

# Negative predictive value of provocation tests for nonsteroidal anti-inflammatory drugs in children

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## ABSTRACT

**Background:** After antibiotics, nonsteroidal anti-inflammatory drugs (NSAID) are one of the leading drug classes responsible for hypersensitivity reactions in children. The drug provocation test (DPT) is the criterion standard for diagnosis.

**Objective:** The aim of the present study was to determine the negative predictive values (NPV) of DPTs with NSAIDs in pediatric patients and to evaluate their attitudes toward NSAID use after a negative DPT result.

**Methods:** The study included all patients who had undergone DPTs between January 1, 2014, and December 31, 2018, in our pediatric allergy clinic for suspected NSAID hypersensitivity reaction and who had a negative result for the suspected agent. Those patients who could be contacted were asked whether the patient had used the same drug again since the DPT and, if so, whether he or she had a reaction. Patients who were reported to have had a reaction were invited to the clinic for reevaluation. Based on the findings from this retesting, the NPVs of the DPTs with NSAIDs were calculated.

**Results:** During the 5-year study period, DPT results were negative for 230 suspected agents in 215 patients. Of these, 143 patients (66.5%) were able to be contacted. A total of 108 patients (75.5%) had used the tested NSAIDs at least once after the provocation test, and five patients (4.6%) reported a reaction on reexposure. Four of these patients declined reevaluation, one patient exhibited no reaction in a second DPT. Therefore, the NPV was calculated as 96.3% (94.3% for ibuprofen, and 100% for paracetamol).

**Conclusion:** The NPVs of DPTs with NSAIDs, especially of paracetamol DPT, is high in children. This finding should reassure the parents of patients who may require NSAID therapy again.

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Nonsteroidal anti-inflammatory drugs (NSAID) are one of the leading drug classes responsible for hypersensitivity reactions (HR) in children.<sup>1,2</sup> The prevalence of NSAID HRs in the general population is between 0.6 and 5.7%.<sup>3</sup> The pharmacologic effects of NSAIDs are on the inhibition of cyclooxygenase (COX) 1 and COX-2 enzyme systems. COX enzymes have a role in the synthesis of prostanoids.<sup>4</sup> The most commonly implicated culprit NSAIDs in young children are ibuprofen and paracetamol.<sup>5,6</sup> Paracetamol and ibuprofen are member of the para-aminophenol and propionic acid derivatives group of NSAIDs, respectively and they make COX-1 and COX-2 inhibitor.<sup>7</sup>

In the pediatric population, NSAID HR usually presents with cutaneous manifestations.<sup>1,6</sup> Therefore, it is difficult to distinguish the symptoms from the underlying febrile illness, *e.g.*, acute idiopathic urticaria, from a potential HR.<sup>8</sup> The drug provocation test (DPT) is the criterion standard for diagnosis. A

negative DPT result is accepted as confirming current tolerance.<sup>9</sup> However, some patients may experience repeated reactions to the same drug despite negative DPT results. False-negative DPT results may occur due to the slow increment in drug dosage during the test, the absence of cofactors (*e.g.*, recent infection), other medications, and physical exercise, or another cause of the recurrent reaction.<sup>9–14</sup>

Even after a negative DPT result, some patients or their parents do not want to use the suspect drug again due to fear of another reaction. When considering the limited number of NSAIDs used by children, the ability to use these agents again, without fear, after a negative test result is especially important in the pediatric population. Therefore, determining the negative predictive value (NPV) is important to reassure that patients can safely use the drug after a negative DPT result. The NPVs of DPTs with NSAIDs have been reported as 96.7% and 97.8% in adults<sup>13,14</sup> but have not been well studied in children. The aim of the present study was to determine the NPVs of DPTs with NSAIDs in pediatric patients and to evaluate their attitudes toward NSAID use after negative DPT results.

## METHODS

The study included all the patients who had undergone DPTs for suspected NSAID HR and who had a

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**Table 1 Characteristics of the patients who were contacted after NSAID DPT ( $n = 143$ ) and those who could not be contacted ( $n = 72$ )**

|                                                  | Patients Contacted After Negative NSAID DPT | Patients Who Could Not Be Contacted after NSAID DPT | <i>p</i> |
|--------------------------------------------------|---------------------------------------------|-----------------------------------------------------|----------|
| Males, $n$ (%) <sup>*</sup>                      | 81 (56.6)                                   | 51 (70.8)                                           | 0.044    |
| Age at reaction, median (IQR), mo                | 69.1 (45.1–119)                             | 80.2 (50.6–135.4)                                   | 0.32     |
| Age at provocation, median (IQR), mo             | 77.2 (51.9–132.8)                           | 82.3 (56.9–138.7)                                   | 0.48     |
| Comorbid asthma, $n$ (%) <sup>*</sup>            | 22 (15.4)                                   | 18 (25)                                             | 0.087    |
| Comorbid chronic urticaria, $n$ (%) <sup>*</sup> | 5 (3.5)                                     | 2 (2.8)                                             | 0.077    |
| Suspected drug, $n$ (%) <sup>*</sup>             |                                             |                                                     |          |
| Ibuprofen ( $n = 123$ )                          | 88 (61.5)                                   | 35 (48.6)                                           |          |
| Paracetamol ( $n = 64$ )                         | 42 (29.4)                                   | 22 (30.5)                                           |          |
| Ibuprofen and paracetamol ( $n = 15$ )           | 6 (4.2)                                     | 9 (12.5)                                            |          |
| Aspirin ( $n = 2$ )                              | 2 (1.4)                                     | 0                                                   |          |
| Dexketoprofen ( $n = 2$ )                        | 2 (1.4)                                     | 0                                                   |          |
| Naproxen ( $n = 5$ )                             | 1 (0.7)                                     | 4 (5.5)                                             |          |
| Metamizole ( $n = 1$ )                           | 1 (0.7)                                     | 0                                                   |          |
| Etodolac ( $n = 1$ )                             | 1 (0.7)                                     | 0                                                   |          |
| Flurbiprofen ( $n = 1$ )                         | 0                                           | 1 (1.4)                                             |          |
| Ketoprofen ( $n = 1$ )                           | 0                                           | 1 (1.4)                                             |          |
| Presenting symptoms, $n$ (%) <sup>*</sup>        |                                             |                                                     |          |
| Skin symptoms                                    | 132 (92.3)                                  | 66 (91.6)                                           |          |
| Anaphylaxis                                      | 11 (7.7)                                    | 5 (6.94)                                            |          |
| Isolated respiratory symptoms                    | 0                                           | 1 (1.4)                                             |          |

NSAID = Nonsteroidal anti-inflammatory drug; DPT = drug provocation test; IQR = interquartile range.

<sup>\*</sup>Percentage values are calculated by columns.

negative result for the suspected agent in our pediatric allergy clinic between January 1, 2014, and December 31, 2018. The local ethics committee approved the study design and protocols. Patients whose parents or caretakers were contacted by telephone at least three months after a DPT that was performed with the suspected agent and with a negative result were included in the study. Those who could be contacted were asked whether the patient had used the same drug again since the DPT and, if so, whether the patient had a reaction. Patients who were reported to have another reaction were invited to the clinic for reevaluation. Based on the findings from this retesting, the NPV of DPT with NSAIDs was calculated.

#### Diagnostic Evaluation at Initial and during Reassessment

At initial presentation, a detailed history was taken, including the spectrum and timing of symptoms, dose and route of administration, list of concomitant

medications, history and timing of previous reactions, and previously tolerated NSAIDs. The patient's family members were also asked about previous aspirin use and any associated reactions. Coexisting chronic diseases, especially asthma, chronic rhinosinusitis, nasal polyps, and chronic spontaneous urticaria, and a family history of drug allergy and allergic diseases were recorded. When the patient's history of suspected reaction was consistent with drug hypersensitivity, oral provocation tests with the suspected drug were recommended at least one month after the initial reaction. Use of drugs that could affect the tests was discontinued a week before the test. Written informed consent was obtained from the patient's legal guardians.

#### DPTs

DPTs were performed to confirm hypersensitivity to the culprit drug. All tests were conducted in strict accordance with the European Network of Drug Allergy guidelines for drug DPTs.<sup>15</sup> The suspected drug was

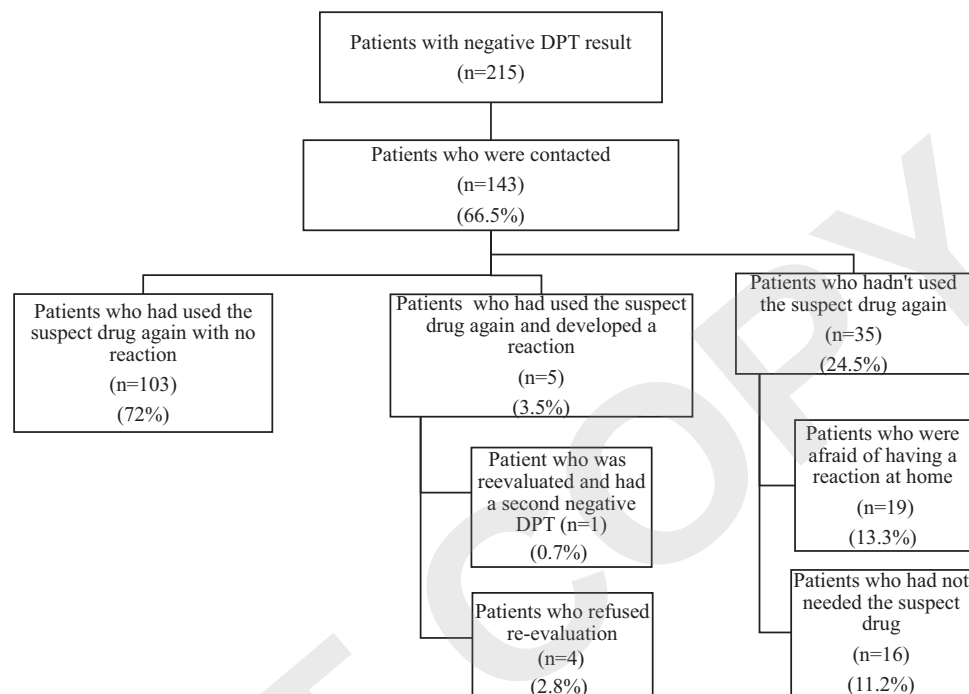


**Figure 1.** Algorithm of the study.

administered orally, divided into 3–5 doses every hour, until a cumulative dose close to the age- and weight-adjusted daily dose of the drug was achieved. The DPT results were considered positive if any objective symptoms or signs were documented and/or if there was a >15% decrease in the forced expiratory volume (FEV1) in the first second of expiration during the DPT.<sup>16</sup> The patients' family members were asked to contact the physician 24 hours after DPT to identify any delayed reaction.

**Statistical Methods.** Statistical analyses were performed by using SPSS 22 (IBM Corp., Armonk, NY). The numbers and percentages are reported for discrete variables, and means  $\pm$  standard deviations for continuous variables. Data sets that were normally distributed are presented as means  $\pm$  standard deviations, whereas non-normally distributed data are expressed as medians and interquartile ranges (IQR). A *p* value of <0.05 was considered statistically significant.

## RESULTS

During the 5-year study period, the DPT results were negative for 230 suspected agents in 215 patients, 132 (61.4%) of whom were boys. Their median (IQR) age was 72.3 months (45.9–121 months). Ibuprofen (*n* = 138 [60%]) and paracetamol (*n* = 79 [34.3%]) were the suspected agents that most frequently gave negative results. The list of suspected agents are listed in Table 1. Presenting symptoms were skin symptoms (rash, angioedema, and urticaria) in 198 patients (92.09%), anaphylaxis in 16 patients (7.44%), and respiratory symptoms only in one patient (0.46%). Of 215

patients with negative DPT results, 143 (66.5%) could be contacted (Fig. 1). The characteristics of the patients who could and could not be contacted are presented in Table 1. Of these 143 patients, 35 had not used the suspected drug again after the negative DPT result: 19 (13.3%) were afraid of having a reaction at home and 16 had not needed the tested NSAID (11.2%).

A total of 108 patients (75.5%) had used the tested NSAIDs at least once after the provocation test. Except for etodolac (only one patient's suspect agent), the NSAID most frequently used again was paracetamol (40/48 patients [83.3%]), and none of these patients reported a reaction on reexposure. This was followed by ibuprofen (70/94 patients [74.5%]); four of these patients reported a reaction on reexposure. The characteristics of patients who experienced a reaction to ibuprofen after negative DPT results are given in Table 2. None of these patients agreed to reevaluation. Another patient who had a negative DPT result with etodolac reported respiratory symptoms after using multiple drugs, including, *e.g.*, etodolac. However, he exhibited no reaction with a second DPT with etodolac. As a result, the NPV was calculated as 96.3% (104/108 patients). To mention separately, the NPV was calculated for paracetamol as being 100% (40/40 patients) but as 94.3% for ibuprofen (66/70 patients).

## DISCUSSION

In this study, our evaluation of 215 patients with a history of suspected NSAID HR who had negative DPT results with the suspect drug yielded an NPV of 96.3%. Also, this ratio was 100% for the NPV of

Table 2 Characteristics of patients who reported a reaction after a negative DPT ( $n = 4$ )

| Patient No.<br>(age, mo/sex) | Time between<br>First Reaction<br>and First DPT | Age at Initial<br>Reaction, mo | Suspected<br>Agent | Symptoms of<br>Initial Reaction | Symptoms of Reaction<br>after Negative DPT<br>Result |
|------------------------------|-------------------------------------------------|--------------------------------|--------------------|---------------------------------|------------------------------------------------------|
| 1 (93/M)                     | 5 wk                                            | 74.15                          | Ibuprofen          | Facial angioedema               | Periorbital angioedema                               |
| 2 (55/M)                     | 13 mo                                           | 12.62                          | Ibuprofen          | Angioedema on the<br>hands      | Rash                                                 |
| 3 (156/F)                    | 5 wk                                            | 111.08                         | Ibuprofen          | Urticaria                       | Urticaria                                            |
| 4 (165/M)                    | 2 y                                             | 104.87                         | Ibuprofen          | Rash                            | Rash                                                 |

DPT = Drug provocation test.

paracetamol and 94.3% for the NPV of ibuprofen. NSAIDs are often used to reduce fever in children. Eruptions suspected to be NSAID HR may be caused by an underlying acute febrile illness, and the prevalence of confirmed NSAID HR among these children is reported to be as low as 16.9 to 27%.<sup>5,6,8,17</sup> Similarly, in our study, the most common presenting symptoms were cutaneous symptoms, and the vast majority of these patients had negative test results. Although it is generally assumed that symptoms caused by underlying infections are the cause of negative DPT results, we also had 16 patients (7.44%) who presented with a history of anaphylaxis and with a negative DPT result; eight reported that they had used the same NSAID again after a negative DPT result. This demonstrated the importance of DPTs in the definitive diagnosis because children's histories may be confusing.

There are only a few studies<sup>13,14</sup> in the literature on NPVs of DPTs with NSAIDs. Negative provocation test results are important to reassure the patients and their physicians with regard to later use of the drug.<sup>14</sup> However, in real life, the patients may avoid using the drug again. The frequency of avoidance was reported as 53.5% in one adult study,<sup>13</sup> whereas another study showed that, of 89% of patients who used an NSAID again, only 41.4% used the same drug.<sup>14</sup> In our study, 75.5% of the patients used the suspect drug again. The higher rate in our study compared with adult studies was attributable to the frequent need for NSAID treatment for fever, pain, and inflammation in pediatric patients.

Febrile illness is more common in children than in adults, and there are also fewer NSAIDs that can be used in children. Thirty-five patients had not used the same NSAID again since the negative DPT result, with the most common reason being fear of an HR (54.3%). The rate of repeated use of a NSAID after a negative DPT result was highest for paracetamol, at 83.3% (40/48 patients). Also the NPV was calculated for the paracetamol as 100%. Similarly, it was reported in an adult study that patients with a negative paracetamol

challenge had a higher repeated use rate (68.6%), and it was noted that paracetamol was regarded as a low-risk molecule.<sup>14</sup> This perspective seemed to be similar for children.

Some patients with negative DPT results may still react with reexposure, a phenomenon that has been associated with the slowly increasing drug doses and the absence of cofactors such as infections, comedications, and physical exercise during provocation.<sup>9-12</sup> Determining NPV is important for counseling the patient with regard to repeated use of the same drug. In a study by DeFrance *et al.*<sup>13</sup> that evaluated NPV in adults, five of 139 patient with a negative NSAID challenge reported a reaction on reexposure. Although the initial NPV was 96.4% (134/139 patients), only three patients had a reaction when retested with the same NSAID, for a final NPV of 97.8%. Bommarito *et al.*<sup>14</sup> reported in their study that 142 patients had negative NSAID provocation test results and that 111 of them (78.17%) could be contacted. Of these, 46 patients took the suspect NSAID again and two reported reactions, which yielded an NPV of 96.7%.

To our knowledge, the studies of evaluating only NSAID use after negative DPT results and reaction rates after reexposure with the same drug among children are limited. In another study conducted in our clinic on NPVs for  $\beta$ -lactam and other drugs in children, 91 patients took the same test-negative drug, 20 of whom had been tested with NSAID. Only one of these 20 patients reported a reaction but had another negative result in the retest.<sup>18</sup> In the present study, the NPV was calculated as 96.3%, and, to mention separately, NPV was calculated for paracetamol as 100% and as 94.3% for ibuprofen. The NPV of NSAIDs was high, but, especially, the ratio of paracetamol was better, which supports that paracetamol is a low-risk molecule.

In the present study, five of 143 contacted patients reported a new reaction with reexposure to the same drug; four of the reactions were mild (urticaria and angioedema). One of these patients had JIA (juvenile idiopathic arthritis) as a chronic illness, and there was

confusion about whether the reaction was due to JIA or to NSAIDs. Only the one patient who reported respiratory symptoms on reexposure agreed to be reevaluated, and this patient also had a negative result on the retest. Similarly, in the study by Defrance et al,<sup>13</sup> five patients reported a reaction after reexposure and none were severe, including urticaria in three patients, angioedema in one patient, and undefined cutaneous reaction in one patient. In our previous study on NPV in pediatric patients, one patient reported a new reaction after using the same NSAID, and his reaction was limited to cutaneous symptoms.<sup>18</sup> The limitation in our study was that we were unable to retest four patients who defined a reaction after a negative test result. Unfortunately, the tests could not be repeated because the parents of these patient did not accept the offer to retest.

## CONCLUSION

Our results indicated an NPV of 96.3% (paracetamol, 100%; ibuprofen, 94.3%) for NSAID DPTs in children, and this ratio is high in children, especially for paracetamol. Analgesic and anti-inflammatory treatment is important in daily life. Some patients may fear having a new reaction and avoid using the same drug. However, they may have difficulties finding another way to alleviate their symptoms if alternative NSAID agents are not available. In fact, the NPV of NSAID DPT is high and the patients' new reactions were not severe, only cutaneous symptoms. Based on these results, we can reassure patients that they can safely continue using the same drug. However, it is also necessary to warn patients and their families that reactions can occur after negative provocation testing.

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