Journal of Pain and Relief

Rey-Matias et al., J Pain Relief 2018, 7:3
DOI: 10.4172/2167-0846.1000319

Research Article Open Access

Effectiveness and Safety of Oral Dexketoprofen for Mild to Moderate Pain among Filipino Adults: A Post-marketing Surveillance Study

Reynaldo R Rey Matias*, Carl Froilan D Leochico and Grace S Nilo

Department of Physical and Rehabilitation Medicine, St. Luke's Medical Center, Quezon City, Philippines

***Corresponding Author:** Reynaldo R Rey Matias, Department of Physical and Rehabilitation Medicine, St. Luke's Medical Center, Quezon City, Philippines, Tel: +632 723 0301; E-mail: drreymatias@gmail.com

Received date: April 27, 2018; **Accepted date:** May 2, 2018; **Published date:** May 9, 2018

Abstract

Background: Studies abroad demonstrate the effectiveness and safety of dexketoprofen in various therapeutic indications. However, there has been no related study on our local population.

Objectives: To evaluate the effectiveness and safety of oral dexketoprofen among Filipino adults in the treatment of mild to moderate acute pain due to musculoskeletal causes (such as osteoarthritis and low back pain), post-operative pain, headache, or dysmenorrhea in primary health care setting in the Philippines.

Methods: This was a prospective observational study. Drug prescription by attending physicians was based on the drug's Summary of Product Characteristics, which included its indications, contraindications, and precautions. Dosage prescriptions varied, depending on the nature and severity of pain on initial consultation, and physicians' clinical judgment. Effectiveness was evaluated using Wong-Baker faces pain rating scale, clinical global impressions scale, and efficacy index; while safety was evaluated according to incidence and severity of adverse events.

Results: Osteoarthritis and low back pain were the most common conditions seen by the physicians during the study period. Majority received the recommended dosage and duration of the medicine, which was 51-75 milligrams of dexketoprofen a day (56.2%) for at least 1 week (57.5%). On follow-up, there was statistically significant improvement ($p<0.0001$) in pain scores among patients, regardless of medical condition and dexketoprofen dosage and duration. There was low (2.8%) incidence of adverse events in the study population. Majority of side effects did not significantly interfere with daily functioning of patients.

Conclusion: This study demonstrated the effectiveness and safety of oral dexketoprofen in various therapeutic indications. Majority experienced moderate or marked therapeutic effect with no to minimal side effect. No serious adverse event from intake of non-steroidal anti-inflammatory drug, particularly related to gastrointestinal and nervous system disorders was noted.

Keywords: Dexketoprofen; Effectiveness; Safety; Postmarketing surveillance

Introduction

Pain is the most common reason for consultation in primary care centers [1]. When not adequately addressed, pain can lead to loss of productivity and decrease in quality of life. Hence, it is necessary to treat pain aggressively with the least invasive treatment modality that is both effective and safe. For mild to moderate pain, non-steroidal anti-inflammatory drugs (NSAID) remain as first-line in the World Health Organization analgesic ladder [2]. NSAIDs represent a large heterogeneous group of compounds used for treatment of inflammatory and painful conditions that can either be musculoskeletal or non-musculoskeletal in etiology. Their antiphlogistic, analgesic, and antipyretic actions are principally based on their ability to inhibit cyclooxygenase, which is the key enzyme in the production of prostaglandins from arachidonic acid [3].

Dexketoprofen is a recently developed NSAID with fast and powerful antiphlogistic action, accompanied by lesser gastric side effects than Ketoprofen [4]. It has slow-release formulation that can produce good penetration into joint space, confirmed by persistent therapeutic concentrations in serum and synovial fluid. Thus it can be administered as low as once a day to a maximum of three times a day, leading to improved compliance especially among patients with polypharmacy for comorbid diseases.

Musculoskeletal conditions, which are frequently characterized by pain and inflammation, are among the leading indications of NSAIDs. The musculoskeletal diseases commonly studied when evaluating the efficacy and safety of dexketoprofen were low back pain, osteoarthritis of hands and knees, ankle sprain, and lower limb trauma [5-9]. Postoperative pain serves as another important model of acute pain in the evaluation of analgesic efficacy and speed of action. In this model of pain, NSAIDs and opioids act synergistically to produce balanced, multimodal analgesia [10]. Other important models of pain include headache and dysmenorrhea, wherein prostaglandins play a pathogenic role; thus NSAIDs are clearly indicated [11].

When conducting post-marketing surveillance, both effectiveness and safety should receive equal emphasis. Several studies abroad show that there is no significant difference between dexketoprofen and other control analgesics in terms of effectiveness, and incidence and profile

of adverse events in various therapeutic indications [12-16]. Therefore, the present study aimed to achieve the following objectives:

- To evaluate the effectiveness of oral dexketoprofen in the treatment of mild to moderate acute pain due to musculoskeletal causes (such as osteoarthritis and low back pain), post-operative pain, headache, or dysmenorrhea in local primary health care setting, as measured by Wong-Baker faces pain rating scale, clinical global impressions scale, and efficacy index; and
- To evaluate safety outcomes according to incidence and severity of adverse events among Filipino patients.

Methodology

This prospective observational study was conducted over a period of 23 months involving a cohort of patients seen in private clinics in different regions of the country and managed with oral dexketoprofen for mild to moderate acute pain due to any of the following causes: osteoarthritis, low back pain, post-operative pain, headache, or dysmenorrhea. The study was approved by the national Food and Drug Administration of the Department of Health. Good clinical practice guidelines were observed throughout the study.

Study procedure

Drug prescription by attending physicians was based on their clinical judgment and knowledge of the drug's Summary of Product Characteristics, which included its indications, contraindications, and precautions [17]. The physicians explained the dosage, potential benefits, and adverse effects of the drug to their patients. Dosage prescriptions varied, depending on the nature and severity of pain on initial consultation. Recommended dosage was generally one 12.5 milligram-tablet every 4 to 6 hours, or one 25 milligram-tablet every 8 hours taken 30 minutes before meal, or as long as total daily dose did not exceed 75 milligrams for healthy patients, or 50 milligrams for those with known mild hepatic or renal dysfunction.

The case report form had 3 main parts: 1) Patient's Clinico-Demographic Profile (including age, sex, weight, occupation, reason for consultation, dosage of oral dexketoprofen prescribed, duration of drug intake, co-morbid diseases, and polypharmacy); 2) Effectiveness Outcomes (including pain score, global improvement score, and efficacy index); and Safety Outcomes (including description and date of adverse events, causal relationship with dexketoprofen intake, severity, and measures taken).

Effectiveness assessment

Effectiveness was assessed based on the following outcomes

Pain score: Physicians obtained subjective pain reports of patients at baseline and follow-up (i.e. after completing 7 days of drug intake, unless a patient presented with adverse event/s necessitating earlier follow-up and/or premature discontinuance of the drug). Based on Wong-Baker faces pain rating scale, pain scores were interpreted according to the following levels of severity: (0) "no pain;" (1) "mild, annoying pain;" (2) "nagging, uncomfortable, troublesome pain;" (3) "distressing, miserable pain;" (4) "intense, dreadful, horrible pain;" and (5) "worst possible, unbearable, excruciating pain."

Clinical Global Impressions (CGI) scale: At baseline, physicians answered the question, "How ill is my patient at this time," according to the following 7-point Likert scale: (1) normal/ not at all ill; (2) borderline ill; (3) mildly ill; (4) moderately ill; (5) markedly ill; (6) severely ill; and (7) among the most extremely ill patients. The physician's response to the CGI-Severity (CGI-S) scale reflected different domains, including physician-observed and patient-reported symptoms, pain-related behavior, and clinical dysfunction during the past 7 days prior to initial consultation [18]. On follow-up, physicians performed their re-evaluation and rated their patients' level of clinical change relative to baseline according to the CGI-Improvement (CGI-I) scale: (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse; and (7) very much worse [18].

Efficacy index: At baseline and follow-up, presence or absence of certain physical examination findings (i.e. swelling, deformity, tenderness, warmth, crepitus, joint effusion, and muscle atrophy) were documented among patients with musculoskeletal complaints (i.e. muscle and/or joint pains). Lastly as part of CGI-Efficacy Index, which plotted the therapeutic effect against adverse effects in a 4 × 4 table (Table 1), physicians reported their patients overall clinical outcomes according to their re-evaluation [19].

Therapeutic effect	Side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
Marked-Vast Improvement. Completely or nearly completely remission of all symptoms				
Moderate-Decided improvement. Partial remission of symptoms				
Minimal-Slight improvement which doesn't alter status of care of patient				
Unchanged or Worse				

Table 1: Clinical Global Impression scale-efficacy index [19].

Safety assessment

Safety was assessed based on patient reports of adverse events according to frequency, severity, and causality. Each adverse event was classified as non-serious or serious based on the drug's Summary of Product Characteristics; the latter is defined as an event leading to life-threatening medical condition, persistent incapacity, prolonged

hospitalization, or death [17]. For any serious adverse event deemed causally related to dexketoprofen intake, physicians were instructed to immediately notify *A. Menarini* Philippines, Inc. for further investigation, intervention, and documentation. Causal relationship between study medication and adverse event was classified as "not related," "unlikely," "possibly," "probably"or"definitely related" according to the modified algorithm by Karch and Lasagna [20].

Treatment of data

Descriptive statistics (i.e. frequency with percentage, mean with standard deviation, median, and range) was performed on demographic and clinical outcomes data, wherever applicable. Data analysis on safety assessment was performed based on the Safety Population, which included all patients who received at least one dose of the study medication during the observation period. All data related to safety assessment (i.e. serious or non-serious adverse events, causal relationship with intake of study medication, premature discontinuance of the drug, and concomitant medication, when needed for adverse event) of the safety population was reported in accordance to the standard operating procedure of the manufacturing company. Analytical statistics using chi-square test was performed on data related to effectiveness outcomes in the intention-to-treat population. All data were reported at 95% confidence interval.

Results

A total of 870 case report forms were submitted and analyzed. Table 2 shows the baseline characteristics of the patients.

Patients had a median (interquartile range) age of 42 (30-54) years, and weight of 62 (55-70) kilograms (Table 2). Majorities were females (54.3%), and were employed for skilled work (29.3%). The conditions that were seen by the physicians during the study were (in order of decreasing frequency): Peripheral muscle and/or joint pains (i.e. osteoarthritis) (53.4%); axial pain (i.e. low back pain) (18.7%); post-operative pain (7.5%); headache (6.6%); and dysmenorrhea (5.3%). More than half of the population received a daily dose of 51-75 milligrams of dexketoprofen (56.2%). Treatment compliance was high, such that majority followed their physician's advice to take the medication for at least 1 week (57.5%). Those who took it for less than 7 days discontinued either due to early pain relief or onset of adverse events; while those who took it for 2 weeks either due to persistent pain or fear of pain recurrence. About 1 out of 5 patients had at least 1 comorbid condition (23.7%), and took their other prescription drugs (37.7%) that were not for pain.

Baseline Characteristics	All Patients (N=870)
Demographic characteristics	
Age, years	
Mean ± SD	42.7 ± 15.2
Range	30-54
Median	42
Sex	
Female	472 (54.3)
Male	383 (44.0)
Missing data	15 (1.7)
Weight, kg	
Mean ± SD	62.9 ± 11.9
Range	55 – 70
Median	62
Occupation	
Skilled work	255 (29.3)
Unemployed	220 (25.3)
Office work	209 (24.0)
Manual labor	96 (11.0)
Missing data	90 (10.3)
Clinical characteristics	
Chief complaint/Pain condition	
Peripheral muscle and/or joint pains	465 (53.4)
Axial pain (i.e. low back pain)	163 (18.7)
Post-operative pain	65 (7.5)
Headache	57 (6.6)
Dysmenorrhea	46 (5.3)
Missing data	74 (8.5)
Daily dosage of dexketoprofen	
<25 mg	2 (0.23)
25-50 mg	359 (41.3)
51-75 mg	489 (56.2)
Missing data	20 (2.3)
Duration of treatment	
1-3 days	161 (18.5)
4-6 days	145 (16.7)
At least 1 week	500 (57.5)
At least 2 weeks	22 (2.5)
Missing data	42 (4.8)
With comorbid condition/s	206 (23.7)
With other prescribed non-pain medication/s	328 (37.7)

Table 2: Demographic and clinical profile of patients.

Effectiveness Outcomes

"Distressing, miserable" was the overall top pain description (36.3%) of patients at baseline. Majority of patients regardless of disease had baseline pain that ranged from "nagging, uncomfortable, and troublesome"to"intense, dreadful, and horrible." Some patients,

especially those with peripheral muscle and/or joint pains (i.e. osteoarthritis), described their pain as "worst, unbearable, excruciating."

On follow-up, majority reported to have had either "no pain" or "mild, annoying" pain, and there was neither report of "intense, dreadful, horrible" nor "worst, unbearable, excruciating" pain. The difference in pain reports between baseline and follow-up periods was statistically significant ($p<0.0001$, Mann-Whitney U test) in all pain conditions.

Two hundred fifty physicians were able to indicate the scores of their patients at baseline and follow-up using the Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I) scales, respectively. At baseline, majority of patients were either "moderately ill" (36.4%) or "mildly ill" (28.4%) (Table 3). On follow-up, 54% of patients had "very much improved," while the rest either had "much improved" (27.6%), "minimally improved" (5.2%), or "no change" (1.2%) (Table 3). Overall, 86.8% of the population had improved, regardless of degree of improvement. There was no report of worsening from baseline.

Severity at Baseline (based on CGI-S)		**Change from Baseline to Follow-up (based on CGI-I)**	
Level	n (%)	Level	n (%)
Normal/ not at all ill	28 (11.2)	Very much improved	135 (54.0)
Borderline ill	6 (2.4)	Much improved	69 (27.6)
Mildly ill	71 (28.4)	Minimally improved	13 (5.2)
Moderately ill	91 (36.4)	No change	3 (1.20)
Markedly ill	20 (8.0)	Minimally worse	0 (0.0)
Severely ill	5 (2.0)	Much worse	0 (0.0)
Among the most extremely ill	8 (3.2)	Very much worse	0 (0.0)
Missing data	21 (8.4)	Missing data	30 (12.0)

Table 3: Results of the Clinical Global Impressions scale (CGI): Severity (CGI-S) and improvement (CGI-I) (N=250).

Among patients with peripheral myalgia and/or arthralgia (i.e. osteoarthritis), which was the most common pain condition (n=465) in the study population, certain clinical parameters were evaluated at baseline and follow-up (Table 4). At baseline, majority of patients presented with tenderness (77.4%), warmth (42.8%), and swelling (41.9%) on affected areas. As shown in Table 4, all clinical findings, except for muscle atrophy, were significantly lesser ($p<0.05$) on follow-up.

Clinical Findings	**Baseline**	**Follow-up**	**p-value***
Crepitus	37 (8.0)	10 (2.2)	<0.0001
Deformity	29 (6.2)	15 (3.2)	0.031
Joint effusion	13 (2.8)	2 (0.4)	0.004
Muscle atrophy	6 (1.3)	5 (1.1)	0.762
Swelling	195 (41.9)	16 (3.4)	<0.0001
Tenderness	360 (77.4)	20 (4.3)	<0.0001
Warmth	199 (42.8)	4 (0.9)	<0.0001
*p-value was computed using Chi-Square Test. Values in boldface are statistically significant at 95% confidence interval.			

Table 4: Clinical findings among patients with peripheral muscle and/or joint pains (N=465) at baseline and follow-up.

Furthermore, the CGI-Efficacy Index (Table 5) showed that majority (56.4%) had marked therapeutic effect with no side effect on follow-up. Approximately 11% either had marked improvement with side effect that did not significantly interfere with functioning or moderate improvement without side effect (Table 5). On the other hand, 1.3% (3 out of 230 patients) did not improve.

Therapeutic Effect	Side Effect			
	None	Did not significantly interfere with functioning	Significantly interfered with functioning	Outweighed therapeutic effect
Marked-Vast improvement. Complete or nearly complete remission of all symptoms.	141 (56.4)	28 (11.2)	1 (0.4)	12 (4.8)
Moderate-Decided improvement. Partial remission of symptoms.	27 (10.8)	13 (5.2)	1 (0.4)	3 (1.2)
Minimal-Slight improvement, which did not alter status of care.	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Unchanged or worse	0 (0.0)	2 (0.8)	1 (0.4)	0 (0.0)
*20 missing or unclear data obtained from 250 physicians, who answered CGI-S & CGI-I.				

Table 5: Results of the Clinical Global Impressions scale-efficacy index (N=230*).

Safety Outcomes

As shown in Table 6, 2.8% of the population reported at least one adverse event (AE), which most commonly occurred among patients with low back pain (9 cases), peripheral muscle and/or joint pains like osteoarthritis (5 cases); and headache (4 cases). Patients treated for headache reported the highest proportion of adverse events (4 out of 57 cases; or 7.0%), followed by those with dysmenorrhea (3 out of 46 cases; or 6.5%), and low back pain (9 out of 163 cases; or 5.5%). Adverse events were most commonly related to the gastrointestinal tract (i.e. bloatedness, constipation, epigastric pain, or hypogastric pain) (7 out of 870 cases; 0.8%) and nervous system (i.e. dizziness, nausea, or insomnia) (6 out of 870 cases; 0.7%) (Table 6). Majority of AEs were classified as non-serious (Table 7). One case of serious AE that necessitated hospital admission was related to hyperglycemia in a patient with low back pain. The other 4 serious AEs were unclassified or lacked adequate information in the physicians case report forms.

Outcomes	Pain Conditions						Total
	Peripheral Muscle or joint Pain n=467	Low back pain n=163	Post-operative Pain n=65	Headache n= 57	Dysmenorrhea n=46	Missing Data n=74	
Number of patients with at least one AE	5 (1.1)	9 (5.5)	0 (0.0)	4 (7.0)	3 (6.5)	3 (4.1)	24 (2.8)
AE: Bloatedness	0	1	0	0	0	0	1
Constipation	0	1	0	0	0	0	1
Dizziness	1	1	0	2	0	0	4
Epigastric pain	2	1	0	0	0	0	3
Fever	0	1	0	0	0	0	1
Hyperglycemia	1	0	0	0	0	0	1
Hypertension	0	0	0	1	0	0	1
Hypogastric pain	0	0	0	0	2	0	2
Insomnia	0	0	0	1	0	0	1
Nausea	0	1	0	0	0	0	1
Periorbital edema	0	0	0	0	0	1	1
Pruritus	1	0	0	0	0	0	1
Uneasiness	0	1	0	0	0	0	1
Unclassified	0	2	0	0	1	2	5
AE: Adverse Event							

Table 6: Safety outcomes across pain conditions.

Approximately 71% of the AEs were either "not" (7 out of 24) or "possibly" (10 out of 24) related to dexketoprofen intake, and 16.7% were classified as "definitely related" (Table 7). Among the 4 patients who developed AEs "definitely related" to drug intake, 1 had fever, 1 had periorbital edema, 1 had disturbance in the gastrointestinal tract (i.e. bloatedness), and the other 1 was unclassified or undetailed.

	Severity of AE			Causal Relationship with Dexketoprofen Intake				
Adverse Events (n)	**Non-Serious AE n=17**	**Serious AE n=5**	**Missing Data n=2**	**Not Related n=7**	**Possibly n=10**	**Probably n=1**	**Definitely Related n=4**	**Missing Data n=2**
Bloatedness (1)	1	0	0	0	0	0	1	0
Constipation (1)	1	0	0	1	0	0	0	0
Dizziness (4)	3	0	1	0	3	0	0	1
Epigastric pain (3)	3	0	0	0	2	1	0	0
Fever (1)	1	0	0	0	0	0	1	0
Hyperglycemia (1)	0	1	0	1	0	0	0	0
Hypertension (1)	0	0	1	0	0	0	0	1
Hypogastric pain (2)	2	0	0	2	0	0	0	0
Insomnia (1)	1	0	0	0	1	0	0	0
Nausea (1)	1	0	0	0	1	0	0	0
Periorbital edema (1)	1	0	0	0	0	0	1	0
Pruritus (1)	1	0	0	0	1	0	0	0
Uneasiness (1)	1	0	0	1	0	0	0	0
Unclassified (5)	1	4	0	2	2	0	1	0
AE: Adverse Event								

Table 7: Severity of adverse events (N=24) and causal relationship with Dexketoprofen intake.

Discussion

Musculoskeletal conditions, particularly osteoarthritis and low back pain, were the most common conditions seen by physicians throughout the study period. Majority received the recommended dosage and duration of the medicine, which was 51-75 milligrams of dexketoprofen a day (56.2%) for at least 1 week (57.5%). On follow-up, there was statistically significant improvement ($p<0.0001$) in pain scores among patients, regardless of medical condition and dexketoprofen dosage and duration. There was low (2.8%) incidence of adverse events in the study population. Majority of these adverse events did not significantly interfere with daily functioning of patients (Table 5).

Osteoarthritis, which remains to be one of the most common musculoskeletal conditions managed in ambulatory clinics, causes somatic type of pain. It is considered an important standard for measuring analgesic efficacy, especially in acute exacerbations [6-7]. Low-back pain and its consequent restriction on mobility is likewise a common condition, wherein inflammation of soft tissues and paralumbar spasm can be addressed by NSAIDs [21]. A medicine's fast onset of action is crucial in the prevention of antalgic postures, which might delay recovery or cause more pain.

In general, the frequency and severity of adverse events (AEs) reported in this local study were comparable in previous studies abroad [2,8,13]. Majority of AEs were classified as non-serious. The incidence and profile of AEs remain within the expected range for a drug of this pharmacological class, being mild gastrointestinal adverse reactions (i.e. bloatedness, constipation, epigastric pain, or hypogastric pain) as most frequent, followed by neurologic disorders system (i.e. dizziness, nausea, or insomnia), which were similar to related studies [2,8]. In our study, it is worth noting that no serious adverse event, particularly gastrointestinal bleeding, myocardial infarction, or death, was reported.

Limitations of the study include data collection that had missing data or unclear responses. For instance, there were 4 serious AEs that could have been classified if there were more details provided by the physician-participants. In addition, there was limitation in the return-rate of responses in terms of the CGI (Clinical Global Impressions) scales, wherein only 250 physicians were able to report the scores of their patients. Since the case report forms were designed to protect the anonymity of patients and physicians alike, there was no provision for information on contact details to clarify vague or missing responses. Recall bias might have also affected the accuracy of responses of both patients and physicians. We also do not discount the possibility of over- or underreporting of both therapeutic effect and adverse events from either party. Moreover since the study was conducted in private clinics, physicians might have committed selection bias of patients who seemed to be more cooperative and compliant than the rest. Hawthorne effect might have influenced the outcomes to lean more towards benefit than risk. Therefore, it is recommended that

aforementioned limitations be addressed in future related studies to improve the methods and prevent bias. Future studies can also compare dexketoprofen with other commonly prescribed non-steroidal anti-inflammatory medications with respect to effectiveness and safety.

Conclusion

In conclusion, majority of the study population experienced moderate or marked therapeutic effect with no to minimal side effect. The most common conditions that were relieved with oral dexketoprofen included musculoskeletal complaints, such as osteoarthritis and low back pain. This post-marketing surveillance provides a view of the effectiveness and safety of the medication.

References

1. Torres RDS, Marques KS, Leal KDR (2015) Main reasons for medical consultations in family healthcare units in the city of Recife, Brazil: A cross-sectional study. Sao Paulo Med J.
2. Carne X, Rios J, Torres F (2009) Postmarketing cohort study to assess the safety profile of oral dexketoprofen trometamol for mild to moderate acute pain treatment in primary care. Methods Find Exp Clin Pharmacol 31: 533-540.
3. Vane JR (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 231: 232-235.
4. Carrabba M, Chevallard M (1987) Ketoprofen lysine in rheumatoid arthritis: Efficacy and tolerability of two therapeutic schedules with evaluation of synovial prostaglandin levels. Current Ther Res 42: 706.
5. Brzeziński K, Wordliczek J (2013) Comparison of the efficacy of dexketoprofen and diclofenac in treatment of non-specific low back pain. Ann Agric Environ Med 52-56.
6. Beltran J, Martin-Mola E, Figueroa M (1998) Comparison of dexketoprofen trometamol and ketoprofen in the treatment of osteoarthritis of the knee. J Clin Pharmacol 38: 74S-80S.
7. Rovetta G, Monteforte P (2001) Dexketoprofen-trometamol in patients with osteoarthritis of the hands. Minerva Ortop Traumatol 52: 27-30.
8. Moore RA, Barden J (2008) Systematic review of dexketoprofen in acute and chronic pain. BMC Clinical Pharmacology 8: 11.
9. Leman P, Kapadia Y, Herington J (2003) Randomised controlled trial of the onset of analgesic efficacy of dexketoprofen and diclofenac in lower limb injury. Emerg Med J 20: 511-513.
10. McQuay H, Moore A, Justins D (1997) Treating acute pain in hospital. BMJ 314: 1531-1535.
11. Bandolier-Evidence based thinking about health care. Dysmenorrhoea.
12. Zapata A, Cegarra F, Artigas R (2000) Dexketoprofen versus tramadol: Randomized double-blind trial in patients with postoperative pain. 7th World conference on clinical pharmacology & therapeutics. Florence, Italy. Br J Clin Pharmacol 223.
13. Marenco JL, Perez M, Navarro FJ (2000) A multicenter, randomised, double-blind study to compare the efficacy and tolerability of dexketoprofen trometamol versus diclofenac in the symptomatic treatment of knee osteoarthritis. Clin Drug Invest 19: 247-56.
14. Rovetta G, Monteforte P (2001) Dexketoprofen-trometamol in morning stiffness induced in nodal osteoarthritis of the hands. Minerva Ortop 52: 27.
15. Barbanoj Rodriguez MJ, Arbos RM, Amaro SR (2008) Dexketoprofen trometamol: Clinical evidence supporting its role as a painkiller. Expert Rev Neurother 8: 1625-1640.
16. Iohom G, Walsh M, Higgins G, Shorten G (2002) Effect of perioperative administration of dexketoprofen on opioid requirements and inflammatory response following elective hip arthroplasty. Br J Anaesth 88: 520-526.
17. Summary of product characteristics of dexketoprofen trometamol (Ketesse).
18. Busner J, Targum SD (2007) The clinical global impressions scale applying a research tool in clinical practice. Psychiatry (Edgmont) 4: 28-37.
19. Guy W (2000) Clinical Global Impressions (CGI) Scale, Handbook of Psychiatric Measures (1st Edn). Washington, DC: American Psychiatric Association.
20. Karch F, Lasagna L (1977) Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 21: 247-254.
21. Deyo RA, Weinstein JN (2001) Low back pain. N Engl J Med 344: 363-370.