The efficacy and toleration of celecoxib (Celebrex®) in the treatment of osteoarthritis in Nigeria: A multicentre study

*S. O. Ogunlade[1], L. M. Oginni[2], H. C. Nwadiaro[3], O. Popoola[4], U. N. Enweani[5], B. O. Onabowale[6] and A. S. Dogunro[7]

[1]*Department of Orthopaedic and Traumatology, University College Hospital, Ibadan*
[2]*Department of Orthopaedic and Traumatology Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife*
[3]*Orthopaedic and Traumatology Unit, University of Jos Teaching Hospital, Jos*
[4]*National Orthopaedic Hospital, Dala, Kano,*
[5]*National Orthopaedic Hospital, Enugu*
[6]*National Orthopaedic Hospital, Igbobi,*
[7]*Pfizer Specialities Ltd., Lagos.*

Summary

Background: **Non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) are effective in terms of pain relief and improving function in osteoarthritis. The advent of cyclooxygenase-2 (Cox-2) specific inhibitor, celecoxib, in the treatment of osteoarthritis has shown similar efficacy in relieving pain in osteoarthritis with low incidence of GI (Gastrointestinal) symptoms.**

Objective: **To determine the efficacy and toleration of celecoxib in treatment of osteoarthritis in Nigerian population.**

Methods: **Eighty patients were recruited from six tertiary health institutions scattered over Nigeria. A fixed dose of 200 mg celecoxib was administered daily with patient seen on the second and six weeks after commencement of study. Efficacy of the drug and safety were assessed during the study.**

Results: **The patients had a mean age of 57.8years with a standard deviation of 13.3 year. The mean weight was 74.7±14.9kg while the female sex constituted the majority (73.8%) of the patients.**

Using the physician global assessment of osteoarthritis instrument, 36.3% of the patients were rated as having poor arthritis score at baseline. This value reduced to 2.6% at second visit and 0.00% at end of the study respectively.

There was no significant difference between the vital signs, haematological indices, renal and hepatic function at baseline and the final visit. There was no case of serious adverse effect.

Conclusion: **The study showed statistically significant improvements in the symptoms of osteoarthristis following the administration of Celecoxib 200mg daily for six weeks.**

Key-words: ***Efficacy, Toleration, Osteoarthritis, Celecoxib (Celebrex®).***

Résumé

Introduction: Des drogues non-sélectives, non-stériodales et anti inflammatoires (NSAIDS) sont efficaces du point de vue du soulagement et amélioration des fonctions dans l'oésteorthrite. Avec l'arrivée de cyclooxygenase - 2(cox-2) inhibiteur célécoxib, dans la prise en charge d'ostéoarthrite a indique l'efficacité semblable dans le soulagement en ostéoarthrite avec une faible incidence GL (Gastointestinal) des symptomes.

Objectif: Déterminer l'efficacité et la tolérance du célécoxibe dans la prise en charge d'ostéoarthrite chez la population nigériane.

Méthode: Quarante quatre patients ont été recrutés venant de six centres sanitaires tertiaires çà et là au Nigéria. Une dose fixe de 200mg célécoxibe a été administrée de façon quotidienne. Après la deuzième et sixième semaine on a étudie les patients après le commencement de cette étude. Le sans danger et efficacité de la drogue ont été évalués au cours de cette étude.

Résultats: L'âge moyen des patients était 57,8 ans, avec un écart type de 13,3 ans. Le poids moyen était 74,7± 14,9kg tandis que le sexe féminin constitue le majorité (73,8%) des patients. À travers l'utilisation d'instrument d'ostéoarthrite d'évaluation globale des médecines 36,3% des patients ont été notés; ils avaient un score mauvais d'arthrite à partir de la ligne de fuite. Cette valeur a diminué au 2,6% au cours de la deuzieme visite et 0,00% apres cette étude respectivement.

Il n'y avait aucun écart important entre les signes de vie, indices hématologique, fonction hépatique et rénale a partir de la ligne de fuite et de la dernière visite et 0,00% après cette étude respectivement.

Il n'y avait aucun écart important entre les signes de vie, indices hématologique, fonction hépatique et rénale a partir de la ligne de fuite et de la dernière visite. Il n'y avait aucum cas d'effet sérieux et adverse.

Conclusion: Cette étude a démontré une amélioration statyistiquement importante dans le symptôme d'ostéoaartyhrite à la suite de l'administration de 200gm de célécoxibe d'une façon quotidine pendant six semaines.

Introduction

Osteoarthritis is one of the most frequent causes of physical disability among adults, and it is the most prevalent musculoskeletal condition that results in joints pain with nearly 70% of the population greater than 65 years of age demonstrating radiographic evidence of the disease[1]

In Nigeria, the knee joint is the most frequently affected joint followed by osteoarthritis of the hip which is commonly secondary to identifiable factors[2,3]. Pain is the most common symptom in patients with osteoarthritis presenting in the hospital.[2,3] The symptoms of osteoarthritis (OA) may be relieved in some patients by the use of simple analgesics in conjunction with life style changes involving joint protection and exercise[4]. However, many patients do not achieve adequate relief of symptoms with these measures and usually require further medications in the like of the non-steroidal anti-inflammatory drugs (NSAIDs)[5].

Recent studies suggest that patients prefer NSAIDs to

*Correspondence

simple analgesic and that such drugs are more effective in terms of relieving pain and improving function[6].

The widespread use of NSAIDs has raised the issue of safety and tolerability, the most common side effect is the development of dyspeptic symptoms that appear to affect all ages and may occur in up to a third of patients treated[7,8].

The gastroduodenal toxicity of NSAIDs is related to the inhibition of the prostaglandins involved in the maintenance of gastroduodenal mucosal integrity[9].

The isolation of two isoforms of cyclooxygenase led to the recognition that prostaglandins involved in upper gastrointestinal (GI) mucosal protection were produced by Cox-1 whereas those produced by Cox-2 were responsible for mediating, pain and inflammation[9,10].

The above observation led to the introduction of celecoxib as the first of a new class of Cox-2 specific inhibitors, which would have effective anti-arthritis effect but lack the gastrointestinal toxicity. This study evaluates the efficacy and toleration of celecoxib in the treatment of osteoarthritis in a Nigerian population, as against other population where such studies had been previously documented.

Subjects and methods

A total of 80 patients with osteoarthritis of the knee, hip and hand were recruited into the study from six tertiary health institutions scattered all over Nigeria to participate in an open label fixed dose clinical trial assessing the efficacy and safety of celecoxib. The hospitals included in project are University College Hospital, Ibadan, University of Jos Teaching Hospital Jos, Obafemi Awolowo Teaching Hospital Ile-Ife, National Orthopaedic Hospital Dala Kano, National Orthopaedic Hospital Enugu and National Orthopaedic Hospital Igbobi Lagos.

Patients recruited either had OA of the knee or hip or hand and these diagnoses were made according to the guidelines of the American College of Rheumatology[11].

To be eligible, a newly diagnosed patient must have had the OA for a minimum of six months while returning patients must be in OA flare without the use of NSAID for a minimum period of two weeks. A written informed consent was obtained from every patient. Patients were excluded if they had active gastrointestinal disease, chronic or acute renal or hepatic diseases, arthritis other than osteoarthritis and, known hypersensitivity to celecoxib and sulfonamides. Women were excluded if they were pregnant or were lactating. Equally excluded from the study were patients who had used steroid and intra articular hyaluronic acid within the past three months. Each participating institution obtained written ethics committee approval before the start of the study.

Patients were required to take the study medication of 200mg Celecoxib daily for six weeks. There were two follow up clinic visits, at week two and at week six which was the end of the study. At each visit, the following were performed: a thorough physical examination, assessment of the Visual Analogue Scale for pain and the physician and patient assessment of arthritis, and each patient functional capacity. Patients were instructed to report all adverse events experienced while on the study medication. Ethical approval were obtained in all the hospitals before commencement of the study.

Assessments

Primary efficacy end points included the patient's assessment of arthritic pain using a visual analogue score: from 0mm (no pain) to 100mm (worst pain), the Patient's & Physician Global Assessment of Arthritis (both using five point score from very good to very poor) and the functional capacity which has three classes.

Safety assessment included recording of adverse events as complained by the patients and or observed by the physicians. Further safety assessment was made by evaluating changes in some laboratory values post treatment.

Statistical analysis

The data submitted for statistical analysis was on a well-structured questionnaire and standard laboratory record forms completed for each of the patient in the trial. The statistical package EPI-INFO version 6.0 was used for the data entry. The data file was subsequently converted to ASCII code to facilitate statistical analysis using the stat Pac gold statistical package.

Percentages and proportion were used to describe categorical variables such as the patients' social interaction, drug and non-drug treatments, medical history, physical examination and arthritis history and assessments. Descriptive statistics such as means (0), standard deviation (d) and range were used to summarize numerical data like age, height, weight, vital signs, laboratory data and assessment of pain on the visual analogue scale.

Chi-square test was used to examine the significance of association between any two categorical variables, applying the Yates's correction where necessary and the Fischer's exact test where appropriate. For paired observation, the McNamara's test was used to investigate the significance of change in arthritis status after drug use. The paired Student's t-test was used to assess changes in numerical data between any two visits. The differences between second and baseline data and final and baseline data for numerical variables were examined for significance using the paired t- test. All statistical tests were two tailed carried out at 5% probability level.

Results

Demographics

A total of eighty patients (Table 1) were recruited to participate in the trial. Female patients were in the majority constituting 73.8% of the total population. All studied patients were black. The mean age is 57.8 years with standard deviation (SD±) 13.3. There was no statistical difference in the age of the two sexes. The table also shows the weight and height in relation to sex.

All patients in this trial have osteoarthritis as the primary diagnosis. A high proportion of the patients (73.8%) had knee joint involvement, knee/hip were together reported in 8.8% of the patients while the least reported joint involvement was the hand (1.3%). Although there appears to be a similarity in the pattern of the distribution of joint involvement by sex, the observed sex differences was statistically significant ($P > 0.05$). While a higher proportion of females

Table 1 Summary statistics of the subjects' Age, Weight and Height by sex

Parameters	Statistics	Sex			t-test	P-value
		Male	Female	Both		
Age (yrs)	Mean (0)	54.05	59.15	57.81	1.53	0.13
	S. D. (δ)	15.02	12.43	13.26		
	Sample size (n)	21	59	80		
Weight (kg)	Mean (0)	73.60	75.14	74.74	0.40	0.70
	S. D. (δ)	16.51	14.14	14.89		
	Sample size (n)	20	57	77		
Height (cm)	Mean (0)	168.45	159.84	162.08	4.76	0.0001
	S. D. (δ)	8.62	6.30	7.89		
	Sample size (n)	20	57	77		

Table 2 Distribution of the patients' arthritis history/diagnosis by sex

Arthritis history	Sex				Both sexes			P-value
	Male		Female					
	Freq.	%	Freq.	%	Freq.	%	X^2	
Primary Diagnosis								
Oeteoarthritis	21	100.0	59	100.0	80	100.0	0.00	1.00
Joint involvement								
Knee	11	52.4	48	81.4	59	73.8		
Hand	1	4.8	0	0.0	1	1.3		
Hip	7	33.3	6	10.2	13	16.3	9.71	0.02
Knee/Hip	2	9.5	5	8.5	7	8.8		
Side of body								
Right side	7	33.3	25	42.4	32	40.0		
Left side	5	23.8	11	18.6	16	20.0	0.58	0.75
Both sides	9	42.9	23	39.0	32	40.0		
Functional capacity								
Class I	0	0.0	0	0.0	0	0.0		
Class II	14	66.7	26	44.1	40	50.0	2.32	0.13
Class III	7	33.3	33	55.9	40	50.0		
Class IV	0	0.0	0	0.0	0	0.0		

Table 3 Physician and patient global assessment of arthritis

Assessment	Visit							
	Baseline		Second		Final		X^2	P-value
	Freq.	%	Freq.	%	Freq.	%		
Physicians' global assessment of osteoarthritis								
Very good	0	0.0	0	0.0	9	12.0		
Good	6	7.5	37	48.1	51	68.0	116.91	0.00001
Fair	45	56.3	38	49.4	15	20.0		
Poor	29	36.3	2	2.6	0	0.0		
Very poor	0	0.0	0	0.0	0	0.0		
Patients' global assessment of osteoarthritis								
Very good	0	0.0	0	0.0	5	6.7		
Good	3	3.8	35	45.5	53	70.7	116.14	0.000001
Fair	44	55.0	38	49.4	17	22.7		
Poor	32	40.0	4	5.2	0	0.0		
Very poor	1	1.3	0	0.0	0	0.0		

Table 4 Summary of the visual pain analogue by each visit

Summary measure for VAS	Visits				
	Baseline	Second	Final	F-test	P-value
Mean (0)	67.64	44.34	28.13	131.66	0.000001
S. D (δ)	14.24	15.34	15.34		
Range	23.0 - 100.0	10.0 - 100.0	0.0 - 75.0		
Sample size	80	77	75		

Table 5 Summary of adverse events

Adverse event	Second visit (Frequency)	Final visit (Frequency)
Infection (Malaria fever)	5	4
Headache	3	1
Diarrhoea	2	0
Dizziness	2	1
Itching	2	0

(81.4% versus 52.4) reported the knee, the reverse was in the proportion of males reporting the hip (33.3% versus 10.2%).

Arthritis assessment

Using the Physician global assessment instrument, 36% of the patients had their arthritis assessed as poor at baseline. This percentage decreased significantly to only 2.6% at the second visit, with only two weeks of medication. At the end of the study, none of the patients had a poor assessment by any of the investigators while 80% of the patients were assessed as either good or very good. Similar trend was observed with the patient global assessment of arthritis ($p < 0.05$). Table 3 shows these changes.

Table 4 shows the sharp reduction in mean value of the Visual Analogue Scale (VAS) as recorded at baseline through the final visit. The mean value of 67.64 ± 14.24 at baseline was reduced significantly to 44.34 ± 15.34 at the second visit and 28.13 ± 15.38 at the final visit ($p < 0.05$).

Toleration and safety

There was no statistically significant difference between the baseline value of all vital signs measured as compared to the second and final visits in all patients. The laboratory assessments of the liver functions, full blood counts and urea and electrolytes were normal in all patients pre and post study.

The adverse events observed during the course of the study are as recorded in Table 5. There was no serious adverse event and none of the patients was withdrawn on account of adverse event.

Discussion

This 6-week study in a representative population of patients with OA of the knee, the ankle and the hand demonstrates that Celecoxib is efficacious in relieving the signs and symptoms of the disease. Efficacy over the study period was established across a broad range of parameters assessing pain and function and, thus the depth of pain relief was assessed using the VAS and the global assessment of arthritis. These end-points showed statistically significant changes when the values at baseline were compared with subsequent values during the study period. These efficacy data thus corroborate and expand on those in other reported studies.[4,12,13]

Published studies indicate that celecoxib exhibits better gastrointestinal (GI) safety and tolerability than non-selective NSAIDs [7,14,15]. We were unable to confirm this because most of our centers had no facilities for upper GI endoscopies and furthermore, this was an open label non-comparative study. In spite of this however, it is reasonable to assume that celecoxib may not be associated with significant upper GI toxicity because none of our patients gave any adverse event that might suggest upper GI toxicity despite direct inquiries. Some studies had shown that some patients on long-term therapy with the non-selective NSAIDs develop high blood pressure [14,17]. The investigators took extra care to monitor the blood pressure of the patients at the various visits and observed no change in the value of the systolic and diastolic pressures at those visits.

Similarly, the renal and hepatic functions were not significantly affected. The measured electrolytes and urea, urinalysis hepatic transaminases and bilirubin in these patients showed no variation pre and post dosing with celecoxib.

At the final visit only six patients had an adverse event and the most common event was malaria fever, which was taken not to be drug related.

Conclusion

This study adds to the expanding literature establishing that celecoxib, a specific inhibitor of cyclo-oxygenase-2 is effective in relieving symptoms of osteoarthritis with the possible added benefit of good upper GI tolerability and lack of hepatic and renal toxicity.

Funding/Support

This study was funded by Pfizer specialities limited, Lagos.

References

1. Lane NE Pain management in osteoarthritis. The role of cox-2 inhibitors. Journal of Rheumatology 1997; 24: 20-24.

2. Adebajo AO. Pattern of osteoarthristis in a West African Teaching Hospital: Annals of the Rheumatic Diseases 1991;

50: 20-22.

3. Ebong WW, Lawson EAL. Pattern of osteoarthritis of the Hip in Nigerians. East African Medical Journal.1978; 55: 81-84.

4. McKenna F, Borenstain D, Wendt H, Wallemark C, Leftkowith JB Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. A placebo controlled randomised, double blind comparison scan J Rheumatol 2001; 30: 11-18.

5. Hochbery MC, Altman RO, Brandt KD, Clark BM, Dieppe PA. Griffin MR et al. Guidelines for the medical management of osteoarthritis of the knee. Arthritis Rheum 1995; 38: 1541-6.

6. Wolfe F, Zhao S, Lane N. Preference for NSAIDs over acetaminophen by rheumatic diseases patients: a survey of 1799 patients with OA, RA, and fibromyalgia. Arthritis Rheum 2000; 43: 378-85.

7. Bensen WG, Zhao DR, Burke TA, Zabinski RA, Makuch RW, Maugrath C et al. Upper gastrointestinal tolerability of celecoxib cox-2 specific inhibitor, compared to naproxen and diclofenac. Rheumatol 2001; 27: 1876–83.

8. Singh G, Ramey DR. NSAID induced gastrointestinal complication the ARAMIS perspective-1997 J Rheumatol 1998-25 suppl 51: 8-16.

9. Warner TD, Gruliano F,Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity a full in vitro analysis Proc Natl Acad Sci 1999; 96: 7563-68.

10. Masferrer JL, Zweife BS, Manning PT, Hauser SD, Leahy KM, Smith WG, et al. Selective inhibition of inducible cyclo-oxygenase 2 in Vivo is anti-inflammation and non ulcerogenic. Proc Natl Acad Sci USA 1994; 91: 3228-32.

11. Altman R, Asch E, Bloch D, Bole G, Borenstain D, Brandt K, et al. Development of Criteria for the Classification and reporting of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American Rheumatism Association Arthritis Rheum 1986; 29: 1039-49.

12. Clemett D, Goa KL. Celecoxib A Review of its use in osteoarthritis, Rheumatoid Arthritis and Acute pain. Drugs 2000 Apr; 59: 957-980.

13. Lichtenstain DR, Wolfe MM. cox-2 selective NSAIDs New and Improved? JAMA 2000; 284: 1297-99.

14. Simon LS, Weaver A L, Graham DY, Kivitz AJ, Lipsky PE , Hubbard RC et al. Anti inflammatory and upper gastro intestinal effects of celecoxib in rheumatoid arthritis: a randomised controlled trial. JAMA 1999; 282: 1921-8.

15. Silverstein FE, Farch G, Goldstein JL, Simon LS, Pincus T , Whelton A et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. JAMA 2000; 284: 1247-55.

16. Whelton A, white WB, Bell AE, Puma JA, Fort JG. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > 65years of age with systemic hypertension and osteoarthritis AMJ Cardiol 2002; 90: 959 – 63.

17. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomised, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients AM J Ther 2001; 8: 85-95.