A Post Marketing Survey on the Side-effects of Loxoprofen

SARANATRA WAIKAKUL, M.D.*,
WARAPORN WAIKAKUL, M.D.**,

Abstract

A survey study of the efficacy and side-effects of loxoprofen in orthopaedic outpatient clinics was carried out from January 1995 to December 1997. There were 1206 patients (569 males and 637 females) with an average age of 56.4 ± 14.9 years. The youngest was 43 and the oldest was 79 years. About 36 per cent of the patients had underlying diseases and 31 per cent were receiving other medications as well as loxoprofen.

About 91 per cent of the patients were satisfied with loxoprofen in terms of pain control and decreased inflammation. However, 8.4 per cent had side-effects, the most common being GI and CNS disturbances. Some patients (0.24%) had GI bleeding and needed hospitalization. The high risk patients were female older than 60 years who had used loxoprofen continuously for more than 6 weeks. However, we conclude that loxoprofen is an effective NSAID with few side-effects.

Key word : NSAIDS, Post-marketing Survey, Loxoprofen

Loxoprofen (Loxonin®, Sankyo), a non-steroidal anti-inflammatory drug related to phenyl-proprionic acid[1], became available in Thailand in 1993. It is used in the management of many painful rheumatological and acute injury conditions[2-4]. Its efficacy can be compared to more commonly used non-steroidal anti-inflammatory drugs but it has fewer side-effects, especially on renal function[5-8]. This study was carried out to investigate the clinical side-effects of loxoprofen in a large group of patients after it had been used in Thailand for 4 years.

PATIENTS AND METHOD

The study was carried out as a prospective survey at Siriraj and Sriwichai Hospitals. All

* Department of Orthopaedic Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700,
** Department of Anesthesiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

patients who received loxoprofen, on appropriate clinical grounds, were eligible for registration in the study. Registration information included biodata, concurrent illness and drug therapy, the reasons for prescribing loxoprofen, and the dosage.

Follow-up visits took place at the end of the first, second, fourth and sixth weeks after the first medication. All patients were followed-up for at least 1 year. At the end of the study, at the 1 year follow-up, the patients were re-evaluated by direct visit, telephone call or questionnaire. At each visit, current dosage, occurrence of side-effects, other medical events, reason for discontinuing loxoprofen, and subjective evaluation of the efficacy of the drug by the patients, were recorded. Any evidence from clinical signs and symptoms and laboratory tests that might have indicated side-effects of loxoprofen was recorded and the drug was discontinued immediately. This prospective study was modified from the published post marketing surveillance guidelines[9] because it was not carried out or suggested by any drug company. The study began in January 1995 and ended in December 1997.

RESULTS

There were 1206 patients in the study, 569 males and 637 females. The average age was 56.4 ± 14.9 years. The youngest was 43 and the oldest was 79 years. Most of the patients had degenerative joint disease (38%), or cumulative trauma disorders (24%) (Table 1). Underlying diseases or co-existing illnesses were observed in 434 patients (36%) and the most common was cardiovascular conditions in 269, followed by endocrine conditions in 152, and disorders of the respiratory system in 13 patients. Loxoprofen was not used in those patients who had peptic ulcer, renal and hepatic disorders. At entry, 374 patients or 31 per cent had concomitant medication for underlying diseases and co-existing illnesses.

The most common reason for the prescription of loxoprofen was lack of effectiveness of previous nonsteroidal anti-inflammatory drugs in 892 patients (74%). The remaining 314 patients received loxoprofen as the first nonsteroidal anti-inflammatory drug for their present illness.

At the initial visit there were 811 patients who received loxoprofen together with antacids, H_2-blockers or sucrafate, and there were 395 patients who received loxoprofen alone. At first, all patients received loxoprofen 60 mg three times a day after meals. Then, the doses were adjusted to optimize the efficacy in each patient using the minimum dosage[10]. During the 2nd week of treatment, 29 patients (2%) needed more loxoprofen than 180 mg/day while 46 patients (4%) needed less (Table 2). Loxoprofen was discontinued in 42 patients (3%) because the patients had improved so much that only paracetamol was needed to control pain and discomfort (Table 2). After 2 weeks of treatment, loxoprofen was reduced in 459 patients (38%) and 377 patients were able to use only paracetamol for pain control. After 6 weeks of treatment, most of the patients who had degenerative joint disease, cumulative trauma disorders, myofascial pain syndrome and acute injuries showed so much improvement that loxoprofen could be discontinued. Only 184 patients needed loxoprofen for more than 6 weeks. These patients had rheumatoid arthritis (11), seronegative arthritis (10), cumulative trauma disorders (61), myofascial pain syndrome (57) and degenerative joint disease (45).

Table 1. Presenting illness generating prescription of loxoprofen.

Condition	No. of patients n = 1206	Sex		Mean duration of illness (years)	
		Male n = 569	Female n = 637	Male	Female
Degenerative joint diseases	461	217	244	3.8 (< 1 - 50)	4.1 (< 1 - 52)
Cumulative trauma disorders	298	141	157	0.4 (< 1 - 10)	0.3 (< 1 - 5)
Myofascial pain syndrome	234	110	124	0.6 (< 1 - 12)	0.8 (< 1 - 15)
Acute injuries	156	74	82	within 7 days after injuries	
Rheumatoid arthritis	11	5	6	1.4 (< 1 - 15)	2.1 (< 1 - 29)
Seronegative arthritis	10	4	6	2.1 (< 1 - 20)	2.2 (< 1 - 25)
Miscellaneous	36	18	18	0.2 (< 1 - 15)	0.2 (< 1 - 20)

Table 2. Changes in dosage of loxoprofen at each follow-up period.

Dosage	No. of patients					
	During 1st week n = 1206	During 2nd week n = 1152	During 2nd to 4th week n = 1140	During 4th to 6th week n = 1132	During 6th week to 1 year n = 1121	
					Using loxoprofen <2 weeks	Using loxoprofen >2 weeks
> 180 mg/day	-	29	-	-	-	-
180 mg/day	1206	1035	681	405	111	34
120 mg/day	-	46	82	129	19	37
Loxoprofen was discontinued because of improvement of illness	-	42	377	598	920	
Loxoprofen was discontinued because of side-effects	54	12	8	11	17	(Total 102)

Table 3. Relationship between sex, age and the side-effects in the patients who experienced only 1 side-effect.

Sex and Age	Male, n = 19		Female, n = 48		Total
Types of side-effects	≤ 60 years	> 60 years	≤ 60 years	> 60 years	
GI disturbance	4	13	15	24	56
Kidney disturbance	-	-	-	1	1
CNS disturbance	1	1	4	2	8
ANS disturbance	-	-	-	1	1
Dermatologic disorders	-	-	1	-	1
Total	5	14	20	28	67

Global evaluation by the patients revealed that loxoprofen was a good drug in terms of pain control, decreasing inflammation and improving daily activities in 1105 patients or 91.6 per cent. Sixty patients (4.9%) felt that the drug was not a good anti-inflammatory and analgesic agent although all had some improvement in pain and inflammation. They were not satisfied with loxoprofen. The remaining 41 patients (3.4%) felt that the drug was ineffective.

One hundred and two patients (8.4%) had side-effects and the drug was discontinued (Table 2). All had at least one side-effect. Twenty-eight of these patients were male and 74 were female. Eighty-six of these patients had mild side-effects and 16 had moderate to severe side-effects which needed medical treatment. However, 3 patients who had severe side-effects were hospitalized with gastrointestinal bleeding but none needed blood transfusion. No patient had a permanent problem because of the side-effects. Sixty-seven patients, 19 males and 48 females had only 1 side-effect, the most common being GI disturbance (Table 3). Side-effects were common in female patients who were older than 60 (Table 3). Thirty-three patients experienced 2 side-effects and the common combined side-effects

Table 4. Relationship between sex, age and the side-effects in the patients who experience 2 side-effects.

Sex and Age	Male, n = 9		Female, n = 24		Total
Types of side-effects	≤ 60 years	> 60 years	≤ 60 years	> 60 years	
GI and CNS disturbance	2	5	9	11	27
GI and ANS disturbance	1	-	-	2	3
GI and kidney disturbance	-	1	1	1	3
Total	3	6	10	14	33

Table 5. Characteristics of patients with and without side-effects.

Characteristics	No. of patients with side-effects n = 102	No. of patients without side-effect n = 1104	P-value
Sex : Male	28	530	$x^2 = 4.69$
: Female	74	574	$p < 0.05$
Age : ≤ 60 years	38	564	$x^2 = 6.60$
: > 60 years	64	540	$p < 0.05$
Using Antacids, H2 Blockers or Sucrafate			
: Yes	8	803	$x^2 = 175.58$
: No	94	301	$p < 0.05$
Regular Alcoholic Consumption			
: Yes	12	2	$x^2 = 99.30$
: No	90	1102	$p < 0.05$
Regular Smoking			
: Yes	9	2	$x^2 = 67.89$
: No	93	1102	$p < 0.05$
Diet : Regular	56	1082	$x^2 = 318.03$
: Irregular	46	22	$p < 0.05$
Duration of Loxoprofen Administration Continuously			
: ≤ 6 weeks	13	1009	$x^2 = 446.6$
: > 6 weeks	89	95	$p < 0.05$

were GI and CNS disturbances (Table 4). These side-effects were also commonly found in female patients who were older than 60 years and 1 patient needed hospitalization. Two female patients had 3 combined side-effects which were GI, CNS and kidney disturbances. Both needed hospitalization because of GI bleeding. So, there were 92 patients or 90 per cent who had GI side-effects with definite bleeding in 3 patients. Thirty eight patients had CNS disturbance. The patients most at risk were female patients who were older than 60 years, having irregular meals and using loxoprofen for longer than 6 weeks (Table 5). Antacids, H2-blockers and sucrafate could reduce GI symptoms (Table 5). However, the use of these drugs did not prevent GI bleeding because one third of the patients who had GI bleeding and who needed hospitalization had also received a H2-blocker as well as the loxoprofen.

DISCUSSION

Biodata of the patients in this study was comparable to other post-marketing surveillances (11-14). About half of our patients were females older than 60 years. About 80 per cent of our patients had osteoarthritis and function disorders of the musculoskeletal system including cumulative trauma disorders and myofacial pain syndrome. Underlying or co-existing diseases were observed in 36 per cent

of our patients. This was similar to other studies, most of which reported these diseases in about 30 to 40 per cent of their patients[3,11-14].

Overall side-effects usually were found less in those studies which were operated by drug companies and did not contribute significantly to the drug safety[5]. So, this study was carried out without any drug company support. Ordinary orthopaedic outpatient clinics were used to collect data from an unselected group of patients. Hence, the results have general application. However, since most of the side-effects were documented by subjective evaluation, they may have been overestimated. Hence, the data presented here may represent the maximum incidence of the side-effects of the use of loxoprofen in ordinary orthopaedic outpatient clinics.

The overall incidence of side-effects of loxoprofen in this study was 8.4 per cent which is rather low compared to other non-steroidal anti-inflammatory drugs which have reported side-effects of 8 to 20 per cent[10-17]. GI disturbance was the most common side-effect. It was observed in 92 patients (7.6%) and 3 patients (0.24%) had significant GI bleeding and needed hospitalization. These figures were smaller than other non-steroidal anti-inflammatory drugs and are comparable to some COX 2 preferential drugs[10-17]. The use of antacid, H2-blokers or sucrafate could significantly reduce the incidence of GI side-effect but not the GI bleeding (Table 5). This finding is similar to other clinical trials[18,19]. Other side-effects such as kidney, ANS and dermatologic disturbance were also low except CNS disturbance which was similar to the other drugs[10-17]. This drug is safe in terms of influencing kidney functions. Only 4 patients or 0.3 per cent had edema but none had abnormal blood chemistry which reflected renal function disturbance. The edema disappeared after the drug was discontinued.

About 31 per cent of the patients had significant improvement in pain and inflammation after 2 weeks of medication and about 76 per cent could discontinue the drug after 6 weeks of medication because of the improvement. Furthermore, subjective evaluation by the patients indicated that 91.4 per cent were satisfied with its effects.

SUMMARY

Loxoprofen in an oral dosage of 180 mg per day is a safe non-steroidal anti-inflammatory drug for general orthopaedic patients who have pain and inflammation in the musculoskeletal system. However, careful monitoring is necessary if the drug is used in female patients older than 60 years and if the drug is used continuously for more than 6 weeks.

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อุบัติการณ์ภาวะแทรกซ้อนและฤทธิ์อันไม่พึงประสงค์จากยาลอคโซโปรเฟน หลังมีจำหน่ายในประเทศไทย

สารเนตร ไวคกุล, พ.บ., วราภรณ์ ไวคกุล, พ.บ.***

ได้ศึกษาประสิทธิภาพและภาวะแทรกซ้อนของการใช้ยา loxoprofen ในผู้ป่วยทั่วไปที่มารับการรักษาทางศัลยกรรมกระดูกและข้อจำนวน 1206 ราย เป็นชาย 569 ราย และหญิง 637 ราย, อายุเฉลี่ย 56.4 ± 14.9 ปี และมีพิสัยอยู่ระหว่าง 43 ถึง 79 ปี ติดตามผลการใช้ยาในผู้ป่วยแต่ละรายไม่น้อยกว่า 1 ปี พบว่าผู้ป่วย 91.4% พอใจต่อยานี้ในการบรรเทาอาการปวดและการอักเสบ มีภาวะแทรกซ้อนเกิดขึ้นในผู้ป่วย 102 ราย คิดเป็นร้อยละ 8.4 ส่วนใหญ่เกิดกับทางเดินอาหาร คิดเป็นร้อยละ 7.6 และเกิดภาวะแทรกซ้อนรุนแรงร้อยละ 0.24 ผู้ป่วยที่มักเกิดอาการได้แก่ ผู้ป่วยหญิงที่มีอายุมากกว่า 60 ปี และใช้ยาติดต่อกันเกิน 6 สัปดาห์ ภาวะแทรกซ้อนรองลงมาคือ การรบกวนของระบบประสาทกลาง มี 38 ราย หรือร้อยละ 3.1 ภาวะแทรกซ้อนทางไตพบน้อยเพียงร้อยละ 0.3 loxoprofen เป็นยาต้านการอักเสบที่ค่อนข้างปลอดภัย

คำสำคัญ : ยาต้านการอักเสบ, ภาวะแทรกซ้อนจากการใช้ยาต้านการอักเสบ

* ภาควิชาศัลยศาสตร์ออร์โธปิดิคส์และกายภาพบำบัด, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล กรุงเทพ ฯ 10700
** ภาควิชาวิสัญญีวิทยา, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400