



Short communication

Nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease phenotype: Topical NSAID and asthma control – A possible oversight link



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ARTICLE INFO

Article history:

Received 16 February 2016

Received in revised form

22 June 2016

Accepted 6 July 2016

Available online 9 July 2016

Keywords:

Aspirin-exacerbated respiratory disease

Non-steroidal anti-inflammatory drug

hypersensitivity

ABSTRACT

Background: Patients with aspirin-exacerbated respiratory disease (AERD) also recently known as nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (NERD) must avoid aspirin and all other oral NSAIDs. The effect of topical NSAID (tNSAID), especially salicylates which are commonly present in topical medicated preparations, on asthma control of this phenotype is studied.

Methods: The study inclusion criteria were adults with: 1) NSAID hypersensitivity; 2) nasal polyposis/chronic rhinosinusitis; 3) not well-/poorly controlled asthma and 4) exposure to tNSAID. Patients were given verbal and written instructions to cease tNSAIDs exposure and asthma control was evaluated during the 6 months prior and after intervention.

Results: There were eleven patients (ten females) with a mean age of 56.5 (range 37–71) years. Prior known oral NSAIDs hypersensitivity included aspirin (5), mefenamic acid (2), diclofenac (2), Synflex (2) and ibuprofen (1). All, except 2, had arthropathies or spinal disorders and were using tNSAID for a mean of 4.2 years. One, four and six patients were using over-the-counter medicated oil containing salicylates, NSAID gel/plasters and both respectively. All patients had cutaneous, with 4 having concomitant inhalational exposure to these tNSAIDs. The mean duration of asthma diagnosis and uncontrolled asthma were 25.2 and 4.5 years respectively. Except for 2 patients, there was no change in asthma maintenance medications pre and post-intervention. Asthma control significantly ($p < 0.05$) improved based on pre and post-intervention ACT score, number of exacerbations, FEV₁ were 14.9 and 22.1, 1.9 and 0.43, 1.28L and 1.67L respectively.

Conclusions: It is paramount to eliminate not only oral but topical NSAID exposure in NERD phenotype asthmatic patients. When a long-standing asthma progressed to uncontrolled, a meticulous evaluation of tNSAIDs exposure is warranted especially if the patient has developed chronic pain.

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1. Background

Patients with aspirin-exacerbated respiratory disease (AERD) phenotype asthma must avoid aspirin (acetylsalicylate) and all other oral NSAIDs. The effect of topical non-steroidal anti-inflammatory drugs (tNSAID), especially methyl salicylate commonly present in topical medicated preparations, on asthma control of AERD phenotype has not been previously studied and we aim to analyse this association in this case series.

2. Methods

The study inclusion criteria were adults with: 1) NSAID hypersensitivity; 2) nasal polyposis or chronic rhinosinusitis; 3) not well-controlled (defined as Asthma Control Test, ACT, score of 16–19) or poorly controlled asthma (defined as ACT score of 15 or less), and 4) exposure to tNSAID. Patients were given verbal and written instructions to cease tNSAID exposure and asthma control was evaluated six months prior and after intervention was conducted from January 2012 to October 2015. Pre- and post-intervention asthma control were evaluated based on 1) ACT score; 2) number of exacerbations defined as acute episodes requiring nebulised bronchodilator and a burst course of systemic corticosteroids, and 3) forced expiratory volume at 1 s (FEV₁). Paired *t*-test was applied

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and a p value of <0.05 was taken as statistical significant.

Study approval was obtained from the Ethics Committee and Hospital Institutional Review Board (number 2015/2759) and waivers of consent from patients.

3. Results

There were eleven patients, ten females with a mean age of 56.5 years (Table 1). The racial demographics are similar to the national's data. All, except two patients, had arthropathies or spinal disorders. They were using tNSAIDs intermittently ranging from a few times a week to a year, for a mean of 4.2 years and all, except three, were using over-the-counter medicated oil containing 8–31% methyl salicylate. The most common route of tNSAID exposure was cutaneous (all patients) followed by inhalation (four patients), and oral mucous membrane (one patient). The mean duration of asthma diagnosis and uncontrolled asthma were 25.2 and 4.5 years respectively. The latter is not significantly different from the mean duration of tNSAID exposure. Three patients had life threatening asthma exacerbations related to topical medicated oil exposure. Following intervention significant improvement in asthma control based on ACT score, exacerbations rate, and lung function was evident (Table 2). All patients were on montelukast. Two patients had their asthma medications tapered down post-intervention, while the rest maintained stable asthma medication prescriptions.

4. Discussion

Aspirin-exacerbated respiratory disease (AERD) is a syndrome characterised by adult-onset asthma, nasal polyposis or chronic rhinosinusitis and, acute upper and lower respiratory tract inflammatory reactions to ingestion of aspirin (acetylsalicylic acid) and other cyclooxygenase-1 (COX-1)-inhibiting NSAIDs [1,2]. It has also been previously referred to as Samter or Aspirin triad (asthma, nasal polyposis, and aspirin/NSAID intolerance), and more recently, the term NSAID-exacerbated respiratory disease (NERD) [1,3]. The term NERD was proposed to stress the fact that the fundamental issue in these patients is not drug hypersensitivity, but the underlying chronic inflammatory respiratory disease only occasionally exacerbated by aspirin or other NSAIDs. The prevalence of NERD is

Table 2

Asthma control during the 6 months prior and 6 months post intervention.

	Asthma control		
	ACT ^a score	Exacerbations ^b , n	FEV ₁ (L)
Pre-intervention	14.9	1.9	1.28
Post-intervention	22.1	0.43	1.67
p-value	<0.01	<0.01	0.03

^a ACT: Asthma Control Test. A score of ≥ 20 is well-controlled, 16–19 is not well-controlled and ≤ 15 is poorly controlled asthma.

^b Exacerbations were defined as acute episodes requiring nebulised bronchodilator and a burst course of systemic corticosteroids.

7% in adult asthmatic patients and doubles in those with severe asthma [2]. This highlights the importance of recognising this subset of asthmatics. The prevalence did not appear to have any specific ethnic or regional variation [2]. Patients with NERD have increased morbidity typified by more emergency department visits, hospitalisations, life-threatening episodes, and glucocorticosteroid bursts when compared with those in patients with aspirin-tolerant asthma [2,3]. Hypersensitivity reactions in patients with NERD can be severe, with case reports of serious adverse events and death as a result of NSAID exposure. In patients with NERD, the use of all NSAIDs is contraindicated by the United States Food and Drug Administration and United Kingdom Medicines and Healthcare Products Regulatory Agency [4].

The pathophysiology of NERD is a non-immunological phenomenon which involves acquired dysregulation in arachidonic acid metabolism resulting in an imbalance between pro-inflammatory and anti-inflammatory mediators, leading to chronic airway inflammation [1]. COX-1-inhibiting NSAID acutely exacerbates this imbalance leading to mast cell activation [5]. Leukotriene-modifying agents, such as montelukast and zileuton, are a pivotal part of the management of all patients with NERD to mitigate the underlying dysregulation of leukotriene production [4] and also to protect patients from severe exacerbations due to fortuitous NSAID exposure. Aspirin desensitisation has been shown to be a useful measure and in up to 60–70% of these patients the response may help in easing the dependence on inhaled and/or systemic glucocorticosteroids [1].

Salicylates are found in many over-the-counter topical

Table 1
Clinical and medication profile.

	Age years	Known drug reactions	Pertinent comorbidities		NSAIDs exposed		
			Diagnoses ^a	Duration	Duration	Type	Route
1	58	Synflex, Acetaminophen Penicillin	Callus Headaches	1 year 3 years	2 years	AXE oil ^c (16%MS**), Corn removal solution (8%MS), Ibuprofen gel & plaster	Skin
2	53	Aspirin, Synflex, Acetaminophen	OA knees	3 years	3 years		Skin
3	37 ^b	Mefenamic acid, Tramadol	PID Oral ulcers	10 years 3 years	10 years	AXE oil, Ketoprofen gel, Choline salicylate (8.7%) oral gel	Skin, oral mucosa, inhalation
4	56	Aspirin, Mefenamic acid, Tetracycline	Spondylosis	2 years	5 years	Thai boxing oil (31%MS), Ketorolac & Ketoprofen plaster & gel	Skin
5	66	Aspirin, Acetaminophen	RA	9 years	8 years	AXE oil, Thai boxing oil, Counterpain cream (10.2%MS), Ketoprofen gel & plaster	Skin, inhalation
6	47	Ibuprofen	Spinal stenosis	5 years	4 years	AXE oil, Ketoprofen & Piroxicam gel,	Skin
7	43 ^b	Diclofenac	Rhinitis	2 years	2 days	AXE oil	Skin, inhalation
8	58 ^b	Diclofenac	OA knees	2 years	2 years	AXE oil, Counterpain cream, Bengay gel (15%MS)	Skin, inhalation
9	56	Aspirin, Amoxycillin, Clarithromycin	OA knees	1 year	1 year	Thai boxing oil	Skin
10	45	Ketoprofen	Meniscus tear	7 years	7 years	Ketoprofen, Piroxicam gel & plaster	Skin
11	71	Aspirin, Amoxicillin, Tetracycline	OA hip	4years	3 years	Tiger balm cream (15%MS), Ketoprofen, Piroxicam gel & plaster	Skin

^a OA: Osteoarthritis; PID: Prolapsed intervertebral disc; RA: Rheumatoid arthritis.

^b Had severe acute asthmatic exacerbations from medicated oil exposure.

^c AXE oil: AXE (Singapore) brand medicated oil containing 16% methyl salicylate (MS**).

applications because of its keratinolytic and analgesic properties to treat pain and aches (e.g. AXE brand medicated oil from Singapore and Thai boxing oil from Thailand, which contain 16% and 31% of methyl salicylate respectively), oral ulcers (Bonjela gel which contains 10.6% of choline salicylate), acne, calluses, warts, dandruffs, psoriasis, and onychomycosis. Salicylates are also found in some antiseptic preparations and exfoliating body and face cleansers. The liniment is also inhaled to relief giddiness, nausea, colds, and nasal congestion. Moreover, salicylates are also found in foods such as berries, pineapples, citrus fruits, potatoes, curry, and spices. These may lead to intolerance reactions [6] and potentially affect asthma control. Many over-the-counter topical preparations for analgesia also contain other forms of NSAID with COX-1 inhibitors such as piroxicam, ketorolac, ketoprofen, and ibuprofen. Systemic effects can occur from absorption via ocular, gastrointestinal, cutaneous, and inhalation (including environmental sources) routes [6–8]. There are only a couple of case reports on acute respiratory reactions to tNSAID preparations from plasters (published in Japanese) and ophthalmic application [7]. The significant improvement in asthma control of patients with NERD in this study suggests that it may be due to the inadvertent exposure of NSAIDs via these routes that have contributed to the lesser controlled and increased risk of life-threatening asthma attacks. This is conceivable as the threshold dose of aspirin during oral challenge, defined as the smallest dose evoking a significant fall in forced expiratory volume in one second (FEV1), seems to be an individual feature of a patient and varies from 10 mg (or even lower dose) up to 600 mg [9].

5. Conclusion

The term NERD (NSAID-exacerbated respiratory disease) would be a better one than AERD as the former encompasses all NSAIDs including aspirin. Patients with NERD should avoid all aspirin-containing compounds and other analgesics that have the potential to inhibit the COX-1 enzyme, unless they have been desensitised to aspirin. It is paramount to eliminate not only systemic but also topical NSAID exposure in NERD phenotype asthmatic patients. When a long-standing asthma progresses to not well or poorly controlled, a meticulous evaluation of tNSAID exposure is warranted especially if the patient has developed chronic pain in the interim. Drug desensitisation followed by daily NSAID therapy may be beneficial in carefully selected patients with NERD and conditions requiring daily NSAID therapy that cannot be treated with selective COX-2 inhibitors [4]. Genetic profiling [10] before complete clinical manifestations of NERD phenotype asthma may reduce the morbidity burden, which can be potentially fatal,

through simple avoidance intervention in this most well-defined asthma phenotype cluster group.

Ethics approval and consent to participate

Study approval was obtained from the Ethics Committee and Hospital Institutional Review Board (number 2015/2759) and waivers of consent from patients.

Competing interests

Nil.

Funding

Nil.

Acknowledgements

Nil.

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