                              | 13                | 69                | 82                |
| MPE <sup>4</sup>                                         | 3                 | 19                | 22                |
| Urticaria (only)                                         | 9                 | 20                | 29                |
| Angioed/urticaria                                        | 3                 | 3                 | 6                 |
| Laryngeal oedema                                         | 1                 | 30                | 31                |
| ENT/pulmonary <sup>5</sup>                               | 4                 | 5                 | 9                 |
| Others                                                   | 0                 | 11                | 11                |
| Atopy/allergy                                            |                   |                   |                   |
| Positive skin tests                                      | 7 (53.8%)         | 31 (43.7%)        | 38 (45.2%)        |
| Asymptomatic                                             | 2                 | 20                | 22                |
| Allergic asthma                                          | 1                 | 6                 | 7                 |
| Allergic rhinitis                                        | 1                 | 7                 | 8                 |
| Food allergy                                             | 4                 | 4                 | 8                 |
| Insect sting allergy                                     | 1                 | 0                 | 1                 |

<sup>1</sup>: median (25–75 percentiles); <sup>2</sup>: immediate = occurring within the first hour after drug intake; <sup>3</sup>: skin eruptions of any type, generalized in most cases; <sup>4</sup>: MPE: maculo-papular eruptions; <sup>5</sup>: rhinitis and/or bronchospasms, all during an anaphylactic shock.

Therefore, single-blinded placebo-controlled oral provocation tests (OPT) were carried out in 82 thoroughly informed patients, under strict hospital surveillance (starting with 1 mg and ending with 1000 mg, with 30 minute time increments). None of the patients were on  $\beta$ -blocker, immunosuppressant medication or anti-allergic drugs at the time of the challenge. If no reaction occurred after reaching the cumulative dose of 1910 mg (within 3 h), the patient stayed in the allergy department for two more hours (giving a total OPT duration of 5 h). If a reaction occurred, 40–60 mg of prednisolone and 10 mg of cetirizine or 120 mg of fexofenadine were given orally and the patient left the department after complete clearing of the reaction. Anaphylaxis was treated by subcutaneous epinephrine. Non-reactors were informed of a possible delayed reaction and were asked to come back should this occur.

## Results

### Clinical history

Most of the patients experienced skin eruptions 82/84 (97.6%), with 10 cases of anaphylactic shock (11.9%). Twenty-six

(30.9%) reactions were immediate (occurring within the first hour after drug intake), 53 (63.1%) non-immediate and five could not remember (Table 1). Thirty-eight patients were atopic (e.g. had positive skin prick tests to aeroallergens), two patients were allergic to another drug ( $\beta$ -lactams and quinolones) and three patients had aspirin/ibuprofen hypersensitivity.

### Oral provocation test

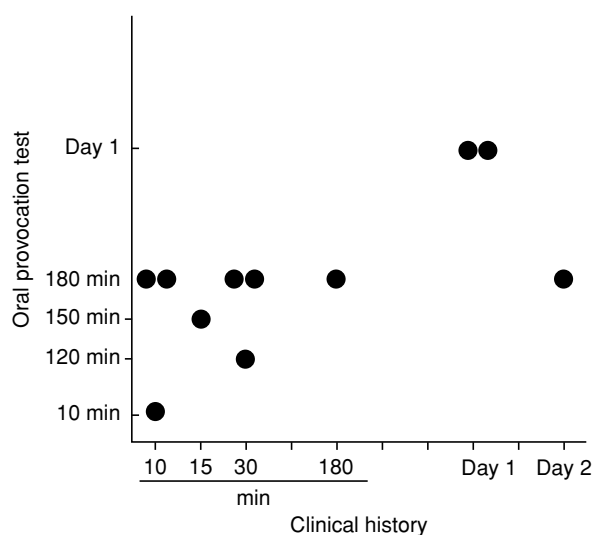
OPT enabled us to differentiate true hypersensitivity to paracetamol. Only 11 OPT were positive. The two patients not tested (due to a history of life-threatening reaction to paracetamol) were included in the positive group. Thus, 13 (15.5%) patients had a diagnosis of paracetamol hypersensitivity and 71 (84.5%) had not. All of the subjects with hypersensitivity to paracetamol had skin eruptions, five with anaphylactic shock. Out of the total positive patients 9/13 had immediate reactions (Table 2).

Using OPT, 10 out of 11 patients had the same, but milder, symptoms and of a shorter duration (because of a quick corrective treatment – data not shown). The chronology was slightly more delayed in 7/11 patients, identical in 3/11 and shorter in 1/11 (Fig. 1). During OPT, only one reaction was immediate (e.g. within the first hour after drug intake), although

**Table 2.** Clinical manifestations and OPT results of the 13 patients allergic to paracetamol

| Age<br>(years) | Sex | Clinical history |                   |                            |                         |               | Time<br>delay <sup>4</sup><br>(months) | OPT<br>mg <sup>5</sup> | Symptoms                                     |
|----------------|-----|------------------|-------------------|----------------------------|-------------------------|---------------|----------------------------------------|------------------------|----------------------------------------------|
|                |     | Symptoms         |                   |                            | Chronology <sup>3</sup> |               |                                        |                        |                                              |
|                |     | Shock            | Skin <sup>1</sup> | ENT/<br>pulm. <sup>2</sup> | Immediate               | Non-immediate |                                        |                        |                                              |
| 43             | F   | –                | MPE               | –                          | +                       | –             | 11                                     | 910                    | MPE                                          |
| 39             | F   | +                | Urt               | +                          | +                       | –             | 4                                      | 410                    | Dyspnea, rhinitis,<br>palmo-plantar pruritus |
| 47             | F   | +                | Urt               | +                          | +                       | –             | 2                                      | 160                    | Urt                                          |
| 20             | M   | –                | Urt               | –                          | +                       | –             | 12                                     | 1910                   | Urt                                          |
| 12             | F   | +                | Urt               | –                          | +                       | –             | 48                                     | ND                     |                                              |
| 40             | F   | –                | Urt               | –                          | –                       | +             | 96                                     | 910                    | Urt                                          |
| 58             | F   | –                | MPE               | –                          | +                       | –             | 4                                      | ND                     |                                              |
| 49             | M   | +                | Urt               | +                          | +                       | –             | 5                                      | 410                    | Anaphylactic shock, Urt                      |
| 33             | F   | –                | MPE               | –                          | –                       | +             | Unknown                                | 1910                   | MPE                                          |
| 33             | F   | –                | Urt               | +                          | –                       | +             | 11                                     | 1910                   | Urt                                          |
| 52             | M   | –                | Urt               | –                          | –                       | +             | 48                                     | 910                    | Urt                                          |
| 24             | F   | –                | Urt               | –                          | +                       | –             | 1                                      | 910                    | Urt                                          |
| 33             | F   | +                | Urt               | +                          | +                       | –             | 2                                      | 910                    | Urt, dyspnea                                 |

<sup>1</sup>: MPE: maculopapular eruption, Urt: urticaria; <sup>2</sup>: bronchospasm, rhinitis, laryngeal oedema; <sup>3</sup>: time elapsed from last drug intake to first symptoms (immediate = less than 1 h, non-immediate = more than 1 h); <sup>4</sup>: Time delay from clinical history to oral provocation test (OPT); <sup>5</sup>: cumulative dose of paracetamol reached before onset of symptoms; ND: not done.

**Fig. 1.** Onset of the symptoms of paracetamol hypersensitivity: comparison between clinical history and oral provocation test.

seven patients experienced an immediate reaction on clinical history (Fig. 1). The severity of the reaction during OPT did not depend on the time that elapsed between clinical history and OPT. Patients who experienced immediate reactions in anamnesis reacted to smaller doses during OPT as compared to patients with a non-immediate reaction (medium dose of 370 mg vs. 1410 mg). The 4/5 patients who experienced anaphylactic shock with skin symptoms and laryngeal edema in anamnesis and who had OPT reacted to smaller doses of paracetamol (mean 472 mg) than those of the other patients (mean 1338 mg). The reactions which occurred after the patients had left the allergy department (3/11) were all mild in intensity and quickly controlled by oral antihistamines. The drug allergy work up for

the paracetamol tolerant patients went on with the other drugs taken together with the paracetamol during clinical history (data not shown).

In both groups, whether allergic to paracetamol or not: (i) the frequency of atopy was similar (7/13 (53.8%) and 31/71 (43.7%)), (ii) the sex ratio was not different (M/F 0.3 and 0.5), (iii) 0/13 (0%) and 2/71 (2.8%), respectively, were allergic to more than one drug ( $\beta$ -lactams and quinolones,  $P > 0.05$ ), and (iv) 3/13 (23.1%) and 0/71 (0%) had aspirin/ibuprofen hypersensitivity ( $P = 0.003$ ).

## Discussion

The clinical history of hypersensitivity to paracetamol (acetaminophen) is rarely sufficient to set a firm diagnosis; therefore only OPT can confirm this. Careful OPT reproduces the same symptoms (never more severe) with identical or slightly delayed chronology in all but one of the cases. Progression of the OPT and strict surveillance is, however, crucial since one patient experienced an anaphylactic shock as severe as that of the clinical history. For the other patients, especially the one who suffered from anaphylactic shock or laryngeal edema, rapid treatment (as soon as prodromic symptoms appear) should avoid the repetition of the whole clinical picture. These patients were polymedicamented during clinical history and only OPT could detect the culprit drug. Any drug provocation test should be performed placebo-controlled, single-blinded, and, in certain situations, even double-blinded. This is especially important if subjective symptoms were the predominant symptoms.

In this paper, we have not referred to the mechanisms of paracetamol hypersensitivity. It has rarely been studied whether specific IgE or T cells are involved. Vidal et al. [2] is one rare example of the search for specific IgE to paracetamol (technique

not detailed in the paper) in a patient who experienced an anaphylactic shock 60 min after drug intake. Results were negative. de Paramo et al. [7] found positive skin prick tests with paracetamol and specific IgE to paracetamol (radioimmunoassay using commercial acetaminophen conjugated with serum human albumin and coupled to cyanogen-bromide-activated filter paper disks) in the serum from two out of four patients. We looked for specific IgE (radioimmunoassay using commercial acetaminophen coupled to sepharose) in six of our patients with immediate reactions and positive OPT; they were all negative (data not shown). Intradermal tests have also rarely been performed. They were negative, for example, in one patient with urticaria 90 min after a paracetamol intake [1]. They were negative (at 10 mg/mL) in two of our patients with immediate hypersensitivity (data not shown). Ibanez et al. [4] performed patch tests in their three patients experiencing maculopapular eruptions a few hours after drug intake. They were all positive. In few cases, cross-reactions between aspirin, other non-steroidal anti-inflammatory drugs and paracetamol exist and are explained by cyclooxygenase enzyme inhibition [8]. Three of our patients could well be included in this pathomechanism. This is a true risk factor, and in patients with proven hypersensitivity to paracetamol, one should look for aspirin hypersensitivity. The other classical risk factors frequently analysed for drug hypersensitivity such as atopy and sex are not risk factors for paracetamol hypersensitivity in our study.

A thorough diagnostic procedure in drug hypersensitivity, including careful provocation tests, is very rarely performed. In the case of suspicion of paracetamol hypersensitivity, it allows to set up a firm diagnosis since very few patients (15.5% in our study) are truly allergic. For clinicians who have no access to OPT, because skin tests [1, 4, 7] and available biological tests (including specific IgE [2, 7], histamine and leukotriene release [9, 10] and lymphocyte transformation test [11]) are rarely helpful for the diagnosis of paracetamol allergy, the delivery of a list of drugs to avoid and of possible other analgesic and anti-pyretic alternatives should be prepared, keeping

in mind that the patient may also be hypersensitive to non-steroidal anti-inflammatory drugs.

## References

- 1 Ownby DR. Acetaminophen-induced urticaria and tolerance of ibuprofen in an eight-year-old child. *J Allergy Clin Immunol* 1997; 99:151–2.
- 2 Vidal C, Pérez Carral C, Gonzalez Quintela A. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 1997; 79:320–1.
- 3 Leung R, Plomley R, Czarny D. Paracetamol anaphylaxis. *Clin Exp Allergy* 1992; 22:831–3.
- 4 Ibanez MD, Alonso E, Munoz MC, Martinez E, Laso MT. Delayed hypersensitivity reaction to paracetamol (acetaminophen). *Allergy* 1996; 51:121–3.
- 5 Moneret-Vautrin DA, Morisset M, Humbert JC, Beaudouin E, Tupin N, Plantier L. Acetaminophen-induced rhabdomyolysis. *Allergy* 1999; 54:1115–6.
- 6 Grunwald MH, Stricker O, Haelvy S, Alkan M, Levy R. Impaired neutrophil functions in patients with leukocytoclastic vasculitis. *Int J Dermatol* 1997; 36:509–13.
- 7 de Paramo BJ, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosmes EL. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 2000; 85:508–11.
- 8 Settiple RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995; 96:480–5.
- 9 Demoly P, Lebel B, Messaad D et al. Predictive capacity of histamine release for the diagnosis of drug allergy. *Allergy* 1999; 54:500–6.
- 10 Lebel B, Messaad D, Rongier M, Kvedariene V, Bousquet J, Demoly P. Cysteinyl-leukotriene release test (CAST) in the diagnosis of immediate drug reactions. *Allergy* 2001; 56:688–92.
- 11 Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy* 1997; 27:175–81.