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Non-Approved Uses of Celecoxib and Indomethacin: Pharmacy Students' Knowledge and Opinions

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Abstract:

A survey was conducted among first-year pharmacy students at Howard University College of Pharmacy to measure their level of knowledge and gauge their opinion regarding the off-label uses of two non-steroidal anti-inflammatory drugs (NSAIDs), indomethacin and celecoxib. The average level of knowledge on indomethacin and celecoxib was 36.2% and 31.2%, respectively. Among the five knowledge-based questions on each of these drugs, the highest correct response rate was obtained on indomethacin dosing at 72.9%, and 64.7% on the class of drugs celecoxib belongs to. In the responses to questions on indomethacin, the highest correct response of 72.9% was significantly higher (p<0.05) than responses to other knowledge-based questions, except for the knowledge level on the class of drugs (59.5%; p=0.3257). In the same manner, the correct response rate of 64.7% for the class of drugs that celecoxib belongs to was significantly higher than the response rates for the other questions (p<0.05), except when compared to the response to the question whether hyperplastic polyps and serrated polyps can develop into cancer (41.2%, p=0.0883). The opinions of the students varied, with a majority (55.9%) agreeing that serious diseases should be treated with non-approved medications. In the case of indomethacin, 35.5% of the respondents believed that because of toxicity issues, it should not be used outside the approved indications, while 27.8% believed that the safety has been established and can be used outside the approved use. Most respondents (55.9%) on celecoxib thought colorectal cancer is a serious disease and can be treated with non-approved drugs.

Keywords: *first-year pharmacy students, celecoxib, indomethacin, knowledge, opinion.*

Introduction

Off-label use of drugs involves using unapproved drug dosage forms and dose levels for drugs otherwise approved for certain indications by US Food and Drug Administration (FDA). It also involves prescribing and ordering drugs for unapproved indications. Although FDA does not allow

pharmaceutical companies to promote off-label uses of drugs, it is common practice among healthcare professionals to prescribe medications that purportedly benefit patients in various healthcare settings. The rationale followed by practitioners to use medications for unapproved indications ranges from that of life-threatening illnesses, same indications but not approved for specific patient populations such as pediatric, and geriatric patients, to medications within the same class of drugs (Veettil et al., 2019). However, the practice entails legal liabilities for healthcare practitioners. It is interesting to note that medications such as tricyclic antidepressants are used as a standard first-line treatment for neuropathic pain, although they do not have approval for such indication. In the same manner, aspirin is commonly used for prophylaxis of coronary disease in high-risk patients without approval for this indication (Wittich et al., 2012). As much as 20% of prescribed drugs, and about 50% in some specialty services are used in an off-label manner (Field, 2008). According to a report by Radley et al., about 70% of off-label uses of drugs are not supported by robust scientific evidence. The study also found out that off-label use was most common among certain cardiac drugs and anticonvulsants, with gabapentin and amitriptyline hydrochloride accounting for over 80% of such use (Radley et al., 2006).

Some non-steroidal anti-inflammatory drugs are used for off-label indications. A systematic review by Zhou et al (2018) looked at the role of celecoxib in the treatment of colorectal cancer. After analyzing 12 trials involving 621 patients, the authors concluded that celecoxib showed some improvement in colorectal patients, but did not show effects on overall response rate, disease control rate, or survival indices. Therefore, the review indicated that there are potential benefits in patients with resectable colon cancer (Zhou et al., 2018; Grfffin, 2010). Another study comprising three controlled randomized trials (4,420 patients) and three post-trial studies (2,159 patients) showed that celecoxib significantly reduced the incidence of colorectal adenomas in a dose-dependent manner (Veetil, et.al., 2019).

A few medications such as immunosuppressive agents and corticosteroids suppress the progression of systemic lupus erythematosus (SLE) and NSAIDs such as indomethacin and others are used to alleviate swelling, pain, and stiffness. Indomethacin is FDA-approved for indications such as acute pain, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis, and gouty arthritis (Munjal & Allam, 2023). Although it can potentially alleviate pain in SLE, there is no specific FDA- approved indication for its use in SLE.

In two previous papers, we reported on the knowledge and opinion of pharmacy students on the off-label uses of metformin and cimetidine in the management of colorectal cancer (Montgomery et al., 2022; Brown et al., 2022). In this paper, we evaluate the overall knowledge and opinion of HU College of Pharmacy first-year pharmacy students on unapproved off-label uses of the non-steroidal anti-inflammatory drugs indomethacin and celecoxib.

Methods

The survey was conducted among Howard University College of Pharmacy first-year professional students. In the celecoxib group, the survey enrolled 34, and in the indomethacin group 37 student participants. The survey questionnaire was administered during a drug information course given by one of us, BH. The demographic data and responses to knowledge-based and opinion questions were analyzed using Qualtrics. The survey consisted of 8 demographics, 5 each of knowledge-based and opinion-based questions. For the knowledge-based questions, a 4-point Likert scale (1=strongly agree; 2=agree; 3 = disagree; 4=strongly disagree) was utilized to score responses. The responses were then aggregated as 'agree" and "disagree," respectively. A mean Likert score was computed by dividing the respective scores by the total number of respondents (n=34 for celecoxib, and n=37, for indomethacin). Demographic data, including

age, gender, state of residence, work experience, annual income, and education were collected through the survey. Results were analyzed using IBM SPSS, and statistical analysis was performed by using a crosstab. A two-tailed Fisher exact test was used to determine statistical significance.

Results and Discussion

Most of the survey participants in both indomethacin (62.2%; *n*=23) and celecoxib (61.8%, *n*=21) groups were females, with the majority (>79%) in both groups being in the 18 to 24 years of age range. It is to be noted that 3 in each group did not respond to the age demographic question. More than 73% in both groups had completed a four-year degree program prior to joining Howard University College of Pharmacy program. Only 32.4% of the respondents in either group held prior pharmacy-related jobs. Responses to other demographic questions were also recorded (Table 1).

Table 1. Demographic Data of Survey Respondents*

Indomethacin respondents [*n* (%)]		Celecoxib respondents [*n* (%)]
Gender:		
Male	14 (37.8)	13 (38.2)
Female	23 (62.2)	21 (61.8)
Age (years)		
18-24	30 (81.1)	27 (79.4)
25-34	No response (8.1)	No response (8.8)
>35	4 (10.8)	4 (11.8)
State of residence before joining HU COP:		
Washington, D.C.	2 (5.4)	0 (0)
Maryland	9 (24.3)	8 (23.5)
Virginia	6 (16.2)	6 (17.6)
Other states	20 (54.1)	20 (58.9)
Work prior to joining HU COP		
Yes	32 (86.5)	30 (88.2)
No	5 (13.5)	4 (11.8)
Annual Income in USD[1]		
<10,000	11(29.7)	10 (29.4)
10,000-19,999	2 (5.4)	2 (5.9)
20,000-29,999	5 (13.5)	4 (11.7)
30,000-39,999	7 (18.9)	7 (20.6)
40,000-49,999	4 (10.8)	4 (11.7)
>49.999	5 (13.5)	5 (14.7)
Type of work:		
Pharmacy-related	12 (32.4)	11 (32.4)
Non-pharmacy-related	19 (51.4)	17 (50.0)
Not answered	6 (16.2)	6 (17.6)
Years worked prior to COP		
< 1 year	3 (8.1)	3 (8.8)
1-3 years	18 (48.6)	16 (47.1)
4-5 years	3 (8.1)	2 (5.9)
>5 years	10 (27.0)	10 (29.4)
Highest education level before joining pharmacy school:		
Some college	4 (10.8)	4 (11.8)
Tow-year degree	3 (8.1)	3 (8.8)
Four-year degree	28 (75.7)	25 (73.5)
Professional degree	2 (5.4)	2 (5.9)

Note: *Three respondents in the indomethacin group and 2 in the celecoxib group did not answer income-level questions; 4 in the indomethacin group and 3 in the celecoxib group did not answer years of work questions.

The highest correct response rate to knowledge-based questions was registered for the dose of indomethacin (72.9%), while 22 (64.7%) respondents correctly identified that celecoxib belongs to selective cyclooxygenase (COX) inhibitor class of drugs (Tables 2, 3). In the indomethacin group, the lowest correct response (n=5, 13.5%) was obtained for not identifying gastrointestinal side effects as a common side effect of the drug (Table 3). Only 4 respondents (13.5%) in the celecoxib group correctly believed that patients with polyps larger in size are at a high risk of cancer. (Table 2). The correct response rate was spread in the range of 13.5% to 72.9% for the indomethacin group, and 13.5% to 64.7% in the celecoxib group. (Tables 2, 3). Within the indomethacin group, the highest correct response rate of 72.9% (n=27) was significantly higher (p=0.0001) than the correct response of 16.2% (n=6) for question 1 (Table 3). Likewise, it was also significantly higher than the correct responses to questions 3 (19.4%) and 5 (13.5%) [p<0.0001 in each case]. However, when compared to question 4 (correct response rate, 59.5%), there was no statistical difference (p=0.3257). Within the celecoxib group, statistical differences were noted when the highest response rate (64.7%) was compared with correct response rates for questions 2 (17.6%, p=0.0002), and 3 (17.6%, p=0.0005), and 5 (13.5%, p=0.0001). The overall correct response rates for the two groups, 31.2% for celecoxib and 36.2% for indomethacin, were not statistically different.

Table 2. Responses to Knowledge-Based Survey Statements on Celecoxib[1]

	Survey statement	SA/A	DA/SDA	Correct responses [n, (%)][2]	Mean LKS±S.D.
1	Celecoxib belongs to a class called selective COX inhibitors	22	12	22 (64.7)	2.15±1.11
2	Colorectal adenomas can either be cancerous or non-cancerous	6	28	6 (17.6)	3.03±0.84
3	Adenocarcinomas are the most common type of colorectal cancer and originate in the granular tissues	7	27	7 (19.4)	3.14±0.80
4	Hyperplastic polyps and serrated polyps cannot develop into cancer	14	20	14 (41.2)	2.58±0.85
5	Patients with polyps larger in size are at a higher risk of cancer	4	30	4 (13.5)	3.64±3.51

Note: [1]Abbreviations: SA=strongly agree; A=agree; DA=disagree; SDA=strongly disagree; LKS=Likert Score; S.D.= standard deviation. [2]The average correct response rate is 31.2%.

Celecoxib belongs to the selective COX inhibitors class of drugs, which is widely known and extensively discussed in advertisements and literature. However, only approximately two-thirds of the participants agreed with the statement. A significant number of respondents showed a low percentage of agreement in answering questions related to the characteristics of colorectal cancer (Table 2). Colorectal adenomas, which are precancerous polyps that form in the colon or rectum, can exhibit both cancerous and non-cancerous properties depending on specific characteristics. While most colorectal adenomas are benign and do not pose an immediate threat of spreading, they still carry the risk of developing into cancer if left untreated. However, a small percentage of adenomas can undergo malignant transformation, acquiring genetic mutations that enable uncontrolled growth and invasion of surrounding tissues, leading to the development of colorectal cancer. Factors such as size, number, and histological characteristics play a role in determining the likelihood of malignant transformation. To mitigate the risk of adenomas progressing to cancer, it is

recommended to undergo regular screening and surveillance, including colonoscopies for detection and removal, particularly for individuals with a history of adenomas or other risk factors.

Table 3. Responses to Knowledge-Based Survey Statements on Indomethacin[1,2]

	Survey statement	SA/A	DA/SDA	Correct responses [*n*, (%)][3]	Mean LKS±S.D.
1	Systemic lupus erythematosus (SLE) has several effective FDA- approved medications	6	31	6 (16.2)	3.27±0.72
2	The maximum dose of oral indomethacin is 150 mg three times daily	10	27	27 (72.9)	3.14±0.93
3	SLE is a nerve-related disease that causes severe pain[3]	7	29	7 (19.4)	3.17±0.80
4	Indomethacin belongs to a class of drugs called anticoagulants	15	22	22 (59.5)	2.73±1.06
5	One of the common side effects of indomethacin is gastrointestinal bleeding	5	32	5 (13.5)	3.35±0.78

Note: [1]Abbreviations: SA=strongly agree; A=agree; DA=disagree; SDA=strongly disagree; LKS=Likert Score; S.D.= standard deviation. [2]One student did not provide an answer to item 3. [3]The average correct response rate is 36.2%.

There is a range of FDA-approved medications available for the treatment of SLE. Less than 1 in 5 of the survey participants were aware of this fact (Table 3). The medications used for SLE are designed not only to address the underlying disease but also to manage symptoms, alleviate inflammation, and regulate the overactive immune response characteristic of SLE. Treatment for SLE typically involves a customized combination of medications that are tailored to the individual's unique symptoms and disease stage. The wording of statement 5 (Table 3) may have caused confusion as it implied that SLE is primarily a nerve-related disease. While SLE is indeed an autoimmune disease that can impact various organs and systems, including the nervous system, it is not primarily classified as a nerve-related condition. The pain experienced in SLE is typically a consequence of factors such as inflammation, joint and muscle involvement, or other related complications. However, SLE can, in certain cases, affect the nervous system and give rise to neurological symptoms such as cognitive dysfunction, seizures, or peripheral neuropathy. Only 13.5% of participants agreed that gastrointestinal bleeding is a known side effect of indomethacin (Table 3). Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) commonly used to relieve pain, inflammation, and fever. While it can be effective in managing these symptoms, it can also cause irritation and damage to the lining of the stomach and intestines, leading to gastrointestinal complications such as bleeding. This risk is higher in individuals who are elderly, have a history of gastrointestinal issues, or take indomethacin for prolonged periods or at high doses.

The opinions expressed regarding the off-label uses of celecoxib and indomethacin varied across the questionnaire items. The majority in the celecoxib group (55.9%) agreed that as a serious disease, cancer should be treated with non-approved medications. This opinion was at variance with the agree response (20.6%) to the statement that cancer can be treated with celecoxib with known side effects. Most respondents (70.6%) would not want to defer to physicians the decision about using non-approved drugs for cancer, and yet only 11.8% think patients have the right to take celecoxib regardless of its approval status (Table 4). Most respondents in the indomethacin group (68.6%) disagree with the statement that indomethacin is

a cheaper option for treating SLE, and most (72.2%) do not support its use outside of approved indications. Only 24.3% think SLE has many treatment options and they do not recommend indomethacin for it, while 35.1% think it gives false hope to these patients. 35.5% of the respondents do not believe in the use of indomethacin due to its toxicity (Table 5).

Table 4. Responses to opinion-related survey questionnaire statements on celecoxib

Survey Statement		Responses	
		Agree (n, %)	**Disagree (n, %)**
1	Cancer is a serious disease and should be treated with a non-approved medication	19 (55.9)	15 (44.1)
2	Most cancers do not have drugs to cure them. Thus, I support the use of any possible drugs even if they are not approved by the FDA	8 (23.5)	26 (76.5)
3	Patients have the right to choose whether they should take celecoxib regardless of approval status	4 (11.8)	30 (88.2)
4	Cancer is a serious disease and I support the use of any drug such as celecoxib with known side effects	7 (20.6)	27 (79.4)
5	I believe I will leave the decision to the prescribing physician who has more detailed information about the patient to decide on the use of a non-approved drug	10 (29.4)	24 (70.6)

Table 5. Responses to opinion-related survey questionnaire statements on indomethacin

Survey Statement		Responses*	
		Agree (n, %)	**Disagree (n, %)**
1	I do not believe in the use of indomethacin outside of the recommended use because of its toxicity	11 (35.5)	25 (65.5)
2	Systemic lupus erythematosus (SLE) has many treatment options. I do not recommend using indomethacin over other medications	9 (24.3)	28 (75.7)
3	Indomethacin gives false hope to patients who are looking for relief from adverse reactions to medications associated with SLE	13 (35.1)	24 (65.9)
4	Indomethacin has been on the market for over half a century and its safety has been established and I believe in recommending it even outside of its approved uses	10 (27.8)	26 (72.2)
5	I support the use of indomethacin assuming it is a much cheaper option for the treatment of SLE	11 (31.4)	24 (68.6)

Note: *Survey respondents who did not provide answers were excluded from the calculation

In the celecoxib group, the survey statements 1 to 5 focused on eliciting the opinions of the survey participants regarding the use of non-approved use of drugs for the management of cancer-related illness (Table 4). While it is true that not all types of cancer have a definitive cure, significant advancements have been made in the development of cancer treatments, including FDA-approved drugs, targeted therapies, immunotherapies, and other treatment modalities. Statement 5 inquires if the participant pharmacy students agreed with leaving the decision to the prescribing physician. In general, pharmacists play a crucial role in medication safety. While it is important to respect the expertise of the prescribing physician, it is equally important to consider the available evidence and regulatory guidelines surrounding the use of drugs. Non-approved drugs may have limited evidence regarding their safety and efficacy, as they have not undergone the rigorous evaluation and approval process of regulatory agencies like the FDA. In such cases, the pharmacist can contribute to patient care by ensuring that the prescribing physician is well-informed about the potential risks and benefits

of the non-approved drug, including any available evidence or clinical data. Collaboration between healthcare professionals, including open communication and shared decision-making, is crucial to provide the best possible care for the patient. Ultimately, the final decision on using a non-approved drug should be made collectively by the healthcare team, while taking into consideration the patient's individual circumstances, available treatment options, and the best available evidence.

Survey Limitations

The close-ended nature of the questionnaire statements may have contributed to bias and overall low knowledge score on celecoxib and indomethacin. In the same manner, it might have skewed the opinions of the survey participants.

Conclusion

A survey conducted among pharmacy students showed an overall 36.2% knowledge level rate on off-label uses of celecoxib, and a-31.2% rate on indomethacin. The survey respondents fared well in identifying the drug class of celecoxib (64.7%) and the dose of indomethacin (72.9%). On the other knowledge-based questions, the respondents scored low. The survey results identified deficient areas in their knowledge on off-label uses of celecoxib and indomethacin. Opinions of the survey participants were inconsistent across the questionnaire items.

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