Original Article

Prescribing patterns of celecoxib and prescribers' perceptions among three general hospitals in Northern Malaysia

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ABSTRACT

Objectives: This paper describes the clinical use of celecoxib in three major, government-subsidized hospitals across Northern Malaysia. Doctors' perceptions of issues related to celecoxib and other nonsteroidal anti-inflammatory drugs (NSAIDs) were assessed concurrently. **Materials and Methods:** A total of 365 patients receiving prescriptions containing celecoxib in 2012 were recruited. Their medical records were screened for celecoxib-related information including its indications, risk factors for gastrointestinal bleeding and cardiovascular comorbidities. A self-reported, six-item questionnaire was used to investigate the perceptions of 211 doctors. **Results:** Patients within a wide range of ages had received celecoxib (15-94 years). General acute pain (23.6%), general chronic pain (20.3%), and osteoarthritis (12.3%) were the most common indications. Less than one-third of patients prescribed with celecoxib (31.5%) were found to have one or more risk factors for gastrointestinal complications. Advanced age (≥65 years) was identified as the most common risk factor (14.8%). Approximately one-third of them (32.4%) were having one or more cardiovascular comorbidities including hypertension and chronic heart diseases. Majority of the doctors (53.1%) believed that celecoxib is more efficacious than conventional NSAIDs in reducing pain and inflammation. The awareness of its better gastrointestinal safety profile was exceptionally high (92.4%) and it remained as the most important factor to consider during prescribing (65.9%). **Conclusion:** Overall, this study revealed the prescribing patterns of celecoxib among the government-subsidized hospitals in Northern Malaysia. Certain issues like its high usage in patients without gastrointestinal risk factors and in those with cardiovascular comorbidities may require a review from clinical perspectives.

Key words: Celecoxib, Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2inhibitors, Northern Malaysia, Hospitals

INTRODUCTION

Celecoxib (Celebrex®), one of the most well-known cyclooxygenase-2 (COX-2) inhibitors, has been widely used for a wide range of morbidities since its launch in the late 1990s. The growing portion of the healthcare cost on this expensive medication had raised a concern worldwide.[1,2] It is currently approved in the National Drug Formulary of the Ministry of Health Malaysia for four indications: Osteoarthritis (OA), rheumatoid arthritis (RA), general acute pain, and ankylosing spondylitis.[3] Spending on celecoxib among government-subsidized hospitals in Kedah State had taken up approximately 76% ($0.12 million USD) of the total expenditure on nonsteroidal anti-inflammatory drugs (NSAIDs) in 2012. To date, no reviews were

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found in the literature of its prescribing patterns in Malaysia.

Since celecoxib was marketed, it has been consistently proven to have similar efficacy to the nonselective NSAIDs in OA and RA.[4] A subsequent trial had confirmed that both dosages of celecoxib (200 and 400 mg daily) were as effective as naproxen and diclofenac in OA.[5] Comparable to naproxen, twice-daily 200 mg celecoxib was proven to improve the functional status and overall health-related quality of life among the RA patients.[6] The antiinflammatory effect of celecoxib to improve both pain control and function in patients with ankylosing spondylitis has also been well-established.[7,8] Its signs and symptoms were equally well-controlled by once-daily 400 mg celecoxib and twice-daily 50 mg naproxen.[8] Furthermore, numerous trials had demonstrated the similar efficacy of celecoxib to traditional NSAIDs in postoperative and other types of acute pain.[9,10] Considering the impact of cost, celecoxib is economically attractive in patients with high risk of gastrointestinal events by lowering the overall medical expenditure.[11]

Including those taking COX-2 inhibitors, upper gastrointestinal events (UGIEs) occur in 1 of every 20 NSAID users and in 1 of every 7 older adults using NSAIDs. The reported annual incidence of UGIE among NSAID users was 2.0-4.5%.[12] Due to the nonselective mechanisms of action, nonselective NSAIDs are associated with higher rates of severe UGIE including perforation, ulceration, and bleeding.[13] Pharmacologically, celecoxib acts via selective inhibition of COX-2 and, therefore, provides better safety profile with regards to GI complications compared with nonselective NSAIDs.[12] A meta-analysis involving five randomized clinical trials proved that celecoxib had led to a relative risk reduction of 79% and 57% in combined gastroduodenal ulcers and peptic ulcer bleedings, respectively.[13] Besides that, it had fewer discontinuations for gastrointestinal events than did traditional NSAIDs. Compared with both traditional NSAID alone and its combination with a proton pump inhibitor (PPI), celecoxib was also associated with relatively low rates of dyspepsia, abdominal pain, nausea, and gastroesophageal reflux disease.[14,15]

However, there were arguments for the small absolute benefits brought by celecoxib.[16] As estimated by two major safety trials, the annual incidence of serious GI complications among the traditional NSAIDs users was only 1.4%. Celecoxib was able to reduce the relative risk of these events by another 50% (number need to treat = 125-130)[17,18] Furthermore, the US Food and Drug Administration (FDA) and some other reviews had highlighted that the benefits of celecoxib after 6 months were not fully demonstrated in these analysis, placing doubt on the rationale of its chronic use in clinical practices.[16] In fact, prescribers have been encouraged by the Malaysian Drug Control Authority (DCA) to use the lowest effective dose of celecoxib for the shortest duration consistent with patient treatment goals.[19]

Among the most commonly reported adverse drug reactions related to celecoxib in Malaysia are skin disorders.[20] The reported incidence of rash, pruritis, and urticaria was collectively lower than 5%.[4] However, as a sulfonamide COX-2 inhibitor, celecoxib has been associated with some severe skin reaction cases including erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis.[20,21] On top of that, risk of cardiovascular events related to celecoxib is another major concern and remains controversial. A meta-analysis had proposed an increased risk of celecoxib in causing cardiovascular death, myocardial infarction (MI), stroke, heart failure, and thromboembolic events compared with placebo.[22] The most significant determinant was a history of such cardiovascular disease within 1 year prior to celecoxib treatment.[23] Furthermore, the effects of celecoxib in sodium retention and elevation of blood pressure especially among the elder patients were well-established.[24]

The aim of this study was to describe the prescribing patterns of celecoxib in three major hospitals in Kedah State. The results are helpful to answer certain important questions regarding the demographic background and clinical situations of patients taking this medication. Doctors' perceptions of issues related to celecoxib and other NSAIDs were assessed concurrently.

MATERIALS AND METHODS

Study design and setting

This study was designed as a multicenter, cross-sectional study that comprised of two parts. First was the investigation of background and clinical conditions of patients receiving celecoxib using their past medical records. A survey was conducted concurrently to assess the perceptions of doctors toward some commonly discussed issues. This study had targeted three of the major, government-subsidized hospitals across Northern Malaysia. All of them were

tertiary hospitals providing multidisciplinary medical services with a large patient population.

Study population and sample size

For his or her medical record to be assessed, a patient should have received at least one prescription containing celecoxib throughout 2012. Both clinic and warded patients were included. In 2012, a total of 7136 patients had received celecoxib. Using Daniel's formula with finite population corrected, the projected sample size needed was 350 patients based on the estimation that only 60% of them had taken this medication for a justifiable reason. The level of confidence and precision were fixed at 95% and 5%, respectively.[25]

To be eligible to participate in the survey, respondents must have been a medical doctor in one of these three hospitals. Visiting specialists and medical postgraduate students were excluded from study. Of approximately 800 doctors in these hospitals, it was estimated that at least 80% might have agreed with the gastrointestinal benefits brought by celecoxib. By applying the same formula, the sample size of respondents needed was 189 doctors. The total number of respondents was increased to account for a 20% nonresponse rate.

Data collection

This study was registered with the National Medical Research Registry and approved by the Medical Research Ethics Committee. A data collection form was developed using the criteria modified from two regional audits of COX-2 inhibitor and NSAID use in UK and Australia.[16,26] Information collected included demographic data, indication for use, dosage, risk factors for gastrointestinal complications, coprescribed low-dose aspirin, use of gastroprotective agents (GPAs) and cardiovascular comorbidities. A full list of patients receiving celecoxib in 2011 was constructed based on the information provided by each hospital. Patients were selected via systematic random sampling for their medical records to be screened.

To conduct the survey, a self-reported, six-item questionnaire was constructed. All questions were given multiple options of answers. They were designed mainly to investigate the prescribers' perceptions toward the effectiveness of celecoxib, its benefits compared with nonselective NSAIDs, and safety issues with regards to its long-term use in patients with cardiovascular comorbidities. On top of that, factors influencing their choice of NSAIDs, frequency of using celecoxib, and their preferred choice for patients with risk for gastrointestinal bleeding were studied. To confirm its content validity, this questionnaire was reviewed by a panel of fifteen physicians. Using Lawshe's method, the projected content validity ratio for each question was above 0.49 (ranging from 0.60 to 1.00).[27] A pilot test was then conducted to assess the test-retest reliability of questionnaire. A total of 25 respondents had participated to complete the survey twice with a 2-week interval. The values of kappa agreement for six items ranged from 0.50 to 0.87.

Statistical analysis

Results were analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0. All categorical data were expressed as frequencies and percentages. Pearson's Chi-square and Fisher's exact tests were used to assess the associations between doctors' perceptions and their clinical experiences. The levels of significance were fixed at 5%.

RESULTS

Prescribing patterns of celecoxib

A total of 365 medical records were screened. Patients within a wide range of ages had received celecoxib (15-94 years). Those below the age of 65 years comprised 79.2% of the group. Almost half of them had taken celecoxib at a dose of 200 mg once daily (47.1%), followed by 200 mg twice daily (21.9%), 200 mg on an "as required" basis (21.9%), and 400 mg once daily (9.0%). Approximately, 6.6% of patients had received celecoxib for a period longer than 180 day.

The main indications of celecoxib are listed in Table 1. The most common indication was nonspecific acute pain which was defined as the use of celecoxib in an unspecified type of pain for less than 30 days. Specific indications approved by the Ministry of Health Malaysia including OA, RA, and ankylosing spondylitis had taken up less than one-third (27.1%) of the total usage.

Potential risk factors for gastrointestinal complications among the celecoxib users are summarized in Table 2. Results showed that more than two-third of them were free from any risk factors. A small group was having more than one risk factor. Advanced age was the most common risk factor. Those taking "high-risk" medications including warfarin, corticosteroids, and nonselective NSAIDs comprised 8.8% of the whole group.

Among the most common cardiovascular comorbidities were hypertension (32.6%) and chronic or ischemic heart diseases (1.6%). Renal impairment (creatinine clearance lower than 60 mL per minute) was found in 1.4% of patients. Approximately, 6.5% of patients were coprescribed with low-dose aspirin (75-150 mg daily) for its cardioprotective properties.

In addition, a total of 11.5% of patients were prescribed with oral GPAs concurrently. These medications included ranitidine (5.5%), pantoprazole (2.2%), esomeprazole (1.9%), magnesium-based antacid (1.1%), and omeprazole (0.8%).

Doctors' perceptions

Of 230 questionnaires distributed, only 211 were completed and returned (response rate: 91.7%). Respondents with the age below 30 years comprised 61.1% of the group. Majority of them were practicing in these hospitals as house officers who were undergoing internship training (52.1%), followed by fully-registered medical officers (33.2%) and specialists (14.7%). Approximately half of them had a clinical experience of 1-5 years (49.3%), followed by less than 1 year (28.4%), greater than 10 years (13.3) and 6-10 years (9.0%).

The most important factors which influenced the doctors to choose between non-selective NSAIDs and COX-2 inhibitors during prescribing were their gastrointestinal safety profiles (65.9%), efficacy (23.7%), cardiovascular safety profiles (3.8%), and the consultant's opinion (3.8%). Only 0.9% of doctors believed that the impact of cost should be prioritized during prescribing. Approximately one-third of respondents (28.9%) admitted that they had chosen celecoxib over other nonselective NSAIDs in more than 50% of the times.

The doctors' perceptions of certain most commonly discussed issues related to celecoxib are summarized in Table 3. Most of the respondents believed that celecoxib was more efficacious than other nonselective NSAIDs in reducing inflammation and pain. Almost all of them agreed that celecoxib as a COX-2 inhibitor provided a better gastrointestinal safety profile. This might have reflected their preference towards the use of COX-2 inhibitors in patients with high risk for gastrointestinal bleeding. Less than two-third of this group were concerned about the potential risk for cardiovascular events brought by celecoxib. House officers and the more experienced doctors including medical officers and specialists did not

Table 1: Indications of celecoxib (*n*=365)

Indication for celecoxib	Frequency	Percentage
Nonspecific acute pain	86	23.6
Chronic pain including neuralgia	74	20.3
OA*	45	12.3
Acute postoperational pain	43	11.8
Ankylosing spondylitis	38	10.4
Sports injury/dislocation	30	8.2
Malignant pain	23	6.3
RA*	16	4.4
Degenerative bone diseases	10	2.7

*OA=Osteoarthritis, RA=Rheumatoid arthritis

Table 2: Potential risk factors for gastrointestinal complications in patients taking celecoxib (*n*=365)

Risk factor	Frequency	Percentage
Age greater than 65 years	54	14.8
Taking warfarin or corticosteroid concurrently	20	5.5
Taking high dose of non-selective NSAID previously	12	3.3
History of gastritis or other gastrointestinal complications	7	1.9
More than one risk factor	22	6.0
Without any risk factor	250	68.5

NSAID=Nonsteroidal anti-inflammatory drugs

Table 3: Doctors perceptions of celecoxib-related issues

Celecoxib-related issue	Categories	Total respondent [*n* (%)]*			*P* value†
		Group 1 (*n*=110)	Group 2 (*n*=101)	Overall (*n*=221)	
Efficacy as anti-inflammatory and analgesic agent compared to nonselective NSAIDs	More effective	57 (51.8)	55 (54.5)	112 (53.1)	0.410
	Equally effective	38 (34.5)	38 (37.6)	76 (36.0)	
	Less effective	15 (13.6)	8 (7.9)	23 (10.9)	
Better gastrointestinal safety profile compared to non-selective NSAIDs	Yes	99 (90.0)	96 (95.0)	195 (92.4)	0.166
	No	11 (10.0)	5 (5.0)	16 (7.6)	
Higher risk of cardiovascular events compared to those not taking celecoxib/NSAIDs	Yes	67 (60.9)	69 (68.3)	136 (64.5)	0.261
	No	43 (39.1)	32 (31.7)	75 (35.5)	
Preferred agents to use in patients with high risk for gastrointestinal bleeding	Nonselective NSAIDs+GPAs	17 (15.5)	8 (7.9)	25 (11.8)	0.091
	COX-2 inhibitor	93 (84.5)	93 (92.1)	186 (88.2)	

*Group 1: House officers; Group 2: Medical officers and specialists, †Pearson's Chi-square and Fisher's exact tests to assess the associations between doctors' perceptions and their clinical experiences. COX-2=Cyclooxygenase-2, GPAs=Gastroprotective agents, NSAIDs=Nonsteroidal anti-inflammatory drugs

significantly differed in their perceptions toward any of these issues.

DISCUSSION

This is the first evaluation of celecoxib use from clinical perspectives in Malaysia. It is also one of the first local studies which have comprehensively described the prescribers' perceptions and concerns toward celecoxib-related issues. Compared with previous studies which demonstrated the COX-2 inhibitor use mainly in OA and RA (72-76.2%), our results showed a relatively high usage of celecoxib in nonspecific acute and chronic pain (43.6%).[16,26] It was only used for OA and RA in 16.7% of cases. Though celecoxib was approved by the Ministry of Health Malaysia for four indications, it had been widely used for a variety of medical conditions [Table 1]. This was, however, not surprising considering the high usage of nonselective NSAIDs for many other indications.

Compared with the Australian audit, a greater proportion of our patients had taken celecoxib at doses greater than 200 mg daily (30.9% vs. 20%). On top of that, more of them had taken it on a fixed schedule basis (78.1% vs. 50%).[16] This was attributable to the local practices that used celecoxib widely for more complicated chronic conditions, including ankylosing spondylitis, malignant pain, and degenerative bone diseases. The prolonged use of celecoxib beyond 6 months among 6.6% of our patients was also of concern. As described by the US FDA, unpublished data of the CLASS trial had actually demonstrated an association of celecoxib with a similar number of ulcer complications as diclofenac and ibuprofen by week 65.[28] The necessity of long-term celecoxib treatment among this small group should be ensured.

The percentage of our patients below 65 of years receiving celecoxib was much higher than that of a nationwide survey in Finland (79.2% vs. 58%); moreover, the latter showed the total usage of two COX-2 inhibitors.[1] It was questionable that this young group could benefit most from celecoxib treatment. Besides that, the proportion of our patients with another two identifiable risk factors for gastrointestinal complications was relatively low compared with that of the Australian Audit: Having history of severe gastrointestinal complications (1.9% vs. 17.4%) and taking warfarin or corticosteroids concurrently (5.5% vs. 10.2%).[16] Only a very small number of our patients had a history of taking high-dose, nonselective NSAIDs (3.3%) before they were given celecoxib. Overall, the high usage of celecoxib among patients without any noticeable risk factor (68.5%) may require a review from the clinical perspectives.

The presence of comorbidities among celecoxib users has been consistently attracting attention. Comparable to the Australian audit, approximately one-third of the celecoxib users (32.6%) were hypertensive. However, our patients had a lower incidence of renal impairment (1.4% vs. 5.9%) and chronic heart diseases (1.6% vs. 8.5%).[16] There is a lack of improved safety data reported in patients with these morbidities which will most likely be aggravated by COX-2 inhibitors. This is the group who may need to be closely monitored for their disease progression.

Furthermore, a small group of our patients using celecoxib (6.5%) was coprescribed with low-dose aspirin. As described in numerous trials of COX-2 inhibitors, the reduction of risk of developing severe gastrointestinal complications compared to non-selective NSAIDs is not statistically significant once the patients are taking low-dose aspirin concurrently.[9] Our patients had also indicated a lower rate of using GPAs with celecoxib than did those in the Australian audit (11.5% vs. 33%).[16] In fact, the benefits of combinational treatment with COX-2 inhibitors and PPIs were only demonstrated among the very high risk patients who had a history of ulcer bleeding.[29] No evidence was available for other conditions and the use of other GPAs with celecoxib.

As would be expected, the safety profile of NSAIDs was the most important factor to be considered by doctors during prescribing. Consistent with a US survey, more than 90% of respondents believed that celecoxib as a COX-2 inhibitor had carried a lower risk of gastrointestinal side effects. In both studies, approximately one-third of respondents had also addressed their concerns towards the risk of cardiovascular events.[30] On top of that, celecoxib was perceived by majority of respondents to be more effective than non-selective NSAIDs in reducing inflammation and pain. It was most likely that heavy promotion of its "better safety profile" had been mistakenly interpreted as "better efficacy". In fact, studies have been consistently proving that both types of NSAIDs are equally efficacious.[3-10]

Comparable to those in the US survey, almost one-fourth of respondents reported that they would choose COX-2 inhibitors over traditional NSAIDs more commonly during prescribing.[30] For patients with a high risk for

gastrointestinal complications, majority of respondents tend to use celecoxib over the combination of nonselective NSAIDs and PPIs. Using COX-2 inhibitor in such cases was proven to be more cost-effective. Another issue worthy of discussion is the assessment of associations between doctors' perceptions and their clinical experiences. Results showed that perceptions of doctors toward both efficacy and safety profile of celecoxib were not influenced by their clinical experiences.

In interpreting information from medical records, the limitations of this study must be considered. The reasons why some patients were given celecoxib and GPAs were unclear or unrecorded. These cases were categorized as "nonspecific acute pain" or "chronic pain" based on the duration of treatment. GPAs were considered as the adjunctive treatment to reduce gastrointestinal side effects of celecoxib. As data were collected retrospectively, we were also unable to identify the specific reasons why prescribers had chosen celecoxib over nonselective NSAIDs in some particular cases. In addition, recall bias was almost unavoidable in the survey. Respondents might have difficulties to recall their experiences in certain questions like "the frequency they had chosen celecoxib over other NSAIDs" and the "most important factor to consider during prescribing".

CONCLUSION

Overall, this study revealed the prescribing patterns of celecoxib among the government-subsidized hospitals in Northern Malaysia. Certain issues like its high usage in patients without gastrointestinal risk factors and in those with cardiovascular comorbidities may require a review from clinical perspectives. Safety profile of NSAIDs is the major concern of doctors during prescribing. The benefit of celecoxib in reducing gastrointestinal complications is well-recognized by doctors. Majority of them believed that celecoxib was more efficacious in reducing inflammation and pain that other NSAIDs despite the evidence shown in numerous studies. This study had also demonstrated that perceptions of doctors toward both efficacy and safety profile of celecoxib were not influenced by their clinical experiences.

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