Syddansk Universitet

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ASA/NSAID intolerance

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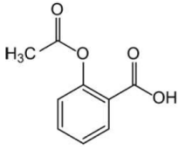
Pharmacological classification

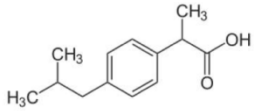
Table 1 Pharmacological classification of antipyretic non-opioid analgesics with typical examples (from Beubler E [6])[a]

Antipyretics	Class		Typical example
Non-steroidal anti-inflammatory drug	Salicylic acid derivatives	–	Acetylsalicylic acid
			Sulfasalazine
	Acetic acid derivatives	–	Diclofenac
			Acemetacin
			Indomethacin
	Propionic acid derivatives	–	Dexibuprofen
			Ibuprofen
			Naproxen
			Ketoprofen
			Flurbiprofen
	Enolic acid derivatives	Oxicams	Meloxicam
			Lornoxicam
			Piroxicam
		Pyrazolones	Phenylbutazone
			Propyphenazone (historically)
			Metamizole = dipyrone
	Fenamates		Mefenamic acid
	Selective COX-2 inhibitors		Celecoxib
Para-aminophenol			Paracetamol = acetaminophen

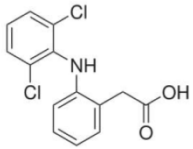
[a]Note: Most COX-2 inhibitors were withdrawn from the market because of a major pharmaceutical scandal at the beginning of this millennium in which class-specific cardiovascular side effects were downplayed in licensing trials [28]. Hence, celecoxib remains the only widely available COX-2 inhibitor



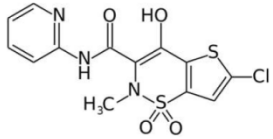
Acetylsalicylic acid



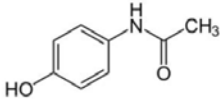
Ibuprofen



Diclofenac



Lornoxicam



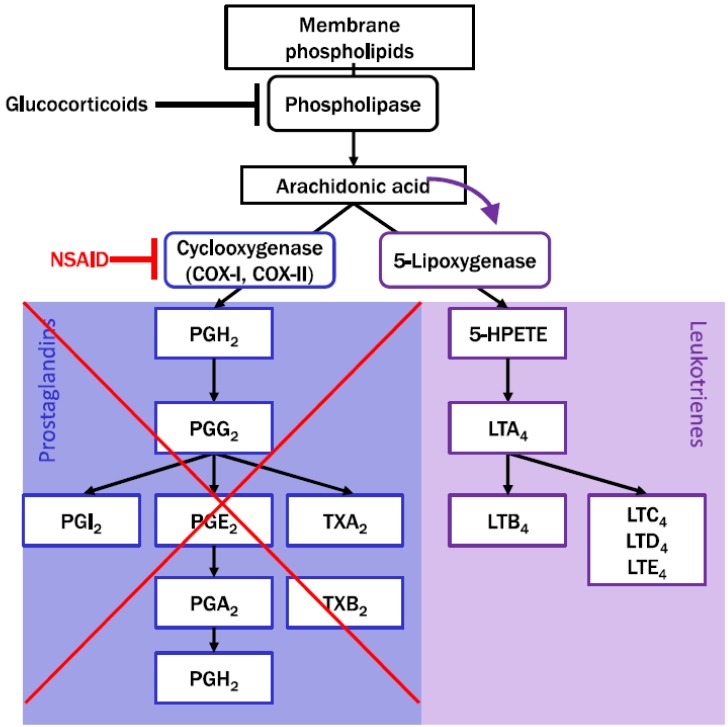
Paracetamol = Acetaminophen

Wöhrl S. Allergo J Int 2018

Mechanism

NSAID

- Chemically diverse substances
- All inhibit the enzyme cyclooxygenase-1 (COX-1) and to lesser extent COX-2
- Acts on the arachidonic acid metabolism- influencing the balance between leukotrienes and prostaglandins
- In NERD, NECD, NIUA cross-reactivity is mediated via COX blockage – mechanism differs from ”truly allergic” SNIDR, SNIUAA (no cross-reactivity)



Wöhrl S. Allergo J Int 2018

Classification hypersensitivity NSAID

Table 2 Novel classification of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (1, 101) (modified)

Type of reaction	Clinical manifestation	Timing of reaction	Underlying disease	Cross-reactivity	Putative mechanism	
NSAIDs-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea and/or nasal congestion/ rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/rhinosinusitis	Cross-reactive	Nonallergic	Cox-1 inhibition
NSAIDs-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		Chronic urticaria			Cox-1 inhibition
NSAIDs-induced urticaria/ angioedema (NIUA)	Wheals and/or angioedema		No underlying chronic diseases			Unknown, probably COX-1 inhibition
Single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals/angioedema/anaphylaxis		No underlying chronic diseases	Non-cross-reactive	Allergic	IgE-mediated
Single-NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (e.g., fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually more than 24 h after exposure)	No underlying chronic diseases			T-cell mediated

- NECD, NIUA and NERD most common
- SNIUAA very rare (Propyphenazone – historically (pyrazolones), rarely acetic acid derivatives (Diclonfenac), propionic acid derivatives (Ibuprofen, Ketoprofen, Naproxen))
- SNIDR rare - most common MDE, ACD (Diclofenac topically), FDE, SCAR

Kowalski et al Allergy 2013

Prevalence NSAID hypersensitivity

- 1-2% of the general population
- Among patients with asthma and CRS with nasal polyps 20-42%
- Among patients with urticaria 20-30%

White. NEJM 2018
Erbagci et al. J Derm 2004

Diagnosis

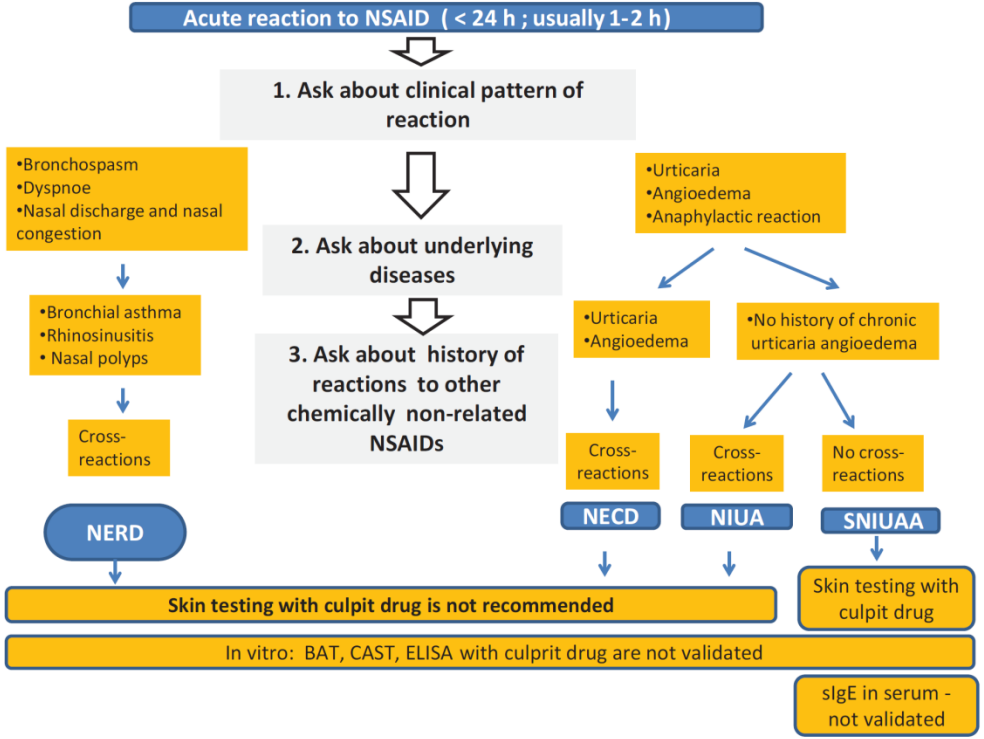


Figure 1 Algorithm for the diagnosis of acute forms of nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity.

Kowalski et al. Allergy 2013

Diagnosis

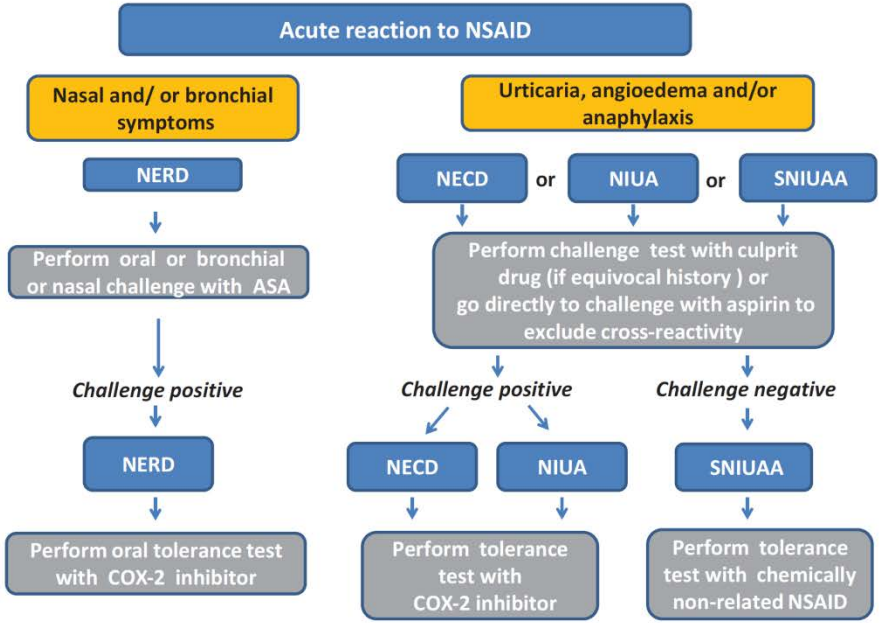


Figure 2 Provocation challenges in patients with a history of acute reactions to nonsteroidal anti-inflammatory drugs (NSAIDs).

There is no formal consensus on the oral provocation protocol.

Kowalski et al. Allergy 2013

Nissen et al. Clinical and Translational Allergy (2015) 5:10
DOI 10.1186/s13601-015-0052-0

Clinical and Translational Allergy

RESEARCH Open Access

Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs): classification of a Danish patient cohort according to EAACI/ENDA guidelines

Christoffer V Nissen, Carsten Bindslev-Jensen and Charlotte G Mortz*

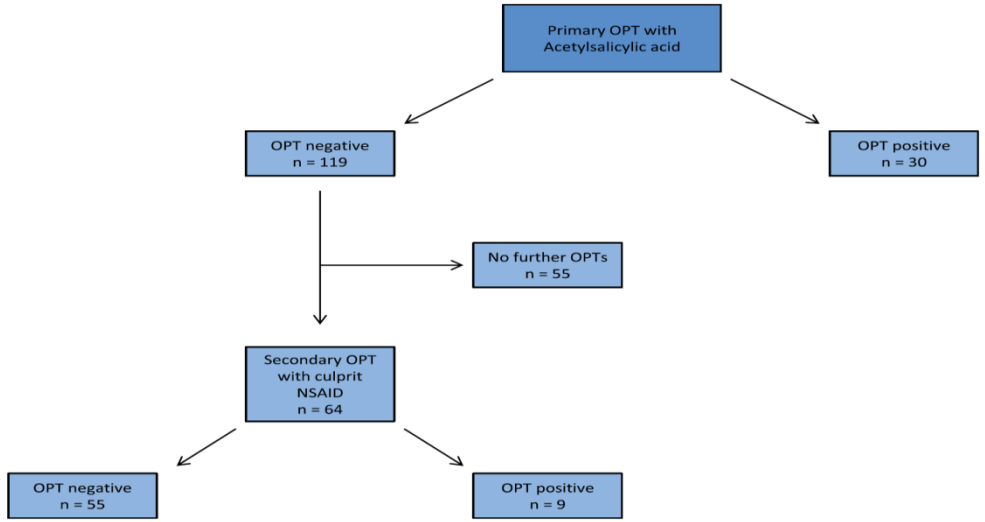


Figure 1 Approach to OPTs in 149 patients suspected of NSAID hypersensitivity. All patients performed a primary OPT with acetylsalicylic acid. If the primary OPT was negative, and ASA not was the culprit drug, a secondary OPT was performed with the culprit NSAID according to case history. See Figure 2 for details about the secondary OPT. OPTs = oral provocation tests.

26% (39/149) positive OPT

Study year 2002-2011

Nissen *et al. Clinical and Translational Allergy* (2015) 5:10
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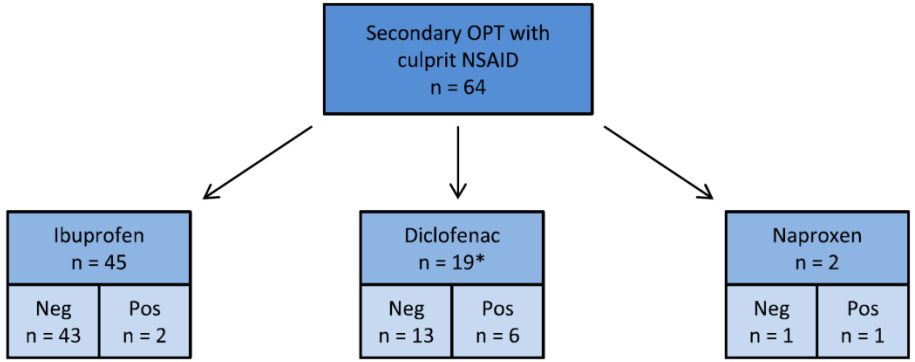

Figure 2 Results of secondary oral provocation test (OPT) with culprit NSAID. Sixty-six OPTs were performed in 64 patients with a negative challenge for ASA. Nine patients had a positive secondary OPT. *Two patients had a history of multiple reactions after intake of several NSAIDs and underwent provocation tests with ibuprofen and diclofenac, both of which were negative. OPTs = oral provocation tests.

Study year
2002-2011

ASA/ NSAID

Table 4 Characteristics of 39 patients with positive OPT according to the EAACI/ENDA classification [12]

Type of reaction	Clinical manifestation	Timing of reaction	Underlying disease	Cross-reactivity	Putative mechanism	Patients n = 38*
NSAIDs-exacerbated respitoratory disease (NERD)	Bronchial obstruction, dyspnea and/or nasal congestion/rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/rhinosinuitis/ nasal polyps	Cross-reactive	Non-allergic COX-1 Inhibition	9
NSAIDs-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		Chronic urticaria	Cross-reactive	Non-allergic COX-1 Inhibition	14
NSAIDs-induced urticaria/angioedema (NIUA)	Wheals and/or angioedema		No underlying chronic diseases	Cross-reactive	Non-allergic Unknown, probably COX-1 inhibition	6
Single NSAID-induced urticaria/ angioedema and anaphylaxis (SNIUAA)	Wheals/angioedema/anaphylaxis		No underlying chronic diseases	Single drug induced	Allergic IgE-mediated	9
Single-NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (e.g., fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually more than 24 h after exposure)	No underlying chronic diseases	Single drug or multiple drug induced	Allergic T-cell mediated	0

*1 patient could not be classified.

Nissen et al, CTA 2015

Nasal symptoms in patients with NSAID hypersensitivity*

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14 with NERD;
1 no CRS but asthma
2/13 with CRS no visible polyps at rhinoscopy

Table 1. Characteristics of 46 patients with NSAID hypersensitivity according to the EAACI/ENDA classification.

Type of reaction	Clinical manifestation	Timing of reaction	Underlying disease	Cross-reactivity	Putative mechanism	Patients (number having CRS)
NSAIDs-exacerbated respiratory disease (NERD)	Broncial obstruction, dyspnea and/or nasal congestion/ rhinorrhea	Acute	Asthma/ rhinosinusitis/ nasal polyps	Cross-reactive	Non-allergic COX-1 inhibition	14* (13)
NSAIDs-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema	-	Chronic urti-carial	Cross-reactive	Non-allergic COX-1 inhibition	6** (1)
NSAIDs-induced urticarial/angioe-dema (NIUA)	Wheals and/or angioedema	-	No underlying chronic disease	Cross-reactive	Non-allergic un-known, probably COX-1 inhibition	19*** (2)
Single NSAID-induced urticarial/ angioedema and anaphylaxis (SNIUAA)	Wheals/ angioedema/ anaphylaxis	-	No underlying chronic disease	Single drug induced	Allergic IgE-mediated	7 (3)
Single-NSAID induced delayed reactions (SNIDR)	Various symptoms and organs involved (e.g. fixed drug eruption, SJS/TEN, nephritis)	Delayed	No underlying chronic disease	Single drug or multiple drug induced	Allergic T-cell mediated	0

*Six patients had overlap of cutaneous symptoms, ** One patient had overlap of respiratory symptoms, *** Two patients had overlap of respiratory symptoms.

19/46 (41%) CRS based on EPOS 2012

Nasal endoscopy, smell test, (CT)

Study year 2013-2016

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CRS versus no CRS

Table 2. Results comparing patients with and without CRS and patients with CRSwNP and CRSsNP (Range).

	No CRS	CRS overall	p	CRSsNP	CRSwNP	p
Number of patients	27	19	-	7	12	-
Mean age	43 (20-75)	44 (19-65)	0.89	47 (33-60)	42 (19-65)	0.45
Female	13	10	0.77	4	6	0.76
Current smokers	11	6	0.53	2	4	0.83
Asthma	3	15	0.00	4	11	0.08
SNOT 22 score	17 (0-49)	39 (7-77)	0.00	34 (24-42)	42 (7-77)	0.07
Smell test score	10 (6-12)	7 (0-12)	0.01	11 (10-12)	5 (0-11)	0.00
Previous sinus surgery	0	7	0.00	0	7	0.01
Number of patients receiving nasal steroid	2	12	0.00	3	9	0.16
Number of patients receiving nasal/sinus surgery	2*	8	0.01	0	8	0.01

* Only septumplasty.

Lange et al, Rhinology online 2019

Sino Nasal Outcome test 22 (QoL)

Table 3. Mean score SNOT 22 total and mean score SNOT 22 subdomains.

	No CRS	CRS overall	p	CRSsNP	CRSwNP	p
SNOT 22 total	17	39	0.00	34	42	0.07
Nasal symptoms	7.9	20,7	0.00	16.1	23.3	0.04
Otologic symptoms	1.3	2.7	0.01	2.3	2.9	0.32
Sleep symptoms	4.8	8.5	0.02	8.6	8.4	0.97
Emotional symptoms	2.6	7.3	0.00	6.9	7.5	0.97

Maximum range: SNOT 22 total: 0-110, nasal symptoms: 0-45, otologic symptoms: 0-15, sleep symptoms: 0-25, emotional symptoms: 0-25.

Reference general Danish population: 10 (Lange et al 2013)

Lange et al, Rhinology online 2019

Danish recommendation

Patients with NSAID hypersensitivity

- 41% CRS with affected QoL, reduced sense of smell and need for treatment of sino-nasal problems
- Recommended screened for sino-nasal symptoms and ENT evaluation

Lange et al, Rhinology online 2019

Desensitization?

Indication for ASA/NSAID treatment e.g. CV disease, rheumatologic disease
Recurrence prevention in nasal polyps

Asthma Symptoms?

Evidence NERD

Decrease in CRS symptoms (grade 1A)

Decrease in nasal corticosteroid use (grade 2B)

Reduction in recurrence of nasal polyps (grade 2B)

Decrease in the need for revision surgery (grade 2B)*

In a subset decreased asthma symptoms and improved asthma control (grade 1B)

*Once every 3th year to once every 9th year

EAACI position paper NERD, Kowalski et al Allergy 2018

Recommendation NERD

TABLE 2 Recommended oral aspirin challenge/desensitization protocol (modified from A. White and DD Stevenson IACNA 2013[71])

Time	Day 1	Day 2
9:00 AM	20-40 mg	100-160 mg
11:00 AM	40-60 mg	160-325 mg
01:00 PM	60-100 mg	325 mg

- Sinus surgery and desensitization 4 (6-12) weeks after the operation is recommended
- Oral (nasal, bronchial, IV)
- Maintenance dose ranges from 300-1300 mg, most 300 mg
- Side effects mainly GI
- Recommed H. pylori eradication, PPI, H2 blockers during treatment
- Montelukast reduce bronchial but not nasal symptoms during desensitization

EAACI position paper NERD, Kowalski et al. Allergy 2018
Klimek et al. Curr Allergy Asthma rep 2014

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Differential diagnosis

- Urticaria/angioedema
- Asthma
- Others?

Conclusion

- ASA/NSAID hypersensitivity a common drug reaction, different subtypes
- Need for ENT evaluation
- The NERD group may benefit from desensitization
- Remember that NSAID may be a co-factor!