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Long-Term Use and Tolerability of Etodolac In Patients With Non-Steroidal Anti-Inflammatory Drug Induced Urticaria and Angioedema

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Özet

Giriş: Nonsteroidal Anti-inflamatuar ilaçlarla (NSAİİ) indüklenen ürtiker/anjioödem (Ü/AÖ), siklooksijenaz-1 (COX-1) enzimlerinin inhibisyonu ile gerçekleşir. Bu nedenle, NSAİİ-Ü/AÖ' i olan hastalarda bir COX-2 inhibitörü olan etodolakın uzun dönem tolere edilebilirliğini inceledik.
Yöntem: NSAİİ-Ü/AÖ öyküsü olan hastalara, kümülatif 400 mg dozda etodolac ile placebo kontrollü tek-kör oral yükleme yapıldı. Plasebo verildikten sonra bir saat aralarla, aktif ilacın dörtte bir ve dörtte üç bölünmüş dozları uygulandı. Bu testten yaklaşık 20 ay sonra hastaları tekrar aradık.
Bulgular: Altmış yedi hasta (ortalama yaş 42,22±12,56 yıl) çalışmaya alındı. İlaç reaksiyon süresi ortalama 89,53±79,91 aydı. En sık komorbid hastalık hipertansiyon (HT) ve en sık suçlu ajan dipirondu. Onyedisi (%25.37) dışında tüm olgularımızın çoklu ilaç alerjisi vardı ama 15 (%22.38) olgu neden olan ilacın adını bilmiyordu. Hiç bir hastada plasebo ile reaksiyon gözlenmedi. Hafif Ü/AÖ gelişen altı hastada (%8.95) geçen ortalama zaman kümülatif doz 400 mg etodolak uygulandıktan bir saat sonraydı. Geriye kalan 61 (%9105) hasta terapötik dozu tolere etti. Testten ortalama 20 ay sonra olguları tekrar çağırdık. Etodolak kullanıp kullanmadıklarını ve bu ajana bağlı alerjik reaksiyon geliştirip geliştirmediklerini sorduk. Sadece bir hasta etodolak alınca reaksiyon rapor etti.
Sonuçlar: Bu çalışma göstermektedir ki, 400 mg etodolak, NSAİİ-Ü/AÖ tanılı hastalarda güvenli bir alternatiftir.

Anahtar Kelimeler: Etodolak, NSAİİ, Ürtiker, Anjioödem.

Abstract

Background: Non-Steroidal Anti-Inflammatory Drug (NSAID) induced Urticaria/Angioedema (U/AE) is mediated by inhibition of cyclooxygenase-1 (COX-1) enzymes. In this respect, we investigated the safety and long-term tolerability of etodolac, a COX-2 inhibitor, in patients with NSAID-U/AE.
Methods: Patients with NSAID-U/AE history underwent a single-blind, placebo-controlled oral challenge with a cumulative dose of 400 mg etodolac. After administration of plasebo, one-quarter and three-quarter divided doses of the active drug were administered at 1-h intervals. We called patients averagely 20 months after the work-up.
Results: Sixty-seven patients (Mean age was 42,22±12,56 years) were recruited. Mean duration of drug reaction was 89,53±79.91 months. The most common comorbid disease was hypertension (HT) and the most frequent responsible agent was dipyrone. Except for 17 (25.37%) patients all of our patients were multi-reactors, but 15 (22.38%) patients did not know the name of culprit drug but they had multi-reactors history. No reaction to placebo was observed in any of the patients. Mean duration of time elapsed for development of mild U/AE in six patients (8.95%) was 1 hour after the last administration of cumulative dose of 400 mg etodolac. The remaining 61 patients (91.05%) well-tolerated the therapeutic dose. We called patients averagely 20 months after the work-up. We interrogated that whether they used etodolac or not and had allergic reaction related to this agent. Only one patient reported a reaction when etodolac was taken.
Conclusions: This study indicates that 400 mg etodolac is a safe alternative in patients suffering from NSAID-U/AE.

Keywords: Etodolac, NSAID, Urticaria, Angioedema.

INTRODUCTION

Drug hypersensitivity reactions are observed in up to 7% of the general population and that are classified into three subtypes: i. Non-immunological reactions. ii. IgE-mediated allergic reactions. iii. Non-immediate allergic reactions (1-4).

NSAIDs are cause of the second most common drug hypersensitivity reactions, approximately 21–25% of these reactions and after antibiotics hypersensitivity (2,5,6). Hypersensitivity reactions to NSAIDs have been classified in different 4 categories (7,8). i. NSAID-exacerbated respiratory disease. ii. NSAID-exacerbated cutaneous disease in patients with chronic idiopathic urticaria. iii. Urticaria and/or angioedema, and anaphylaxis induced by a single NSAID. The clinical symptoms are induced by a single NSAID group or by only one drug from a specific group. There is good tolerance to other chemically unrelated NSAIDs in these patients (9-11). iiii. Multiple NSAID-induced U/AE in patients not having pre-existing chronic urticaria (7). The symptoms are induced by different NSAIDs that are not chemically related, named as cross-intolerance (CI) or non-allergic hypersensitivity (6,7). Most studies on CI to NSAIDs have focused on respiratory responses with the inhibition of the cyclooxygenase enzyme (COX) and has been attributed to their inhibitory effect on COX-1 enzyme (6,12,13). This mechanism has also been proposed for cases of urticaria and angio-oedema induced by several NSAIDs (14). In vitro methods have not been sufficiently validated (15-16). Demonstration of drug allergy with a complete drug allergy work up

including a detailed clinical history and physical examination and drug provocation tests is required to avoid relapses. This work up is composed of a review of the EAACI/ENDA and GA2LEN/HANNA recommends that the diagnosis should be confirmed with a drug provocation test in cases of multiple NSAID-induced U/AE, Drug provocation test (DPT) is the gold standard in the diagnosis of drug allergy and is carried out for either correct diagnosis or therapeutic purposes and also to find safe alternatives (17,18). These tests are potentially dangerous and must be performed under medical monitoring in specialized hospital centers (19). Selective COX-2 inhibitors are good choices in patients with or without chronic idiopathic urticaria.

We investigated the safety and the long-term tolerability of etodolac, a COX-2 inhibitor, in patients with NSAID-U/AE.

PATIENTS AND METHODS

Inclusion criteria: Patients who had at least two episodes of NSAIDs induced U/AE.

Exclusion criteria: Patients younger than 18 years or older than 80 years of age. Patients with diagnosis of chronic idiopathic urticaria or acute recurrent urticaria not related to NSAID intake. Pregnant or breastfeeding patients. Patients taking beta-blockers or angiotensin converting enzyme inhibitors. Patients, with contraindications for epinephrine administration. Patients who had acute infections, auto-immune and/or underlying cardiac, hepatic or renal diseases that contraindicated a drug provocation test. Subjects with psycho-somatic disorders and patients who tolerated different unrelated NSAIDs. Patients were instructed to stop antihistamine medications one week before.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the relevant Ethics Committees.

Data of 67 patients with NSAIDs induced U/AE with and without concurrent underlying diseases that presented to Izmir Ataturk Education and Training Hospital between January 2010 and October 2012 were retrospectively reviewed. Patient age, gender, characteristics of NSAID hypersensitivity, underlying diseases and diagnostic work-up findings were obtained.

Oral drug provocation test

Subjects with reliable or documented history of analgesic hipersensitivity underwent a single-blind, placebo-controlled oral challenge with a cumulative dose of 400 mg Etodolac. First, placebo was given. Then, increasing doses of NSAIDs were administered orally at 1 h intervals one-quarter and three-quarter divided doses the active drug were given. During the challenge procedure, blood pressure, forced expiratory volume in the first second (FEV1) values, skin, ocular, nasal and bronchial syptoms were monitored after drug dose was given. If cutaneous and/or respiratory symptoms, cardiac or bronchial symptoms appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during drug administration, the therapeutic dose was achieved. The patients were kept under medical surveillance for up to 2 h after completing the test if negative. The test was defined as negative if no adverse reaction occurred in 24 h. We contacted our patients by phone after a mean period of 20.05±7.94 months to question whether they had reactions with etodolac use after the test.

Statistical analysis

The statistical analyses were performed by SPSS ver. 16.0 computer software. Results are expressed as mean values±standard deviation.

RESULTS

In this study, we carried out drug provocation test with etodolac in 67 (50 women and 17 men) patients with NSAIDs induced U/AE. Mean age was 42.22±12.56. We followed up these patients for a mean duration of 20.05±7.94 months. We were able to reach all of patients enrolled in the present study by phone. We interrogated whether they used etodolac or not and had allergic reaction related to this agent (Table 1).

Table 1. Demographics and disease characteristics of the study group

Gender Male Female	 17 (25.37%) 50 (74.62%)
Age, mean (years)	42.22±12.56
Mean follow-up time	20.05±7.94
The number of reactions 2 3 4 ≥5	 12 (17.9%) 13 (19.4%) 9 (15.78%) 33 (49.25%)
Previous reactions, n (%) Single cutaneous involvement ≥ 2 organ involvements	 46 (68.65%) 21 (31.34%)
Atopy rate, n (%)	20 (29.85%)
Underlying diseases Hypertension Rhinitis Asthma Goiter Diabetes Mellitus Aspirin Exacerbated Respiratory Diseases Migraine	 11 (16.41%) 11 (16.41%) 9 (13.43%) 7 (10.44%) 6 (8.9%) 6(8.9%) 1 (1.4%)
Culprit drug Dipyrone- Pyrazolone (COX-1) Paracetamol-Para-aminofenoles (COX-3) Aspirin-Salisilat (COX-1) Flurbiprofen-Profen (COX-1, 2) Naproxen-Profen (COX-1, 2) Diclofenac sodium-Fenil asetik (COX-1, 2) Dextropropoxyphene-Profen (COX-1, 2) Ketoprofen-Profen (COX-1, 2) Ibuprofen-Profen (COX-1,	 23 (34.32%) 20 (29.85%) 16 (23.88%) 14 (20.89%) 11 (16.41%) 10 (14.92%) 1 (1.4%) 1 (1.4%) 1 (1.4%)

2)	
Antibiotic hypersensitivity in history	7 (10.44%)
Reaction with unknown drug	15 (22.38%)
Single NSAID reactors (n, %)	17 (25.37%)

Twelve (17.9%) patients had two episodes of reactions with NSAIDs, 13 (19.4%) patiens had three, 9 (15.78%) patients had four and 33 (49.25%) patients had 5 or more episodes of reaction with NSAID. Forty six (68.65%) patients had cutaneous reaction, and 21 (31.34%) patients had 2 or more organ involvement. The rate of atopy was 20 (29.85%). Underlying disease; 11 (16.41%) patients had HT, 11 (16.41%) patients had rhinitis, 9 (13.43%) patients had asthma, 7 (10.44%) patients had goiter, 6 (8.9%) patients had Diabetes Mellitus, 6 (8.9%) patients had aspirin exacerbated respiratory diseases, 1 (1.4%) patient had migraine. Culprits drugs were dipyrone, paracetamol, aspirin, flurbiprofen, naproxen, diclofenac sodium, dextropropoxyphene, ketoprofen and ibuprofen (Table 1). Except for 17 (25.37%) patients all our patients were multi-reactors, but 15 (22.38%) patients did not know the name of culprit drug but they had multi-reactors history. No reaction to placebo was observed in any of the patients.

Table 2. Characteristics of patients with a positive reaction to etodolac

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, gender	39, M	54, F	53, F	43, F	37, F	55, F
Organ involvement	Multis ystem	Multis ystem	Multis ystem	Multis ystem	Multis ystem	Multis ystem
Reaction numbers	≥5	≥5	2	≥5	≥5	≥5
Atopy	+	+	-	-	-	-
Underlying diseases	Rhinitis	-	*DM, **HT, Goiter	Rhinitis, AERD	-	Asthma Rhinitis AERD
Culprit drug	Flurbiprofen Naproxen Diclofenac	Reaction with unknown drug	Paracetamol Dipyrone	Flurbiprofen Paracetamol Aspirin Dipyrone	Paracetamol Aspirin Dipyrone	Aspirin Dipyrone

*DM-Diabetes Mellitus, **HT-Hypertension, ***AERD-Aspirin Exacerbated Asthma

Six of 67 patients (8.95%) developed mild U/AE, after a cumulative dose of 400mg of etodolac (Table 2). The remaining subjects 61 (91.05%) tolerated perfectly etodolac challenge. They had history of reactions multi-system organ involvement during the reactions of hypersensitivity. Five patients explained 5 or higher hypersensitivity reactions in their life with NSAID induced reaction. Three patients had underlying diseases mainly rhinitis, two of them had AERD and also one patient had asthma and one patient had DM, HT and goiter. One patient didn't know the culprit drug. The most common culprit drug was dipyrone, followed by aspirin, flurbiprofen, paracetamol, naproxen, diclofenac.

DISCUSSION

NSAID hypersensitivity can be common (20). COX-2 inhibitors are the most suitable alternative drugs in patients with NSAID induced U/AE. It is recommended to avoid the culprit analgesics in patients with NSAID induced U/AE and DPT is carried out in order to find safe alternatives and also excluding cross-reactivity of related drugs (21). Nimesulide is the first marketed selective COX-2 inhibitors and has been shown to be a safe alternative in these patients (22-26). Rofecoxib and celecoxib were other selective COX-2 inhibitors that provide better results in these patients but were withdrawn from the market due to adverse effects in 2003 (27-34). Other COX-2 inhibitors such as meloxicam, valdecoxibe, etoricoxibe, and parecoxibe were published to be safe in these patients (35-42). Etodolac is one of the COX-2 inhibitors been shown to be effective in the treatment of rheumatological diseases (43). Studies demonstrated that etodolac is a selective COX-2 inhibitor similar to celecoxib and other "COX-2 inhibitors (44). We applied DPTs with etodolac to patients with NSAID hypersensitivity in order to find safe alternatives for their analgesic/anti-inflammatory needs and demonstrated that 61 (91.05%) of patients tolerated a 400 mg therapeutic dose of etodolac. None of our patients reported having taken etodolac before. The reactions seen in only six of patients were usually mild and after a full therapeutic dose of the drug. Among the patients who developed a reaction, one was male, four had comorbid conditions. The reactions observed were cutaneous and mainly observed within the first hour following the administration of full therapeutic doses. While some studies documented some factors to be a risk for developing such reactions to alternative COX-2 inhibitors, such as; female gender, atopy, history of anaphylactic reactions with culprit drug, other study did not (36,45-47). Five of our patients were female. Only one of our patient was male. Two patients had atopy but others had not. No patients the history of anaphylactic reaction with NSAIDs. Celik et al. published with good success rates for safe uses of nimesulide (92%), meloxicam (91%), celecoxib (100%) and rofecoxib (99%) (24,26,30,32). Our results was 91.05% with etodolac. Netsi et al. reported that the safety of meloxicam in 148 patients with clinical history of U/AE after ingestion of different NSAIDs. Two patients (1.35%) reacted to a total dose of 7.5mg (48). Similarly, Domingo et al. reported that five patients (4.62%) developed reactions to meloxicam challenge among 108 patients with histories of NSAID-induced cutaneous reactions, and these reactions were defined as ‘‘slight urticaria’’ of cutaneous type (35). Naoko et al. showed that the most frequently intolerated drugs was etodolac (53.3%), acetaminophen (38.5%), meloxicam (33%). This study showed that among the NSAIDs that were investigated in this study is meloxicam seems to be better tolerated than etodolac between two selective COX-2 inhibitors (49). Moreover, in this study, acetaminophen was better tolerated than etodolac.

Reports have shown that up to 20% of subjects with cross-intolerance may also be intolerant to paracetamol (50). However in our study etodolac was tolerated by 20 patients who described paracetamol as the culprit drug.

We contacted the patients after a mean duration of 20 months after the initial provocation test. Only one patient had a reaction with etodolac during this period despite a negative provocation test so the negative predictive value after oral provocation test was 98.4% in our study. The clinical reaction described in this patient was urticaria and angioedema which occured after third or forth drug dose. Defrance et al. showed that the negative predictive value of drug provocation tests with NSAIDs is high in the study with a 6 month follow up period (over 96%) (51).

In the present study, we found that the majority of patients (91.05%) with NSAID-induced U⁄AE perfectly tolerated a 400-mg therapeutic dose of etodolac. In conclusion, in NSAID-reactive individuals, etodolac could be the first choice as an alternative NSAID.

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