



ORDINE PROVINCIALE
DEI MEDICI CHIRURGHI E
DEGLI ODONTOIATRI
DI VENEZIA



CORSO DI FARMACOALLERGOLOGIA: SPUNTI DI DISCUSSIONE SULLE ALLERGIE AI FARMACI

LE REAZIONI ALLERGICHE AI FANS

Patrizia Bonadonna e Andrea Zancanaro

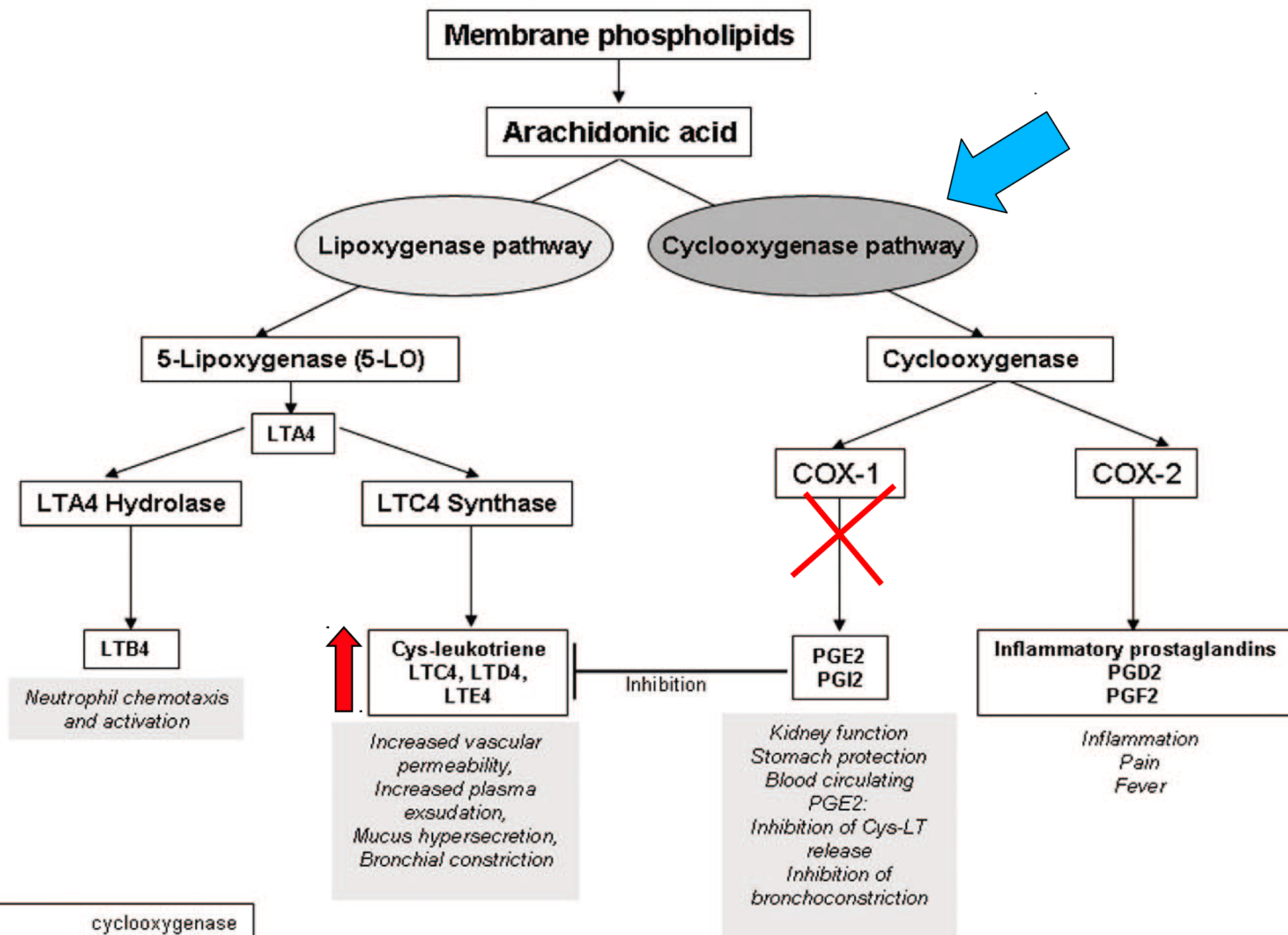




Elenco dei prodotti da banco più venduti in Italia 1° semestre 2018

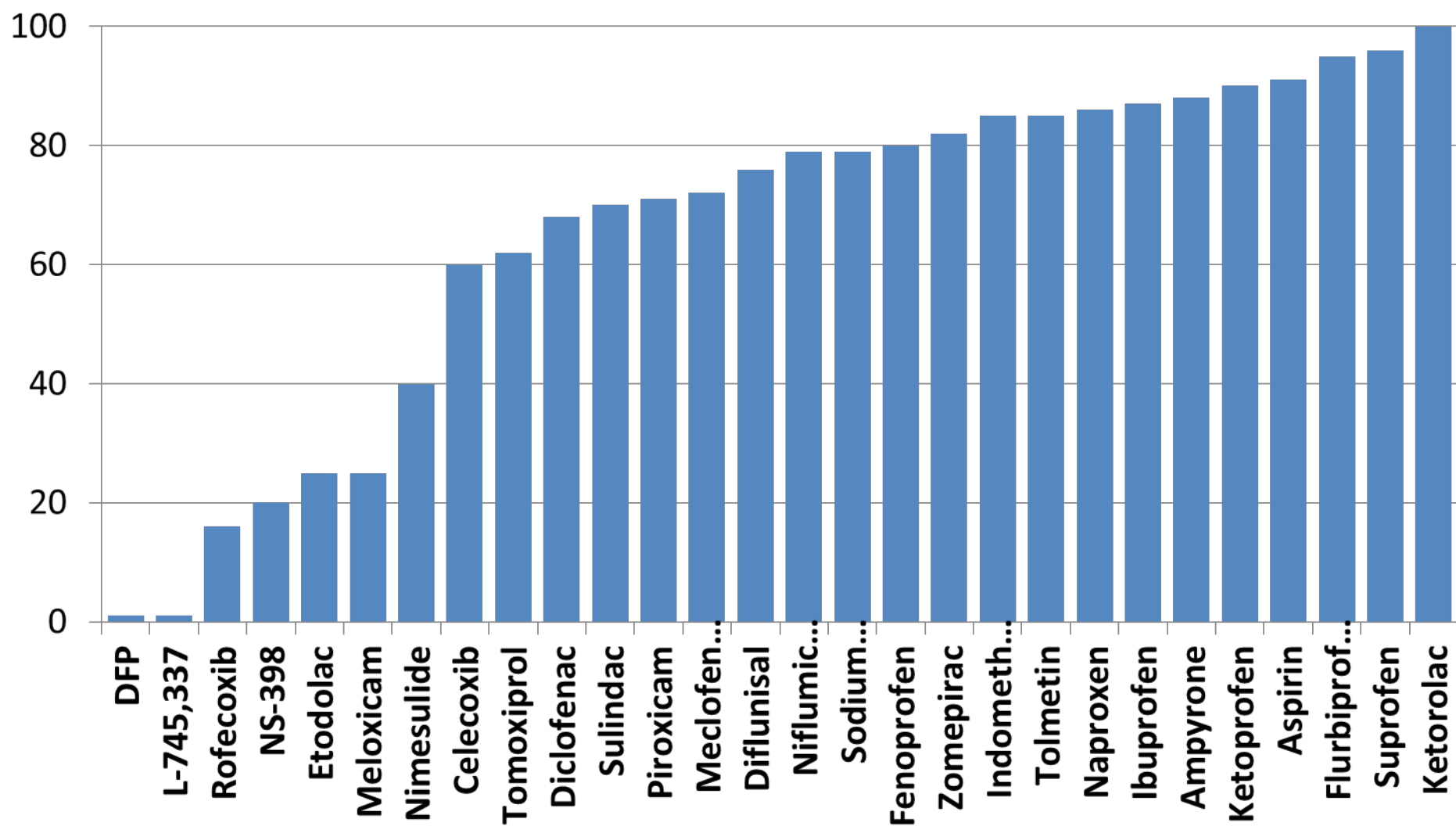


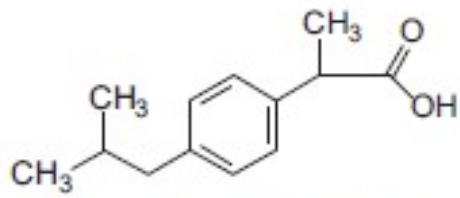
- 6,3 milioni di confezioni di Tachipirina (varie formulazioni)
- 2,9 milioni di confezioni di Enterogermina
- 1,8 milioni di confezioni di Rinazina spray nasale
- 1,8 milioni di confezioni di Aspirina effervescente
- 1,2 milioni di tubetti di Voltaren gel
- 1,2 milioni di Okitask
- 1 milione di scatole di Moment compresse
- 65000 di confezioni di Nurofen Sciroppo pediatrico



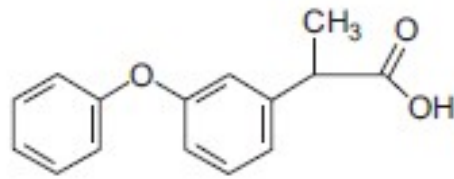
COX	cyclooxygenase
LT	leukotrien
PG	prostaglandin
CYS	cysteiny

Percentuale di inibizione della COX-1 da parte di vari FANS

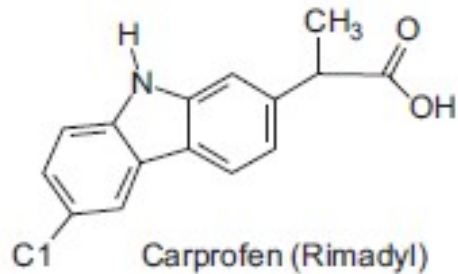




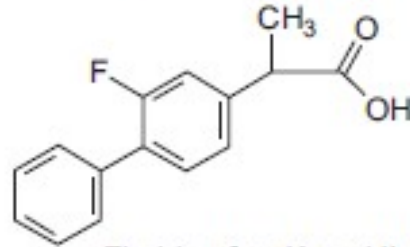
Ibuprofen (Motrin)



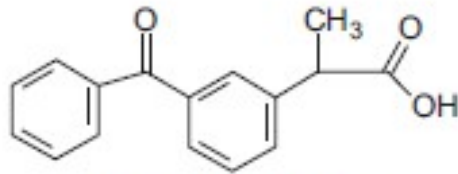
Fenoprofen



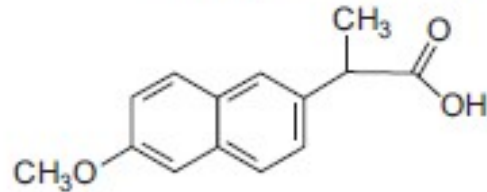
Carprofen (Rimadyl)



Flurbiprofen (Ansaid)

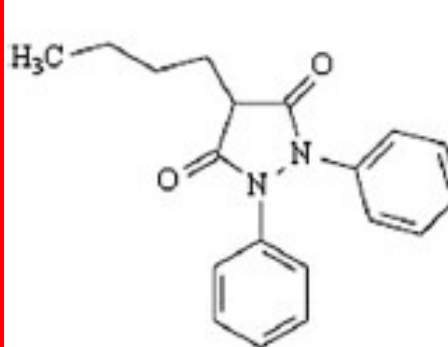
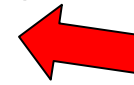


Ketoprofen (Orudis)

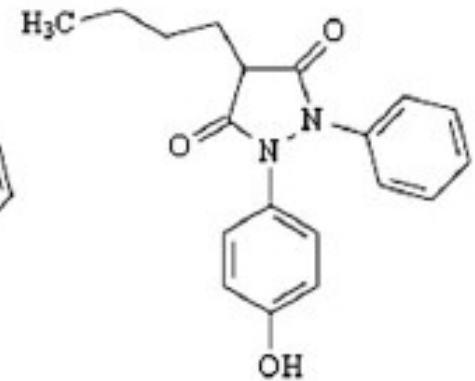


Naproxen (Aleve, Anaprox)

**Es DERIVATI DALL'ACIDO
PROPIONICO**



Phenylbutazone

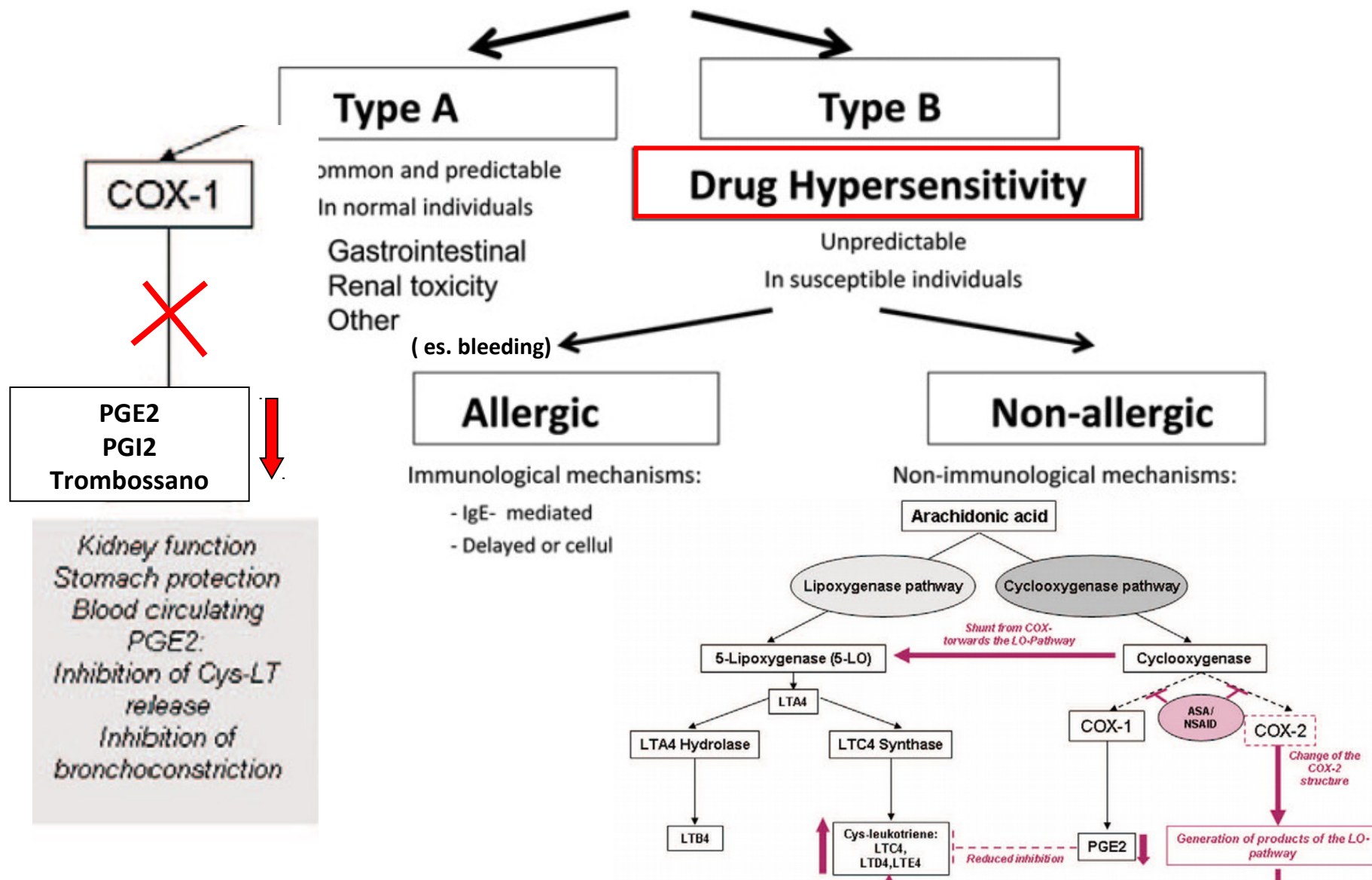


Oxyphenbutazone

NSAIDs grouped in classes determined by similar chemical structures

Group	Drugs
Salicylic acid derivatives	Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfalazine, olsalazine
Para-aminophenol derivatives	Acetaminophen
Indol and indene acetic acids	Indomethacin, sulindac, etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Arylpropionic acid	Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin
Anthranilic acid (fenamates)	Mefenamic acid, meclofenamic acid
Enolic acid	Oxicams (piroxicam, tenoxicam), pyrazolidinediones (phenylbutazone, oxyfentathrazone)
Alkalones	Nabumetone
Pyrazolic derivatives	Antipyrine, aminopyrine, dipyrrone

Adverse Reactions to NSAIDs



Epidemiologia NSAID- induced hypersensitivity reactions (IHR)

- **Prevalenza: 0,3% - 5,7%**
- **Rappresentano la 2° causa più comune di reazioni di ipersensibilità ai farmaci**
- **Prevalenza tra gli adulti asmatici (questionario): 4,3-11%**
- **Prevalenza tra gli adulti asmatici (challenge) : 21 %**
- **Prevalenza delle manifestazioni cutanee da FANS: 0,3%**
- **Prevalenza delle reazioni di ipersensibilità ai FANS nei pazienti con orticaria cronica: 27-35%**

Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA[#] and GA2LEN/HANNA*

M. L. Kowalski¹, J. S. Makowska¹, M. Blanca², S. Bavbek³, G. Bochenek⁴, J. P. Bousquet⁶, G. Celik³, P. Demoly⁷, E. B. Gomes⁸, E. Nizankowska-Mogilniczka⁵ | *Allergy 2011*

Timing of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism
Acute (immediate to several hours after exposure)	Rhinitis/asthma	Cross-reactive	Asthma/rhinosinusitis/nasal polyps	Inhibition of COX-1
	Urticaria/angioedema	Cross-reactive	Chronic urticaria	Inhibition of COX-1
	Urticaria/angioedema	Multiple NSAIDs-induced	No underlying chronic disease (in some patients, the reaction to NSAIDs may precede development of chronic urticaria)	Unknown Presumably related to COX-1 inhibition
	Urticaria/angioedema/anaphylaxis	Single drug-induced	Atopy Food allergy Drug allergy	IgE-mediated
Delayed (more than 24 h after exposure)	Fixed drug eruptions. Severe bullous skin reaction Maculopapular drug eruptions Pneumonitis Aseptic meningitis Nephritis Contact and photocontact dermatitis	Single drug or multiple drug-induced	Usually no	T-cell-mediated (Type IV) Cytotoxic T cells NK cells Other

Reazioni di Ipersensibilità ai FANS di tipo Immediato/Acuto

**Cross-reattività
tra FANS**

Rinite e asma esacerbati da FANS (AERD)	+
Orticaria/angioedema da FANS in CU	+
Orticaria/angioedema da singolo farmaco	-
Orticaria/angioedema da più FANS	+
Anafilassi da singolo FANS (IgE-mediata)	-
Reaz Mista cutanea + respiratoria	+/-

Reazioni di Ipersensibilità ai FANS di tipo Immediato/Acuto

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Reazioni di Ipersensibilità ai FANS di tipo Immediato/Acuto

Cross-reattività
tra FANS

**Rinite e asma esacerbati da FANS
(AERD)**

+

- **Triade ASA o Triade Samter Widal o asma Triad o **Aspirin- Exacerbated Respiratory Disease****
- **Evitare completamente il farmaco non necessariamente altera la progressione della sottostante malattia**
- **Sintomi: rinorrea, dispnea e broncostruizione dopo assunzione del FANS**

Prevalence of AERD

- 0.5 -1.9 % in **normal population**
- 4.3-11% (questionnaires)
- 8-21% among **adult asthmatics** (challenge)
- 5% in **children (0-18) asthmatics** (challenge)

- 30-40% in CRS with **nasal polyposis (history)**
- 60-85% in CRS with **nasal polyposis (challenge)**

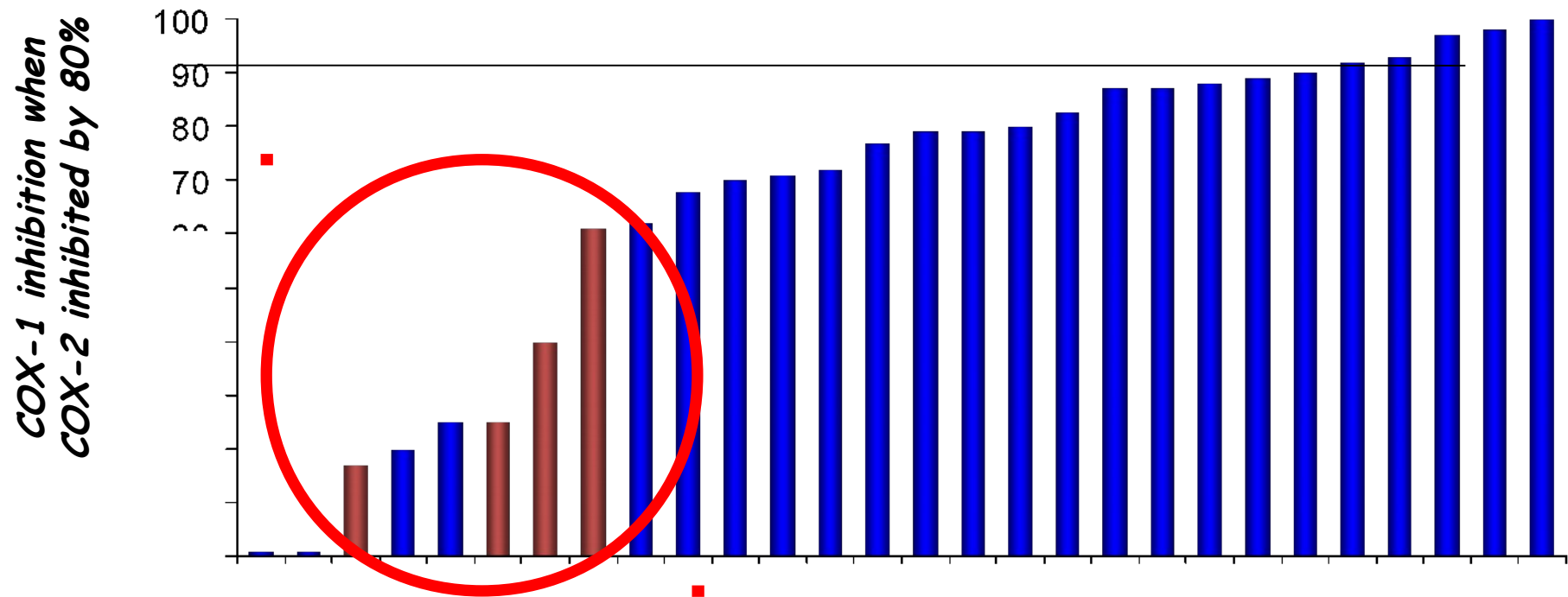
- F/M 2.3:1 in EU and 3:2 ratio in USA
- No racial or ethnic predilection
- Family histories are rare (1-6%), early diagnosis
- **Atopy 34-64%**

Atopy and AERD

- **The risk of AERD is eight times higher in people with allergic rhinitis than in those without it**
(Hedman et al. Int J Epidemiol 1999; 28: 717)
- **Allergic conditions and serum IgE levels were higher in asthmatic patients with AERD than those who tolerated aspirin**
(Kolyoncu et al. Allergy 1999; 54: 428)
- **Atopy is a risk factor for NSAIDs sensitivity**
(Sancez-Borges et al. Ann Allergy Asthma Immunol 2000; 84: 101)

Gestione del paziente con AERD: Scelta del farmaco alternativo

COX-2-selective inhibitors



Group A: NSAIDs cross-reacting in majority of hypersensitive patients (60–100%)

Ibuprofen	Etololac
Indomethacin	Diclofenac
Sulindac	Ketoprofen
Naproxen	Flurbiprofen
Fenoprofen	Piroxicam
Meclofenamate	Nabumetone
Ketorolac	Mefenamic acid

Group B: NSAIDs cross-reacting in minority of hypersensitive patients (2–10%)

Rhinitis/asthma type
acetaminophen (doses below 1000 mg)
meloxicam
nimesulide
Urticaria/angioedema type
acetaminophen
meloxicam
nimesulide
selective COX-2 inhibitors (celecoxib, rofecoxib)

Group C: NSAIDs well tolerated by all hypersensitive patients*

Rhinitis/asthma type
selective cyclooxygenase inhibitors (celecoxib, parvocoxib)
trisalicylate, salsalate
Urticaria/angioedema type
new selective COX-2 inhibitors (etoricoxib, pavocoxib)

ML Kowalski
Allergy 2011

Da evitare
Alta cross-reattività

- Si possono usare ma senza superare le dosi (Es. Paracet. ≤ 500 mg)
- Eseguire test di tolleranza

Clinical and pathologic perspectives on aspirin sensitivity and asthma

Stevenson & Szczeklik JACI 2006;118 : 773

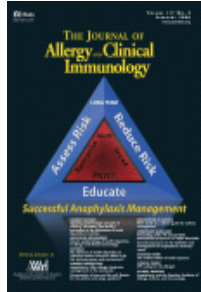


TABLE III. Selective COX-2 inhibitors preferentially inhibit COX-2

Celecoxib (Celebrex)*

Rofecoxib (Vioxx)†

Valdecoxib (Bextra)†

Etoricoxib (Arcoxia)‡

Parecoxib (Dynastat)‡

Lumiracoxib (Prexige)‡

Tolerability of coxibs

Author	N	Drug	Dosage	Reactors, n (%)
Sánchez Borges, 2001	20	Celecoxib	200	4 (20)
		Rofecoxib	25	1 (5)
Valero, 2002	58	Rofecoxib	50	1 (1.7)
Munoz-Bellido, 2003	61	Rofecoxib	47	1 (1.6)
Perrone, 2003	216	Rofecoxib	25	1 (0.46)
Senna, 2004	52	Celecoxib	200	4 (7.6)
	52	Rofecoxib	25	1 (1.9)
Nettis, 2005	141	Etoricoxib	90	2 (1.4)
Sánchez Borges, 2005a	54	Celecoxib	200	6 (11.1)
	56	Etoricoxib	120	4 (7.1)
Sánchez Borges, 2005b	28	Rofecoxib	50	2 (7.1)
		Valdecoxib	40	1 (3.5)
Viola, 2005	120	Celecoxib	200	1 (1.1)

- **Donna di 55 anni**

- **6 mesi prima: orticaria generalizzata , vomito e sincope 2 h dopo l'assunzione di una compressa di Naprossene**

- **Anamnesi Patologica Remota:**

- Rinite e Congiuntivite in primavera : allergica al polline di betulla e graminacee
- Soffre di gastrite cronica

- **Ha avuto alcuni episodi di orticaria cronica , ma in questo periodo era in remissione**



**.....abbiamo quindi sottoposto la
paziente ad un test di scatenamento
con un antinfiammatorio alternativo**



2010

ORIGINAL ARTICLE

EUR ANN ALLERGY CLIN IMMUNOL

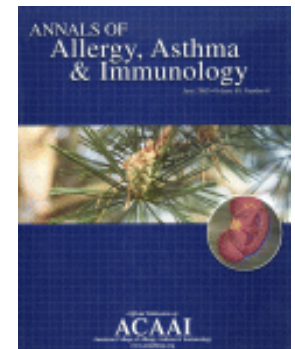
VOL 42, N 6, 216-220, 2010

M. PAGANI¹, P. BONADONNA², A. DAMA³, G.E. SENNA³, P.P. VESCOVI¹, A. ANTICO¹

Long-term tolerability of etoricoxib in different types of NSAID-intolerant subjects

Safety of etoricoxib, a new cyclooxygenase 2 inhibitor, in patients with nonsteroidal anti-inflammatory drug-induced urticaria and angioedema

Mario Sánchez-Borges, MD*†; Fernan Caballero-Fonseca, MD*‡; and Arnaldo Capriles-Hulett, MD*‡



**Ann Allergy
Asthma Immunol.
2005**



**Int Arch Allergy
Immunol. 2007**

Etoricoxib tolerability in patients with hypersensitivity to nonsteroidal anti-inflammatory drugs.

Viola M, Quaratino D, Gaeta F, Caruso C, Valluzzi R, Romano A.

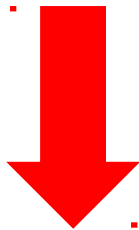
Challenge test

1° gg : Placebo



Dopo circa 40' pz. presenta: sensazione di "malessere" e prurito "sine materia"

2° gg : Etoricoxib



< 1 h

Anafilassi

« Potrebbe spiegarmi in dettaglio tutto quello che ha ingerito durante il test...»



« subito prima di iniziare il test ho mangiato una bananae come al solito ,quando devo assumere un antinfiammatorio ho assunto una compressa di rabeprazolo!»

Skin Tests



BANANA

- **Prick test (estratti commerciali) : Negativi**
- **Prick by prick (frutto fresco): Negativo**
- **IgE specifiche: Negative**
- **Challenge test: Negativo**

I 10 principi attivi più prescritti a livello nazionale

Principio attivo	incidenza sul n. confezioni 2010	diff. rispetto confezioni 2009
lansoprazolo	4,04%	+2,29%
acido acetilsalicilico	2,95%	+4,23%
omeprazolo	2,54%	+18,31%
ramipril	2,40%	+7,98%
pantoprazolo sodico sesquidrato	2,34%	+26,36%
metformina cloridrato	2,07%	+12,46%
amlodipina besilato	1,93%	+4,97%
amoxicillina triidrato/potassio clavulanato	1,73%	-2,27%
furosemide	1,71%	+5,13%
ceftriaxone disodico	1,44%	-1,19%

Inibitori di Pompa

- Omeprazolo (1989)
- Lansoprazolo (1995)
- Pantoprazolo (1997)
- Rabrepazolo (1999)
- Esomeprazolo (2002)

Reazioni Avverse minori: 1%- 3%

- cefalea
- diarrea
- nausea
- vertigini
- **rush (0,5% - 1.1%)**

Reazioni Avverse maggiori: rari (case reports)

- nefrite (*omeprazolo*)
- epatite (*omeprazolo e lansoprazolo*)
- disturbi visivi (*omeprazolo e pantoprazolo*)

THE LANCET

Volume 345, Number 8044 • October 1992 • Published weekly • Sunday 1 June 1993

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- 1004 **Pharmacology**: the new penicillins
- 1005 **Pharmacology**: the new penicillins

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Pharmaceutical industry
page 1046

Acute disseminated epidermal necrosis due to omeprazole

SIR,—A 72-year-old woman started omeprazole 20 mg daily for dyspeptic symptoms unresponsive to antacids. She was disabled by a previous hemiplegia, cardiac failure, agoraphobia, and travel sickness, and she was taking long-term medication for heart failure and depression. 2 weeks after starting omeprazole she developed a rash on the arms which became very extensive on trunk and proximal limbs over the following 4 weeks, at which stage she was referred here. The omeprazole had not been discontinued at an early stage in view of the beneficial effect on the gastro-oesophageal symptoms.

1992

“...up “to August 1992 the *Committee on Safety of Medicines* has received 223 reports of cutaneous reactions to omeprazole including 6 erythema multiforme and 8 patterns of blisterings”

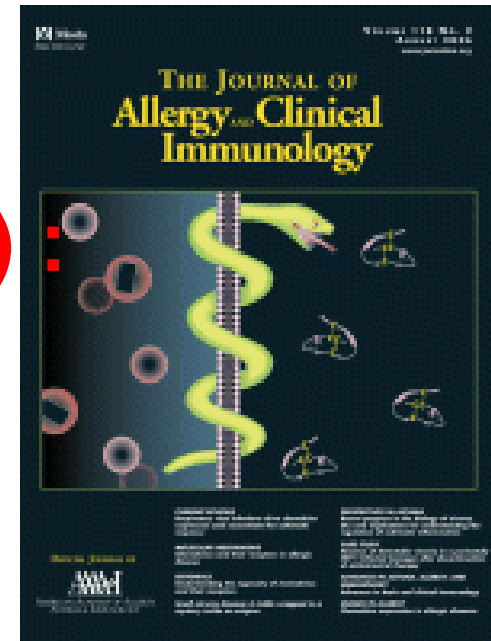
Anaphylaxis to omeprazole

Jan Paul Ottervanger, MD,^a Rita A. S. Phaff, MD,^b

Erik G. J. Vermeulen, MD,^c and Bruno H. Ch. Stricker, MB, PhD^a

Rijswijk and Rotterdam, The Netherlands

Prick test Omeprazolo (4mg/ml)
Positivo = Pomfo + Eritema



1996

Hypersensitivity to proton pump inhibitors: Diagnostic accuracy of skin tests compared to oral provocation test

JACI 2012

Patrizia Bonadonna, MD^{a}*

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Oscar Bortolami, PhD^b

Andreas Bircher, MD^c

Kathrin Scherer, MD^c

Annick Barbaud, MD^d

Giovanni Passalacqua, MD^e

Mauro Pagani, MD^f



Allergy

EUROPEAN JOURNAL OF ALLERGY
AND CLINICAL IMMUNOLOGY



ORIGINAL ARTICLE

EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Immediate-type hypersensitivity reactions to proton pump inhibitors: usefulness of skin tests in the diagnosis and assessment of cross-reactivity

S. Kepil Özdemir¹, İ. Yılmaz¹, Ö. Aydın¹, S. Büyüköztürk², A. Gelincik², M. Demirtürk², D. Erdoğan², Ş. Cömert³, T. Erdoğan³, G. Karakaya³, A. F. Kalyoncu³, F. Öner Erkekol⁴, A. B. Dursun⁴, Z. Mısırlıgil¹ & S. Bavbek¹

2013

Test cutanei per inibitori di pompa

Drug	Prick (40 mg/ml)	Id 0,04 mg/ml	Id 0,4 mg/ml
OMEPRAZOLE	neg	neg	neg
ESOMEPRAZOLE	neg	neg	neg
PANTOPRAZOLE	neg	neg	neg
Drug	Prick	Id	Id
LANSOPRAZOLE (30 mg/ml)	neg	/	/
RABEPRAZOLE (40 mg/ml)	positive	/	/

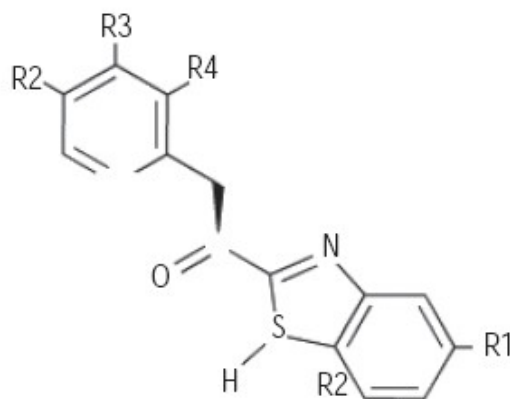
- **Ripetizione del Challenge Test con Etoricoxib**
- **Challenge test con Naprossene**



Tollerati entrambi

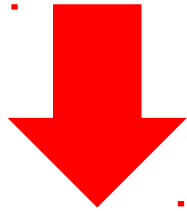


Cross-reattività tra PPI



	R1	R2	R3	R4
Omeprazole	-OCH ₃	-CH ₃	-CH ₃	-CH ₃
Lansoprazole	-	-	-OCH ₂ -CF ₃	-CH ₃
Pantoprazole	-OCF ₂ H	-	-OCH ₃	-OCH ₃
Rabeprazole	-	-	-O(CH ₂) ₃ -OCH ₃	-CH ₃
Esomeprazole	-OCH ₃	-CH ₃	-OCH ₃	-CH ₃

**Challenge Test con 40 mg
di Pantoprazole**



Tollerato



Diagnosi finale

**Anafilassi da rabeprazolo in
paziente che tollera i farmaci
anti-infiammatori.**

Azienda Ospedaliera Universitaria Integrata di Verona



Collaborations with:

Unità Operativa di Allergologia

Dr. Gianenrico Senna
Dr. Patrizia Bonadonna
Dr. Michele Schiappoli
Dr.ssa Annarita Dama
Dr. Marco Caminati
Dr.ssa Elisa Olivieri

- **Dr.ssa Roberta Zanotti**
Gruppo Interdisciplinare Mastocitosi
- **Dr. Giovanni Passalacqua**
Università di Genova
- **Dr.ssa Beatrice Caruso**
Laboratorio Vr
- **Dr. ssa Giovanna Zanoni**
Immunologia Vr
- **Dr.ssa Carla Lombardo**
- **Dr. Mauro Pagani**