



Oral Provocation Test in Non-Steroidal Anti-Inflammatory Drug Hypersensitive Patients Referred to Singapore General Hospital

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Abstract

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed classes of drugs and are easily accessible as over-the-counter anti-inflammatory drugs in Singapore. NSAIDs hypersensitivity is the second most common referral to allergy clinic in a tertiary referral centre. **Methods:** Referred patients with history of NSAID intolerance were underwent open challenge with 1) putative NSAID to confirm the diagnosis; 2) Aspirin to determine the cross-reactivity or 3) selective cyclooxygenase-2 (COX-2) inhibitor to identify the suitable alternative. Data were analysed retrospectively. **Results:** Over a 4-year period (2010-2014), a total of 127 patients (mean age SD 40.7 +/- 15.2) underwent a total of 155 open-labelled NSAIDs oral provocation tests (OPT). Overall positive challenge rate is 26.5% (41 out of 155). Despite having a clinical relevant history of causative, only 29.4% (20 out of 68) had positive OPT to putative NSAIDs. Using selective COX-2 inhibitor challenge for assessing the tolerability of suitable alternative, we found only 8.8% (5 out of 57) positive challenge. **Conclusions:** In our 4-year patients cohort with history of NSAIDs of intolerance, positive OPT rate of 26.5% in confirming diagnosis of NSAIDs hypersensitivity. The intolerance to selective COX-2 inhibitor was found in 8.8% of patients with non-steroidal anti-inflammatory drugs hypersensitivity patients.

Subject Areas

Allergy & Clinical Immunology

Keywords

Non-Steroidal, Anti-Inflammatory Drugs, Hypersensitivity, Cyclooxygenase 2

1. Introduction

Non-steroidal Anti-inflammatory drugs (NSAIDs) are commonly used analgesics and the prevalence to NSAIDs hypersensitivity ranging from 0.3% - 2.5% of the general population [1] [2]. However, the prevalence of NSAIDs hypersensitivity is higher up to 30% in patients with underlying asthma, nasal polyposis and chronic urticaria [2] [3]. After beta lactam hypersensitivity, NSAID is ranked at second or third most common cause of drug hypersensitivity reaction based on the study populations [2] [4]. NSAIDs attribute 24.6% of adverse drug reactions among Singaporean children [5].

NSAIDs are heterogeneous group of compounds and they can be sub grouped depending on their heterogenic chemical structures, however, they share the ability to inhibit cyclooxygenase (COX) enzymes (COX 1 and COX 2). The widely describe mechanism of action of NSAIDs involves inhibition of prostaglandin production via inhibition of the cyclooxygenase (COX) pathway of arachidonic acid metabolism resulting increase in production of cysteinyl leukotrienes. Moreover, NSAIDs induce wide spectrum of adverse reaction related to their pharmacological reaction. The array of hypersensitivity symptoms varies from cutaneous (urticaria with or without angioedema), respiratory symptoms (rhinitis with or without dyspnoea) and anaphylactic reaction.

For patient with NSAIDs hypersensitivity, the tests to diagnose NSAIDs hypersensitivity are still limited. Controlled oral provocation test is the only definitive way to diagnose the reactions caused by non-steroidal anti-inflammatory drugs (NSAIDs) [6]. The tolerability to COX-2 inhibitors in patients with NSAIDs hypersensitivity has been shown in different studies [7] [8]. In clinical practice, controlled challenge of selective COX-2 inhibitor should consider to determine the tolerability in NSAID hypersensitivity patient.

2. Methods

This study was a retrospective review of patients seen at Allergy center, Singapore General Hospital, Singapore. The work was reviewed and approved by the Sing Health Centralised Institutional Review Board (CIRB). The referred patients with history of NSAID-induced urticarial, angioedema or anaphylaxis underwent open challenge with 1) putative NSAID to confirm the diagnosis, 2) Aspirin to determine the cross-reactivity or 3) selective cyclooxygenase-2 (COX-2) inhibitor to identify the suitable alternative.

2.1. Patients

The clinical records of adult patients referred to our allergy clinic for evaluation after developing dermatologic or respiratory side effects associated with the use of NSAIDs over a 4-year period, from 2010 and 2014 were reviewed.

We included all adult patients with age 18 year old and above (n = 127) with mean age, 40.7 +/- SD 15.2 and 81 women (63.8% of all patients) who were referred to our allergy clinic for evaluation after developing dermatologic or respiratory side effects associated with the use of NSAID. We excluded patients whose

notes were irretrievable data (n = 3). Patients who experienced severe cutaneous reaction such as Steven-Johnson syndrome, Toxic epidermal necrolysis and pregnant woman were not offered a drug provocation test.

Patients with suspected hypersensitivity to NSAIDs were evaluated by an allergist and were offered oral provocation test. Patients were included in the study if they have a hypersensitivity to one or more NSAIDs and underwent an oral provocation test. Data of previous NSAIDs exposure, tolerability to other group of NSAIDs or paracetamol, background atopy and concomitant medical diseases were recorded in the patient case note.

2.2. Controlled Oral Provocation Test

All included patients were subjected to open oral provocation test with either 1) putative NSAID to confirm the diagnosis or 2) Aspirin to determine the cross-reactivity or 3) selective cyclooxygenase-2 (COX-2) inhibitor to identify the suitable alternative. Where the diagnosis could not be convincingly made on history per se, hypersensitivity to NSAIDs was confirmed by conducting an oral provocation test with either putative NSAID or Aspirin. The oral challenges were performed at outpatient challenge clinic. Prior to the oral challenge, anti-histamines were stopped for 5 days while the use of beta blocker and ACEI were suspended for one day. Patients were interviewed and examined before obtaining informed consent for drug challenge.

Incremental dose of challenged NSAIDs were administered at 30 minutes interval according to the challenge protocol. The challenges were only considered positive if the patient developed objective symptoms [9]. Patients were monitored for 2 hours after the last challenge dose.

If no symptoms developed during the oral provocation test, patients were advised to monitor for the late reaction. All patients were contacted via phone the next day of challenge to determine any reaction after 2 hours of monitoring.

3. Results

The clinical data of 127 patients (mean age SD 40.7 +/- 15.2) who underwent open-labelled NSAIDs oral provocation tests (OPT) was reviewed. Total of 155 open-labelled NSAIDs oral provocation tests (OPT) were conducted. Patients demographics consisted of female (81, 63.8%) with majority Chinese ethnic group (102, 80.3%) followed by Malay (15, 11.8%), Indian (6, 4.7%) and others ethnic group (4, 3.1%). The demographic and clinical characterizations of the study group, as well as the drugs suspected to cause hypersensitivity reaction are shown in **Table 1**.

Among various NSAIDs, Diclofenac (20.2%) and Naproxen (19.7%) were the two commonest reported culprits NSAIDs. In 32 (25.2%) patients, more than two eliciting different groups of NSAIDs were recorded to cause hypersensitivity reactions. However, 27 (21.3%) patients reported to tolerate different groups of NSAIDs and 78 (61.45) did not try to take other NSAIDs after their first reaction to a NSAID. Moreover, hypersensitivity to Paracetamol was found in 40 (31.5%)

of patients.

Of the 127 patients, 19 (15%) had history of asthma, 9 (7.1%) allergic rhinitis, 10 (7.9%) patients have underlying angioedema and urticaria unrelated to intake of NSAIDs, 2 (1.6%) have chronic rhinosinusitis and 3 (2.4%) have NSAIDs exacerbated respiratory disease.

In term of initial reaction (see **Figure 1**), urticaria and/or angioedema was the most frequently reported symptom (85%), among which 59.8% were isolated periorbital angioedema. Reaction involving the airways *i.e.*, asthma with or without a naso-ocular symptoms were rare (7%). Anaphylaxis was reported by 4 (3.1%) patients together with other concomitant drugs.

Among 155 challenges: 68 (43.9%) Putative NSAIDs challenge, 30 (19.4%) Aspirin challenge and 57 (36.8%) selective COX-2 inhibitor challenge, see **Figure 2**. Overall positive challenge rate is 26.5% (41 out of 155). Despite having a clinical relevant history of causative, only 29.4% (20 out of 68) had positive OPT to putative NSAIDs. Aspirin challenge resulted in 53.3% (16 out of 30) positive challenge, hence confirming the diagnosis of cross reactivity to various group of NSAIDs, see **Table 2**.

After completion of the either confirmation or detection of cross reactivity among NSAID challenge, 29 (22.8%) patients underwent for second challenge to

Table 1. Demographic and characteristic of patients.

	Patients (n = 127)
Gender (male/female) n (%)	46/81 (36.2%/63.8%)
Age (years) (mean+/- SD)	40.7 +/- SD 15.2
Reaction to 1 NSAID n (%)	95 (74.8%)
Reaction to various NSAIDs n (%)	32 (25.2%)
Reaction to paracetamol	40 (31.5%)
Background history of Atopy	
Asthma	19 (15%)
CSU ± Angioedema	10 (7.9%)
Allergic rhinitis	9 (7.1%)
Chronic Rhinosinusitis	2 (1.6%)
NSAIDs exacerbated respiratory disease	3 (2.4%)

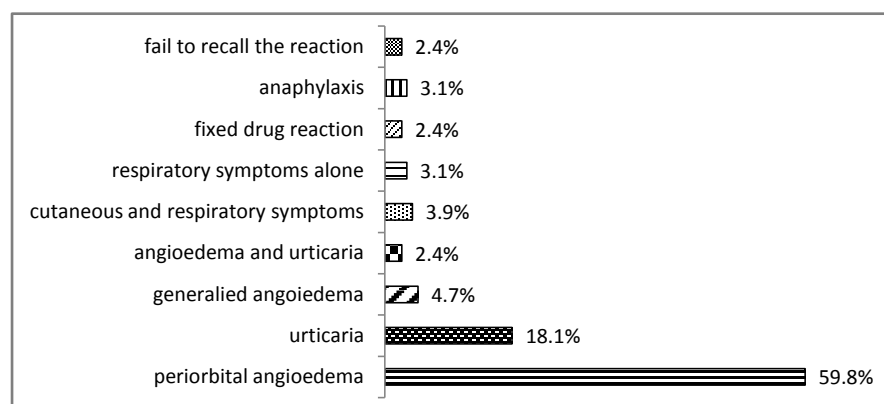


Figure 1. Percentage of initial reaction in different clinical features.

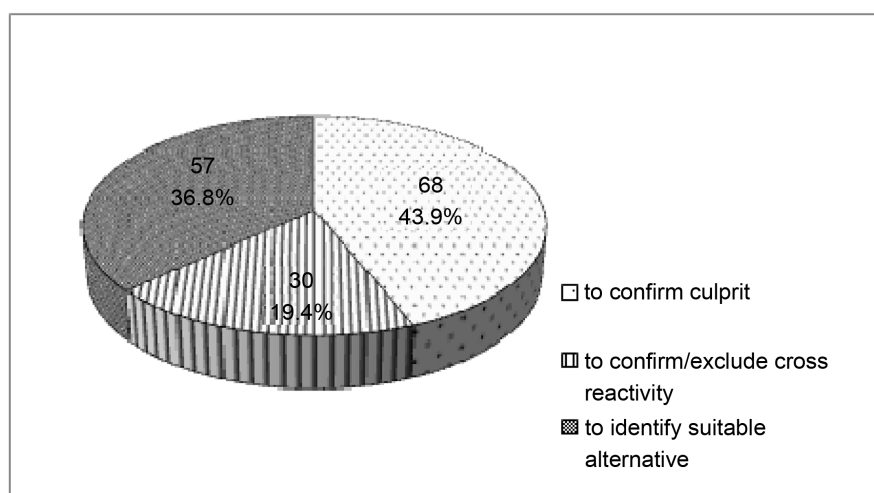


Figure 2. Percentage showing indication for challenge.

Table 2. Percentage of positive and negative challenge result.

Indication for challenge	Reaction to challenge	
	Positive N (%)	Negative N (%)
To confirm culprit	20 (29.4)	48 (70.6)
Confirm/exclude cross reactivity	16 (53.3)	14 (46.7)
Suitable alternative	5 (8.8)	52 (91.2)

identify the suitable alternative. Overall, selective COX-2 inhibitors such as Etoricoxib and Celecoxib were tested in 51 (87.93%) and 6 (10.34%) of challenges meant for identification of suitable alternative NSAIDs respectively.

Using selective COX-2 inhibitors for identification of suitable alternative, we found only 8.8% (5 out of 57) positive challenge. For the anaphylaxis cases, cautious OPT with putative NSAIDs were done in 75% (3 out of 4) patients. None reaction were found.

4. Conclusions

NSAIDs are widely used analgesia in adults and they are most frequently involved in drugs hypersensitivity reaction. The clinical manifestation of NSAIDs hypersensitivity is varied depending on the individual's background associated atopy. Clinically significant allergic diseases were noted in 33.9% of patients; with majority has history of asthma 15%. Overall, periorbital oedema and urticarial (59.8% and 18.9% respectively) were the commonest initial presenting symptoms. The culprit NSAIDs are majority COX-1 inhibitor in our study.

In the absence of laboratory and other available diagnostic tests such as validated skin test for NSAIDs hypersensitivity, the gold standard for the diagnosis of NSAIDs hypersensitivity is the OPT. Our 4-year patients cohort with positive OPT rate of 26.5% confirmed diagnosis of NSAIDs hypersensitivity including challenge with selective COX-2 inhibitors. The positive rate was 36.7% (36 of 98) in patients underwent for either confirmation of hypersensitivity or cross-reac-

tivity among NSAIDs. In practical setting, patients who are confirmed hypersensitivity to NSAIDs are advised to avoid all NSAIDs. However, patient with diagnosis of cross-reactivity to NSAIDs and Paracetamol has limited choice for the treatment of fever and pain. Hence, those patients are offered to have challenge with selective COX-2 inhibitors.

The selective COX-2 inhibitors are considered to be the safest suitable alternative in Asian population as study by Lanora GV *et al.* [8]. The percentages of cross reactivity to COX-2 inhibitor in patients with multiple NSAIDs hypersensitivity are varied from 0% to 10% depend on different coxib molecules [10] [11] [12]. In our study, etoricoxib was predominantly used over other COX-2 inhibitors as a secondly challenge alternative drug, giving the fact that Etoricoxib inhibits much higher COX-2 selectivity than Celecoxib [13]. Similarly, our study showed that 8.8% of NSAIDs hypersensitivity patient cross-react with selective COX-2 inhibitors.

The number in our study is limited to determine the association of Paracetamol hypersensitivity in patient with COX-2 inhibitor hypersensitivity. Matucci A *et al.* showed that patients who had Paracetamol hypersensitivity are more likely to react to a COX-2 inhibitor [14]. Our study showed that 5% (2 out of 40) of patient with Paracetamol hypersensitivity are cross reacted to selective COX-2 inhibitor.

According to our study, selective COX-2 inhibitor will be the potential alternative for patient with NSAIDs hypersensitivity. In view of cross reactivity among small proportion of the patients, challenge with selective COX-2 inhibitor in NSAID hypersensitivity patient should perform in the controlled setting to confirm the tolerability.

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