Non-Steroidal Anti Inflammatory Drugs: Overview of reports of Over The Counter (OTC) products

Introduction

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) are agents with potent anti-inflammatory, analgesic, and antipyretic properties. NSAIDs are potent inhibitors of cyclooxygenase activity, which causes a reduction in the formation of prostaglandin, prostacyclin and thromboxane product, all of which are mediators of inflammation.
NSAIDs are indicated for *rheumatic pain, muscle pain, headache, tooth pain, symptomatic treatment of primary dysmenorrhea, acute low back pain, pain and fever accompanying flue, pharyngitis and cold* [1]. NSAIDs are available since the seventies in the last century.

Common adverse reactions with NSAIDS are headache, dizziness, vertigo, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, rash and elevation of transaminases [1]. Uncommonly or in rare cases severe reactions are observed, including (bleeding or perforation of a) stomach ulcer, anaphylactic reactions, pancytopenia, interstitial nephritis, renal failure, liver failure, Stevens Johnson syndrome / Toxic Epidermal Necrolysis, heart failure and myocardial infarction [1-4].
In the Netherlands NSAIDs are available on prescription as well as over the counter (OTC) use without prescription. Since the enactment of the Medicines Act of 2007, OTC medicines have been categorized into three categories of legal status of supply. These categories are pharmacy only (PH), Pharmacy and Drugstore only (PDO) and without restriction (GS) respectively. In the Netherlands, classic oral OTC NSAIDs currently available are diclofenac potassium (tablets 12.5 mg and 25 mg), ibuprofen (tablets and capsules 200 mg and 400 mg, suspension 20 mg/ml), ketoprofen (tablet 25 mg) and naproxen (220 mg, 275 mg, 550 mg) [5]. These OTC NSAIDs are sold in pharmacies, drug stores or in supermarkets/service stations, depending on dosage and pack size. Diclofenac 25 mg and naproxen 550 mg are only available in the pharmacy. All other products can be bought in the pharmacy and drugstore, depending on pack size, except ibuprofen 200 mg (maximum 12 tablets), which is available in supermarkets/ services stations as well.

The current observation describes an overview of reported adverse reactions of the above mentioned OTC NSAIDs.

Reports

Selection of OTC NSAIDs
All non-oral NSAIDs were omitted. Current as well as non-current oral NSAIDs were included. Concerning diclofenac, only potassium salts (12,5 mg and 25 mg) were selected. For ibuprofen, all oral forms of 200 mg and 400 mg were included as well as suspension 20 mg/ml. Regarding naproxen all oral strengths were selected, because dosages from 220 mg, 275 mg and even the highest tablet dose of 550 mg (Aleve intense tablet) are available as OTC product; surprisingly lower dosages of 250 mg and 500 mg are only available on prescription. From a medical perspective, these were however also considered relevant and were selected. For ketoprofen 25 mg no reports were available. Therefore, selection was primarily based upon strength of the individual oral OTC NSAID, but from each individual

report it is not evident, if the product was bought as OTC product or if it was supplied on prescription.
On August 8, 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained in total 1842 adverse drug reactions in 1184 patients associated with the use of oral OTC NSAIDs. With diclofenac potassium use 19 patients experienced 36 reactions, with use of ibuprofen 409 patients experienced 619 reactions and with naproxen use 756 patients experienced 1187 reactions. Serious cases were observed in 12 patients (63 %) for diclofenac potassium, in 67 (16 %) patients for ibuprofen and in 114 patients (15 %) for naproxen.

Death
A fatal outcome was reported ten times in total, once in relation to diclofenac K, five times in relation to ibuprofen and four times in relation to naproxen. Details are presented in table 1.

Table 1. Fatal outcome reported with the use of diclofenac K, ibuprofen and naproxen

Patient, Number, Sex, Age, Source	**Drug, daily dose Indication for use**	**Concomitant Medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug, outcome**
A 147627 M, 70 years and older Consumer/ non health professional	diclofenac k 25mg bid	non specified anticoagulans, non specified betablocker	renal failure, death unexplained	< 1 year discontinued fatal
B 27249 M, 51-60 years MAH	paclitaxel 6mg/ml o.d lung carcinoma, ibuprofen 200mg o.d. gemcitabine 200mg o.d. lung carcinoma		gastric ulcer perforation, death nos	4 months discontinued fatal
C 34314 M, 61-70 years Social medicine	ibuprofen 400mg, 16 times daily pain	Calcium carbonate / magnesium carbonate	gastrointestinal tract bleed nos, renal function abnormal	1 day discontinued fatal
D 70570 F, 21-30 years General Practitioner	ibuprofen 400mg o.d-t.i.d. headache		death, viral myocarditis	3 year not applicable fatal
E 104512 F, 70 years and older Specialist doctor	ibuprofen 200mg traumatic injury		death, toxic epidermal necrolysis	days not applicable fatal
F 145416 M, 70 years and older Other health professional	bortezomib 1 mg/mg multiple myeloma, ibuprofen 400 mg o.d. bone pain dexamethasone 20 mg o.d. multiple myeloma		acute cholestatic hepatitis, hepatitis acute, liver failure, itch, jaundice	4.5 months discontinued fatal

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
G 20964 F, 70 years and older Physician with own pharmacy	acenocoumarol 1mg trimethoprim 300mg cystitis, unspecified omeprazol 20mg b.i.d. naproxenum tablet 250mg b.i.d.	tolbutamide furosemide betahistine lactulose syrup hydroxychloroquine paracetamol temazepam isosorbide mononitrate	epistaxis, death nos	2 months unknown fatal
H 30951 M, 61-70 years Specialist doctor	naproxen tablet 250mg, norfloxacin 400mg cystitis, unspecified	enalapril dipyridamol tramadol carbasalate calcium	nephritis interstitial, death nos	1 month unknown fatal
I 70969 unknown, 70 years and older Specialist doctor	naproxen a tablet 250mg		gastrointestinal ulcer	not reported unknown fatal
J82843 M, 70 years and older General Practitioner	etoricoxib 90mg low back pain, naproxen 220mg low back pain	formoterol/ budesonide inhalation, terbutalin inhaler triamcinolone cream	death, gastric haemorrhage	etoricoxib: 3 months naproxen: unknown not reported fatal

Serious reactions

The most frequently reported serious ADRs reported in association with diclofenac K , ibuprofen and naproxen are listed in table 2.

Table 2. Top 10 Serious* reactions for diclofenac K, ibuprofen and naproxen: absolute count and percentage of total number of serious reactions is shown.

diclofenac K			**ibuprofen**			**naproxen**		
PT	n	%	PT	n	%	PT	n	%
Anaphylactic reaction	3	8,8	Angioedema	4	3.3	Anaphylactic shock	15	7,7
Renal impairment	2	5,9	Ulcer	4	3,3	Anaphylactic reaction	9	4,6
Pruritus	2	5,9	Drug interaction	3	2,5	Dyspnea	7	3,6
Liver disorder	2	5,9	Anaphylactic shock	3	2,5	Angioedema	6	3,1
Hypersensitivity	2	5,9	Hypersensitivity	3	2,5	Hypersensitivity	5	2,6
Erythema	1	2,9	Death	3	2,5	Urticaria	4	2,1
Angioedema	1	2,9	Anaphylactic reaction	2	1,7	Swollen tongue	4	2,1
Heart rate increased	1	2,9	Gastrointestinal hemorrhage	2	1,7	Renal failure acute	4	2,1
Hepatic function abnormal	1	2,9	Urticaria	2	1,7	Hypotension	4	2,1
Renal function test abnormal	1	2,9	Renal impairment	2	1,7	Hemorrhage	3	1,5

* Since reporters can only assess the seriousness of the complete report, and not the individual ADRs, it is possible that the table contains non serious ADRs that are part of a serious report

In association with diclofenac K only anaphylactic reaction, renal impairment, pruritus, liver disorder and hypersensitivity were reported more than once. For ibuprofen angioedema and ulcer were reported most frequently. For naproxen anaphylactic shock and anaphylactic reaction were reported most frequently, followed by dyspnea, angioedema and hypersensitivity. Below, some reactions are described in detail, either to ascertain the seriousness of the reported reaction (e.g. anaphylactic reaction/shock), the actual interpretation of the reported reaction (location of ulcer and hemorrhage: gastro-intestinal or elsewhere), impact (drug interaction with the different- or same medications) and/or presence of possible risk factors.

Anaphylactic reaction and anaphylactic shock

The anaphylactic reactions and shocks were almost exclusively reported by health professionals. It concerned both females and males, almost all adults. Reactions on naproxen were seen on the higher doses of 500 mg and 550 mg as well as on lower doses of 220mg, 250 mg and 275 mg; for ibuprofen reactions took place on both 200 mg and 400 mg. A substantial amount of patients had used the suspected drug before without experiencing a reaction, in some patients however, previously less severe reactions had taken place. Latency in most cases was between 15 minutes and 1 hour after intake. Almost all patients were treated with adrenalin, clemastine and/or corticosteroids.

IBUPROFEN

Ulcer
For ibuprofen, ulcer (organ class General disorders) was reported four times on ibuprofen 200 mg; verification revealed this concerned gastro-duodenal ulcers. All were reported by the MAH on four patients (aged 36 till 93) described in a publication in the literature.

Drug Interaction
Three serious reactions of drug interaction with ibuprofen were observed. The first one (48738) concerned a literature report with a pharmaceutical company as sender, regarding a female aged 55, with hyponatraemic coma following administration of desmopressin and ibuprofen with an unknown latency period. Concomitant medication was not reported. Patient was hospitalized and has been treated with water restriction. After 48 hours, patient has recovered.
Case 70073 concerned a poorly documented serious literature report from a MAH upon a person of unknown gender and unknown age, with an increased INR as a drug interaction following administration of ibuprofen, diclofenac, naproxen with acenocoumarol with unknown latency. The patient outcome is unknown. Concomitant medication was not reported.
The third report (156189) concerns a female, aged 57 years, with a convulsion as a result of a drug interaction of ibuprofen 400 mg once daily for ear pain with claritromycine 1000 mg daily for otitis with a latency of less than 1 day for ibuprofen and 4 days for clarithromycin. Diagnostic test in hospital (blood test, CT scan, ECG) showed no abnormalities. Ibuprofen was discontinued, clarithromycin was continued. Patient recovered. Concomitant medication was not reported. Medical history revealed that patient

suffered from mononucleosis. Other factor mentioned was that the event occurred on a warm day during holiday in Italy.

NAPROXEN

Haemorrhage
Three serious reports of haemorrhage (organ class Vascular disorders) in association with naproxen were reported. In one poorly documented report (72438) this concerned a rectal haemorrhage in association with naproxen 500 mg, acenocoumarol and diclofenac/misoprostol. The second report (107169) concerned a report of the MAH based upon a literature publication, in which a large hematoma in the mouth after a surgical procedure for carcinoma was described, in association with naproxen 500 mg twice daily and sertraline 100 mg daily. The male patient, aged 53, had a history of abnormal bleeding in the past. A marked decrease in serotonin level in the platelets was found.
The third report, sent by MAH, based upon a literature publication, was a bleeding, not specified, in combination with pulmonary toxicity, gastrointestinal toxicity and bone marrow depression in association with filgrastim, pegfilgrastim, dexamethasone, capecitabine, bleomycine, allopurinol, cyclophosphamide, not specified coumarine and naproxen.

Reactions grouped by System Organ Class (SOC)

Gastrointestinal reactions were most frequently observed (14%, 20% and 31 % respectively for diclofenac K, ibuprofen and naproxen), but also skin reactions were frequently reported (19 %, 21 % and 16 % respectively). Nervous system disorders were often reported for ibuprofen and naproxen (14 % and 12 % respectively), but not in relation to diclofenac potassium. Also cardiac disorders were only reported in relation to ibuprofen (4 %) and naproxen (3%).

On ibuprofen gastro-intestinal reactions most frequently reported were abdominal (upper) pain (33 times), nausea (20 times) and vomiting (12 times) .Skin reactions on ibuprofen most frequently reported were angioedema (21 times) rash (20 times), erythematous rash (13 times), urticaria (19 times), and alopecia (13 times). Regarding the SOC nervous system disorders, dizziness, headache and somnolence were reported most frequently (18, 16 and 12 times respectively). Cardiac adverse reactions observed mostly were palpitations (11 times) and (peripheral) oedema (together 13 times).

On naproxen gastro-intestinal reactions most frequently reported were abdominal (upper) pain (112 times), nausea (60), diarrhoea (23), constipation (19), vomiting (18), dyspepsia (16) and stomatitis (15). Skin reactions on naproxen reported more than ten times were rash (26), urticaria (21), angioedema (19), erythematous rash (18) and pruritus (15). Regarding nervous system disorders in relation to naproxen, dizziness, somnolence and headache were most frequently reported (39, 33, 31 times respectively). Cardiac disorders reported in association with naproxen consisted mostly of (peripheral) oedema (22 times) and palpitations (13 times).

<u>Severe Gastrointestinal reactions</u>

In the System Organ Class Gastrointestinal disorders, several preferred terms refer to severe reactions. In total 29 severe GI reactions in 29 patients were reported, 1 for diclofenac K, 7 for ibuprofen and 21 for naproxen (table 3).

Table 3. Severe Gastrointestinal reactions reported on diclofenac K, ibuprofen and naproxen.

Preferred Term	Diclofenac K	Ibuprofen	naproxen
Gastric perforation	1		
Gastric haemorrhage		1	4
Gastric ulcer		1	3
Gastric ulcer haemorrhage		1	1
Gastric ulcer perforation		1	
Gastrointestinal haemorraghe		2	7
Gastrointestinal ulcer			1
Hematemesis		1	5
Total	**1**	**7**	**21**

Regarding diclofenac K, a female consumer, aged 73, reported a gastric perforation after 2 tablets of diclofenac K 12.5 mg (without stomach protection) probably used for kidney stones. No further information upon risk factors is available.
Concerning ibuprofen, in two male patients reactions were fatal (Patient B and C). All other five reactions occurred in women, three between 21 and 31 years and three between 54 and 60 years. In one patient (43625) a 31 year old female (smoker, alcohol three times a week, up to 7 units) had a gastric ulcer hemorrhage, confirmed by biopsy. In this patient beside ibuprofen 400 mg tid. also paroxetine 20 mg was suspected, with an unknown latency. In all other patients no information upon risk factors (smoking, alcohol, history of ulcer) was available. Doses of ibuprofen were between 400 mg twice and three times daily. In one patient (17353) hematemesis started already after one day, in two other patients gastric ulcer respectively gastric hemorrhage occurred after three months respectively five months use of ibuprofen.

The most severe GI reactions on naproxen took place in patients above 60 years old, with exception of hematemesis in a female, aged 48 years, with a history of oesophageal varices and liver cirrhosis, a 36 year old female with GI haemorrhage after 2 weeks use of naproxen 250 mg twice daily and a 16 year old rheumatic female, who had a gastric haemorrhage one day after starting naproxen 250 mg twice daily. In 3 out of 21 patients, other drugs were also suspected: in case of a rectal GI haemorrhage amoxiciline, in a gastric GI haemorrhage rivaroxaban and etoricoxib in a case of fatal gastric haemorrhage (case J). In 2 other patients drugs were used, which could have contributed to the reactions: In one patient(6780) acetylsalicylic acid and dipyridamol during 2.5 months were used (latency for naproxen 19 days), in another patient (14207) acetylsalicylic acid and paroxetine (latency 3 months)- naproxen had been used for 6 months. In four patients gastric mucosa protective drugs, including proton pump inhibitors and H2-receptorantagonist had been used as concomitant medication. In almost all cases no information on risk factors was available. In half of the reports the latency between the use of naproxen and the severe GI reaction was less than 14 days. The daily dose of naproxen varied between 220 mg till 1000 mg daily.

Discussion and conclusion

OTC NSAIDs are used by a large number of patients. Among these drugs, lower dosages of naproxen and ibuprofen, which are also available in drug stores and supermarkets / service stations (ibuprofen) are the most prominent. In more than twenty years Lareb received a total 1842 adverse reactions on OTC NSAIDs in 1184 patients. In 193 of those patients it concerned serious cases, which is more than 10 %.

On diclofenac K reactions were only reported in 19 patients, on ibuprofen and naproxen 20 -35 times more. For this reason, a comparison of reported adverse reactions between the three drugs is not useful.

Death was reported ten times. Details revealed however that in most reports other causes, including co-medication, might have played a major role. In two reports (B, gastric ulcer and E, Toxic Epidermal Necrolysis), a relation with the OTC NSAID was plausible. In patient C a high intake of 6400 mg ibuprofen was observed in an illiterate patient (the reporter mentioned the OTC availability of a large pack size of 50 tablets as a major contribution to this mistake).

Amongst serious reactions, anaphylactic shock/reactions were most frequently reported, followed by diverse hypersensitivity reactions, including dyspnea, angioedema, urticaria, pruritus and erythema.

The most frequently reported reactions were mild gastrointestinal reactions, skin reactions or reactions on the nervous system, which is in line with the product information. Severe gastrointestinal reactions were reported in 21 patients (< 2 %), in almost half of the patients within two weeks after start. In many old reports no gastric mucosa protection was taken in patients above the age of 60 years. At that time, the guideline regarding stomach protection had not yet been implemented on a wide scale [6].

No cardiac reactions on low dose diclofenac potassium were reported to Lareb, except one case of increased heart rate in combination with other symptoms of an allergic reaction.

In general, the reported reactions on OTC NSAIDs were similar to those mentioned in the SmPCs, including several serious allergic and gastrointestinal reactions.

References

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