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The Frequency Of Nonsteroidal Anti-Inflammatory Drugs Hypersensitivity Reactions In Patiens With Musculoskeletal System Diseases

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Özet

Non-steroid anti-enflamatuar ilaçlar (NSAID), hipersensitivite reaksiyonları, Allerji Kliniklerine başvuran hastalarda sık olarak görülür. COX-1 inhibitörleri genel olarak sorumlu olup, COX-2 inhibitörü ilaçlar bu hastalarda iyi tolere edilir. Bu çalışmada, biz kas-iskelet sistemi hastalıkları olan hastalarda NSAİİ'ler aşırı duyarlılık reaksiyonları sıklığını araştırdık.

Yöntem: Fiziksel Tıp ve Rehabilitasyon (FTR) kliniğine başvuran 175 hasta çalışmaya dahil edildi.

Bulgular: 122 kadın ve 53 erkek hasta çalışmaya alındı. Bu hastaların yaş ortalaması 46,08 ± 15,37 yaşındaydı. En sık görülen hastalık, yumuşak doku hastalıkları, fibromiyalji, ankilozan spondilit, osteoporoz ve travma takip osteoartrit oldu. 62 hastada herhangi bir altta yatan hastalık yok iken, en sık altta yatan hastalık hipertansiyon, rinit, metal alerjisi, diyabet, egzama, kalp hastalığı, böcek alerjisi, böbrek hastalığı ve antibiyotik allerjisi ardından, astım oldu. On hasta hayatlarında NSAID ile aşırı duyarlılık reaksiyonları olduğunu belirtmiştii. 1 hastada romatoid artrit vardı ve bir diğer hastada Sjögren sendromu vardı, 8 hastada osteoartrit vardı. Bir hasta dışında tüm hastalarda çoklu ilaç aşırı duyarlılık reaksiyonu vardı. Sadece bir hastada naproksen hipersensitivitesi olduğunu açıkladı. Sekiz hasta U/AE vardı ve dördünde mide ağrısı ve iki hastada da hipotansiyon ve nefes darlığı şikayeti vardı. İki hastada hipotansiyon vardı ve bunlardan biri de mide ağrısı vardı.

Sonuç: NSAID aşırı duyarlılık reaksiyonları PM & R başvuran hastalarda daha sık olarak görüldüğünü göstermektedir.

Anahtar Kelimeler: NSAII, FTR, aşırı duyarlılık

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAID)-induced hypersensitivity reactions are often seen in practice of allergy departments. Generally the culprit drug is COX-1 inhibitors, COX-2 inhibitor drugs may be well tolerated in such patients. In this study, we investigated the frequency of NSAIDs hypersensitivity reactions in patients with musculoskeletal system diseases.

Methods: One hundred seventy five patients attended to physical medicine and rehabilitation (PM&R) outpatient clinic of our university hospital enrolled in our study.

Results: 122 female and 53 male patients were included to the study. Mean age of these patients was 46.08±15.37 years old. The most common disease was osteoarthritis followed by soft tissue disease, fibromiyalgia, ankylosing spondylitis, osteoporosis and trauma. While 62 patients had no underlying disease, the most common underlying disease was asthma, followed by hypertension, rhinitis, metal allergy, diabetes mellitus, eczema, heart disease, insect allergy, renal disease and antibiotic allergy. Ten patients explained hypersensitivity reactions with NSAIDs in their lives. Eight patients had osteoarthritis, one patient had rheumatoid arthritis and the other one had sjogren syndrome. Except for one patient, all of the patients had multi-drug hypersensitivity reaction. Only one patient explained that she had naproxen hypersensitivity. Eight patients had U/AE and four of them also had stomachache and two patients also had hypotension and dispnea. Two patients had hypotension and one of them also had stomachache.

Conclusions: These results show that NSAIDs hypersensitivity reactions are more often seen in the patients attending PM&R out patient clinics other than that mentioned in the other studies.

Keywords: NSAIDs, PM&R, hypersensitivity.

Introduction

Adverse drugs reactions (ADRs) are one of the most common health problem in allergy departments. The World Health Organization has defined ADRs as ‘‘Harmful, unintended reactions to medicines that occur at doses normally used for treatment” [1]. These reactions can be seen up to 25% of outpatients and 10–20% of hospitalized patients [2-4]. There are 5 adverse drug reactions types that described from type A to E [5]. Type A reactions are predictable reactions that occur based on a known pharmacologic property of a drug. Drug hypersensitivity reactions (DHRs) constitute only a small portion of them and called Type B reactions that are not related to the pharmacologic property of the drug. These reactions can be divided into two types intolerances: Idiosyncratic and immunologic drug reactions [6]. Immunologic drug reactions may be related with IgE-mediated or T-cell dependent reactions [7,8]. The cause of the idiosyncratic drug reactions still unknown. Both of idiosyncratic and immunologic drug reactions can be classified as drug hypersensitivity and consist of approximately up to a third of all ADRs [8,9]. Type C reactions are related to the cumulative dose of a medication and are dependent on both time and dosage

[5]. Type D reactions are time dependent and manifest in a delayed fashion after the initiation of the drug [5]. Type E reactions refer to withdrawal symptoms after discontinuation of the drug [5].

Epidemiologic investigations of drug hypersensitivity reactions are important to evaluate their impact in medicine as well as their burden for affected patients. It has been difficult to determine the true prevalence of DHRs because of problems concerning definition and identification of reactions, besides of lack of population studies in this issue [10]. There are few epidemiologic studies on nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity. Most of these studies are based on hospitalized patients' clinical histories [11-13]. Nevertheless relatively few studies have been performed on ambulatory patients conducted in Physical medicine and rehabilitation (PM&R) departments. We aimed to determine the prevalence and characteristics of NSAIDs hypersensivity in PM&R department outpatients who have very often been taking NSADs. Although the gold standard for drug allergy definition is provocation test with the culprit drug, the characterization of NSAIDs hypersensitivity reactions with this study could give insight to preventive measures potentially useful in reduction of these reactions in this group of patients.

Methods and Results

Our study group included randomized selected 122 female and 53 male patients attended to PM&R outpatient clinic of our university hospital. Mean age of these patients were 46,08±15,37 years old. While 13 of our patients had no education, 96 of them were graduated from primary school, 38 were from secondary school, 26 were from high school and 2 of them were postgraduated. When we evaluated the occupations of the patients, 82 of them were housewife, 29 were worker, 20 were retired, 15 were officer, 11 were student and 18 were in "others" group. 110 of our patients had the diagnosis of osteoarthritis, 9 had soft tissue rheumatism, 8 had fibromiyalgia, 7 had ankylosing spondylitis, 7 had osteoporosis, 5 had trauma, 17 had other diseases. While 62 patients had no underlying disease, asthma (n=28), hypertension (n=26), rhinitis (n=20), metal allergy (n=11), diabetes mellitus (n=7), eczema (n=6), heart disease (n=5), insect allergy (n=4), renal disease (n=2) and antibiotic allergy (n=2) were co-existing diseases. The most common taking drug was Paracetamol followed diclofenac, dextketoprofen, flurbiprofen, dipyrone, etodolac, naproxen, meloxicam, aspirin, pomade and combined preparetes.

Table 1. Demographics and disease characteristics of the study group

Female	122 (69.7%)
Male	53 (30.3%)
Age, mean (years)	46.08±15.37
Education	
None	13 (7.4%)
Primary school	96 (54.9%)
High school	38 (21.7%)
University	26 (14.9%)
Post graduate	2 (1.1%)
Occupation	
Officer	15 (8.6%)
Worker	29 (16.6%)
Housewife	82 (46.9%)
Student	11 (6.3%)
Retired	20 (11.4%)
Other	18 (10.2%)
Type of rheumatic disease	
Inflammatory rheumatic disases RA and AS	11 (6.3%)
Soft tissue rheumatism (tendinitis, bursitis ect)	9 (5.1%)
Fibromiyalgie	8 (4.6%)
Osteoporosis	7 (4%)
Traumatic conditions	5 (2.9%)
Neurological diseases	8 (4.6%)
Peripheral or axial osteoarthritis	110 (62.9%)
Other painful conditions (Familial Mediterranean fever, Syogren syndrome, reflex sympatic distrophy ect)	17 (9.7%)
Underlying diseases (Totally 113)	
Hypertension	26 (14.9%)
Rhinitis	20 (11.4%)
Asthma	28 (16%)
Goiter	2 (1.1%)
Diabetes Mellitus	7 (4%)
Eczema	6 (3.4%)
Cardiac failure	5 (2.9%)
Renal failure	2 (1.1%)
Antiobics allergy	2 (1.1%)
Metal allergy	11 (6.3%)
Insect allergy	4 (2.3%)
The most common taking drugs	
Paracetamol-Para-aminofenoles (COX-3)	104 (22.26%)
Diclofenac sodium-Fenil asetik (COX-1, 2)	101 (21.62%)
Dextketoprofen (COX-1, 2)	64 (13.70%)
Flurbiprofen-Profen (COX-1, 2)	61(13.06%)
Dipyrone- Pyrazolone (COX-1)	25 (5.35%)
Etodolac (COX-2)	25 (5.35%)
Naproxen-Profen (COX-1, 2)	18 (3.85%)
Meloxicam (COX-2)	18 (3.85%)
Aspirin-Salisilat (COX-1)	13 (2.78%)
Pomade	10 (2.14%)
Combined preparates	28 (5.99%)
Type of reactions	
Stomachache	34
Urticaria/AE	3
Urticaria/AE+stomachache	3
Urticaria/AE+dispnea+hypotension +stomachache	1
Urticaria/AE+hypotension+dispnea	1
Hypotension	1
Hypotension+stomachache	1

Table 2. Characteristics of patients with hypersensitivity reactions

Gender/Age	Occupation	Type of the rheumatic disase	Underlying disease	Single or multi reactors	Organ involvement	Other allergic diseases
49y/F	Housewife	Osteoarthritis	HT, DM, HD	Multiple	U/AE+hypotension+dispnea	Insect allergy+asthma
49y/F	Housewife	Osteoarthritis	HT, HD	Multiple	Hypotension	None
57y/F	Retired	Osteoarthritis	HT+renal disease+goiter	Multiple	U/AE+dispnea+hypotension+stomachache	Antibiotic allergy+asthma+insect allergy
43y/F	Housewife	Sjogren Syndrome	None	Multiple	Hypotension+stomachache	Eczema+rhinitis
50y/F	Housewife	RA	None	Multiple	U/AE	None
54y/F	Retired	Osteoarthritis	None	Multiple	U/AE	Metal allergy
66y/M	Officer	Osteoarthritis	Psoriasis	Multiple	U/AE+stomachache	None
57y/F	Housewife	Osteoarthritis	HT, DM, HD	Multiple	U/AE	Rhinitis
48y/F	Housewife	Osteoarthritis	None	Naproxen	U/AE+stomachache	None
44y/F	Housewife	Osteoarthritis	HT	Multiple	U/AE+stomachache	Rhinitis

*HT: Hypertension; **DM: Diabetes Mellitus; *HD: Heart disease; U: Urticaria; AE: Angio edema; RA: Rheumatoid arthritis

Ten patients explained hypersensitivity reactions in their lives with NSAIDs. Seven patients were housewives. Two patients were retired and 1 patient was officer. Eight patients had osteoarthritis, one patient had rheumatoid arthritis and the other one had sjogren syndrome. Except for one patient all of the patients had multi-drug hypersensitivity reaction. Only one patient explained that she had sole naproxen hypersensitivity. Except for four patients the other ones had underlying diseases, mainly hypertension followed by heart failure, diabetes mellitus and also three patients had allergic dieases, first patient had insect allergy and asthma, second patient had insect allergy and asthma with antibiotics allergy, third patient had eczema and rhinitis, two patients had rhinitis and one of them had asthma and insect allergy. One patient had metal allergy, two patients had rhinitis. Six patients had urticaria/angioedema (U/AE) and three of them also had stomachache. One patient had U/AE, dispnea, hypotension, stomachache, the other one had hypotension, dispnea, U/AE. Only one patient had hypotension and the last patient had hypotension and stomachache.

Discussion

NSAIDs are commonly prescribed in patients with painful rheumatic diseases. Considering the conditions of our country, these drugs are not prescribed only by physicians. Some of the patients may obtain these drugs from a pharmacy without having any prescription. NSAIDs have became cheaper and more available in our country due to the latest health and drug policies. So these drugs have been used frequently unnecessary. In this study we analyzed NSAIDs hypersensitivity reaction rates in patients with musculoskeletal system diseases.

The prevalence of drug hypersensitivity in general population remains largely unknown, but it may be estimated that 3-7% of the population experience ADRs [3, 10]. Recently, self reported prevalence of hypersensitivity reactions to drugs in general adult population has been reported in two studies [14, 15]. The prevalences of drug allergy were almost identical in both groups, being 7.7 and 7.8%, respectively. DHRs accounts were 3% to 6% for all hospital admissions and they occur 10% to 15% in hospitalized patients [10]. Escolano et al. determined the prevalence of drug allergies in a population of surgical patients and they asked patients if they were aware of the existence of any episode of allergy to drugs. This study consists of 1,218 patients of whom 159 (13.05%) reported being allergic to drugs. The rate of NSAIDs allergy was 19.3%. The skin was involved in 72.1% of the reactions that were highly likely to have been caused by allergy; 6.9% of these reactions involved the respiratory tract, 4.4% the circulatory system, 12% the skin plus respiratory tract, and 4.4% the skin plus respiratory and circulatory systems [16]. Three patients had only U/AE after taking NSAIDs in our study. Three people had U/AE and stomachache. One patient explained that U/AE and some cardiac syptoms, stomachache and dispnea related to NSAIDs use. One patient had only some cardiac symptoms. One patient had hypotension and stomachache. And finally one patient explained that hypotension, dispnea, U/AE. Dona et. al. evaluated a total of 4460 patients who reported 4994 episodes with a clinical history of DHR over a 6-year period. Based on clinical history, 37% of the episodes were attributed to NSAIDs. Analysis of the 1683 patients (37.45%) finally confirmed as allergic showed the most frequent diagnosis to be hypersensitivity to multiple NSAIDs (47.29%) [17]. In our study only one patient explained single drug allergy with naproxen, the other patients had multidrug hypersensitivity. NSAIDs related cutaneous reactions may affect 0.3% of general population [18]. NSAIDs are the first [19] or the second causes within the drugs [20] for anaphylactic reactions. We found that NSAIDs hypersensitivity reaction rate was 5.71% in patients of PM&R outpatients clinic. This frequence was very high when compared with the literature. We attributed this high frequency to that our study was performed on PM&R patients. We found that thirty four people had stomachache and 10 people had hypersensitivity reaction which were related to NSAIDs.

We analyzed that the most common taken drug was paracetamol and followed by diclofenac. Generally paracetamol has been firstly chosen by physician in mild to moderate painful conditions. Other reason that paracetamol have been chosen that it has low gastric irritation effect. The second common chosen drug was diclofenac in our study. Diclofenac has more efficient and rapid antiinflammatory effect in musculoskeletal system diseases. Although the acetic acid group of NSAIDs (like naproxen, diclofenac, ibuprofen) seems to carry a higher risk of anaphylactic reactions than other groups [21] they have been commonly prescribed in our country. Other group, pyrazolones are the most likely NSAIDs inducing immediate hypersensitivity reactions [22] they have also been taken very often by our patients. Although newly developped cyclooxygenase-2 selective inhibitors can also induce hypersensitivity reactions with a very low, estimated at 0.008%, incidence [23] they have been more rarely used in our country.

According to the treatment guidelines of osteoarthritis, NSAIDs are especially recommended in the cases of moderate to severe pain [24]. Therefore, in accordance with general literature, NSAIDS have been commonly used by females and in the case of degenerative joint diseases. The rate of female patients was 69,7% in our study and all of patients who had NSAID hypersensitivity were female except one. In a study carried out in a population in 2005, the female to male ratio of patients with drug allergy was approximately 2:1 [25]. Other studies have also shown the female predominance [26-29]. It is not well known, whether this is due to a higher consumption of drugs by women compared with men or including genetic predisposition [30]. Consumption of NSAIDs, the most frequent group of drugs involved and confirmed as causing allergy, is more common in women than in men [31-33]. The higher occurrence of NSAID hypersensitivity in women as well as the reactions to placebo are difficult to explain on a pathophysiological basis.

Nowadays NSAID hypersensitivity reactions have frequently diagnosed. After taking NSAID side effect symptoms developing frequently have been attributed to and falsely positive as signs of hypersensitivity. These symptoms may be related to pharmacological side effects of the drug or infectious diseases. So based on patient history of an adverse reaction to NSAID, it has oftenly been adviced to avoid all NSAID. False positive diagnosis of NSAID hypersensitivity causes more prescription of second line medications and causes less efficacy, increased toxicity and loss of money. In our study, thirty four patients explained that they had stomache after taking NSAIDs. These complaints were not related to NSAID hypersensitivity.

The high rate of drug hypersensitivity reaction of NSAIDs has been revealed that hypersensitivity reactions should be questioned when prescribing these drugs to patients in the practice of PM&R. In the cases with chronic pain due to osteoarthritis and other rheumatological diseases NSAIDs with multiple analgesic drugs or variety of NSAIDs, even sometimes consecutive, frequently have been used. Because of the limited information about analgesic drug reactions on PM&R patients in the literature, these reactions can often be ignored. When a drug reaction occurs, the patients usually apply for allergic diseases department although the drug was given by PM&R department. This may result in with the lack of physician's information about the adverse drug reactions on this subject. The results of this study showed that PM&R professionals should change their attitude about drug safety and life-threatening side effects and hypersensitivity reactions of NSAIDs in their practice.

References

1. WHO: International drug monitoring: the role of national centers. Tech Rep Ser: WHO (1972) 498: 1-25.
2. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, Seger DL, Shu K, Federico F, Leape LL and Bates DW: Adverse drug events in ambulatory care. N Engl J Med (2003) 348: 1556-1564.
3. Gomes ER and Demoly P: Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol (2005) 5: 309-316.
4. Lazarou J, Pomeranz BH and Corey PN: Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA (1998) 279: 1200-1205.
5. Edwards IR and Aronson JK: Adverse drug reactions: definitions, diagnosis, and management. Lancet (2000) 356: 1255-1259.
6. Uetrecht J: Idiosyncratic drug reactions: current understanding. Annu Rev Pharmacol Toxicol (2007) 47: 513-539.
7. Demoly P and Hillarie-Buys D: Classification and epidemiology of hypersensitivity drug reactions. Immunol Allergy Clin N Am (2004) 24: 345-6.
8. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P and Williams HC. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol (2004) 113: 832-6.
9. Demoly P and Bousquet J: Epidemiology of drug allergy. Curr Opin Allergy Clin Immunol (2001) 1: 305-310.
10. Gruchalla RS: Drug allergy. J Allergy ClinImmunol (2003) 111: 548-559.
11. Thong BY, Leong KP, Tang CY and Chng HH: Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. Ann Allergy Asthma Immunol (2003) 90: 342–347.
12. Wohrl S, Vigl K and Stingl G: Patients with drug reactions: is it worth testing? Allergy (2006) 61: 928-934.
13. Preton SL, Briceland LL and Lesar TS: Occuracy of penicillin allergy reporting. Am J Hosp Pharm (1994) 51: 79-84.
14. Falcão H, Lunet N, Gomes E, Cunha L and Barros H: Drug allergy in university students from Porto. Portugal Allergy (2003) 58: 1210.
15. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E and Demoly P: Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy (2004) 34: 1597-1601.
16. Escolano F, Bisbe E, Castillo J, López R, Parés N, Arilla M and Castaño J. Drug allergy in a population of surgical patients. Rev Esp Anestesiol Reanim (1998) 45: 425-30.
17. Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F, Salas M, Rondón C, Canto MG and Blanca M. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. J Investig Allergol Clin Immunol (2012) 922: 363-71.
18. Settipane RA, Constantine HP and Settipane GA: Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. Allergy (1980) 35: 149-154.
19. Mullins RJ: Anaphylaxis: risk factors for recurrence. Clin Exp Allergy (2003) 33: 1033-1040.
20. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N and Vierucci A: Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). Ann Allergy Asthma Immunol (2001) 87: 27-32.
21. Quiralte J, Blanco C, Delgado J, Ortega N, Alcntara M, Castillo R, Anguita JL, Sáenz de San Pedro B and Carrillo T: Challenge-based clinical patterns of 223 Spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. J Investig Allergol Clin Immunol (2007) 17: 182-188.
22. Asero R: Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. Clin Exp Allergy (2005) 35: 713-716.
23. Layton D, Marshall V, Boshier A, Friedmann P and Shakir SA: Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. Drug Saf (2006) 29: 687-696.
24. Tuncer T, Çay HF, Kaçar C, Altan L, Atik OŞ, Aydın AT, Ayhan FF, Yanık BÇ, Durmaz B, Eskiyurt N, Genç H, Kutsal YG, Günaydın R, Hepgüler S, Hizmetli S, Kaya T, Kurtaiş Y, Ölmez N, Sarıdoğan M, Sindel D, Tur BS, Sütbeyaz S, Şendur ÖF, Uğurlu H and Ünlü Z. Evidence-Based Recommendations for the Management of Knee Osteoarthritis: A Consensus Report of the Turkish League Against Rheumatism. Turk J Rheumatol (2012) 27: 1-17.

25. Gamboa PM: The epidemiology of drug allergy related consultations in Spanish Allergology Services: Alergologica-2005. J Investig Allergol Clin Immunol (2009) 2: 45-50.
26. Barranco P and Lopez-Serrano MC: General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy (1998) 4: 61-2.
27. Haddi E, Charpin D, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP and Vervloet D. Atopy and systemic reactions to drugs. Allergy (1990) 45: 236-9.
28. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E and Demoly P: Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy (2004) 34: 1597-1601.
29. Macy E and Poon K-YT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med (2009) 122: 778.
30. Adkinson NF Jr, Essayan D, Gruchalla R, Haggerty H, Kawabata T, Sandler JD, Updyke L, Shear NH and Wierda D. Health and Environmental Sciences Institute Task Force. Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. J Allergy ClinImmunol (2002) 3: 461-78.
31. Grimmsmann T and Himmel W: Polypharmacy in primary care practices: an analysis using a large health insurance database. Pharmacoepidemiol Drug Saf (2009) 18: 1206-1213.
32. Rasmussen HM, Sondergaard J, Kampmann JP and Andersen M: General practitioners prefer prescribing indicators based on detailed information on individual patients: a Delphi study. Eur J Clin Pharmacol. (2005); 61: 237-41.
33. Helin-Salmivaara A, Klaukka T and Huupponen R: Heavy users of non-steroidal anti-infl ammatory drugs: a nationwide prescription database study in Finland. Eur J Clin Pharmacol. (2003) 59: 477-482.