

Risk factors for positive paracetamol drug provocation testing and procedure optimization

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Clinical Implications

- In paracetamol drug hypersensitivity, atopy and a history of an immediate reaction were risk factors for a positive drug provocation test result. We propose a simplified data-driven (10%, only in anaphylaxis as index reaction-20%-30%-50% step) protocol with 1-hour intervals, followed by a 1-hour 30-minute observation period.

TO THE EDITOR:

Paracetamol (acetaminophen) drug hypersensitivity reactions (DHRs) are addressed either in studies tackling nonsteroidal anti-inflammatory drugs (NSAIDs) or more rarely, in targeted paracetamol-only articles.^{1,2}

In this study, we describe our experience with paracetamol DHR and drug provocation test (DPT), using a similar methodology as our group has recently used for beta-lactam DPT.³ We used logistic regression to search for risk factors of positive DPT result or anaphylactic events during DPT. We performed survival analysis to detect reactive doses (RDs, expressed as a ratio between the cumulative reactive dose and the total DPT dose for a given patient; ie, the dose reached if DPT was to be completed) and reactive times (R_{time} , the time between the last dose and reaction onset). RD was expressed as a percentage and R_{time} in minutes. The studied event was *occurrence of a reaction during DPT*. Paracetamol DPT performed in our unit was conducted according to an open empirical protocol,⁴ with the following 30-minute incremental doses: (0.1-1 mg in case of an anaphylactic index reaction) 10-50-100-250-500-1000 mg, accounting for 0.5%-3%-8%-20%-47%-100% of a cumulative dose of 1990 mg for an adult with no need of dose adjustment. The same protocol was used for immediate and mild-to-moderate nonimmediate reactions, and general DPT contraindications⁵ were taken into account. For children, the last dose was calculated according to their weight, to reach a total dose corresponding to their personalized daily therapeutic dose (ie, 60 mg/kg/24 h). A compulsory surveillance period of 1 hour 30 minutes followed the last administered dose. The patients (or their parents, in case of children) gave their written informed consent to take part in this study for which approval from the local ethical committee was granted (RECHMPL 18_0434).

Between May 1996 and July 2018, 498 patients with alleged paracetamol DHR were tested by DPT in our unit (of whom 48 tested between 1996 and 2000 and already reported⁶). The patient characteristics are presented in Table I. The clinical manifestations of the index reaction ranged from mostly cutaneous (urticaria and/or

angioedema in 50.7% and maculopapular exanthema in 23.8%) to anaphylaxis in 1 of 5 patients (21.6%, of whom 66 without shock and 42 with shock).

In 55 patients (11%), the DPT result was positive, confirming the diagnosis of DHR. Ten patients (18.2%) were also hypersensitive to NSAIDs (of whom 9 and 1 were considered to have NSAID-induced urticaria and/or angioedema and single NSAID-induced anaphylaxis, respectively). Median RD and R_{time} were 47.7% (interquartile range 25-75 [IQR₂₅₋₇₅], 21.4-100) and 30 minutes (IQR₂₅₋₇₅, 15-50), respectively (Figure 1). Eighty percent of positive patients (44 cases) reacted within 1 hour after the last dose, and all patients reacted within 20 hours (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Two-thirds (35 cases, 63.6%) had not completed the DPT when the reaction occurred and among this subgroup, 20% (7 cases) reacted between 30 minutes and a maximum of 50 minutes after the last administered dose. In a quarter of positive cases (14 patients, 25.5%), DPT elicited anaphylactic events. We identified 2 independent risk factors for positive DPT result: being atopic (odds ratio [OR], 1.9; 95% CI, 1-3.4) and having a clinical history of an immediate reaction (OR, 4; 95% CI, 2.2-7.3). A clinical history of anaphylaxis was associated with a 5-fold increased risk of anaphylactic DPT (OR, 5.1; 95% CI, 1.4-18.4).

The Kaplan-Meier curve for RD (Figure 1) identified 4 sharp drops during DPT, and 2 additional steps (corresponding to RD lower than 5%). Of note, there was no anaphylactic event at low doses, the first one occurring at RD = 21.5% (equivalent to 430 mg paracetamol in adult DPT) (Table I; see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

There was no significant difference between median RD and R_{time} for patients with severe (ie, anaphylactic) versus mild to moderate reactions (cutaneous, rhinoconjunctivitis) during DPT (RD, 47.7% vs 47.7%, and R_{time} , 25 vs 30 minutes, respectively).

Of the 55 positive DPT events, 16 (29.1%) were observed in children, including 3 cases of anaphylaxis elicited at RD = 47%, 64.5%, and 100%. Median RD and R_{time} were 64% (IQR₂₅₋₇₅, 28-100) and 30 minutes (IQR₂₅₋₇₅, 21.25-30) in children, and they were not significantly different from those observed in adults.

Clinical observation of our empirical DPT for paracetamol⁴ led us to conceive that a longer time step than 30 minutes would be optimal, especially for higher doses, to avoid charging the patient with allergen in a too short time lapse. The observation was enhanced by the fact that in at least 20% of cases that reacted before the completion of DPT, the reaction occurred longer than 30 minutes after the last dose (Table I; see Figure E1 in the Online Repository). Our initial DPT protocol, with 30-minute steps, did not allow us to analyze whether the percentage of cases with this profile would be higher if a longer interval had been chosen.

Considering the above, (1) we were able to identify 4 RDs and analyze their safety profiles, (2) anaphylaxis during DPT was elicited (only) at doses above RD = 20%, (3) at least 1 in 5 patients needed more than 30 minutes to react, and (4) a clinical history of anaphylaxis is an independent risk factor (5-fold) for anaphylactic DPT, and we propose the following data-driven

TABLE 1. Patient characteristics

Characteristic	Value
Total no. of patients	498
Sex: female	147 (29.5)
Atopy	170 (34.1)
Asthma	73 (14.6)
Clinical history	
U and/or AE	253 (50.7)
Anaphylaxis	108 (21.8)
Without shock	66 (13.4)
With shock	42 (8.4)
MPE	119 (23.8)
SCAR	0 (0)
Other	16 (3.2)
Unknown	2 (0.5)
Chronology of the index reaction	
Immediate (≤ 1 h)	156 (31.3)
Nonimmediate (> 1 h)	303 (60.8)
Undetermined	39 (7.8)
Patients with a positive DPT result	55 (11.0)
Reactive time, range	5 min–20 h
≤ 30 min	34 (61.8)
30–60 min	10 (18.2)
1–6 h	5 (9.1)
> 6 h	6 (10.9)
Semiology of the positive DPT result	
U and/or AE	34 (61.8)
Anaphylaxis	14 (25.5)
Without shock*	11 (20)
With shock	3 (5.5)
MPE	7 (12.7)
Other	0 (0)

AE, Angioedema; MPE, maculopapular exanthema; SCAR, severe cutaneous adverse reaction; U, urticaria.

Values are n (%).

*One case of isolated bronchial hyperreactivity during DPT was also included in this group.

doses for paracetamol DPT: 20%-30%-50% of the envisioned cumulative dose, corresponding to 3 of the 4 RDs identified on the curve (namely, 20%-50%-100%). In case of anaphylaxis during the index reaction, we propose to add an extra dose, starting at 10% (and after having performed skin tests, see below). We propose 1-hour increments between the doses and a 1-hour 30-minute surveillance period after the last ingested dose. A similar analysis of 182 positive DPT results for beta-lactams revealed that severe reactions already occurred at minute doses, with more than three-quarters of the patients with an anaphylactic shock being identified at an RD of 1% or less.³ Here, all 55 positive DPT results were elicited at doses above RD = 20%, which is close to a 500-mg tablet of paracetamol (which is either a full-unit dose or half a unit dose, according to different habits of intake). We could argue that the 10 patients (Figure 1) with urticaria at low doses could have had anaphylaxis if DPT started at RD above 20%. However, there is a clearly different pattern of response in beta-lactam and paracetamol DPT, respectively. For the former, anaphylaxis during the index reaction is usually due to a therapeutic dose, but during DPT this dose could be

10,000-fold lower,³ underlining low-dose reactivity in these patients. Our results showed that in paracetamol DHR, the doses eliciting severe reactions during DPT are similar or 2-fold lower (see above) to the ones ingested during the index anaphylactic reaction. Different mechanisms leading toward a DHR or reactions to metabolites of paracetamol⁷ compared with beta-lactams can be put forward to explain such differences. At therapeutic doses, paracetamol is rapidly absorbed in the gastrointestinal tract, reaching maximum concentrations between 30 and 60 minutes. Its half-life ranges between 1 and 4 hours and more than 90% of the absorbed drug is metabolized, originating several metabolites. One of the metabolites, N-acetyl-P-benzoquinone imine, is particularly reactive and has the ability of binding to proteins⁵ and is currently regarded as a possible candidate to explain paracetamol DHR.

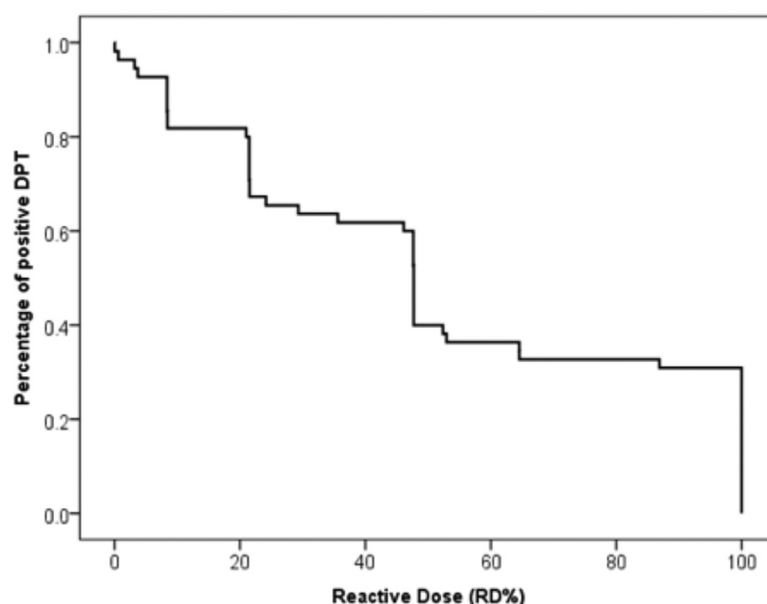
The current protocol results in a cumulative dose in adults of 1990 mg and in children up to 60 mg/kg, delivered over a 2.5- to 3.5-hour time period instead of the typical 12 to 24 hours, respectively. We believe that a lower cumulative dose might have resulted in a lower sensitivity given some patients reacted only after the last dose. However, this relatively high cumulative dose most likely does not result in a decreased specificity. However, in adults with a low body weight and/or patients with underlying liver diseases, adjustment of the envisioned cumulative dose during DPT should be considered to avoid hepatotoxicity.

The time interval of 30 minutes is typically taken in DPT. In reality, some intervals can become longer than 30 minutes due to practical reasons and/or presence of nonobjective symptoms, making the treating physician decide to postpone the following dose. This might have explained the longer interval in 7 of our cases because a preceding itch (n = 3) or sneezing (n = 1) was present within the 30-minute interval in 4 of 7. In published series tackling DPT to paracetamol, time increments are set between 20 minutes and 1 hour, with no additional explanation related to the decision to do either way.

In our experience with DPT, we performed the same dose escalation (30-minute interval between doses) in immediate and mild nonimmediate reactions. For patients with nonimmediate reactions in the index clinical history, longer intervals could be applied but they are barely compatible with 1-day hospitalization. In our study, all 6 patients reacting more than 6 hours after the last dose had had a nonimmediate index reaction. Their DPT reaction was mild cutaneous urticaria/angioedema or maculopapular exanthema. They represent 1.7% of the patients describing a nonimmediate reaction or a reaction of undetermined chronology in this study. Considering all this data, introducing slower dose-escalation in all patients with nonimmediate index reactions does not seem to be either a pragmatic or a safer approach. On the contrary, our data suggest that prolonging the time interval between doses to 1 hour for immediate reactors will minimize the severity of an immediate reaction, at least for a subgroup of patients.

In general, skin testing for paracetamol is not recommended⁸ given its low sensitivity and the fact that most reactions are considered non-IgE-mediated, although limited cases with positive skin test results have been reported.^{8–10} In our cohort, all the patients with an index reaction of anaphylaxis had had negative skin test result before DPT.

It could be argued that the use of open challenges instead of the preferred double-blind placebo-controlled challenges is a drawback of our study. In up to 27% of placebo-challenged



%positive DPT	1.8	7.1	17.9	33.9	60	100
RD (%)	0.05	3.72	8.43	21.52	47.7	100
N, positive DPT (cumul)	1	3 (4)	6 (10)	8 (18)	15 (33)	22 (55)
N, anaphylaxis	0	0	0	3	6 (9)	5 (14)
N, anaphylactic shock	0	0	0	1	2 (3)	0 (3)

FIGURE 1. The Kaplan-Meier curve for RD in patients with a positive DPT result. Below the graph the characteristics at different RDs suggested in our data-driven protocol are outlined, namely, the new and cumulative events provided by each step.

patients a reaction can be observed, although mostly consisting of subjective symptoms of nausea, headache, or itch and only rarely objective symptoms such as urticaria.^{E1} Analogous to the PRACTALL guidelines for food challenges,^{E2} in our study these subjective symptoms were not used as stop signs or interpreted as a positive DPT result.

In our work 89% of patients convinced to have a paracetamol allergy were found not to be paracetamol hypersensitive. Similar results are observed in physician and self-proclaimed drug allergy in which 77%^{E3} to 90%^{E4} of patients tolerate drugs during an allergy workup, indicating an important overreporting of allergy. Currently, valid clinical or *in vitro* biomarkers are missing to efficiently separate these 2 groups and an allergy workup including a DPT remains the criterion standard.

In conclusion, we describe a cohort of patients undergoing provocation testing for paracetamol and observed that a drug hypersensitivity reaction was confirmed in 11% of patients. The RD for anaphylaxis was above 20% in all patients, contrary to observations with beta-lactam allergy. Risk factors for a positive DPT result were atopy and immediate index reaction and on the basis of existing data we propose a simplified (10%, in anaphylaxis as index reaction)-20%-30%-50% step protocol with 1-hour intervals, followed by a 1-hour 30-minute observation period.

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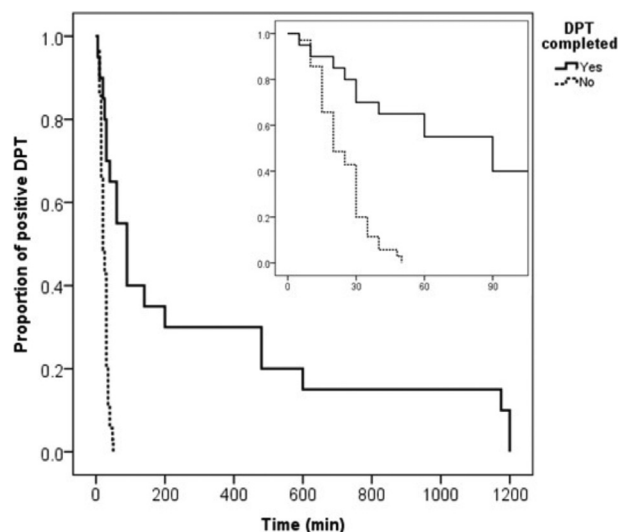


FIGURE E1. The Kaplan-Meier curve for RD in patients with a positive DPT result subdivided into those reacting before completion of the DPT (dotted line) and those after having received all doses (filled line). The inset demonstrates the results from a time range up to 90 minutes. Given the setup of 30-minute incremental steps, most patients reacting during the DPT reacted within 30 minutes, yet 7 patients reacted between 30 and 50 minutes after their last dose. All positive DPT results occurred within 20 hours after the last dose.

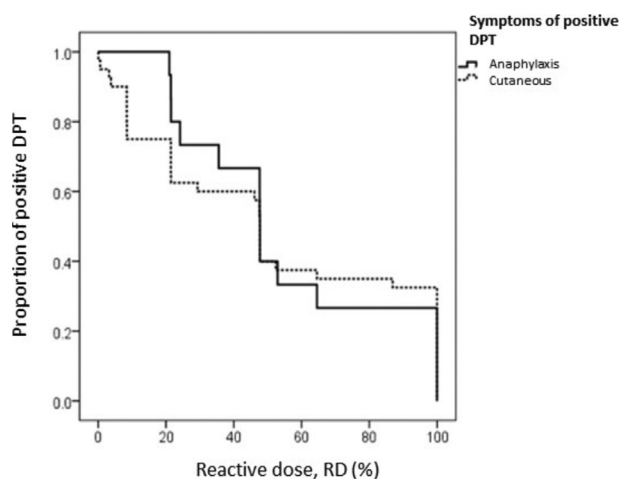


FIGURE E2. The Kaplan-Meier curve for RD in patients with a positive DPT result subdivided into those with isolated mucocutaneous symptoms (urticaria, angioedema, maculopapular exanthema), dotted line, and anaphylaxis, filled line.

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