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Analysis of Cost-Effectiveness of Antihypertensive Therapy in Hypertension Patients at A-Ihsan Regional Public Hospital in 2023

Masyitah Isnaini,[1] Widiah Widiarti,[2] Miski A. Khairinisa[3]

[1]Pharmacist Professional Study Program, Faculty of Pharmacy,
Padjadjaran University, Indonesia
[2]Department of Pharmacy. Al-Ihsan Regional Public Hospital, Bandung, Indonesia
[3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy,
Padjadjaran University, Indonesia

Abstract

Hypertension is a disease that causes an abnormal increase in blood pressure, which causes cardiovascular disease. Long-term hypertension therapy requires large costs. Apart from that, existing antihypertensives are also very varied, so a cost-effectiveness analysis is needed to choose medications that balance costs and advantages. This study aims to determine the most economical antihypertensive medication at Al-Ihsan Regional Public Hospital in Baleendah. Based on patient medical records, this study was carried out retrospectively. Therapy data and treatment costs are the basis for the data collection process. The data is processed descriptively. The reduction in blood pressure that meets the target and the length of stay (LOS) is used to determine how effective the therapy was; the ACER and ICER values are used to determine how cost-effective the procedure was. According to the research findings, the average total cost of group A (ACEI with CCB) is IDR 2,311,000.00, whereas group B (ARB with CCB) is IDR 2,888,823.00. The efficacy of group A (ACEI with CCB) was 83.3%, while group B (ARB with CCB) was 52.4%. The findings showed that among inpatient hypertension patients at Al-Ihsan Regional Public Hospital, group A (ACEI with CCB) was more cost-effective, with an Average Cost Effectiveness Ratio (ACER) value of IDR 27,743,097, than group B (ARB with CCB ACER value of IDR 55,130,209). Based on this study, therapy of group A (ACEI with CCB) offers excellent therapeutic efficacy at a reduced cost. Hospitals are expected to have the ability to handle their spending on hypertension medications appropriately and efficiently

Keywords: Combination of Antihypertensives, Hypertension, Cost-Effectiveness Analysis

Corresponding Author: Miski Aghnia Khairinisa. Department of Pharmacology and Clinical Pharmacy. Faculty of Pharmacy, Universitas Padjadjaran. Email: miski.aghnia@unpad.ac.id
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Introduction

Hypertension is a disease characterized by high blood pressure (BP), which can result in problems such as heart failure, stroke, cardiovascular disease, and renal failure.[1] Systolic blood pressure (SBP) of 140–159 mmHg and diastolic blood pressure (DBP) of 90–99 mmHg are the parameters used to characterize hypertension for stage 1, and SBP values of 160–179 mmHg and DBP values of 100–109 mmHg are used to characterize hypertension for stage 2.[2]

According to the West Java Provincial Health Service, the percentage of people receiving health services for hypertension patients based on BP readings, particularly for Bandung regency, is 82.75%, which is higher than the percentage for West Java Province (70.3%).[3] Hypertension therapy takes longer to be treated and requires many costs.[4] Pharmacoeconomics analyzes medical therapy costs. It deals systematically with the meaning, measurement, and comparison of costs.[5]

Antihypertensive therapy is a common practice at Al-Ihsan Regional Public Hospital. It involves the combination of medications such as calcium channel blockers (CCB) and ACEIs (Angiotensin-Converting Enzyme Inhibitors) or ARBs (Angiotensin Receptor Blockers). Varying drug prices are important when making decisions about whether to use drugs for patients. Cost-effectiveness analysis (CEA) is crucial for recommending the best therapy at an effective cost.[6]

Methods

A descriptive analysis combined with an observational study approach was conducted. A total sampling technique was used in 2023 to collect data retroactively. The data taken was divided into 2 groups: A (ACEI with CCB) and B (ARB with CCB). The pharmacoeconomic study used is Cost-Effective Analysis (CEA), using the perspective of hospitals as health service providers. The Incremental Cost Effectiveness Ratio (ICER) and Average Cost Effectiveness Ratio (ACER) values illustrate the CEA technique. The efficacy and total cost comparison is known as ACER. The total cost used is direct medical costs. Based on the two therapy groups, if one group has lower costs but high effectiveness, it does not require ICER calculations. ICER is calculated if the cost of each intervention is more expensive with high effectiveness or cheaper with low effectiveness.[7]

Data was taken from the medical records installation, management information system, and finances at Al-Ihsan Regional Public Hospital. These costs include the costs of hypertension medication, other medications, medical equipment costs, facility costs, diagnostic costs, and examination costs during hospitalization.

The patient's length of stay (LOS) and BP readings upon admission and discharge from the hospital are used to gauge effectiveness. Patients diagnosed with hypertension and older than 18 years old who were randomized to either group A (ACEI with CCB) or group B (ARB with CCB) for antihypertensive medication met the study's inclusion criteria. The exclusion criteria in this study were incomplete data and pregnant or breastfeeding patients.

Results and Discussion

This study was conducted at Al-Ihsan Regional Public Hospital for 4 months for patients who received the combination of antihypertension therapy (ACEI with CCB and ARB with CCB) in 2023. According to the study's results, twenty-seven patients met the requirements. Table 1 shows the patient characteristic data.

Table 1. Features of the Patient According to Age and Gender

Characteristics	Number (n)	(%)
Gender:		
Male	16	59.26
Female	11	40.74
Total	27	100
Age		
>18-40	1	3.70
>40-60	10	37
>60	16	59.3
Total	27	100

Hypertension patients treated at Al-Ihsan Regional Public Hospital in 2023 who used antihypertensive combination therapy were 16 males (59.26%) and 11 females (40.74%). The number of men who experience hypertension is greater than that of women. Men are more likely to experience BP increases; however, hormonal considerations cause women probably going to develop hypertension after menopause. Therefore, women are more at greater risk than men to experience hypertension during that time.[8]

Based on age, most patients who experienced hypertension were >60 years old (16 patients; 59.3%), >40-60 years old (10 patients;37%), and >18-40 years old (1 patient; 3.7%). The arteries lose their elasticity as people age, which causes structural and functional changes in the blood artery system that raise SBP. This increases the risk of hypertension in people aged 60 to 74.[9] Increasing age causes physiological changes, such as increased sympathetic nerve activity in the elderly.[10] Renal blood flow and glomerular filtration rate are lowered due to impaired renal function and baroreceptor reflex sensitivity. Peripheral vascular resistance rises due to decreased blood vessel flexibility, raising BP.[11]

JNC VIII recommends ACEI, ARB, low-dose thiazide diuretics, or CCB for non-black patients with hypertension. The recommended initial therapy for blacks is low-dose thiazide diuretics, or CCB.[12] ACE inhibitors inhibit ACE from converting angiotensin I to angiotensin II.[13] The decreased angiotensin II production causes increased natriuretic, so BP decreases, and cardiac smooth muscle remodeling is prevented. A decrease in arterial and venous pressure causes a decrease in preload and afterload.[14]

ACE inhibitors can also catalyze the degradation of bradykinin, which provides vasodilation, anti-inflammatory, and anti-fibrinolysis effects.[15] ACE inhibitors do not cause angiotensin I to become angiotensin II. The adrenal medulla releases catecholamines, pre-capillary arterioles, and post-capillary venules constrict, aldosterone is produced and released, cardiac myositis and vascular smooth muscle cells are stimulated to hypertrophy, and norepinephrine reuptake is inhibited.[16]

The pituitary and adrenal cortex produce antidiuretic hormone and aldosterone in response to angiotensin II. Aldosterone activates internal mineralocorticoid receptors, which results in the reabsorption

of salt and water from the atmosphere.[17] The antidiuretic hormone stimulates the creation of aquaporin-2 channels in the collecting duct, leading to selective air reabsorption. The effects of aldosterone and angiotensin II cause adverse cardiac remodeling. Aldosterone and angiotensin-II are lowered by ACE inhibitors, preventing detrimental cardiac remodeling.[18]

Angiotensin II receptor antagonists, also known as ARBs, prevent angiotensin II from acting at particular receptors, especially the AT1 receptors in tissues such as the adrenal gland and smooth muscle. The body's renin-angiotensin-aldosterone system (RAAS) regulates BP and fluid balance. Angiotensin II is a potent hormone that narrows blood vessels. Angiotensin II receptors come in two varieties: AT1 and AT2. Angiotensin II-induced AT1 receptor activation has several effects, including muscle cell proliferation, sodium reabsorption in the kidneys, water retention, and vasoconstriction.[18]

On the other hand, stimulation of the AT2 receptor results in vasodilation and anti-proliferative effects. ARBs inhibit angiotensin II's vasoconstrictive and aldosterone-secreting effects by specifically inhibiting AT1 receptors in organs such as blood vessels and the adrenal gland, all without appreciably changing heart rate. Renin and angiotensin II levels rise in response to AT1 receptor blockade, which increases AT2 receptor stimulation. Unlike ACE inhibitors, ARBs do not inhibit the enzyme that breaks down bradykinin, which promotes vasodilation; hence, they do not affect its levels.[19]

It is believed that ARBs work by lowering adverse effects and potentially improving therapeutic efficacy. By opposing angiotensin II-induced vasoconstriction, water intake, aldosterone release, catecholamine release, and arginine vasopressin release, ARBs displace angiotensin II from angiotensin I receptors and reduce BP.[20] Moreover, ARBs prevent fluid reabsorption.[13] The ARBs exhibit similar clinical characteristics, although variances in their pharmacokinetic profiles may result in discrepancies in efficacy.

The more contemporary ARB medications, like candesartan, olmesartan, telmisartan, and irbesartan. Irbesartan offers longer half-lives and durations of action than its older counterparts, losartan and valsartan. Given their longer duration of action, the newer drugs may make it easier to control BP for the entire day. Valsartan and losartan might necessitate twice-daily dosing, whereas ARBs with longer durations of action do not provide additional benefits when administered more frequently than once daily.[21] As ACE inhibitors and ARBs are examples of typical RAAS pathway inhibitors that function differently from CCBs, combining them should produce complementary or synergistic effects rather than using two drugs that target the same route.[22]

Calcium channel blockers obstruct particular cell membrane channels that allow extracellular calcium to pass through. Although there are several kinds of calcium channels, L-type channels in humans are the primary target of the CCBs that are now in use. CCBs relax the vascular smooth muscle cells, which lowers BP and causes vasodilation by preventing the inward flow of calcium. CCB is divided into two classes, namely non-dihydropyridine and dihydropyridine. Both are based on their physiological effects.

Non-dihydropyridine CCBs in cardiac muscle will reduce contractility and slow down the activity of the sinus pacemaker, namely sinoatrial (SA) and atrioventricular (AV) node conduction velocities.[23]

Table 2. Blood Pressure and Average Total Cost of Therapy for Group A (ACEI with CCB)

Respondent Number	Age	BP at Admission (mmHg)	BP at Discharge (mmHg)	Reached The Target/ No	Total Cost (IDR)
1	52	166/94	127/80	✓	7.330.377
2	40	164/77	145/79	X	781.458
3	68	171/100	128/76	✓	1.453.220
4	62	210/139	144/94	✓	1.548.656
5	70	130/88	124/80	✓	1.824.303
6	49	174/86	125/75	✓	928.207
Total= 6 patients				✓= 5 X= 1	Average= 2.311.000

Table 3. Blood Pressure and Average Total Cost of Therapy for Group B (ARB with CCB)

Respondent Number	Age	BP at Admission (mmHg)	BP at Discharge (mmHg)	Reached The Target/ No	Total Cost (IDR)
1	64	199/80	131/85	✓	884.721
2	69	147/90	122/70	✓	6.246.877
3	59	225/128	147/96	X	2.858.090
4	80	187/78	121/81	✓	10.653.440
5	46	170/100	142/72	X	1.975.258
6	65	203/124	158/82	X	1.766.226
7	49	240/110	178/103	X	2.649.147
8	55	195/60	125/67	✓	1.613.178
9	51	188/103	134/79	✓	1.087.905
10	64	207/80	186/108	X	2.017.599
11	81	163/106	135/83	✓	2.000.628
12	69	159/92	123/70	✓	674.285
13	52	170/85	110/70	✓	1.328.026
14	70	183/91	151/74	X	2.304.844
15	76	172/102	155/108	X	2.398.884
16	47	170/100	122/72	✓	1.456.032
17	73	180/130	120/80	✓	746.163
18	65	230/138	148/84	X	1.836.273
19	54	209/99	184/95	X	2.164.801
20	81	168/91	171/86	X	10.156.113
21	71	161/83	132/81	✓	3.867.798
Total= 21 patients				✓= 11 X= 10	Average= 2.888.823

Table 4. Effectiveness of Hypertension Treatment to Reach Therapeutic Targets

Therapeutic Effectiveness	ACE I with CCB		ARB with CCB	
	Total	%	Total	%
Reached the target	5	83,3	11	52,4
Not reached the target	1	16,7	10	47,6
Total	**6**	**100**	**21**	**100**

Table 5. Distribution of Hypertensive Patients Based on Length of Stay Group A (ACEI with CCB)

Length of Stay	Number (n)	Targeted	Untargeted	%
1-2 days	2	1	1	16.7
3-4 days	4	4	0	66.7
5-6 days	-	-	-	-
≥7 days	-	-	-	-
Total	6	5	1	-
%	-	83.3	16,7	100

Table 6. Distribution of Hypertensive Patients Based on Length of Stay Group B (ARB with CCB)

Length of Stay	Number (n)	Targeted	Untargeted	%
1-2 days	7	6	1	86
3-4 days	11	3	8	27
5-6 days	2	2	0	100
≥7 days	1	0	1	0
Total	21	11	10	-
%	-	52	48	100

Table 7. Overview of ACER Calculations for Antihypertensive Drugs

	Group A	Group B
Average Total Cost (IDR)	2.311.000	2.888.823
Therapeutic Effectiveness (%)	83,3	52,4
ACER (IDR)	27.743,0972	55.130,2099

*ACER = Average Total Cost / Therapeutic Effectiveness

The agents are verapamil and diltiazem. Dihidropiridin CCBs work as peripheral arterial vasodilators, reducing vascular resistance and lowering BP. The agents are amlodipine and nifedipine. A second line from a different class is initiated if monotherapy fails to reach BP targets.[24]

Combining ACEI with CCB or ARB with CCB is considered more effective in controlling BP. In individuals with severe systolic hypertension, benazepril and amlodipine combination therapy was considerably more effective than monotherapy in decreasing SBP and pulse pressure.[22] Some patients cannot take ACEI due to coughing side effects; therefore, ARB is used.[25]

Nearly no hypertensive patient at Al-Ihsan Regional Public Hospital receives monotherapy because their BP doesn't meet the target; instead, a combination of antihypertensives is used as a treatment option. Combinations of ACEI with CCB (group A) and ARB with CCB (group B) were the types of combination therapy used in this investigation.

The patient's BP dropped in accordance with the objective, indicating the efficacy of the treatment. The JNC VII target BP value for hypertensive patients ≥ 60 years of age with no diabetes comorbidities is <150/90 mmHg and <140/90 mmHg for those <60 years of age.[12] The number of patients in group A is shown in Table 2, while Table 3 shows the number of patients in group B.

Based on the study, patients who reached the most therapeutic targets were in Group A (5 patients; 83.3%), while Group B had 11 patients (52.4%) (Table 4). ACEI and CCB use two distinct but complementary functioning mechanisms. Thus, they work well together to lower BP. As a result of peripheral vasodilation, CCB reduces BP. Through elevated renin activity and the synthesis of angiotensin II, CCB also concurrently activates the sympathetic nervous system (SNS). This will impact how well CCB lowers BP.[26] The addition of ACEI offsets the effect of CCB's RAS activation.

Furthermore, the negative sodium balance brought on by CCB amplifies the antihypertensive effects of ACEI. Peripheral edema is the most common side effect associated with CCB. Because venous circulation is less than arterial dilatation, there is a larger transcapillary gradient and capillary leak, which results in this effect. Due to ACEI's ability to dilate veins and arteries and restore normal transcapillary pressure, this impact may be mitigated. As a result, the peripheral edema brought on by CCB decreases.[27]

The combination of ACEI with CCB can more effectively lower cardiovascular mortality and overall mortality than the atenolol/thiazide combination, according to the study of a randomized controlled trial of the prevention of chronic heart disease and other vascular events by blood pressure and cholesterol-lowering in a factorial study design. This study also found that combining ACEI with CCB can quickly and strongly reduce BP in patients with blood pressure above 160 mmHg.[28]

The effectiveness of therapy can also be seen in LOS (Length of Stay). Table 5 shows that group A had treatment with a shorter duration, namely 1-4 days (only 4 days), with a LOS of 3-4 days (66.7%). Meanwhile, in group B (Table 6), there was a treatment duration of 5-6 days for 2 patients and 7 days for 1 patient, with a LOS of 3-4 days (27%). Overall target achievement for group A was 83.3% (Table 5), while group B was 52% (Table 6).

The LOS can be influenced by two factors, namely sociodemographic factors and the

patient's clinical history.[29] To prevent the severity of hypertension, choosing appropriate and effective treatment is very influential. The drug's ability to decrease blood pressure and the patient's improved condition following therapy both affect how long a patient stays in the hospital.[11]

To analyze cost-effectiveness, table 7 shows that the average total cost of group B is greater (IDR 2,888,823) than group A (IDR 2,311,000). This is affected by the price differential between group A and group B antihypertensive drugs. Group A antihypertensive medications have an average cost of IDR 4,765, but group B has IDR 7,952. The total costs are the costs of hypertension medication, other drugs, medical equipment, facility, diagnostic, and examination costs while the patient is being treated at Al-Ihsan Regional Public Hospital.

Table 7 presents the findings of the CEA of antihypertensive medication, utilizing the ACER value. Group A has the cheapest average total cost (IDR 2,311,000) with a higher percentage of therapy effectiveness (83.3%) than group B. These findings are consistent with previous research, which found that ACEI and CCB have an antihypertensive impact that lowers BP and protects against target organ damage with relatively cheap drug costs.[30]

The ACER value (Table 7) obtained based on the reduction in BP in group A was lower (IDR. 27,743.0972) than group B (IDR. 55,130.2099). So, based on the calculation of the ACER value based on the reduction in BP, it can be stated that therapy group A is more cost-effective than group B.

Based on the two therapy groups, group A has lower costs and high effectiveness, so it does not require ICER calculations. ICER calculations can be calculated if the cost of the tap intervention is more expensive with high effectiveness or cheaper with low effectiveness.[7]

Conclusion

Group A's therapy (ACEI with CCB) has good therapeutic effectiveness and lower costs, according to research findings analyzing the cost-efficiency of antihypertensive therapy in inpatients at Al-Ihsan Regional Public Hospital in 2023. These outcomes were attained by contrasting the average overall cost of treatment with its efficacy. Group A's (ACEI with CCB) average total cost is IDR 2,311,000.00 and group B's (ARB with CCB) average total cost is IDR 2,888,823.00.

Group A's therapy was found to be 83.3% successful, while group B's was 52.4%. The outcomes demonstrated that group A was more economical, with an ACER value of IDR 27,743,097 as opposed to IDR 55,130,209 for group B.

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Conflict of Interest

None declare

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Prospect Study of Anti-inflammatory Activity by Identification of *Muntingia calabura* Leaf Infusion

Shenny S.S Permana,[1] Muchamad R.A Yusuf,[1] Aufa A.D Putri,[1] Jasmine Y. Sukmayani,[1] Ratu Z.A.P Sudrajat,[1] Miski A. Khairinisa,[2] Indah S. Wahyuni,[3] Enny Rohmawaty,[4] Muhammad H. Bashari,[4] Ronny Lesmana,[4] Aziiz Mardanarian Rosdianto[1,4]

[1]Veterinary Study Program, Faculty of Medicine, Universitas Padjadjaran, Jatinangor, Indonesia.
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, Indonesia.
[3]Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran, Jatinangor, Indonesia.
[4]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jatinangor, Indonesia.

Abstract

Many diseases occur due to inflammation that is not handled properly. One of the feature of inflammation is swelling or edema. Inflammation can be handled with traditional medicine, such as *Muntingia calabura L.* (*M. calabura L.*) Pharmacologically, this plant extract is reported to have antipyretic, analgesic, anti-inflammatory, antioxidant, and antibacterial. Metabolite compound contained in *M. calabura L.* has the potential as an anti-inflammatory agent. The objective of this study is to ascertain the secondary metabolites contained in *M. calabura L.* leaves infusion. This experimental research method includes the simplicia making and infusion of *M. calabura L.* leaves by cold infusion and phytochemical screening. This study also showed that the infusion of *M. calabura L.* leaves contained flavonoids, alkaloids, and triterpenoids. Overall, the findings indicate potential as an anti-inflammatory agent that requires further investigation, specifically in preclinical testing.

Keywords: Anti-inflammatory, infuse, *M. calabura L*, phytochemical screening

Introduction

Several diseases arise when inflammation symptoms are not promptly and accurately addressed. Osteoarthritis becomes a problem that arises due to inadequately managed inflammation. This condition is prevalent among racehorses and other equine athletes.

It occurs due to repetitive joint trauma, leading to cartilage damage and erosion of bone1. A study found that 33% of thoroughbred racehorses aged 2-3 years suffered from osteoarthritis and lesions in their articular cartilage.[2] Other diseases that can emerge from inflammation in horses is muscle and orthopedic pain, perioperative pain, corneal ulcers, uveitis, laminitis, and gastrointestinal pain (colic).[3] Efforts to prevent the worsening of trauma can be reduced using anti-inflammatory drugs. Indonesia has a wealth of natural medicines and traditional remedies that many people have been using for generations.[4]

Corresponding author: Aziiz M. Rosdianto. Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jatinangor, Indonesia. Email: a.m.rosdianto@unpad.ac.id
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M. calabura L., also known as kersen, belongs to the family Muntingiaaceae and is widely found along the way. This plant typically grows in the wild. Nevertheless, due to its dense foliage, it is deliberately cultivated as a roadside shade tree and an air pollution absorber.[5] This plant is one of the potential candidates for further development as a traditional medicine for anti-inflammatory purposes. Some research journals state that flavonoids are the main constituents in kersen leaves. Flavonoids themselves are polyphenolic compounds with various activities, one of which is anti-inflammatory.[5]

One direct benefit of traditional medicine formulations for the community is the easy availability of these remedies. The demand for plant-based ingredients in traditional medicine is increasing because they are proven healthier and have fewer side effects than chemical-based alternatives. However, a challenge with traditional medicine is the limited knowledge and information about the different types of plants used as ingredients and how to use them effectively.[6]

Based on this information, the primary goal of this study is to identify the secondary metabolites present in the infusion of *M. calabura L.* leaf so that further tests can be carried out in vivo and in vitro as anti-alternative inflammatory drugs.

Methods

This study is a laboratory experiment to discover the secondary metabolites found in *M. calabura L.* leaf infusion (MCLI). This study was conducted at the Chemical Application Laboratory and Services, Universitas Padjadjaran. This research has received approval and authorization from the Research Ethics Committee of Universitas Padjadjaran (Document No. 1066/UN6.KEP/EC/2023).

Research Procedures

Collection and preparation of sample

Samples of *M. calabura L.* were collected from the Sukapura Village in Kiaracondong District, Bandung City, West Java Province. Before further investigation, the sample was recognize at the Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran (Document No. No.212/LBM/IT/VIII/2023). The sample was cleaned of attached dirt, cut into small pieces, and dried in the dryer.

Preparation of M. calabura L. Infusion

The simplicia of *M. calabura L.* leaves (50 g) was extracted with 200mL distilled water (1:4). At room temperature (25-30°C), let it stays for 1 hour before being placed in the refrigerator for 19 hours. Next, the infusion substance was filtered and put into a falcon tube. Adaptive method for cold infusion was followed Farmakope Herbal Indonesia year 2017.

Phytochemical Screening

Phenolic Test

Two grams of sample was mixed with 5 mL methanol. The solution was refined then 5% ferric chloride solution was added. When phenolic compounds are present, a positive outcome is indicated by the formation of a bluish-black color.[7]

Tannins Test

Roughly 2 grams of the plant extract were boiling with 5 mL of distilled water. After that, added 0.1% Ferric chloride to the mixture and watched for the appearance of a greenish-black color, which would suggest that tannins were present.[7]

Alkaloid Test (Wagner's Test)

Two grams of sample was mixed with 5 mL chloroform, then add 5 mL sulphuric acid. Next, put a few drops of Wagner's reagent

into the solution. If a reddish-brown or brown clumpy substance forms, it means the test is positive.[7]

Flavonoid Test

1. Shinoda test: combined 2 grams of the sample with 5 mL of methanol solution. Next, put in a tiny piece of magnesium chunk. Then, added 2 drops of concentrated HCl. When the color turned orange, it meant that there were flavonoids present.
2. Two grams of sample was mixed with 5 mL methanol solution; then plant solution was treated with 2-3 drops of 10% sodium hydroxide solution. The development of a strong yellow color suggests that flavonoids are present.
3. Mixed two grams of the sample with a 5 mL methanol solution and then reacted it with two drops of 2N hydrochloric acid. The sudden appearance of a acute yellow color shows that there are flavonoids present.[7]

Saponins (Foam Test)

Two grams of sample was mixed with 5 mL aquadest, filtered the solution, shaken vigorously for 2 minutes, then reacted with two drops hydrochloride acid 2N. The formation of a persistent froth for 10 minutes indicated the presence of saponins.[7]

Tripernoids and Steroids Tests

Mixed two grams of each sample with ethanol. 2 mL chloroform was extracted with 1 mL chloroform and water (1:1). Then added with 1 mL concentrated sulphuric acid. Reddish-brown coloration indicated the presence of tripernoids. Green, blue, and violet pigment indicated the presence of steroids.[7]

Results and Discussion

Extraction Yield

The cold infusion technique was employed in this research to extract compounds from the leaves of *M. calabura L.*, resulting in an extract yield of 0.1%. The cold infusion technique differs from the hot infusion technique. This method involves using refrigerator temperatures where the sample is left to steep for a minimum of 12-24 hours.[8] A non-thermal extraction method was selected to prevent any potential damage to heat-resistant active metabolits that may be present in the sample. Biological factors (plant part, plant species, location of growth, and harvesting time) and chemical factors (size, hardness, dryness of the material, levels and types of active compounds contained in plant material, type of solvent use, extraction methods) Can affect the quality of the extract.[9]

Table 1. Phytochemical Screening Results

No	Test	Testing Method	Result
1.	Phenolic	$FeCl_3$ reagent 5%	-
2.	Tannins	$FeCl_3$ reagent 1%	-
3.	Flavonoids	Concentrated HCL reagent + Mg	-
		Reagent H_2SO_4 2N	-
		NaOH reagent 10%	+
4.	Saponins	Reagent HCL 2N	-
5.	Triterpenoids		+
	Steroids	Concentrated H_2SO_4 reagent	-
6.	Alkaloids	Wagner's reagent	+

Note: (-) : Not detected | (+) : Detected

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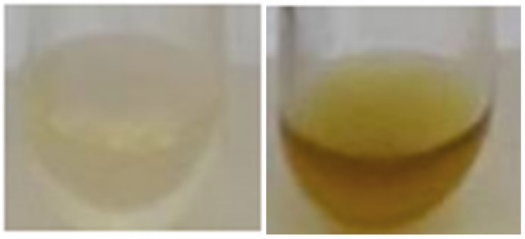

Figure 1. Phytochemical screening results of phenolics coumpounds with 5% ferric chloride solution: (a) before and (b) after adding the reagent.

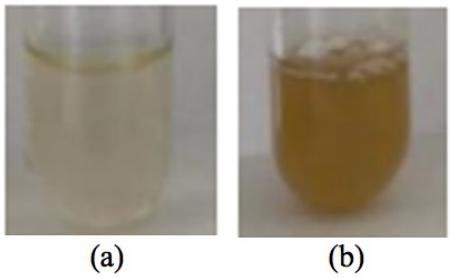

Figure 2. Phytochemical screening results of tannin coumpounds with 1% ferric chloride solution: (a) before and (b) after adding the reagent.

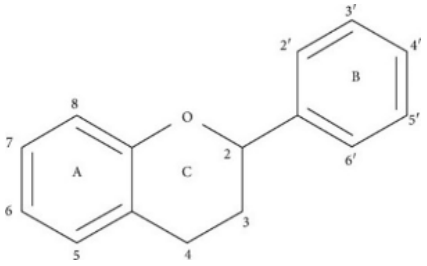

Figure 3. Basic Flavonoids Structure[14]

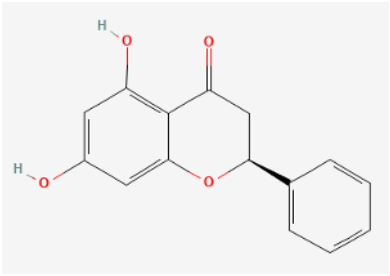

Figure 4. Pinocembrin Structure[21]

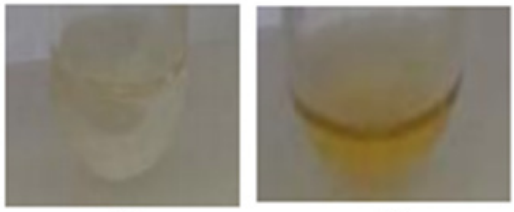

Figure 5. Phytochemical screening results of flavonoids compounds found in 10% sodium hydroxide solution reagent: (a) before and (b) after adding the reagent.

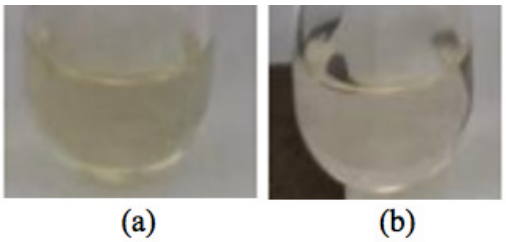

Figure 6. Phytochemical screening results of saponins compounds with hydrochloride acid 2N: (a) and (b) after adding the reagent.

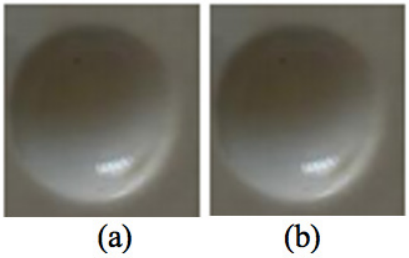

Figure 7. Phytochemical screening results of triterpenoids and steroids compounds with concentrated sulphuric reagent: (a) before and (b) after adding the reagent.

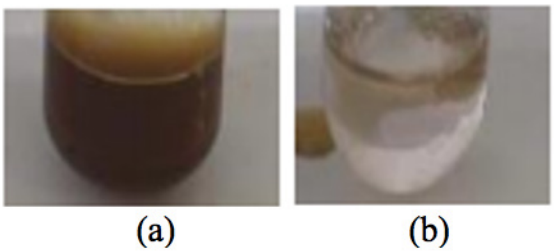

Figure 8. Phytochemical screening results of alkaloids compounds using Wagner's reagent: (a) before and (b) after adding the reagent

Meanwhile, the extraction process employs the infusion method due to its relatively shorter and faster preparation time and the easy availability of materials and tools.[10] Water is a commonly used solvent for extracting active constituents soluble in water from plant materials, despite the drawback of the infusion being susceptible to mold growth.

Phytochemical Screening

The content of secondary metabolite compounds in the leaves through phytochemical screening for the test was phenolics, tannins, flavonoids, saponin, triterpenoids, steroids, and alkaloids showed the following results as in Table 1.

Phenolics

Test for phenolic compounds obtained negative results (Fig. 1). The level of phenolics in plant sources rests on factors such as maturation processes, cultivation techniques, cultivars, growing conditions, and processing and storage conditions, among others.[11]

Phenolic compounds of MCLI that were not detected may have been influenced by extraction method factors. According to a study, Many traditional methods used to extract phenolic compounds from plants, like soxhlet extraction, percolation, and maceration, have their own problems. These include getting only small amounts of the compounds, using a lot of extraction solvents, taking a long time, and creating a lot of waste.

Because of these issues, new methods like Microwave Assisted Extraction. (MAE), (Ulrasonic Assisted Extracytion) Ulrasonic Assisted Extracytion (UAE) , Supercritical Carbon Dioxide (SC-CO2), Enzyme Assisted Extraction (EAE), and Pressure Liquid Extraction (PLE) have come up. These techniques are unconventional but help fix the problems of the methods before12. Therefore, further testing is necessary to identify the phenolic compounds in *M. calabura L.* leaf.

Tannins

Based on the results of a phytochemical test of tannin compounds, MCLI showed negative results. The results showed an acute yellow solution was formed after adding 1% ferric chloride solution, while positive results were obtained if a greenish-black coloration solution was formed. The results of the study can be viewed in Figure 2.

The tannin content in *M. calabura L.* leaves might be low in amounts detectable through cold infusion methods. The analytical methods employed should be highly sensitive to detect tannins at low concentrations. Several advanced technologies, such as microwaves and ultrasonication, have demonstrated the potential to extract tannins efficiently. Additionally, controlling factors like temperature, solid-to-solvent ratio, particle size, source of the material, and extraction time contribute to obtaining higher-quality tannins.[13]

Flavonoid

Previous study reported that *M. calabura L.* leaves extract rich in flavonoid active metabolits, which show a potential anti-inflammatory activity. Flavonoids direct to inhibiting the biosynthesis of prostaglandins (PGE) and lipooxygenase (LOX), which are enzymes involved in the inflammatory process.

Flavonoid compounds are categorized into various subgroups, such as flavones, flavanones, flavans, and biflavans.[15] One of the flavanone compounds found in kersen leaves is pinocembrin.[16] The study states that pinocembrin possesses anti-inflammatory activity and has been demonstrated in various

disease models.[17] Pinocembrin works by decrease of c-Jun N-terminal Kinase levels, p38/MAPK, and NF-kB, thereby inhibiting cytokines products.

In a rheumatoid arthritis rat model, pinocembrin decrease joint erosion and the percentage of inflammatory cells.[18] In the ulcerative colitis animal study, administering high doses of pinocembrin demonstrated therapeutic and anti-inflammatory effects, likely due to inhibiting the NF-kB pathway.[19] Additionally, pinocembrin has shown promising results in respiratory allergic inflammation by reducing Th2-type cytokines (IL-4, IL-5, and IL-13) in bronchoalveolar lavage fluid from sensitized rats through the inhibition of NF-kB activation blocking).[20]

Based on the phytochemical screening test results, positive results were found in a 10% sodium hydroxide solution reagent characterized by acute yellow formation. In the other reagent (Table 1.), negative results were obtained because there was no formation of acute yellow color in the sample. The results of the flavanoid compound test using a 10% sodium hydroxide reagent be seen in Figure 5.

Saponin

Saponins are potent surface-active substances that lead to the formation of foam upon being heated in water. The saponins compounds were not detected in MCLI. The saponins test results can be seen in Figure 6.

These results might occur due to insufficient extraction time and temperature. According to a study, higher temperatures and longer extraction durations increase saponin levels.[22] Additionally, active saponin compounds are more effectively generated when extracted using methanol as a solvent. This results because methanol's universal nature allows it to capture saponins with polar and non-polar groups.[23]

Triterpenoids and steroids

The test results of triterpenoid compounds in *M. calabura L.* leaves using the 1 mL concentrated sulphuric reagent showed that the leaves contained triterpenoids but not steroid compounds in MCLI.

In a study, it is mentioned that the compound group belongs to the triterpenoid class treatment effects on inflammation complex range, which persists for an onset and duration treatment to treated of chronic diseases, including periodontitis, cerebral edema, sepsis, liver injury, gastric ulcer, acute lung injury, allergic reaction.[24] Another group (Escin) showed a significant reduction in inflammation induced in mice in vivo. Moreover, its effects better compared to the positive treatment by NSAID. The Escin mechanism is linked to the glucocorticoid receptor (GR). Through GR activation, escin inhibits the activation of NF-κB, subsequently reducing the release of inflammatory cytokines (TNF-α and IL-1β) along with nitric oxide (NO).

Alkaloids

Based on phytochemical screening results, the MCLI tested showed the presence of alkaloid compounds. This was seen from the formation of brown sediment at the bottom of the test tube from the MCLI. The alkaloid compound test resulting from using Wagner's reagents can be seen in Figure 7.

Several studies have indicated that alkaloids can inhibit various pro-inflammatory factors expression, such as histamine, lipid mediators, cytokines, and enzymes involved in the inflammatory response.[25] Some alkaloids direct mechanism to treated dermatomyositis rheumatoid arthritis, ankylosing spondylitis, myasthenia gravis, ankylosing spondylitis, systemic lupus erythematosus, Behcet's

disease, and other rheumatic immune diseases.[26]

Conclusion

The investigation of this study showed that local *M. calabura L.* contains flavonoids, triterpenoids, and alkaloids and each has the potential to developing for alternative inflammation traetment by natural products.

Prospect Future Studies

The study revealed that the anti-inflammatory potential of the studied medicinal plants. The cold maceration extraction method can be use to obtain more secondary metabolites without damaging heat-sensitive compounds. *Muntingia calabura L.* leaves extract contains a wide range of non-polar, semi-polar, and polar secondary metabolite chemicals. Using the fractional method to separate some of these compounds based on their polarity is better. As anti-inflammatory drugs, further tests can be carried out in vivo and in vitro. By purifying and separating the beneficial components from these plant extracts, we could gain a better understanding of how they function and discover potential ingredients for developing new drugs.

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Conflict of Interest

None declared.

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Evaluation of Antibiotic Use in Pediatric Inpatients at One of Bandung Regional Hospitals in August 2023

Putri Maharani,[1] Imam A. Wicaksono,[2] Falerina Puspita,[3] Hijrah M. Zainudin[3]

[1]Apotechary Program Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia 45363
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia 45363
[3]Bandung Kiwari Regional General Hospital, West Java, Indonesia

Abstract

Adverse Drug Reaction (ADR) is any unfavorable and unexpected drug response in paInfectious diseases are a major concern in the field of health, especially in developing countries like Indonesia. Children are vulnerable to infections because their immune systems are not fully developed. Proper management is necessary for the prevention and treatment of infectious diseases in pediatric patients. Antibiotics are the primary choice for addressing bacterial infections. However, the increased use of antibiotic can contribute to high levels of antimicrobial resistance (AMR), rendering infection treatment ineffective. The evaluation of antibiotic use can be conducted through the Anatomical Therapeutic Chemical (ATC) as the classification system and the Defined Daily Dose (DDD) measurement unit (ATC/DDD), which focuses on the quantity and types of antibiotics used. Although this method provides a quantitative overview, a qualitative approach using the Gyssens method and interviews with relevant parties are necessary for a more in-depth understanding of the rationality of antibiotic use. This study aims to comprehend the patterns of antibiotic use in pediatric inpatients at one of Bandung Regional Hospitals during August 2023. Using a retrospective observational approach, data were collected and processed using the ATC/DDD method. The evaluation results show that cephalosporins is the most commonly used antibiotic group, with cefotaxime being the dominant antibiotic administered intravenously. Quantitative evaluation indicates variations in DDD/100 patient days among different antibiotics, with ciprofloxacin having the highest value and amikacin the lowest. For a comprehensive understanding, qualitative research using the Gyssens method and interviews is necessary to strengthen the evaluation results of antibiotic use. Ultimately, this study provides a thorough perspective on antibiotic use in pediatric inpatients, supporting efforts to control antimicrobial resistance and promote more judicious antibiotic selection.

Keywords: Key words: Keywords: antibiotics; pediatrics; antibiotic use evaluation; WHO indicator ATC/DDD.

Corresponding author: Putri Maharani. Pharmacist Professional Study Program, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia. Email:putri19042@mail.unpad.ac.id
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Introduction

Infectious diseases are a major concern in the field of health, especially in developing countries like Indonesia. Children are more susceptible to infections due to their underdeveloped immune systems.[1] Study conducted by Djaja and Sulistiyowati, reveals that the highest mortality rates in infants and toddlers are caused by infectious diseases. Therefore, concerted efforts are needed for proper prevention and treatment of infectious diseases, especially in pediatric patients.[2]

The primary option to address the issue involves the use of antimicrobials, including antibiotics for bacteria, antifungal drugs, antivirals, and antiprotozoals. Generally, antibiotics are defined as the most commonly used drugs to fight bacterial infections and are considered a remarkable medical discovery of the 20th century. The introduction of antibiotics has transformed therapeutic paradigms, saving millions of lives from bacterial infections.[3,4]

The high rates of antibiotic use and prescription can be one of the contributing factors to the rose of antimicrobial resistance (AMR). AMR is a condition that occurs when bacteria is no longer responding to antibiotics, making treatments ineffective and difficult or not feasible to treat infections. The emergence and spread of antibiotic resistance are driven by various factors, including inherent microbial characteristics and numerous environmental factors involving both prescribers and patients. Factors contributing to antibiotic resistance include population and population's density, ineffective infection control programs, poor compliance, including inappropriate prescriptions and inadequate dosages.[5,6]

Drug Utilization Evaluation (DUE) is performed to assess whether the use of drugs, including antibiotics, is rational. The evaluation can be conducted qualitatively or quantitatively. Qualitative DUE is an approach used to assess the appropriateness of drug use based on predetermined criteria related to prescription and prescription indications. On the other hand, quantitative DUE is performed by classifying drugs based on the Anatomical Therapeutic Chemical (ATC) classification and drug usage in Defined Daily Doses (DDD).[7]

ATC is a classification system categorizing drugs based on therapeutic and pharmacological characteristics. Additionally, DDD is used as a measurement unit related to the ATC code. DDD represents the estimated average daily dose of a drug when used for its main indication in the adult population.[8,9] In pediatric patient groups' cases, DDD can serve as an overall measurement tool when it is difficult to identify warnings or limitations regarding the use of adult-based DDD.[8]

From those explanations above, an evaluation of antibiotic use in children is necessary to monitor and supervise appropriate and rational antibiotic usage. This study aims to understand the patterns of antibiotic use and conduct a quantitative evaluation using the ATC/DDD method in pediatric inpatients at one of Bandung Regional Hospitals in August 2023.

Methods

This study adopts an observational study approach, with data collection conducted retrospectively. The collected data originated from pediatric inpatients at one of the Regional General Hospitals (RSUD) in Bandung, West Java in August 2023, then categorized based on the type of antibiotic, the quantity and potency of antibiotics administered, as well as the total days of patient care. Inclusion criteria includes pediatric inpatients receiving

antibiotic therapy managed by the Pediatric Medical Staff Group (KSM), while exclusion criteria involves antibiotics without ATC codes. The collected data will be processed quantitatively using the ATC/DDD method. ATC codes and DDD values for antibiotics are obtained from the WHO website, which accessible through the link https://www.whocc.no/atc_ddd_index/. DDD calculations are performed for each ATC code, and the DDD calculation formula is as follows.[10]

Total Consumption in DDD[11]:

$$DDD = \frac{Number\ of\ item\ used\ x\ Amount\ of\ drug\ per\ item}{WHO\ recommended\ DDD\ of\ a\ drug\ (g)}$$

DDD/100 patient days is calculated using the formula[11]:

$$\frac{DDD}{100} Patient\ Days = \frac{Total\ Consumtion\ in\ DDD}{Total\ Days\ of\ care\ in\ the\ period} x100$$

Results and Discussion

The antibiotics use in pediatric inpatients were assessed using the ATC/DDD method. The evaluation is conducted by considering the Anatomical Therapeutic Chemical (ATC) codes and the standard Defined Daily Dose (DDD) values for each type of antibiotic. Subsequently, analysis and calculations are performed to obtain the DDD/100 patient-days value.

Table 2.1 shows that there are 10 antibiotic groups used in the treatment of pediatric inpatients at one of the Regional General Hospitals (RSUD) in Bandung, with cephalosporins being the most frequently prescribed category, accounting for 57.41% of the total prescriptions. Another study conducted at Dr. Soebandi Jember Regional General Hospital in the 2017 period indicated that cephalosporins was the most commonly prescribed antibiotic group, with a percentage of 46.22% in the treatment of pediatric inpatients.[12]

Meanwhile, at tertiary care hospital in Pune, Maharashtra for a period of 6 months (October 2018 to April 2019), the antibiotic group Cephalosporins was the most common class of antibiotic prescription (45%), followed by penicillins (27%) prescribed in pediatric wards.[13] Meanwhile, during a 6-month period (October 2018 to April 2019) at a tertiary care hospital in Pune, Maharashtra, cephalosporins were the most commonly administered antibiotic group (45%), followed by penicillins (27%), in pediatric wards.[13] This investigation was also carried out in Abu Dhabi, United Arab Emirates (UAE), a developed country on the West Asian continent. Cefaclor 130 (31.1%), Co-amoxiclav 103 (24.6%), and ceftriaxone 69 (16.9%) were the most commonly prescribed antibiotics in this study, whereas amoxicillin 1 (0.2%) and clarithromycin 2 (0.5%) were the least frequently prescribed.[14]

According to the majority of research, amoxicillin is the most commonly prescribed antibiotic, with broad-spectrum beta-lactams becoming increasingly popular.[15] Furthermore, another study discovered that amoxicillin prescriptions were significantly higher in both the United Kingdom and the Netherlands. [16] Nonetheless, multiple studies have shown that the beta-lactam family is still the most widely administered category of antibiotics. These patterns may be influenced by variations in patient characteristics, doctor prescription behaviors, pharmaceutical costs, and antibiotic prescribing guidelines for a variety of illnesses, including acute sinusitis, acute otitis media, and pharyngitis.[14]

A class of β-lactam antibiotics, Cephalosporins, are currently in their fifth generation. It is originally derived from the fungus Cephalosporium sp. which are a large group of bacterial antimicrobials that work through their β-lactam rings. Beta-lactam

Table 1. Antibiotic Profile Based on Number of Uses and Route of Administration

Class of Antibiotics	Type of Antibiotics	Number of Use	Route of Use (%)		Total Percentage
			Oral	Parenteral	
Cephalosporin	Cefotaxime	603		25.48	
	Ceftazidime	10		0.42	
	Ceftriaxione	376	12.72	15.89	57.41
	Cefixime	301			
	Cefoperazon	69		2.92	
Penicillin	Ampicillin	146		6.17	
	Amoxycillin	29	1.23		14.20
	Cloxacillin	161		6.80	
Carbapenems	Meropenem	243		10.27	10.27
Aminoglycosides	Gentamicin	183		7.73	9.80
	Amikacin	49		2.07	
Nitroimidazole	Metronidazole	71		3.0	3.0
Macrolides	Erythromycin	9	0.38		2.41
	Azithromycin	48	2.03		
Glicopeptide	Vancomycin	39		1.65	1.65
Fluroquinolones	Ciprofloxcacin	20	0.84		1.27
	Levofloxacin	10	0.42	0.42	
Total		2367	17.62	82.82	100

antimicrobials act on susceptible organism in two steps: in the first step, the antibiotic binds to a key receptor called membrane-bound penicillin-binding protein (PBP). This protein plays a vital role I the cell cycle, helping to build peptidoglycan structure of the cell wall. Therefore, inactivation of PBP by the bound antibiotic has an immediate effect in its function. The second steps involves the physiological effects of this receptor-ligand interaction. PBP acts in the cell wall's late phases of peptidoglycan production. As peptidoglycan maintains the integrity of the cell wall in a hypotonic environment, its disruption leads to lysis and cell death.[17–19]

Cephalosporins are divided into five generations based on their efficacy against gram-positive and gram-negative bacteria, as well as their discovery date. Cefazolin, cefadroxil, and cephalexin are first generation cephalosporins that are effective against most gram-positive cocci, such as *staphylococci* and *streptococci,* but have poor gram-negative coverage against *Proteus mirabilis*, *Escherichia coli*, and *Klabsiella pneumonia*. There are two types of second-generation cephalosporins: cefuroxime (cefprozil) and cephamycin (cefmetazole, cefotetan, cefoxitin).[19] In compared with the first generation, second-generation ceplaholsporins show lower action against gram-positive cocci but higher activity against gram-negative bacilli.[20]

Cefotaxime, ceftazidime, ceftriaxone, cefoperazone, and cefixime are third-generation cephalosporins that treat gram-negative infections resistant to prior generations or other β-lactam antimicrobials. Cefepime is a fourth-generation cephalosporin that covers *Streptococcus*

Table 2. Quantity Profile of Antibiotic Use based on the ATC/DDD Method

No	ATC Code	Antibiotics	Delivery Route	Total Grams	Standard DDD	Total DDD	Total LOS	DDD/ 100 *patient days**
1	J01MA02	Ciprofloxacin	O	10	1	10		76.92
2	J01DD04	Ceftriaxone	P	444	2	222		59.04
3	J01CF02	Cloxacillin	P	161	2	80,5		56.69
4	J01CA04	Amoxycillin	O	24.02	1.5	16.01		53.38
5	J01FA10	Azithromycin	O	26.6	0.3	88.67		46.67
6	J01DD08	Cefixime	O	126.5	0.4	310.5		45.39
7	J01DD01	Cefotaxime	P	603	2	150.75		27.162
8	J01DD02	Ceftazidime	P	10	4	2.5		22.73
9	J01MA12	Levofloxacin	P	5	0.5	10		21.28
10	J01DH02	Meropenem	P	243	3	81	2160	13.41
11	J01FA01	Erythromycin	O	21.6	1	21.6		12.71
12	J01DD12	Cefoperazon	P	69	4	19.75		10.23
13	J01XD01	Metronidazole	P	54.5	1.5	23.67		7.63
14	J01CA01	Ampicillin	P	146	6	35.33		5.56
15	J01XA01	Vancomycin	P	19.5	2	9.75		4.18
16	J01GB03	Gentamicin	P	7.32	0.24	30.5		3.76
17	J01GB06	Amikacin	P	12.25	1	12.25		3.21

pneumoniae (S. pneumoniae), methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Pseudomonas aeruginosa*.

This includes β-lactamase-producing gram-negative bacilli, as well as the gram-negative bacteria covered by the third generation. Despite its efficiency against both gram-positive and gram-negative bacteria, Cefepime is only used for severe systemic infections in individuals with multi-resistant pathogens.[21] Fifth-generation cephalosporins cover susceptible gram-positive and gram-negative pathogens, including MRSA and penicillin-resistant *S. pneumoniae*.[22–24]

Cephalosporins are widely used globally because of their broad antibacterial spectrum, low toxicity, and penicillinase resistance. They are frequently prescribed for both preventive and theurapeutic tratments of infections due to their safety in children, low allergenicity, and broad spectrum, which makes it effective against gram-positive and gram-negative bacteria. Cephalosporins are also commonly used as empiric therapy when the cause of illness is unknown, without any laboratory evidence, and often used as part of the initial treatment.[25,26]

In antibiotic prescriptions, there are 8 antibiotic groups consisting of 17 types of antibiotics. The most commonly prescribed antibiotic is cefotaxime (25.48%). Cefotaxime is a third-generation cephalosporin antibiotic widely used in the treatment of infections caused by both gram-negative and gram-positive bacteria, as well as penicillin resistance in pneumococcus. Additionally, cefotaxime can be used as empirical therapy for meningitis in infants and children, treatment of pneumonia, sepsis, and diseases susceptible to infection.[27,28] The use of cefotaxime is more recommended for children, especially neonates, compared to other cephalosporin group such as ceftriaxone because cefotaxime does not affect bilirubin metabolism. Moreover, cefotaxime has lower gastrointestinal side effects compared to ceftriaxone.[12]

In terms of antibiotic administration, the data shows that intravenous administration is the most commonly used route, reaching a percentage of 90.82%. The selection of the antibiotic administration route is based on the location of the infection and efficiency considerations. Intravenous antibiotics administration may be considered for patients with moderate to severe infection levels, in accordance with the guidelines of the Ministry of Health of the Republic of Indonesia in 2011. Intravenous administration is carried out to ensure that antibiotics directly enter the systemic circulation and evenly distribute to infected tissues, aiming for maximum antibiotic effects and optimal healing processes.[29]

The table 2.2 shows the calculation results of DDD/100 patient days indicate that ciprofloxacin has the highest percentage at 76.92%, while amikacin has the lowest percentage at 3.21%. The evaluation of DD/100 patient days for pediatric inpatients shows that antibiotic use is in line with WHO standards. If the DDD value exceeds the WHO standard, it indicates that the antibiotic use is less selective, raising concerns about irrational antibiotic use.[30] However, not all antibiotics with high usage rates have high DDD/100 patient- days values. For example, cefotaxime has the highest usage rate (see Table 2.1), but ciprofloxacin has the highest DDD/100 patient-days value (see Table 2.2).

The difference is affected by the total Length of Stay (LOS) and DDD values. A longer LOS for pediatric patients results in a lower DDD/100 patient-days value for each antibiotic, and vice versa. DDD values depend on the total grams of antibiotics used, determined by the doses given during the hospital stay, which vary in dosage, usage, and duration for each pediatric patient.

Additionally, varitions in WHO DDD standards for different antibiotics also impact DDD values.[8,31] For example, ceftriaxone and cefotaxime, where according to WHO DDDs standards, ceftriaxone has a standard DDD value of 2, and cefotaxime has a standard DDD value of 4 with a total of 603 grams, which is 159 grams more than ceftriaxone. Consequently, in the final results, the DDD value for ceftriaxone is larger than the DDD value for cefotaxime by 150.75.

The evaluation of DDD values doesn't fully explane the reasoning behind antibiotic use. DDD values can estimate the probable irrationality of antibiotic use (the rational parameters being the appropriate drug, indication and dose). To fully assess rational antibiotic use, further studies on other contributing factors are needed.

This study can provide information on the amount of antibiotics used in pediatric patients in one of the regional general hospitals in Bandung. Comparing these findings with similar studies in other hospitals, or even internationally, can provide a basis for considerations to help control antibiotic resistance, improve drug stock management, and develop hospital antibiotic use guidelines.[12,26] However, this method isn't a strict parameter for assessing the rationality of antibiotic use because ATC/DDD only measures the quantity and type of antibiotics used.[32]

A qualitative evaluation using the Gyssens method is needed to assess the appropriateness of antibiotic use, considering factors like indications, efficacy, toxicity, cost, spectrum, duration, dose, interval, rout, and timing of administration. This study has limitations, such as the lack of distribution of antibiotic use grouped by age and gender. Nonetheless, combining quantitative and qualitative

evaluations can provide a foundation for promoting intelligent and responsible antibiotic use in pediatric inpatients.

Recommendations include continuous monitoring and evaluation of drug use to enhance rational use, increased collaboration among healthcare professionals to improve antibiotic quality and prevent resistance, and the development and implementation of formulary system by the pharmacy and therapy committee to regular antibiotic use rationally.

Conclusion

Conclusion from the antibiotic usage profile indicates that cephalosporins (57.41%) and cefotaxime (25.48%) are the most widely used antibiotic groups and types, with the dominant route of administration is intravenous (82.82%). On the other hand, the evaluation of antibiotic usage quantity using the ATC/DDD method indicates that ciprofloxacin has the highest DDD/100 patient-days value at 76.92, while amikacin has the lowest value at 3.21. Interview with pertinent parties and qualitative research utilizing the Gyssens approach is required to obtain more comprehensive understanding of the rationale of antibiotic usage. This is done to strengthen the evaluation results of antibiotic usage in pediatric inpatients at one of Regional General Hospitals in Bandung during August 2023.

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Conflict of Interest

None declared.

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An Observational Study to Compare the Anti Anginal Efficacy of Ranolazine versus Nicorandil in Ischemic Heart Disease Patients Attending a Tertiary care Hospital in Kolkata India

Arup R. Mallick,[1] Pradip Saha,[2] Ishita Sengupta,[3] Gairik Sengupta,[1]*
Paramartha Bhattacharya,[2] Soumya K. Dutta[2]

[1]Department of Pharmacology, Institute of Post Graduate Medical Education and Research, Kolkata, India
[2]Department of Cardiology, Institute of Post Graduate Medical Education and Research, Kolkata, India
[3]Department of Anatomy, Medical College, Kolkata, India

Abstract

Ischemic Heart disease (IHD) occurs due to an imbalance between myocardial oxygen supply and demand. In stable IHD, second-line anti-anginal drugs like Ranolazine and Nicorandil are used as add-on therapy with first-line agents like Nitrates and beta-blockers. Our study compared the efficacy of Ranolazine versus Nicorandil utilizing the patient's responses to Short Seattle Angina Questionnaire (SAQ7) score. A prospective observational study on stable IHD patients attending the cardiology Outpatient Department (OPD) of IPGME&R and SSKM Hospital, Kolkata, with either Ranolazine or Nicorandil as add-on therapy (50 patients in each group). SAQ7 score was recorded at baseline and three follow-up visits (1.5, 3, and 6 months). Adverse effects and the changes in HbA1C levels in diabetic patients among these patients were also compared. There was a significant increase in SAQ7 score in Ranolazine [median (IQR) - 26.50 (25.00 - 29.25) to 32.00 (30.75 - 34.00), $p < 0.0001$] and also in Nicorandil [median (IQR) - 27.00 (24.00 - 30.00) to 32.50 (31.00 - 34.00), $p < 0.0001$] group in third follow up visits from baseline. The comparison between the groups didn't show any significant changes. There were no significant changes in HbA1C levels between the pre and post-treatment period. Adverse effects were more in the Nicorandil group. Both drugs significantly improved IHD patients' symptom control and were well tolerated. There were no significant differences in the change of HbA1C level in Diabetic patients. However, a larger study is required to decide whether these drugs can be used as a single agent alone.

Keywords: Ischemic Heart disease, Ranolazine, Nicorandil, Short Seattle Angina Questionnaire (SAQ7) score

Corresponding author: Gairik Sengupta. 1Department of Pharmacology, Institute of Post Graduate Medical Education & Research, Kolkata, India Email: drgairiksengupta@gmail.com
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Introduction

Ischemic Heart disease (IHD) is a condition characterized by an inadequate supply of blood and oxygen to a portion of the myocardium due to an imbalance between myocardial oxygen supply and demand. The patients typically complain of episodes of chest discomfort, heaviness, or squeezing sensation, and rarely frank pain. Upon clinical suspicion of angina, the patient undergoes several biochemical tests and imaging, i.e., blood tests for lipid profile (total cholesterol, LDL, HDL, and triglycerides), glucose including HbA1C, creatinine, ECG, and Echocardiogram to assess the systolic and diastolic function of heart and cardiovascular system.[1]

The anti-anginal agent Ranolazine exerts its effects without affecting the heart rate, arterial blood flow, or coronary blood flow. Ranolazine inhibits late Na+ current, which may contribute to arrhythmias in IHD patients. Inhibition of this current decreases Na+ dependent Ca2+ overload and its detrimental effects on myocardial ATP hydrolysis and cardiac function.[2]. Few studies revealed that Ranolazine has additional HbA1C lowering effects, which provides additional benefits in Type 2 Diabetes Mellitus patients without any accompanying hypoglycemia.

Nicorandil has nitrate-like (cGMP-dependent) properties and has agonistic action at ATP-sensitive potassium (KATP) channels. It dilates both arterial and venous vascular beds, thereby reducing afterload and preload of the heart. Experimental and clinical studies suggested a cardioprotective effect of Nicorandil mimicking that of ischemic preconditioning. It is a phenomenon in which short periods of ischemia preceding prolonged stopping of perfusion (as in MI) reduce myocardial injury.[1] Trimetazidine, another anti-anginal drug, is a metabolic modulator also known as a partial Fatty Acid Oxidation (pFOX) inhibitor that partially inhibits the fatty acid oxidation pathway in myocardium.[2] Ivabradine is a newer anti-anginal drug causing bradycardia by inhibiting hyperpolarization-activated sodium channels in the sinoatrial node.[3]

Seattle Angina Questionnaire (SAQ) is a validated disease-specific health status instrument for coronary artery disease (CAD) with high test–retes reliability, predictive power, and responsiveness.[4] A shortened version of this instrument, SAQ-7, has also been validated and can be used to evaluate patients with stable CAD.[4] The European Society of Cardiology (ESC) guidelines[5] and National Institute for Health and Care Excellence, UK (NICE) guidelines[6] recommend the use of a second-line anti-anginal drug like Ranolazine, Nicorandil, Trimetazidine or Ivabradine as an add-on therapy in patients inadequately responding or poorly tolerating the first line anti-anginal drugs. While some studies and meta-analyses were conducted with anti-anginal first-line medicines as well as a few second-line drugs, studies comparing the efficacy of Ranolazine versus Nicorandil as an add-on therapy are lacking, especially in India. The present study, therefore, was planned to address this issue involving these two commonly used drugs.

Methods

A prospective observational study with longitudinal follow-up was undertaken with patients attending the cardiology OPD of IPGME&R and SSKM Hospital, Kolkata, India. Patients were recruited according to the inclusion and exclusion criteria stated below. The study period was 18 months from commencement. Fifty patients having stable IHD who received Tab Ranolazine 500 mg twice daily and 50 others who received Tab Nicorandil 5 mg twice daily as add-on therapy were followed up for 6 months with 2 interim follow-up visits at 1.5 months and 3 months.

Inclusion criteria were stable IHD patients of either gender between ages 20-65 years and poorly controlled on any of the first-line anti-anginal agents like nitrates, beta-blockers, or calcium channel blockers.

Exclusion criteria were any life-threatening comorbidity, anemia or critical conditions like acute coronary syndrome or acute heart failure. Baseline demographic and clinical variables were noted. SAQ 7 score was used as an outcome parameter and was recorded at the beginning of the study and each follow-up visit.[6] Primary objective was to assess the anti-anginal efficacy of Ranolazine versus Nicorandil as add-on therapy with first-line anti-anginal-agents in known IHD patients. The secondary objective was to assess changes in HbA1C level caused by both the drugs, if any, and to assess the adverse effects caused by them.

The study commenced after ethical approval from the Institutional Ethics Committee at IPGME&R, Kolkata - India. Written informed consent was taken from all patients and with all respect for their privacy and confidentiality. The study was registered with Clinical Trials Registry-India (CTRI) with reg no. CTRI/2020/10/028644.

Data was analyzed by routine descriptive statistics, namely mean and standard deviation for numerical variables and counts and percentages for categorical variables. Intragroup comparisons were done using a paired T-test for parametric data and a Wilcoxon matched-pairs signed-ranks test for nonparametric data, as applicable. The chi-square test was employed for the intergroup comparison of categorical variables. Analyses were two-tailed, and the level of statistical significance was set at $p< 0.05$ for all comparisons. (Software used: IBM SPSS statistics version 20).

Results and Discussion

Results

Table 1. Baseline age (mean + SD) in Ranolazine group was (53.30 +7.675) years and baseline age in Nicorandil group was (53.20 +6.899) years; $p = 0.9455$.

Table 2. At baseline in Ranolazine group, FBS (mean + SD) was 106.74 + 17.72 where as in Nicorandil group it was 104.64 + 16.86; $p = 0.2435$.

Table 7. Changes in FBS in Ranolazine after 6 months: At baseline in Ranolazine group, the mean + SD of FBS was 106.74 +17.72 and after 6 months of treatment became 106.12 +32.73, $p = 0.0019$.

Table 8. Changes in FBS in Nicorandil after 6 months: At baseline in Nicorandil group, mean + SD of FBS was 104.6 +16.86 and after 6 months of treatment became 104.0 +25.38, $p = 0.0053$

Figure 1. In Ranolazine group 35 were male, 15 female and in Nicorandil group 36 were male and 14 were female; $p > 0.05$.

Figure 2. In Ranolazine group, 20 participants were businessmen, 4 farmers, 7 housewives, 11 retired, 7 service-men, 1 painter. In Nicorandil group,18 participants were businessmen, 4 farmers, 8 housewives, 9 retired, 10 service-men, 1 painter; $p > 0.05$.

Figure 3. About 15 people in the Ranolazine group were diabetics where, whereas 13 people in the Nicorandil group were diabetics. In the Ranolazine group, 20 people had hypertension whereas in the Nicorandil group, 17 patients had hypertension. About 12 people in the Ranolazine group had dyslipidemia where, whereas 9 people in the Nicorandil group had dyslipidemia. In the Ranolazine group, 17 patients had family

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H/O IHD, whereas in the Nicorandil group, 19 people had family H/O IHD.

Figure 4. At baseline in Ranolazine group, PPBS (mean + SD) was 135.0 + 55.34. In Nicorandil group it was (123.1 + 32.55); p = 0.4715

Figure 5. At baseline in the Ranolazine group, total Cholesterol (mean + SD) was 161.7 + 41.73. In Nicorandil group it was 151.7 + 40.30; p = 0.2227.

Figure 6. At baseline in Ranolazine group, the mean + SD of LDL was 51.18 + 14.82. In Nicorandil group it was 50.26 + 13.01; p = 0.9521.

Figure 7. Data analysis was done with patients who completed 6 months of treatments and attended at-least 2 follow-up visits. The baseline age (mean + SD) in the Ranolazine add-on group was 53.30+ 7.675 years, and in the Nicorandil add-on group was 53.20+6.899 years, and there was no significant difference between the two groups (p = 0.9455). In the Ranolazine group, 35 were male, 15 were female, 36 were male and 14 were female in the Nicorandil group. There were no significant differences in gender and occupation between the groups (p > 0.05).

In the Ranolazine group, 17 people had a family history of IHD; in Nicorandil, group 19 had a family history of IHD with no significant difference between groups (p >0.05)). Regarding comorbidities among subjects, in the Ranolazine group, 20 had Hypertension, 15 had Diabetes Mellitus, and 12 had Dyslipidemia, and in the Nicorandil group, 17 had hypertension, 13 had Diabetes Mellitus, and 9 had Dyslipidemia. There was no significant difference between groups (p = 0.1991).

Regarding other laboratory parameters, i.e., Fasting and post-prandial blood sugar (FBS, PPBS), Total Cholesterol, and LDL, there were no significant differences between the groups (p > 0.05). But after 6 months of treatment, in the case of Ranolazine and Nicorandil, there were changes in (mean + SD) FBS, p= 0.0019 and p= 0.0053, respectively, from the baseline. This may not be a reflection of potential anti-diabetic activity as the SD was relatively wide (Fig. 16, Fig. 18). In case of baseline SBP and DBP, there were no significant differences between two groups.

Figure 8. Regarding Seattle Angina Questionnaire 7 score or Short SAQ7 score baseline values were comparable between the study groups.. There were significant differences in SAQ7 score from baseline in both groups separately at 3 and 6 months both (p < 0.0001) but a comparison of changes in SAQ7 score after 3 and 6 months in between the group found no significant difference (p = 0.6257 and p = 0.5301 respectively).

Figure 12. HbA1C: In Ranolazine group among 15 diabetics patients, the mean+ SD of HbA1C was 7.260 +1.137 and after 6 months of treatment the mean+ SD of HbA1C became 7.093 +0.8319, p = 0.7971. In Nicorandil group among 13 diabetics patients, the mean+ SD of HbA1C was 7.054 +0.7264 and after 6 months of treatment became 6.923 + 0.5434, p =0.8491.

Figure 14. Several adverse effects were observed in both groups which were self limiting in nature and didn't require treatment discontinuation. However the number of adverse effects was greater in Nicorandil group with no significant difference between groups regarding any adverse effect.

Figure 16. Changes in SBP in Ranolazine after 6 months: At baseline in Ranolazine group,

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the(mean + SD SBP was 129.8 +15.71 and after 6 months of treatment became 123.4 +9.817, p = 0.0216. Such significant lowering of SBP was not observed in Nicorandil group

Figure 18. The baseline SAQ7 score [median (IQR)] in Ranolazine group was 26.50 (25.00-29.25) which significantly increased to 31.00 (29.00-33.00) and 32.00 (30.75-34.00) after 3 and 6 months of follow–up respectively ($p < 0.0001$ in both the scenario). In case of Nicorandil, the baseline SAQ7 score [median (IQR)] was 27.00 (24.00-30.00) which significantly increased to 31.00 (29.00-33.00) and 32.50 (31.00-34.00) after 3 and 6 months of follow–up respectively ($p < 0.0001$).

In both groups there were few adverse effects, mostly self-limiting and with no significant intergroup difference for any of them. No adverse effect required treatment discontinuation. In Ranolazine group there were altogether 16 adverse effects, most common being dizziness, 8 in number followed by Headache (6) and Palpitations (2). In Nicorandil group also Dizziness was the leading adverse effect, 10 in number followed by Flushing (7) and Palpitations (4). There were altogether 21 adverse effects in Nicorandil group.

Discussion

Ischemic Heart disease (IHD) causes considerable morbidity and mortality across the world and warrants lifestyle modification along with pharmacotherapy with first line anti anginal drugs like nitrates and beta blockers for satisfactory management. Existing guidelines also recommend the use of second line drugs like Ranolazine, Nicorandil, Trimetazidine or Ivabradine as add on therapy in patients inadequately responding or poorly tolerating the first line drugs. While some researches were conducted on these drugs, no study in South East Asia till date has compared these two commonly used drugs Ranolazine and Nicorandil for their efficacy and tolerability. Our study attempted to address this issue using SAQ[7] score for improvement in stable IHD patients. The ARETHA AT observational study[7] (Austria) found a significant reduction in angina frequency and Nitroglycerin consumptions when Ranolazine was used as add on therapy with Calcium channel blockers (CCB) or Beta blockers.

The TERISA trial[8] found that weekly angina frequency was significantly lower with Ranolazine versus placebo. A meta-analysis of randomized controlled trials of Ranolazine, Nicorandil and Ivabradine was conducted where the secondary outcome was the Seattle Angina Questionnaire (SAQ) scores showed Ranolazine and Ivabradine improved 3 of the 5 SAQ scores. Our study also found significant improvement in SAQ score with Ranolazine after 3 months of use but not at 1.5 months. It also recorded a significant reduction of systolic blood pressure upon 6 months of use. Kobara et al[9] had shown that Nicorandil suppresses ischemia-induced norepinephrine release and ventricular arrhythmias in hypertrophic hearts.

In an animal model of myocardial infarction with rats Chen et al[10] found that Nicorandil inhibits TLR4/ MyD88/NF-κB/NLRP3 signaling pathway to reduce pyroptosis. The CHANGE Trial[11] documented that administration of nicorandil before primary percutaneous coronary intervention led to improved myocardial perfusion grade and reduced infarct size in patients with ST segment–elevation myocardial infarction. Tarkin et al[12] found that nicorandil is comparably effective for angina prophylaxis to long-acting nitrates and other conventional anti-anginal drugs. Ito et al[13] showed a beneficial effect of intracoronary nicorandil on microvascular dysfunction after primary percutaneous coronary intervention:

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demonstrated its superiority to nitroglycerin in a cross-over study. Our study has found a significant improvement in stable IHD patients on Nicorandil as add on therapy after 3 months and 6 months of use but not after 1.5 months.

Another meta-analysis involving the effects of Ranolazine on HbA1C in diabetic patients had shown that Ranolazine improves HbA1c without increasing the risk of hypoglycaemia.[14]. However, in our study, among 15 diabetic patients in Ranolazine group and 13 in Nicorandil group no significant change of FBS, PPBS or HBA1C upon 6 months of use was found. Both drugs were well tolerated and no significant difference was found between them in terms of efficacy and tolerability. Moreover, the significant SBP reduction with Ranolazine found in our study was not reported in earlier research conducted and may warrant another study in future regarding the same.

Conclusion

This study shows significant improvements in patients after adding the second line agents for both the drugs with comparable efficacy. No significant changes in HbA1C level between pre and post treatment period in any group was found, though a larger sample size is required to comment on this. The incidences of adverse effects were more in Nicorandil group though none of them was serious enough to warrant treatment discontinuation and both of the drugs seem suitable as second line antianginal agents.

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Conflict of Interest

None declared.

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Table 1. Baseline Characteristics

Characteristics	Number (n)	Number (%)
Sex		
Male	71	71
Female	29	29
Marital Status		
Single	2	2
Married	82	82
Widow	16	16
Age (Years)		
20-35	2	2
36-50	30	30
51-65	68	68
Comorbidities		
Diabetes	28	28
Hypertension	37	37
Dyslipidemia	21	21

Table 2. Baseline Laboratory and Clinical Parameter

Variabel	Ranolazine Add-on Group (n=50)	Nicorandil Add-on Group (n=50)	P-value
FBS (mg/dL) (mean ± SD)	106.74±17.72	104.64±16.86	0.2435
PPBS (mg/dL) (mean ± SD)	135.0±55.34	123.1±32.55	0.4715
Total Cholesterol (mg/dL) (mean ± SD)	161.7 ± 41.73	151.7 ± 40.30	0.2227
LDL (mg/dL) (mean ± SD)	51.18 ± 14.82	50.26 ± 13.01	0.9521
SBP (mmHg) (mean ± SD)	129.8 ± 15.71	128.8 ± 16.24	0.6461
DBP (mmHg) (mean ± SD)	71.80 ± 8.734	74.60± 7.879	0.0770

Table 3. SAQ7 Score [median (IQR)] at Different Time-points of the Study in Both the Group

Groups	SAQ 7 score [median (IQR)]			
Timeline	**Baseline**	**1.5 months**	**3 months**	**6 months**
Ranolazine	26.50 (25.00-29.25)	29.00 (27.25- 32.00)	31.00 (29.00-33.00)	32.00 (30.75-34.00)
Nicorandil	27.00 (24.00-30.00)	29.00 (27.00-31.00)	31.00 (29.00-33.00)	32.50 (31.00-34.00)

Table 4. Changes in SAQ7 Scores Over Time from Baseline Between Ranolazine and Nicorandil [median (IQR)]

Timeline	Ranolazine	Nicorandil	P value
3 months	3.500 (2.000-5.000)	4.000 (3.000-5.250)	0.6257
6 months	5.000 (3.000-7.000)	5.000 (4.000-7.000)	0.5301

Table 5. Changes in HbA1C level (mean + SD) among Diabetic Patients after 6 months

Groups	Baseline	6 months	P value
Ranolazine (n=15)	7.260 ± 1.137	7.093 ±0.8319	0.7971
Nicorandil (n=13)	7.054 ± 0.7264	6.923 ±0.5434	0.8491

Table 6. Adverse Effects

Adverse effects	Ranolazine	Nicorandil
Dizziness	8	10
Headache	6	0
Flushing	0	7
Palpitation	2	4
Total	**16**	**21**

Table 7. Changes in Laboratory and Clinical Parameters in Ranolazine group

Variables	Baseline	6 months	P value
FBS (mg/dl) (mean ± SD)	106.7 ± 17.72	106.12 ± 32.73	**0.0019***
PPBS (mg/dl) (mean ± SD)	132.8 ± 35.76	135.0 ± 55.34	0.1273
Total Cholesterol (mg/dl) (mean ± SD)	161.7 ± 41.73	160.8 ± 36.74	0.9003
LDL (mg/dl) (mean ± SD)	51.18 ± 14.82	51.10 ± 11.88	0.5907
SBP (mmHg) (mean ± SD)	129.8 ± 15.71	123.4 ± 9.817	**0.0216****
DBP (mmHg) (mean ± SD)	71.80 ± 8.734	73.60 ± 7.762	0.2052

* Significant changes observed in FBS after 6 months of treatment (p= 0.0019)
**Significant changes observed in SBP after 6 months of treatment (p= 0.0216)

Table 8. Changes in Laboratory and Clinical Parameters in Nicorandil group

Variables	Baseline	6 months	P value
FBS (mg/dl) (mean ± SD)	104.6 ± 16.86	104.0 ± 25.38	**0.0053***
PPBS (mg/dl) (mean ± SD)	121.8 ± 24.43	123.1 ± 32.55	0.6002
Total Cholesterol (mg/dl) (mean ± SD)	151.7 ± 40.30	149.9 ± 34.60	0.9877
LDL (mg/dl) (mean ± SD)	50.26 ± 13.01	49.94 ± 9.305	0.3681
SBP (mmHg) (mean ± SD)	128.8 ± 16.24	123.0 ± 10.15	0.0768
DBP (mmHg) (mean ± SD)	74.60 ± 7.879	71.40 ± 7.287	0.0561

* Significant changes observed in FBS after 6 months of treatment (p= 0.0053)

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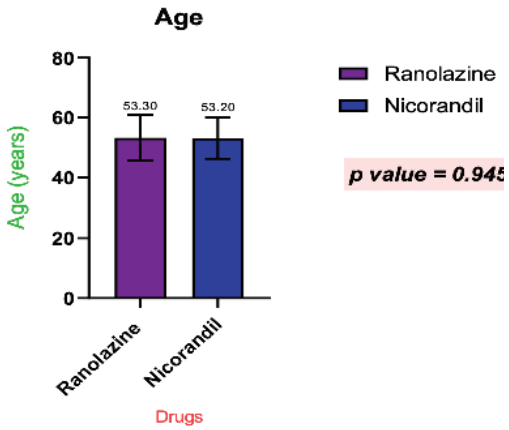

Figure 1. Baseline age (mean + SD) (N=100)

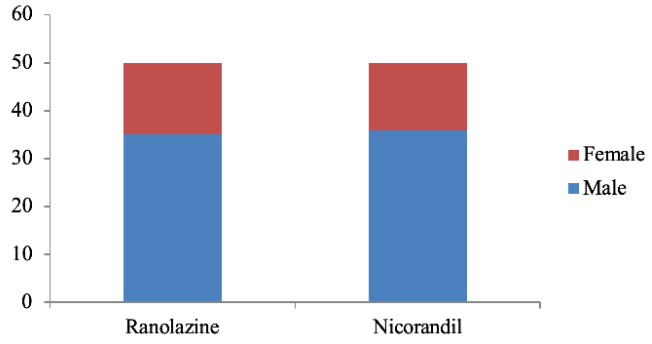

Figure 2. Gender of the Subjects of Both the Group

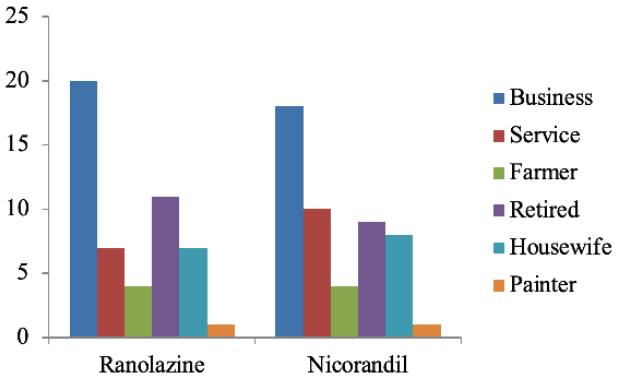

Figure 3. Occupations of the Subjects of both the Group

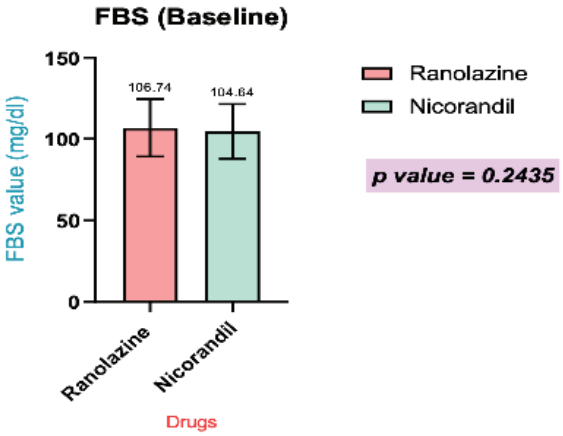

Figure 4. Baseline FBS (mean + SD) (N=100)

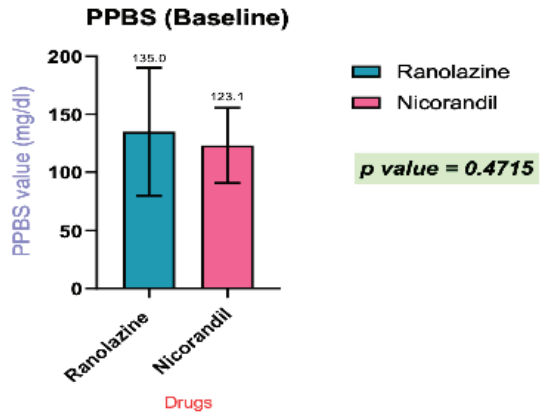

Figure 5. Baseline PPBS (mean + SD) (N=100)

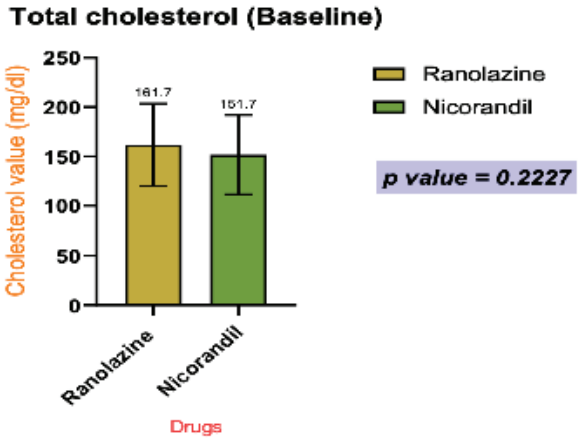

Figure 6. Baseline Total Cholesterol (mean + SD)(N=100)

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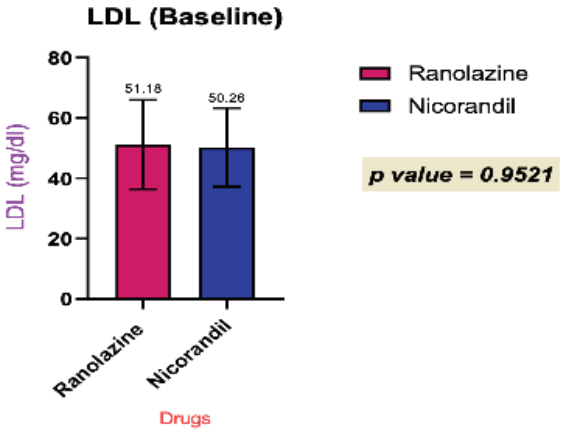

Figure 7. Baseline LDL (mean + SD) (N=100)

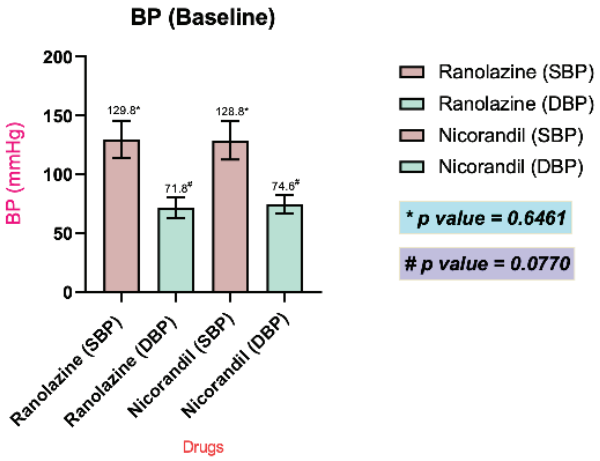

Figure 8. Baseline BP (SBP and DBP) (mean + SD) (N=100

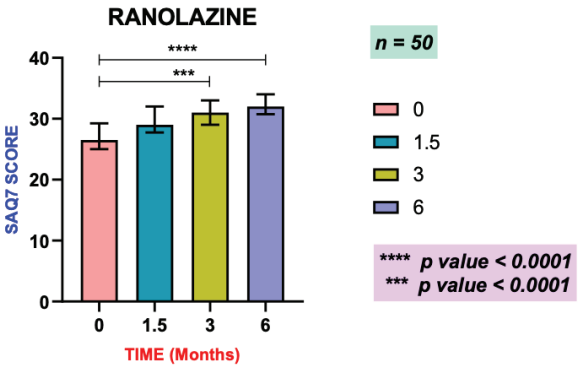

Figure 9. Change of SAQ7 score [median (IQR)] over time with Ranolazine

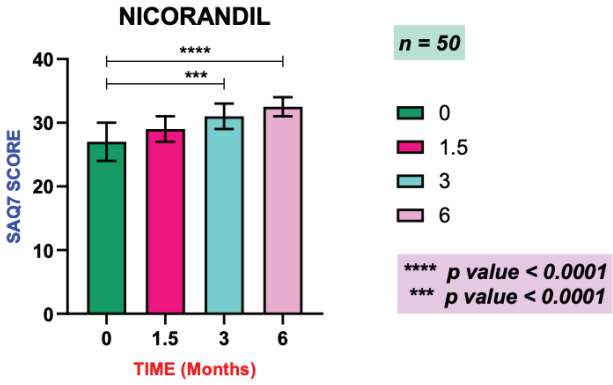

Figure 10. Change of SAQ7 score [median (IQR)] over time with Nicorandil

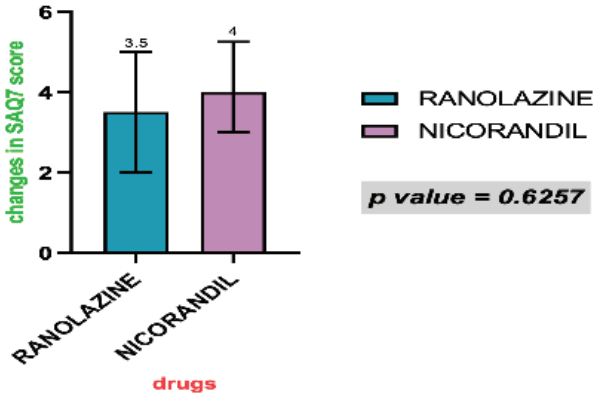

Figure 11. Changes in SAQ7 scores after 3 months between Ranolazine and Nicorandil [median (IQR)]

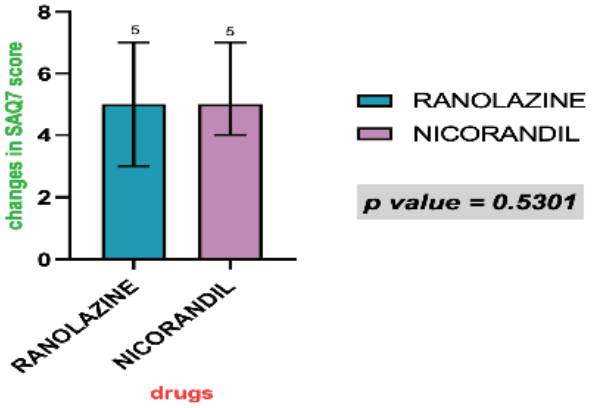

Figure 12. Changes in SAQ7 scores after 6 months between Ranolazine and Nicorandil [median (IQR)]

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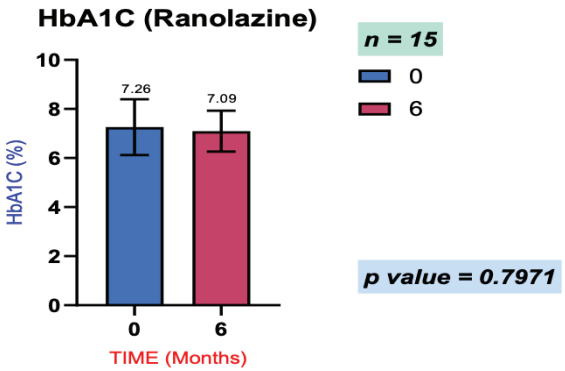

Figure 13. Changes in HbA1C level (mean + SD) among diabetic patients in Ranolazine group after 6 months

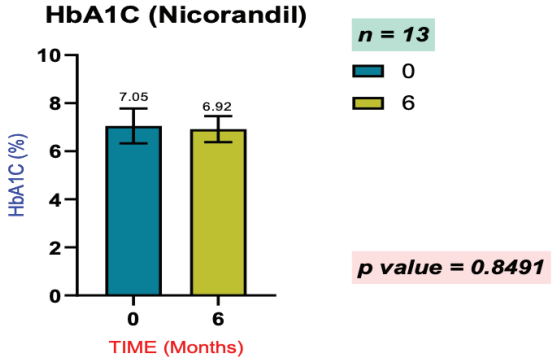

Figure 14. Changes in HbA1C level (mean + SD) among diabetic patients in Nicorandil group after 6 months

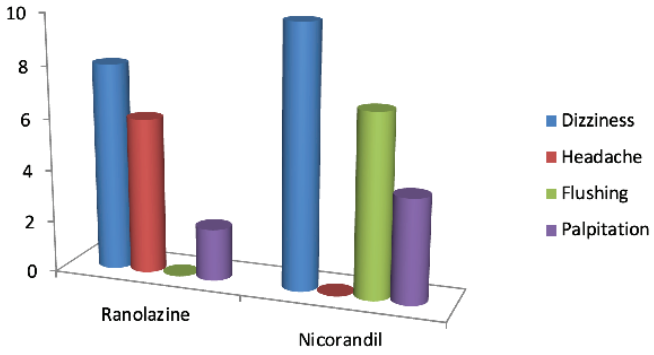

Figure 15. Adverse Effects in both Groups

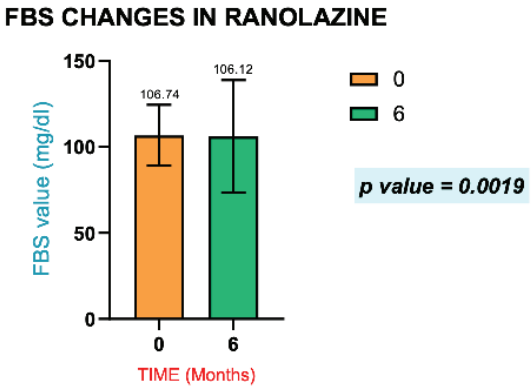

Figure 16. Changes in FBS (mean + SD) in Ranolazine after 6 months

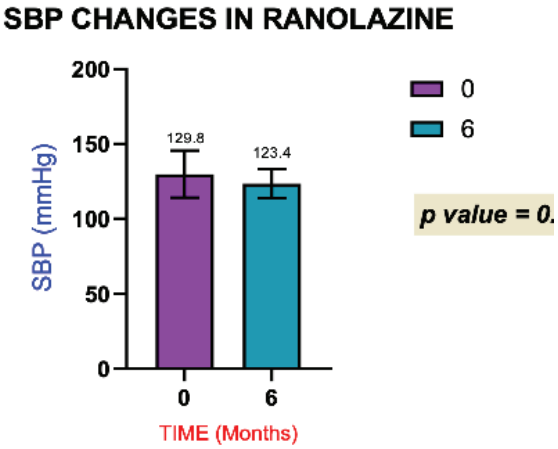

Figure 17. Changes in SBP (mean + SD) in Ranolazine after 6 months.

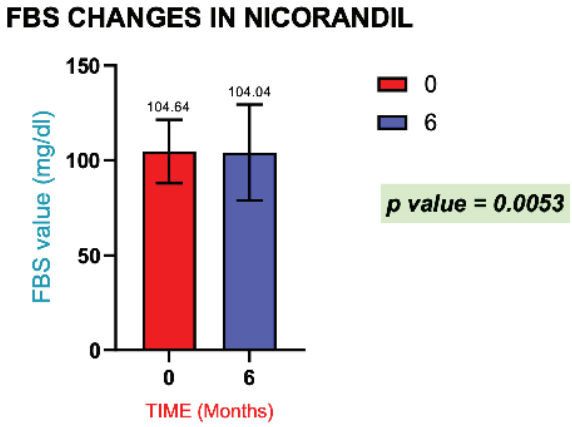

Figure 18. Changes in FBS (mean + SD) in Ranolazine after 6 months

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Prescribing Pattern of Corticosteroid in Dermatologic Disorder at Tertiary Care Teaching Hospital in Western Indian

Zankrut Patel*[1], Dhiren Patel[1], Jatin Patel[2], Sumit Patel[3]

[1]Assistant Professor, Department of Pharmacology, Ananya College of Medicine and research, KIRC campus , Ahmadabad-Mehsana Highway,Kalol,Gandhinagar, India
[2]Associate Professor, Department of Pharmacology, Ananya College of Medicine and research, KIRC campus , Ahmadabad-Mehsana Highway,Kalol,Gandhinagar, India
[3]Professor, Department of Pharmacology, GMERS Medical College Godhara, Panchmahal India

Abstract

Based on their potent immunosuppressive and anti-inflammatory properties, corticosteroids are essential for treating several skin disorders. Due to their lesser systemic toxicity, topical treatments are recommended. The use of corticosteroids in Indian dermatology practice, however, is not well documented. This study aims to analyze the prescribing patterns of corticosteroids for dermatologic disorders. In the outpatient dermatology department of GCS Hospital, Ahmedabad, a cross-sectional, observational study was conducted for six months, from March 2021 to August 2021. We looked at prevalent skin problems and prescribing patterns in 500 prescriptions. A descriptive statistical analysis was done following the compilation of all the data into Microsoft Office Excel. 169 patients (out of 500) received corticosteroids. There were 53% men and 47% women, respectively. The Papulosquamous illness affected 33% of them. The average number of corticosteroids per prescription was 1.17. Out of 198 prescribed corticosteroids, 163 (82.32%) were topical formulations, and 35 (17.67%) were oral. Among the nine different corticosteroids prescribed, clobetasol was given to 29% of patients. Additionally, 39% of patients received a fixed-dose combination (FDC) of corticosteroids, with clobetasol and salicylic acid being the most commonly used FDC. The average cost of corticosteroids per prescription was 135.18 INR, ranging from 4 INR to 468 INR for 15 days of treatment. The mean cost of corticosteroids was significant compared to other concomitant drugs ($P < 0.05$). Topical corticosteroids were more commonly prescribed than oral ones, with psoriasis being the most common indication for topical corticosteroids. Clobetasol and mometasone were the most frequently used topical corticosteroids.

Keywords: Corticosteroids; Dermatology; Prescribing pattern.

Corresponding author: Zankrut Patel. Department of Pharmacology, Ananya College of Medicine and research, KIRC campus , Ahmadabad-Mehsana Highway,Kalol,Gandhinagar, India Email: zankrutmedico27@gmail.com
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Introduction

Skin disorders, affecting all age groups and genders, are a prevalent concern in society, presenting a wide range of symptoms and severity. These conditions can be minor or life-threatening, acute or chronic, painless or painful. Due to their chronic nature, they significantly impact patients' quality of life, financial stability, and social interactions[1]. Common dermatological conditions include fungal infections, dermatitis, psoriasis, urticaria, eczema, and vitiligo[2]. In India, prescribing medications for skin conditions poses challenges, such as inappropriate drug combinations and the overuse of antimicrobial treatments and their combinations with corticosteroids[3]. Due to their potent immunosuppressive and anti-inflammatory properties, corticosteroids are widely prescribed and frequently overprescribed, which can increase the risk of adverse drug reactions. Despite this, corticosteroids remain essential in treating many skin diseases[4].

Glucocorticoids can be administered systemically via intramuscular, intravenous, and oral methods, or locally through topical and intralesional means. Topical corticosteroids come in various forms, including creams, ointments, lotions, and gels[5]. Topical applications are preferred as they allow direct medication delivery to the target organ, dose adjustment based on response, and reduced systemic toxicity[6]. However, adverse effects of topical preparations can include hypertrichosis, purpura, striae, steroid-induced rosacea, and epidermal and dermal thinning[7]. Systemic administration of corticosteroids may lead to serious adverse effects such as immunosuppression, cataracts, glaucoma, hypertension, hyperglycemia, cushingoid characteristics, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, this study aims to examine the prescribing patterns of corticosteroids in dermatological practice, along with other relevant factors.

Methods

The outpatient dermatology department at GCS Medical College, Hospital and Research Center in Ahmedabad, a tertiary care teaching hospital, served as the site for an observational, cross-sectional study. Over six months, from March to August 2021, 500 patients' prescriptions were randomly collected through a bi-weekly survey. Data on patients of all ages and genders who provided written informed consent were gathered and analyzed. The study received prior approval from the Department of Dermatology and the Institutional Ethics Committee. Patients were informed about the study and given a brief explanation following their dermatologist visits. The investigator enrolled each patient by visiting the dermatology outpatient department. A case record form (CRF) was used to document patients' personal information after enrolment. Prescription data were analyzed for demographics, drug usage trends, and the proportion of medications prescribed as corticosteroids, including their specific formulations. The compiled data was entered into Microsoft Office Excel 2010 for descriptive statistical analysis. An independent t-test was applied to compare the costs of corticosteroids and concurrent medications.

Results and Discussion

Skin conditions significantly impact the quality of life, particularly in a country like India, where there are regional variations in climate, social standing, and religious customs. Certain disorders may worsen with seasonal changes; for example, psoriasis and dermatitis often worsen in the winter, while scabies and fungal skin infections are more prevalent in the summer[8]. The prescribing physician gains valuable feedback regarding the sensible use of prescription patterns. Studies like these

are useful for identifying current trends in treatment adherence and usage[9]. In India, corticosteroids are very popular, and their use has increased over time. Even though their rational use is not always apparent, they are continuously produced and sold.

In our study, out of 500 patients, 169 (33.80%) were prescribed corticosteroids. Of these, 142 (84.02%) received one corticosteroid, 25 (14.79%) received two, and only 2 (1.18%) were prescribed three corticosteroids. Each prescription was written using brand names. Out of the 169 patients, 82% received a prescription for topical corticosteroids, while 18% received an oral prescription. Our findings were similar to those of Javsen C et al[10]. and Narwane SP et al[11], who also showed that topical corticosteroids were prescribed more frequently than oral ones. In our study, the majority of patients (46.74%) were between the ages of 21 and 40. Among these, there were slightly more male patients (50.63%) compared to female patients (49.37%). These results were consistent with studies by Ankit et al[12] and Bylappa et al[13].

According to the WHO ICD-10[14] classification, the most prevalent dermatological condition observed was papulosquamous disease of the skin (33.13%), followed by dermatitis and eczema (20.71%), both of which required the prescription of corticosteroids. Our findings aligned with those of Gupta R et al[4], Mukherjee S[15], Sarvanakumar RT, et al[16], and Mirshad PV et al[17]. According to the current study, 33.72% of corticosteroid prescriptions included clobetasol as the most frequently prescribed medication. This finding differs from the study by Javsen C et al[10], where 55% of prescriptions were for betamethasone. In our study, salicylic acid was most commonly combined with topical corticosteroids due to its keratolytic activity and ability to enhance penetration. This is similar to the findings by Khan et al[18] and Sarkar et al.[19], who also reported the use of fusidic acid and clotrimazole in conjunction with topical corticosteroids.

The average total cost per prescription was INR 640, which is slightly higher than the INR 487.50 recorded in a study by Pathak et al[20]. However, some prescriptions had significantly higher costs due to the inclusion of expensive medications such as immunomodulators (tacrolimus) and decapeptide-containing melgain lotion, which raised the overall average cost. Other factors contributing to the high cost include the generally high prices of dermatological products, polypharmacy, and the limited availability of generic medications.

Conclusion

The current study concludes that dermatitis and eczema, which often require corticosteroids, are the most prevalent dermatological disorders, followed by papulosquamous skin diseases. Topical corticosteroids were prescribed more frequently than oral ones, with the highest usage for psoriasis. Mometasone and clobetasol were the most commonly prescribed topical corticosteroids. There were fewer prescriptions for injections listed in the essential medications list and prescribed by their generic names, which may not be a positive indicator. Further research on the safety profile of corticosteroids is necessary.

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Conflict of Interest

None declared.

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Table 1. Demographic Characteristics of Patients

Characteristic	Number (%)
Gender	
Male	90 (53.25%)
Female	79 (46.74%)
Age	
0-20 years	26 (15.38%)
21-40 years	79 (46.74%)
41-60 years	48 (28.40%)
>61 years	16(9.46%)

Table 2. Different Types of Topical Formulations

Formulation	Prescribed number n (%)
Oral	**35(17.67)**
Tablet	35(17.67)
Topical	**163(82.32)**
Ointment	39(23.92)
Cream	68(41.71)
Lotion	48(29.44)
Paste	8(4.90)

Table 3. Steroid-Containing Topical Formulations Fixed Dosage Comnations (FDCs)

Topical steroid	Salicylic acid	Clotrimazole	Calcipotriol	Fusidic acid	Total
Clobetasol	34	0	5	1	40
Betamethasone	0	8	0	11	19
Mometasone	0	0	0	2	2
Hydrocortisone	0	0	0	2	2
Total					63

Table 4. Cost Analysis of the Research Participants Prescription

Cost of Variable	Result (INR)	P value*
1. Total cost/prescription (Mean ± SD)	640.00±397.03	
2. Corticosteroids/prescription (Mean ± SD)	135.18±88.07	<0.0001
3. Concomitant medicine cost/prescription (Mean ± SD)	504.65±411.15	
* P value < 0.05, that is, statistically significant		

Table 5. Cost of Corticosteroids by Subgroup Analysis

Type of prescription	1- Corticosteroids (N=142)	2- Corticosteroids (N=25)	3- Corticosteroids (N=2)
Corticosteroids /prescription Cost in INR (Mean ± SD)	118.73 ± 77.70	226.20 ± 92.34	165.00±0.0
Concomitant medicine cost/prescription **Cost in INR (Mean ± SD)**	531.36 ± 424.42	383.08 ± 305.51	128 ±0.0
P value	**<0.0001**	0.020	-

P value < 0.05 for 1&2 corticosteroids/prescription, that is, statistically significant

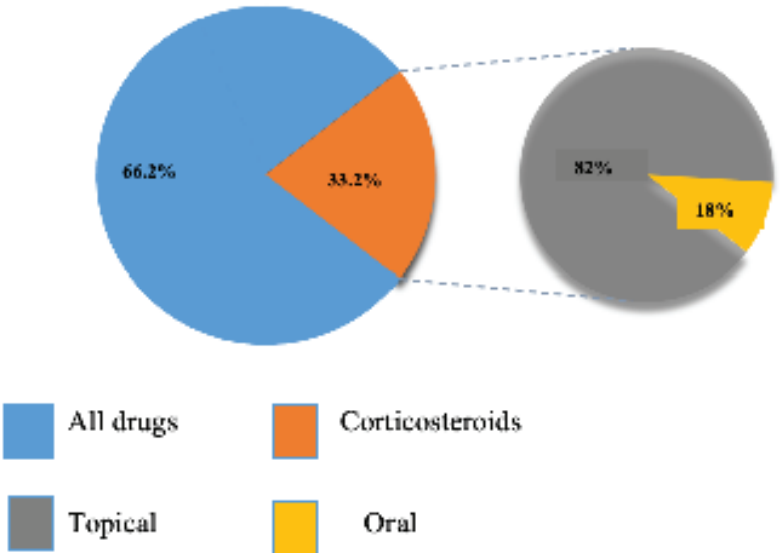

Figure 1. Frequency of Corticosteroid Prescribing

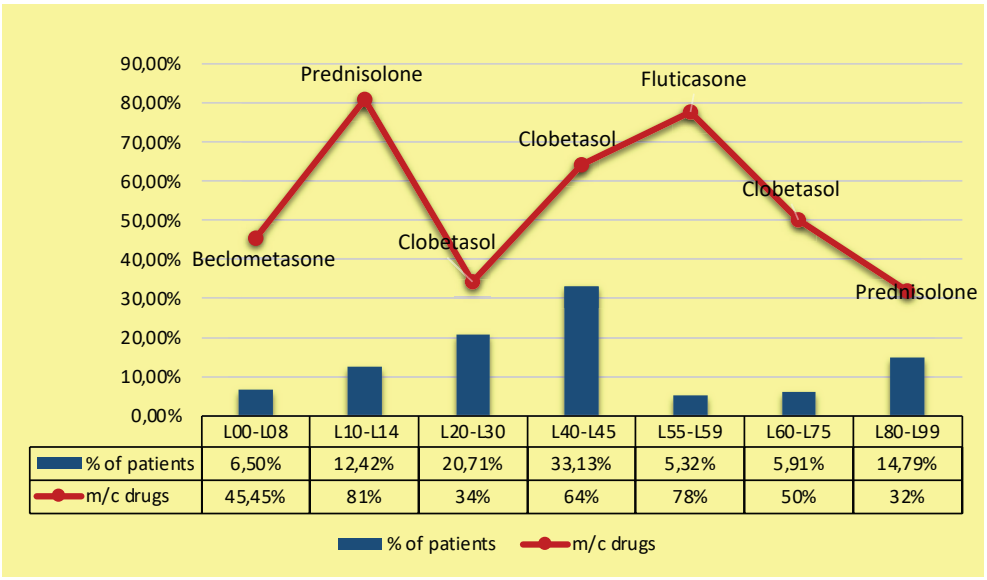

Figure 2. Patient Distribution Based on Diagnosis with the Most Widely Used Corticosteroids Indicated.

- L00-L08 – Infectious disease (Pyoderma ,candidiasis, scabies, herpes zoster)
- L10-L14 – Bullous disorder (pemphigus)
- L20-L30 – Dermatitis and eczema (prurigo, pityriasis alba)
- L40-L45 – Papulosquamous disease (Psoriasis and lichen planus)
- L55-L59 – Radiation related disorder (PMLE)
- L60-L75 – Skin appendages disease (Acne hair loss, alopecia areata,keloid)
- L80-L99 – Other (pigmentation disorder, SLE,insect bite, nutritional deficiency)

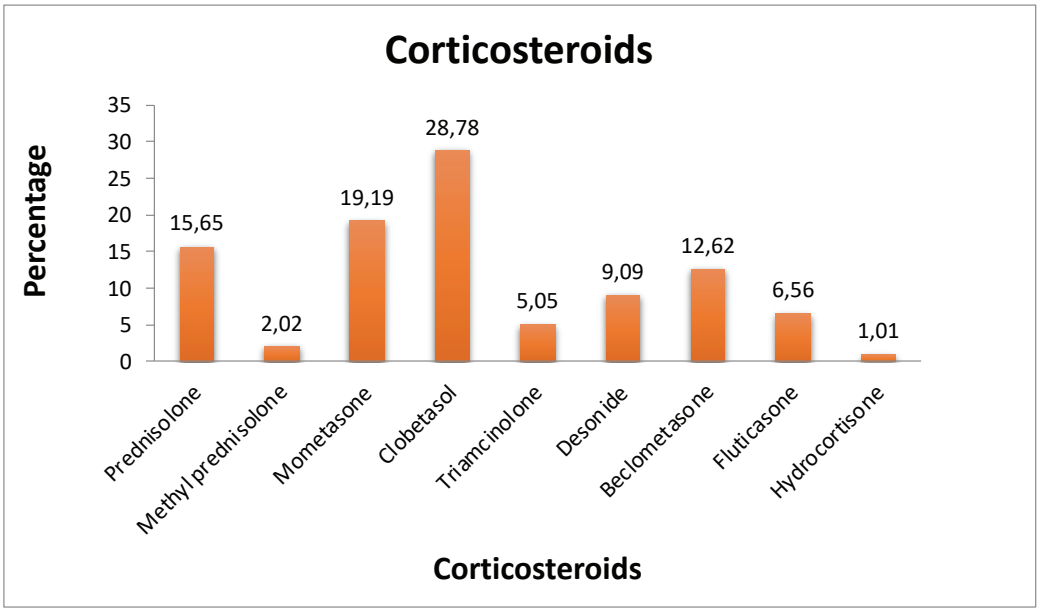

Figure 3. Pattern of Corticosteroid Prescription

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Modeling Hyperglycemia Induction Variants In Mice as Preclinical Test Animals

Setiyo Budi Santoso[1,2]*, Widarika Santi Hapsari[1,2], Deksa Yudha Syach Putra[1]

[1]Department of Pharmacy, Faculty of Health Sciences, Universitas Muhammadiyah Magelang, Indonesia
[2]Collaboration for Pharmacology and Clinical Pharmacy Studies, Universitas Muhammadiyah Magelang, Indonesia

Abstract

Inducing hyperglycemia in animal models is crucial for preclinical research on antidiabetic drug development, especially when genetically diabetic test animals are unavailable. Various methods have been employed to elevate the glycemic levels in test animals. Despite the common use of alloxan monohydrate, streptozotocin, and dextrose monohydrate to induce hyperglycemia in animal models, their comparative effects on glycemic control and pancreatic histopathology remain insufficiently explored. Specifically, the extent of pancreatic impairment induced by these agents, particularly in stable hyperglycemic conditions. This study aims to evaluate and compare the effectiveness of these three agents in inducing hyperglycemia in mice, focusing on their impact on pancreatic histology, in order to identify the most suitable agent for modeling type 2 diabetes based on glycemic stability and minimal pancreatic impairment. Our protocol involved dividing the mice into six groups of five each with a control group. Mice in Groups A and D were exposed to alloxan monohydrate 0.12 mg/gram body weight, Groups B and E to streptozotocin 0.05 mg/gram body weight, and Groups C and F to dextrose monohydrate 6 mg/gram body weight, inducing hyperglycemia for nine days following a seven-day acclimatization period. Pancreatic histopathological examination included assessments of cytoplasmic vacuolization, fat infiltration, and islet deformation. The study found that alloxan monohydrate was more effective than dextrose monohydrate and streptozotocin in inducing and maintaining hyperglycemic stability in mice. Histopathological analysis showed that dextrose monohydrate and streptozotocin posed a lower risk of pancreatic impairment, while alloxan led to noticeable islet deformation and cytoplasmic vacuolization. Our findings suggest that dextrose monohydrate and streptozotocin are preferable for modeling type 2 diabetes due to their stability and relatively mild effects on pancreatic histology.

Keywords: Animal Models; Alloxan Monohydrate; Dextrose Monohydrate; Streptozotocin; Pancreatic Histopathology

Corresponding author: Setio Budi Santoso. Department of Pharmacy, Faculty of Health Sciences, Universitas Muhammadiyah Magelang, Indonesia. Email: sb@unimma.ac.id
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Introduction

Diabetes is now the world's most significant health issue[1,2], and is ruled by hyperglycemia[3,4]. Persistently high glycemic levels may signify an insulin deficiency brought on by the death of pancreatic beta cells, a reduction in glucose receptor sensitivity, or the degradation of tissue receptors[4,5], among other serious implications[6].

Throughout the preclinical stage of developing an anti-diabetic drug, test animals with diabetic pathological characteristics should be readily available[7,8,9]. Mice are among the alternative study animals employed in laboratories[10,11,12], because of their ease of handling[13], excellent adaptability, and physiological similarities to humans[14]. In such studies, diabetic mouse models such as Akita mice, NOD-mice, and Ob-mice are typically employed[15].

To the genetically diabetic test animals is unavailable, alloxan monohydrate and streptozotocin are regularly employed to induce diabetes in mice[15,16]. Alloxan, a toxic glucose analogue, targets pancreatic beta cells via the GLUT2 transporter, generating reactive oxygen species (ROS) that cause oxidative stress and necrosis, impairing insulin secretion[17]. Initially, alloxan induces a transient hypoglycemic phase due to brief insulin stimulation before extensive beta-cell damage occurs[17,18]. In contrast, streptozotocin alkylates DNA in beta cells, inducing stable diabetes through DNA fragmentation, ROS production, and depletion of NAD+ and ATP, leading to irreversible beta-cell damage[19,20].

As demonstrated in prior research, alloxan monohydrate induction for one day increased glycemic levels to 127 mg/dL[21], and induction for three or more days increased it to 164-270 mg/dL[22, 23]. Meanwhile, three days of streptozotocin induction increased the glycemic level to 137 – 273 mg/dL[6,24,25], whereas seven days of dextrose monohydrate induction resulted in a glycemic index of 148 – 155 mg/dL[8,9].

Despite the common use of alloxan monohydrate, streptozotocin, and dextrose monohydrate to induce hyperglycemia in animal models, their comparative effects on glycemic control and pancreatic histopathology remain insufficiently explored. Specifically, the extent of pancreatic impairment induced by these agents, particularly in stable hyperglycemic conditions. This study aims to evaluate and compare the effectiveness of these three agents in inducing hyperglycemia in mice, focusing on their impact on pancreatic histology, in order to identify the most suitable agent for modeling type 2 diabetes based on glycemic stability and minimal pancreatic impairment.

Methods

Materials and equipment

Hyperglycemia-inducing preparations included alloxan monohydrate (Sigma-Aldrich). Louis, MO), streptozotocin (Sigma-Aldrich, St. Louis, USA) and 40% dextrose monohydrate (Otsuka, Malang, Indonesia). Metformin (Dexa Medica Palembang, Indonesia) and Na-CMC (Dai-ichi Kogyo Seiyaku, Kyoto, Japan) were used in the intervention preparations. The induction preparation solvent was citrate buffer (pH 4.5). A glucose strip package and glucometer (easytouch) were used to measure the glycemic index. Consumable supporting protocols included handscoons, 1 ml and 5 ml syringes, blood lancets, and aquadests. Supporting instruments for the protocols include analytical scales, beaker glass, mouse cages, markers, mortars, stampers, and oral probes.

Ethical clearance and animal

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Ethics Committee Ethics of Universitas Gadjah Mada's Faculty of Medicine approved the study protocols. Our study involved 36 male mice of the Balb/c strain with a weight range of 25-30 grammes and gestation period of 2-3 months. All mice were obtained from the Pharmacy Laboratory of Gadjah Mada University, Yogyakarta, Indonesia.

Diabetic-Induced Assay and Evaluation

A total of 36 mice were divided into six groups of five primary test animals and one reserve animal. Following a seven-day acclimatisation period[12], all test groups underwent a nine-day hyperglycemia modelling induction period, followed by a five-day intervention period[11].

To induce hyperglycemia, alloxan 0.12 mg/gram body weight (BW) was administered intraperitoneally in groups A and D, streptozotocin 0.05 mg/gram BW intraperitoneally in groups B and E, and dextrose monohydrate 6 mg/gram BW orally in groups C and F. The induction period lasted nine days in a row[12]. Following hyperglycemia in all subjects, groups A, B, and C were treated with 0.065 g/g BW metformin orally, whereas groups D, E, and F were treated with Na CMC orally (placebo). Indeed, dextrose monohydrate was induced in groups C and F throughout the intervention period[12]. At the end of the acclimatization period, the glycemic index of all mice was measured for the baseline study, then again on the ninth day to evaluate the achievement of hyperglycemia modeling, and on the fourteenth day to demonstrate the stability of the glycemic index following metformin intervention[11].

Histopathology assessment

For pancreatic histopathology assessment, the mice were sacrificed by neck dislocation, and the pancreas was removed and prepared in 10% formalin for histological examination (Bio-Optica). Hematoxylin Eosin (HE) staining was used to prepare and interpret the preparations at the Anatomy and Pathology Laboratory, Faculty of Medicine, Gadjah Mada University. The preparations were examined with an Olympus CX 33 microscope (magnifications of 40x, 100x, and 400x), shot with a SIGMA Full-HD Microscope Camera, and processed with ToupLite for Windows x64 version 2.1.17118.20200518. Pancreatic histopathological examination features included cytoplasmic vacuolization, fat infiltration, and islet deformation, with impairment scales of 0 (none), 1 (mild), 2 (moderate), and 3 (severe)[26].

Results and Discussion

Stability of Glycemic Index Performance

Throughout the nine-day experiment, both groups of alloxan-induced mice demonstrated glycemic indices of 479 mg/dL (Group A) and 363 mg/dL (Group D). In response to the induction of hyperglycemia, Group A, which received a five-day metformin intervention, exhibited a noticeable decrease in glycemic index (333.6 mg/dL). Conversely, Group D, serving as the negative control, exhibited a continued upward trend, reaching a glycemic index of 428 mg/dL (Figure 1).

Similarly, over the nine-day period, both sets of streptozotocin-induced mice showed initial glycemic indices of 181 mg/dL (Group B) and 140 mg/dL (Group E). Following the induction of hyperglycemia, Group B, treated with metformin for five days, displayed a significant reduction in glycemic index to 165 mg/dL. In contrast, Group E, the negative control, exhibited an ongoing elevation, reaching a glycemic index of 245 mg/dL (Figure 2).

In the case of mice induced with dextrose monohydrate, the nine-day period showed initial glycemic indices of 217 mg/dL

(Group C) and 185 mg/dL (Group F). Post-hyperglycemia induction, Group C, undergoing a five-day metformin treatment, demonstrated a notable decrease in glycemic index (176 mg/dL). Meanwhile, Group F, functioning as the negative control, displayed an upward trend, ending at 197 mg/dL (Figure 3).

Based on the main results (Figure 4), the most substantial elevation in glycemic levels throughout the successive induction phase manifested in the following sequence: alloxan (371%), dextrose monohydrate (49%), and streptozotocin (26%). Following the conclusion of the intervention period, the percentage surge in glycemic levels exhibited a reduction across all three models: alloxan (228%), dextrose (21%), and streptozotocin (15%) (Table 1).

The Pancreatic Histopathology Assesment

Based on the histopathological findings, evident damage is observed in pancreatic cells across all three inductions. The escalation in hyperglycemia corresponds to the grading of pancreatic cell impairment. Notably, the control group, devoid of any intervention, exhibited more pronounced damage compared to the groups undergoing metformin intervention (Figure 5).

In the modeling induction accompanied by metformin intervention, the alloxan group exhibited a moderate degree of damage in the parameters of cytoplasmic vacuolation and alterations in islet shape. In contrast, the streptozotocin and dextrose groups demonstrated mild damage in both of these parameters. Notably, there were no indications of lipid infiltration damage in any of the groups subjected to metformin intervention (Table 2).

Conversely, in the modeling induction without metformin intervention (control groups), all three induction model groups manifested severe damage in the parameters of cytoplasmic vacuolation and changes in islet shape (Table 2). In relation to the parameter of lipid infiltration, only the alloxan modeling group displayed mild damage, while the remaining groups showed no discernible signs of damage (Figure 6).

This study compares the effects of alloxan monohydrate, streptozotocin, and dextrose monohydrate on glycemic stability and pancreatic impairment. Empirical data on hyperglycemia-inducing agents are provided to guide researchers in selecting appropriate agents for modeling type 2 diabetes, considering stability and relative impacts on pancreatic histology.

Our findings identify alloxan monohydrate as the most reliable hyperglycemic agent, showing a sustained 228% increase in glycemic levels. Interestingly, dextrose monohydrate demonstrates a higher stability index (21%) compared to streptozotocin (15%). These results expand on previous studies, which mainly documented glycemic elevation ranges for alloxan (164–270 mg/dL)[22,23], streptozotocin (136.8–273.5 mg/dL)[6,24,25], and dextrose monohydrate (148.25–155 mg/dL)[8,9,27].

A significant new discovery in our study points to the high stability index of alloxan monohydrate following metformin intervention is associated with prolonged pancreatic damage, marked by cytoplasmic vacuolation and structural alterations in islet cells. The destructive action of alloxan monohydrate on the pancreas[28,29] leads to reduced insulin levels[4], as it infiltrates beta cells through the GLUT2 transporter, inducing necrosis through reactive oxygen species (ROS) production, generating hydrogen peroxide and hydroxyl radicals[4,16,30].

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Similar to alloxan monohydrate, streptozotocin targets beta cells via GLUT2 transporter[4], leading to necrosis[31], insulin deficiency and hyperglycemia[30,32]. By alkylating DNA in beta cells, it induces DNA fragmentation, ROS production, and NAD^+/ATP depletion, resulting in irreversible pancreatic damage[19,20]. In contrast, dextrose monohydrate exacerbates hyperglycemia[33], which may lead to pancreatic beta cell damage and decreased insulin secretion due to the production of free radicals and reduced hexokinase activity while also compensatory energy sources[8,9].

Our histopathological evaluation highlights cellular responses, particularly cytoplasmic vacuolation, islet shape alterations, and lipid infiltration[26]. The alloxan control group showed the highest vacuolation severity (score 3), indicating major cellular damage[34]. Additionally, islet shape alterations scored 3, suggesting potential impairment in glucose metabolism[35,36,37]. Metformin-treated groups showed no lipid infiltration, suggesting a protective effect[38,39] possibly due to facilitating the regeneration of impaired Langerhans cells[40,41]. According to our findings, as in the majority of pancreatic cells[42], necrotic beta cells disrupt insulin production, leading to hyperglycemia[32], and occurs alongside the depletion of the islets of Langerhans[43].

Conclusion

The study found that alloxan monohydrate was more effective than dextrose monohydrate and streptozotocin in inducing and maintaining hyperglycemic stability in mice. Histopathological analysis showed that dextrose monohydrate and streptozotocin posed a lower risk of pancreatic impairment, while alloxan led to noticeable islet deformation and cytoplasmic vacuolization. Our findings suggest that dextrose monohydrate and streptozotocin are preferable for modeling type 2 diabetes due to their stability and relatively mild effects on pancreatic histology.

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Conflict of Interest

None declared.

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Table 1. Percentage increase in glycemic levels in mice induced with alloxan monohydrate (A), streptozotocin (B), and dextrose monohydrate (C) over nine days, along with subsequent stability after a five-day metformin intervention.

Treatment Group	Induction Variant Glycemic	Index (Percentage Increase)		
		Baseline	Day-9	Day-14
A	Alloxan Monohydrate	102±12 (-)	479±75 (371%)	334±141 (228%)
B	Streptozocotin	144±20 (-)	181±41 (26%)	165±37 (15%)
C	Dekstrosa Monohydrat	145±32 (-)	217±40 (49%)	176±13 (21%)

Table 2. Histopathological evaluation of pancreatic tissue parameters in representative test animal treatment groups.

Treatment	Histopathological Evaluation Parameters		
	Cytoplasmic Vacuolation	Islet Shape Changes	Lipid Infiltration
Modeling Induction with Metformin Intervention			
Alloxan Monohydrate **(a)**	2	2	0
Streptozocotin **(b)**	1	1	0
Dekstrose Monohydrat **(c)**	1	1	0
Modeling Induction (Control)			
Alloxan Monohydrate **(d)**	3	3	1
Streptozocotin **(e)**	3	3	0
Dekstrose Monohydrat **(f)**	3	3	0

Value Interpretation: Normal Morphology (0), Mild Impairment (1), Moderate Impairment (2), Severe Impairment (3).

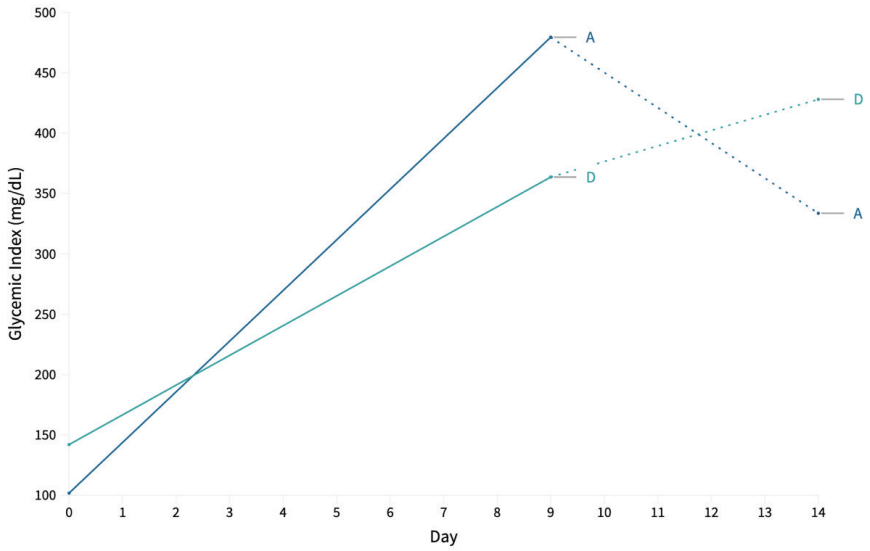

Figure 1. Measurement results of glycemic index in alloxan monohydrate-induced mice within the metformin intervention group (Group A) and the Control Group (Group D).

Solid lines depict the glycemic achievement progression after the induction phase (day-9), and dashed lines represent the stability of glycemic index attainment after the five-day intervention (day-14).

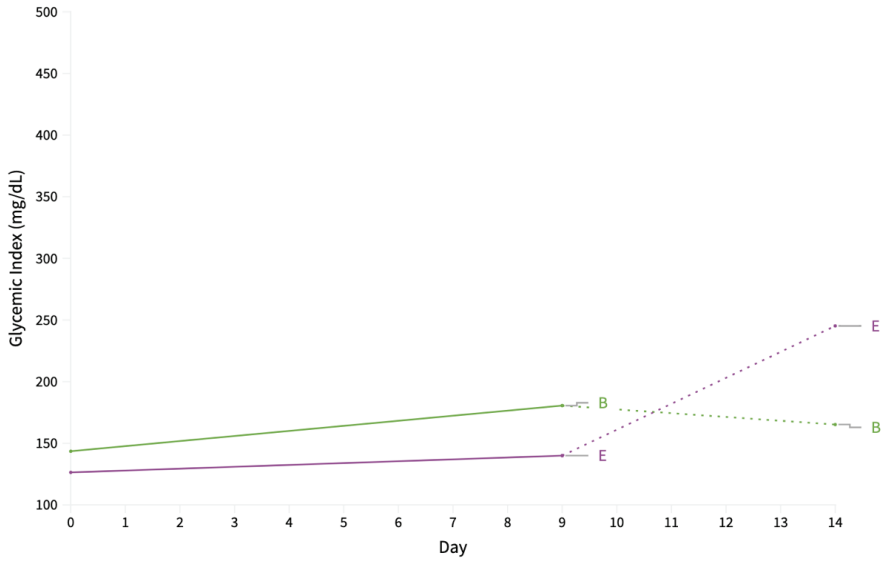

Figure 2. Measurement results of glycemic index in streptozotocin-induced mice within the metformin intervention group (Group B) and the control group (Group E).

Solid lines depict the glycemic achievement progression after the induction phase (day-9), and dashed lines represent the stability of glycemic index attainment after the five-day intervention (day-14).

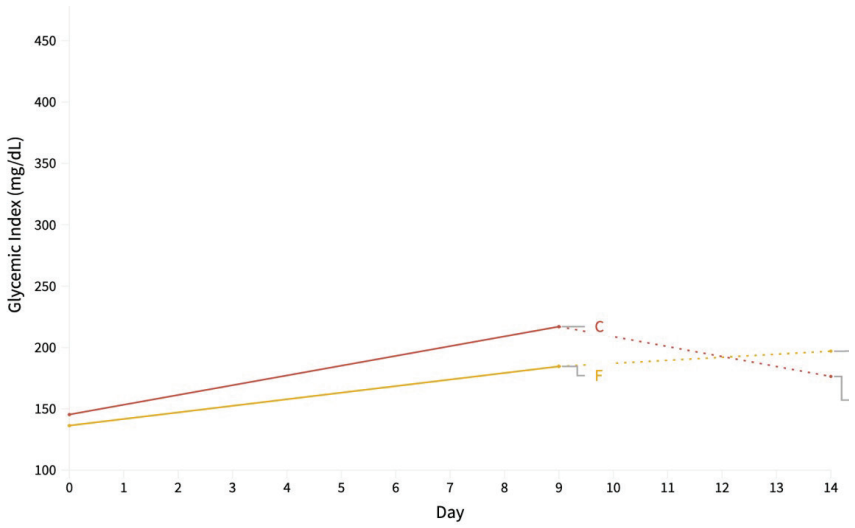

Figure 3. Measurement results of glycemic index in dextrose monohydrate-induced mice within the metformin intervention group (Group C) and the control group (Group F).

Solid lines depict the glycemic achievement progression after the induction phase (day-9), and dashed lines represent the stability of glycemic index attainment after the five-day intervention (day-14).

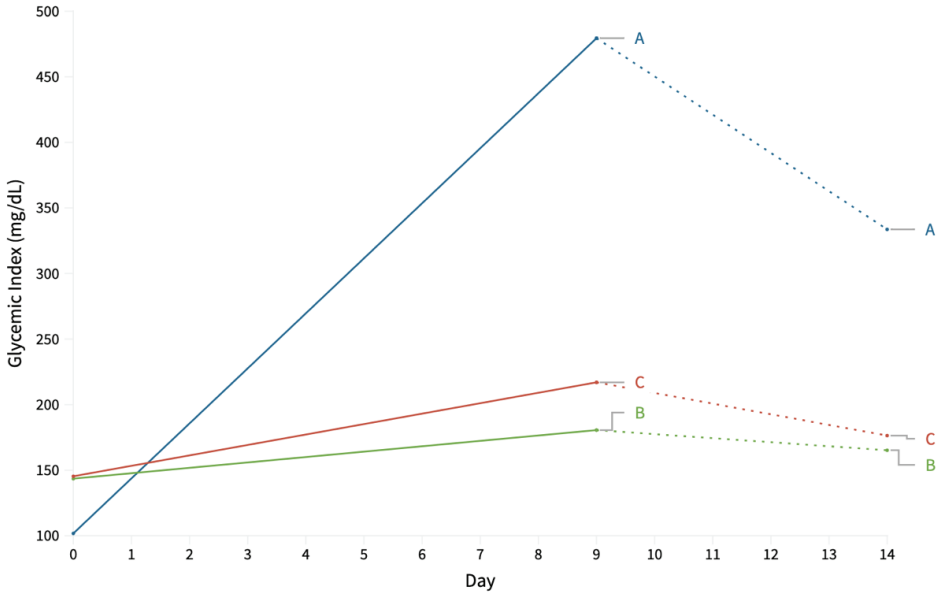

Figure 4. Glycemic index measurements in mice encompassed three distinct induction modalities: alloxan monohydrate (A), streptozotocin (B), and dextrose monohydrate (C).

Continuous lines illustrate the progression of glycemic attainment post the induction phase (day 9), while dashed lines delineate the stability of glycemic index achievement subsequent to the five-day intervention (day 14).

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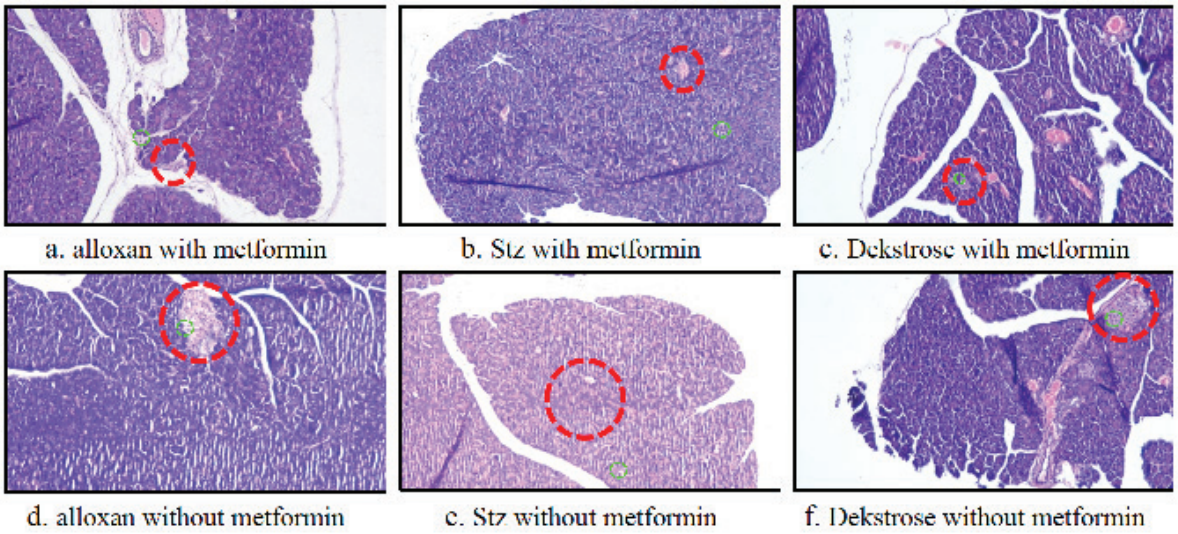

Figure 5. Histopathological examination of pancreatic tissue (100x magnification) in representative samples from six induction variants: alloxan (a and d), streptozotocin (b and e), dextrose (c and f).

Groups a, b, and c underwent metformin intervention, whereas groups d, e, and f were utilized as controls. Islet shape alterations are denoted by red circles, and cytoplasmic vacuolation is indicated by green circles.

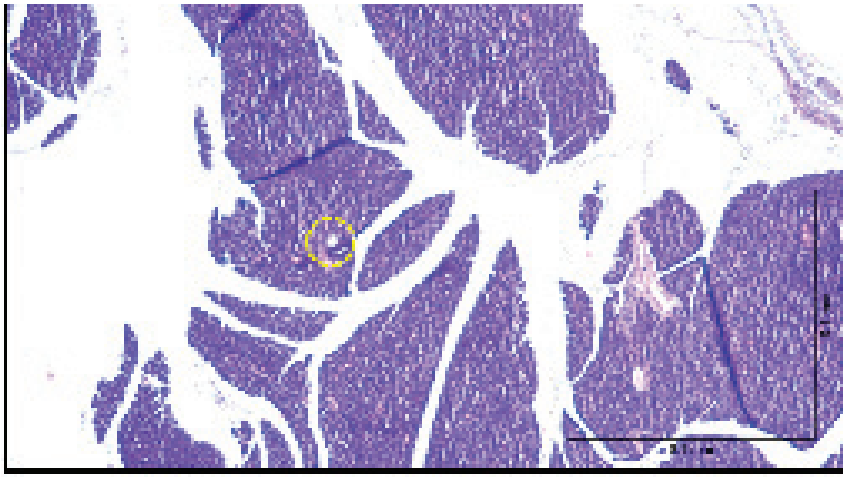

Figure 6. Histopathological examination of pancreatic tissue (40x Magnification) in representative samples of test animals subjected to alloxan induction as the control.

The area of mild lipid infiltration is demarcated by the yellow circle.

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Adverse Events of Bedaquiline Drug Use in the Treatment of Multidrug-Resistant Tuberculosis (MDR TB) Patients: A Review

Nabilah A. Nihlah,[1] Bilqis N. Almattin,[1] Imam A. Wicaksono[2]

[1]Pharmacist Professional Study Program, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia

Abstract

Adverse Drug Reaction (ADR) is any unfavorable and unexpected drug response in patients dosed for prevention, diagnosis, or therapy. Tuberculosis is a contagious infectious disease caused by the bacterium Mycobacterium tuberculosis. Multi-drug resistance Tuberculosis (MDR TB) is caused by bacteria that are resistant to the two most powerful first-line anti-TB drugs - isoniazid and rifampicin; cases of resistance to both drugs result in worse treatment outcomes, longer treatment duration, high costs, and various other complications. All medications used to treat MDR TB patients have the potential to cause mild, moderate, and severe side effects, especially Bedaquiline. This article will explain information on drug side effects that occur in patients treated with MDR TB and Bedaquiline. The data was collected and discussed from primary journals through Google Scholar and PubMed online databases. Bedaquiline has the potential to cause side effects such as QT interval prolongation or irregular heart rhythm, cardiac arrhythmia, gastrointestinal disorders, joint and muscle pain, hearing loss, acne, and chest pain. Therefore, treatment of MDR TB with Bedaquiline requires monitoring to ensure patient compliance and early detection of possible side effects to ensure the safety and effectiveness of treatment.

Keywords: Adverse Drug Reaction, tuberculosis, MDR TB, bedaquiline

Corresponding author: Nabilah Azka Nihlah. Pharmacist Professional Study Program, Faculty of Pharmacy, Padjadjaran University, West Java, Indonesia. Email: nabilah18005@mail.unpad.ac.id
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Introduction

Tuberculosis (TB) is an infectious disease usually caused by Mycobacterium tuberculosis. TB typically affects the lungs (pulmonary TB) but can also affect other body parts such as the central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, and bones and joints. Standard treatment for patient TB is a 6-9 month regimen with four first-line drugs - isoniazid, rifampicin, ethambutol, and pyrazinamide. Many of the medications used to treat TB, especially second-line drugs, often have substantial toxicity profiles.[1] Backup many medicines are given together due to drug resistance, increasing overall toxicity through drug interactions.

Adverse Drug Reaction (ADR) can generally be classified into two types based on pharmacological effects and predictability. First, ADR type A is an undesirable reaction that can occur in everyone with a therapeutic dose, a pharmacological effect that can be predicted (predictable). The effect is dose-related and easy to overcome. Usually, this type of reaction has been recognized before the drug is released on the market. Secondly, type B ADR is unwanted reactions unrelated to the drug's pharmacological effects, so these reactions cannot be predicted and are not observed during the pharmacological and toxicological screening of the drug before the drug is marketed.[2,3]

Monitoring of adverse drug events is monitoring each patient's response to an undesirable drug, which occurs at the usual dose used in humans for prophylactic, diagnostic, and therapeutic purposes on drugs licensed to be marketed.[4] It is also used to detect or identify ADR as early as possible, especially those that are unrecognized, severe, and infrequent, as well as determine the frequency and incidence of known and newly discovered, prevent the recurrence of adverse drug reactions, and identify drugs or drug interactions that have a high potential to cause ADR.[5]

Based on the electronic platform of the Indonesian Food and Drug Authority data reported in 2021, there was a frequency of ADR in Indonesia with a total reporting of 8,691 cases, of which 4,842 came from reports from health workers and 3,847 from the pharmaceutical industry. Based on the reported data, ten pharmacological subgroups of drugs were suspected of causing ADR from the 2021 health worker report, the largest of which is the Drugs For Treatment Of TB group, followed by the Quinolone Antibacterial group. Of the ten active substances of the most reported ADR cases, there were three active substances reported, which were dominated by drugs for the treatment of TB, namely Bedaquiline (BDQ), Levofloxacin, and Clofazimine.[6]

Meanwhile, based on The Electronic Health Record (EHR) data reported in 2022, there was a frequency of adverse drug reactions in Indonesia with a total reporting of 10,749 cases, of which 6,852 were from health worker reports, and 3,897 were from pharmaceutical industry reports. Where the most reported cases of adverse drug events are suspected to be drugs used in the treatment of TB. From the reports recorded, there are ten active drug substances suspected of causing the most ADR reported in 2022, which are dominated by drugs for the treatment of TB, namely BDQ, Levofloxacin, Clofazimine, Cycloserine, Pyridoxine, Linezolid, and Ethambutol.[7]

Based on the EHR data reported, there is a drug that is thought to cause the most cases of adverse events, namely the drug BDQ,

which has the most reports, namely in 2021, as much as 17% or around 1477 out of 8,691 cases and 2022 as much as 1,353 out of 10,749 cases. Therefore, this journal will provide information on ADR in MDR TB treatment and using BDQ. The main objective of this literature review is to contribute to the scientific understanding of adverse events using BDQ in treating patients with MDR TB.

Methods

All primary data was collected and discussed in primary literature journals through online databases on Google Scholar and PubMed. The search was conducted by combining the keywords "BDQ," "TB-MDR," "Pharmacovigilance TB-MDR," and "Pharmacovigilance TB-MDR BDQ." The primary data sources used included research journals published in national and international journals.

The journals were screened with inclusion criteria of articles related to MDR TB treatment using BDQ and published in 2014-2024, as well as exclusion criteria of repository and review articles. Based on the keywords of this research, the results of searching journal libraries on Google Scholar and PubMed, journal libraries numbering 3,050; 1,273; 1,660; 5,559; 115, and 24 articles for each keyword were obtained.

Results and Discussion

TB is a contagious infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) infection. This *M. tuberculosis* bacteria is a rod-shaped bacteria with acid-resistant properties, also often called Acid Resistant Bacilli. TB is an infectious disease that is the leading cause of death worldwide.[17]

Based on information related to drug side effects that occur in patients with MDR TB patients in the form of depression, nausea, vomiting, dyspepsia, arthralgia, hepatotoxicity, ototoxicity, peripheral neuropathy, electrolyte depletion, renal impairment, hepatic impairment, erythrocytosis, myelosuppression, QT prolongation or irregular heart rhythm, psychiatric/psychiatric disorders, neurology, insomnia, depression, confusion, hearing impairment, digestive disorders, and visual impairment.[8–10]. Information related to drug side effect studies in MDR TB regimens can be seen in Table 1.1.

The goal of TB treatment is one of the most efficient efforts to prevent further spread of *M. tuberculosis* bacteria. The treatment regimen for TB disease is divided into 2 stages, namely the initial/intensive stage, which is treatment given every day for 2 months and aims to reduce the number of germs in the body.

Drugs such as Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), and Ethambutol (E); then proceed to the advanced stage of treatment, which is treatment given every day for 4 months which aims to kill the remaining germs still in the body with drugs such as Isoniazid and Rifampicin.[18]

TB patients are classified based on the results of sensitivity testing to antibiotics used in anti-TB drug therapy regimens. The categories include monoresistant, which refers to resistance to one type of first-line anti-TB drug, and poliresistant, which means resistance to more than one type of first-line anti-TB drug, excluding isoniazid (H) and rifampicin (R) simultaneously, such as resistance to isoniazid and ethambutol. Multidrug-resistant TB (MDR TB) is characterized by resistance to at least both isoniazid (H) and rifampicin (R) simultaneously.

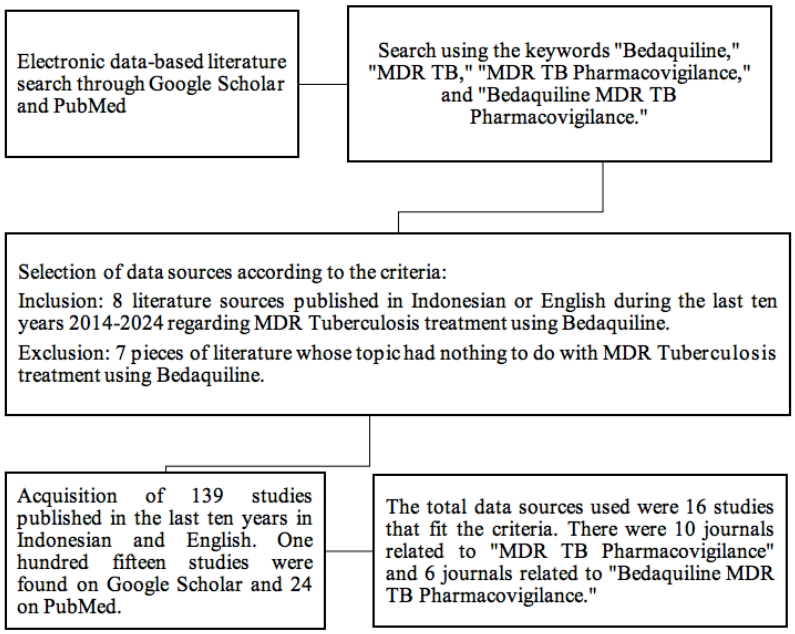

Figure 1. Methods

Extensively drug-resistant TB (XDR TB) refers to MDR TB that is also resistant to one of the fluoroquinolones and one of the second-line injectable drugs (kanamycin, capreomycin, and amikacin). Rifampicin-resistant TB (RR TB) is defined as resistance to rifampicin, confirmed by either genotyping (rapid test) or phenotyping (conventional) methods, with or without resistance to other anti-TB drugs. TB patients with rifampicin resistance have the possibility of developing resistance to other drugs, such as MR TB, PR TB, MDR TB, and XDR TB, that are proven to be resistant to rifampicin.[18]
Intensive Phase : 2 months H - R - Z - E
Advanced Phase : 4 months H - R

Multidrug-Resistant Tuberculosis (MDR TB)
MDR TB is a condition in which a patient has TB disease but has developed resistance to the drugs isoniazid and rifampicin simultaneously with or without resistance to other first-line drugs, both of which are the most effective drugs in TB treatment. There are two regimens for the treatment of MDR TB, namely long-term and short-term therapy regimens.[19]

Patients with cases of resistance to both drugs will have worse treatment outcomes, higher mortality rates, longer treatment duration (about two years), high costs, and various other complications, so the treatment of MDR TB is more complicated than drug-sensitive TB. Therefore, monitoring is needed to ensure that patients undertake treatment well.[17]

MDR TB treatment is started with at least five TB drugs that effective and at least three medications for the remainder of therapy after BDQ is discontinued.[20] Treatment for MDR TB patients generally involves short-term treatment using a combination of 7 drugs given daily for 4-6 months: Bedaquiline (Bdq), Levofloxacin (Lfx), Clofazimine (Cfz), high-dose Isoniazid (H), Pyrazinamide (Z), Ethambutol (E), and Ethionamide (Eto); or a 4-drug combination given daily for 5 months of Levofloxacin (Lfx), Clofazimine (Cfz), Pyrazinamide (Z), and Ethambutol (E); then given long-term treatment with a combination of 5 drugs given daily for 6 months using Bedaquiline (Bdq), Levofloxacin (Lfx), Clofazimine (Cfz) or Cicloserine (Cs), Pyrazinamide (Z);

or can also use a combination of 4 drugs given daily for 14 months, namely Levofloxacin (Lfx), Clofazimine (Cfz) or Cicloserine (Cs), Pyrazinamide (Z).[20]

Intensive Phase
4-6 months Bdq - Lfx - Cfz - H - Z - E - Eto / 5 months Lfx - Cfz - Z - E
Advanced Phase
6 months Bdq - Lfx - Lzd - Cfz or Cs - Z / 14 months Lfx - Lzd - Cfz or Cs - Z

ADRs during MDR TB treatment are more common in male. In addition, there is a high incidence of ADRs in patients with HIV co-infection and those receiving injectable drugs as part of their treatment regimen due to long-term treatment, which can decrease patient adherence.[21] Monitoring the occurrence of drug side effects is very important during MDR TB treatment. All anti-TB drugs used for MDR TB patients can cause mild to severe side effects. Health workers should continuously monitor and immediately act if side effects are found.

Some of the side effects of drugs that are also found in patients treated with MDR TB are strong joint and muscle pain.[22] Studies show that side effects are managed with pharmacological and non-pharmacological interventions. Side effects also do not always lead to temporary or permanent discontinuation of MDR TB treatment, nor do they negatively affect treatment outcomes. This highlights the importance of continuous monitoring and prompt action in the event of adverse events so that treatment can be continued.[23]

MDR TB patients often have comorbidities or additional medical conditions. Some common comorbidities include diabetes, kidney disease, liver disease, HIV/AIDS, and immune disorders. These extra conditions can complicate the treatment of MDR TB and increase the risk of side effects. Therefore, more careful management and personalized therapy is required.[23]

Bedaquiline
Bedaquiline (BDQ) is used in the treatment of MDR TB and is the first new anti-TB drug to be introduced to the market in nearly 50 years. It belongs to the diarylquinoline category and has a novel mechanism of action against *M. tuberculosis*. In Indonesia, BDQ was only registered with the Food and Drug Administration in 2018, and there are limited studies systematically investigating the use of BDQ in MDR TB therapy.[19]

This review reflects some of the prospects and challenges faced using BDQ for TB therapy. One major obstacle is the high cost of the drug, which may limit its accessibility in low- and middle-income countries. In addition, further research is needed to refine the dose and duration of BDQ treatment and identify biomarkers that can predict response to treatment and potential side effects.

On the other hand, BDQ's prospects show promising potential. It is highly effective in treating MDR TB, and there is a possibility of utilizing it in combination with other drugs to improve treatment effectiveness. In addition, ongoing studies are also exploring the potential use of BDQ in addressing other mycobacterium infections, including non-tuberculous mycobacterium lung diseases. These analyses imply that BDQ could have a significant role in global initiatives to fight drug-resistant TB 24. From the search results for reference journals, information on the drug BDQ can be seen in Table 1.2.

BDQ is a diarylquinoline that works by a novel mechanism inhibiting adenosine triphosphate synthesis in bacterial microenvironments, disrupting bacterial energy metabolism. The

use of BDQ occurs as part of a short-term treatment regimen for patients with MDR TB. Such patients receive a combination of seven drugs administered daily over 4-6 months.[25] The application of BDQ in the clinical management of MDR TB has brought encouraging results. Studies have shown that BDQ-containing therapeutic regimens produce positive results in most patients, while its tolerability over prolonged treatment periods is generally satisfactory.[24]

BDQ Therapy Regimen / Interval

Treatment for MDR TB involves the use of more potent drug combinations and a longer duration of treatment compared to standard TB therapy. Typically, MDR TB therapy involves administering drugs such as fluoroquinolones, aminoglycosides, and cycloserine, as well as other drugs such as linezolid, clofazimine, and BDQ. The duration of MDR TB treatment is generally longer, ranging from 18 to 24 months, and can be adjusted depending on the patient's response to treatment. Close supervision and regular monitoring are required in MDR TB therapy to ensure patient adherence to treatment and detect possible adverse effects.[26]

The use of BDQ to treat MDR TB provides good synergy when combined with other anti-TB antibiotics. Some combinations that have been tested for efficacy include:

1. BDQ and delamanid (Dlm): shown promising results for MDR/XDR TB patients, but be aware of the possibility of higher cardiac toxicity.
2. BDQ and pyrazinamide: shown to suppress bioenergy and deplete the energy reserves of TB cells, thereby reducing the burden of infection.
3. BDQ and cephalosporins enhanced BDQ's bactericidal activity against *M. tuberculosis*.
4. BDQ and pretomanid have a strong synergistic effect on MDR TB.
5. The combination of BDQ, pretomanid, and linezolid showed high culture conversion rates and low relapse rates for extensively resistant TB.[24]

Pharmacodynamics / Mechanism of Action of Bedaquiline

BDQ is the latest drug the World Health Organization (WHO) recommended for treating MDR TB in 2013. BDQ works as an ATP synthase inhibitor that affects microbial membranes and became the first drug to receive the Food and Drug Administration's (FDA) approval for TB treatment after more than 40 years. BDQ is integrated into combination therapy for MDR TB patients who do not respond to standard treatment.[26]

BDQ is an anti-TB drug that operates by inhibiting ATP synthase, an enzyme crucial in microbial energy metabolism. In this way, BDQ interferes with the energy production process required by TB bacteria for survival. Because of this, BDQ is an efficient drug in treating TB that is unresponsive to standard treatment. Moreover, BDQ also has lipophilic properties that allow it to penetrate the cell membrane of TB bacteria more efficiently. Combining these two mechanisms of action makes BDQ the first choice in treating MDR TB.[36]

BDQ utilizes its antimicrobial activity by inhibiting the synthesis of ATP in *M. tuberculosis*. The drug targets the central region of the enzyme's c subunit, disrupting the energy production process and arresting the micro-development of the bacteria, ultimately leading to death. This unique mechanism of action makes BBQ a promising addition to the existing arsenal of anti-TB agents, especially in regions where MDR TB is standard.[25]

Pharmacokinetics of Bedaquiline

BDQ was administered orally and underwent rapid absorption, reaching a peak time to maximum plasma concentration (Tmax) within 4 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased with the BDQ dose, showing a linear pharmacokinetic profile up to 700 mg. BDQ has a high plasma protein level (>99%) and is metabolized primarily in the liver via the enzyme CYP3A4. The major metabolite of BDQ, M2, also has activity against *M. tuberculosis*. BDQ and its metabolites are eliminated mainly through feces, with small amounts excreted through urine. The pharmacokinetics of BDQ are not influenced by factors such as age, gender, or race.[25]

BDQ is metabolized via cytochrome P450 enzyme isoenzyme 3A4, which catalyzes N-demethylation to form metabolite M2, whose activity is approximately three to six times that of BDQ. Although M2 circulates at concentrations 10 times lower than BDQ, the potential risk of toxicity makes it a cause for concern. Preclinical trials have shown that M2 has a more substantial phospholipidosis-inducing effect and is more cytotoxic than BDQ. M2 concentrations were also associated with QT interval prolongation then undergoes an N-demethylation process, most likely executed by the same enzyme.

Although excretion of BDQ through the kidneys is considered less significant, excretion through the feces does occur. BDQ and M2 have high protein binding rates, exceeding 99.9% and 99.7%, respectively. The safety of BDQ use involves several aspects, including its ability to cause moderate QT interval prolongation and an unexplained increase in mortality observed in one randomized phase II trial. The approved BDQ use regimen includes a 2-week loading phase at a dose of 400 mg daily, followed by a dose of 200 mg three times a week until week 24.[27]

Information related to BDQ's ADME profile can be described as follows:

- Absorption: oral ingestion, increases when taken with food, aiming to optimize efficiency and absorption. The time to reach the peak concentration in plasma is about 4-6 hours.
- Distribution: high degree of distribution into tissues and bind to blood transport proteins. The distribution of BDQ within the body allows exploitation of its bactericidal activity against *M. tuberculosis*.
- Metabolism: processes in the liver, mainly through cytochrome P450 enzymes, resulting in the formation of metabolites.
- Excretion: excreted via feces. The drug is eliminated slowly from the body, with a final elimination half-life of about 5.5 months.[24]

Side effects of Bedaquiline

BDQ has potentially severe side effects, such as QT interval prolongation and cardiac arrhythmias. The QT interval measures the time for blood to be pumped by the heart, and its prolongation can lead to dangerous heart rhythm disturbances. In addition, BDQ may also cause nausea, vomiting, headache, as well as elevated liver enzymes. Due to these risks, BDQ requires close monitoring and regular examination of patients to detect symptoms of side effects.[26]

Based on data from the Indonesian Ministry of Health, BDQ has the potential to cause several side effects, such as joint pain and muscle pain, joint and muscle inflammation, liver function disorders, gastrointestinal complaints, and cardiac disorders such as QT interval prolongation, irregular and dangerous

heartbeats (ventricular arrhythmias).[20]

BDQ can also cause liver function-related side effects; it also has dangerous drug interactions with CYP3A4 inductors and inhibitors, as well as other QT interval-prolonging drugs. In clinical trials, the most common side effects associated with BDQ were nausea, limb pain, bilateral hearing loss, acne, and chest pain.[25]

The use of BDQ with other drugs needs to be done with caution due to potential interactions and side effects. Besides the risk of side effects and drug interactions related to BDQ, there are other essential considerations in its use:

1. BDQ should only be used in combination, as monotherapy can lead to bacterial resistance.
2. Patients with a history of heart disease or who are taking QT-prolonging drugs need to be cautious.
3. Hepatitis patients need extra monitoring because BDQ runs on the liver.
4. There is limited data on the safety and benefits of BDQ for HIV patients.
5. Pregnant and breastfeeding women need special consideration as safety data is limited.
6. A minimum of 6 months and more of BDQ therapy is needed for optimal results, with regular monitoring of liver function, electrolytes, and ECG.

Fatal serious adverse events are reported through SITB by the pharmacy or clinical pharmacy staff or ADR officer-in-charge as soon as possible within 24 hours of the occurrence, while non-fatal serious adverse events are reported no later than 15 days after the occurrence. SITB will inform directly to all interested parties who have access. Meanwhile, non-serious ADRs can be reported through SITB or the EHR page as soon as possible since they are known to have occurred.[18]

Providing information on the occurrence of ADR is the duty of pharmacists, as well as preventing and reducing the incidence of ADR, especially in TB and MDR TB patients who require high compliance by providing information on the correct use of drugs, namely:

1. Take medicine according to the schedule and doctor's recommendations.
2. Avoid drinking alcohol and smoking while taking MDR TB drugs.
3. Get enough rest and avoid overexertion.
4. Eat a balanced and nutritious diet.
5. Drink plenty of water.
6. Manage your intake of salt, sugar, and fat.
7. Control vital signs regularly. Low blood pressure can aggravate nausea and vomiting.
8. Additional vitamins are recommended to treat anemia.
9. Avoid excessive stress, as it can worsen the body's condition.
10. Communicate with your doctor is essential to address side effects and maximize treatment. Compliance is key.

The use of BDQ in the treatment of MDR TB has good potential to improve treatment success rates, but it is essential to be aware of the possibility of drug interactions and side effects in patients. Therefore, it is necessary to monitor and report any adverse drug events, whether mild, moderate, or severe. Through close monitoring, it is hoped that treatment can run safely and effectively according to the goals of MDR TB treatment.

Pharmacists have a role in detecting ADR in patients, recording and exploring data related to ADR, conducting tertiary literature studies, matching ADR data with suspected drug data, searching for information on other reports,

analyzing causality using the Naranjo scale, formulating recommendations to clinicians, making reports, and reporting ADR to the ADR reporting system. This shows that ADR reporting by pharmacists is an essential part of the spontaneous reporting system.[28]

ADR can usually be identified when pharmacists visit patients or provide drug information to counseling patients and others. Each reported ADR will then be observed or collected related to information on drug use history, disease history, possible drugs that cause ADR, and Naranjo scale assessment. ADR reporting by healthcare professionals is done as soon as possible spontaneously when an adverse event occurs.

The minimum types of information that must be submitted in ADR reports are patient-related information in the form of patient initials, age and date and year of birth, gender, and weight; ADR information in the form of ADR description, date of ADR occurrence, date of ADR reported, laboratory test results or other appropriate tests if available, other relevant patient information/history, adverse event outcome; information related to the suspected drug in the form of drug name (active substance and trade name), dose, frequency, and route of drug administration, date of drug start, an indication of drug use.[29]

Information on whether the ADR improved after the drug was stopped or the dose was reduced, batch number, information on whether the ADR occurred when the drug was re-administered, drugs taken with the suspected drug and the date of starting to take the drug; and reporter information in the form of name, address, telephone number, and occupation/profession.[29]

ADR reporting allows for causality assessment of adverse drug events. The causality assessment is the result of evaluating the complaints or clinical manifestations experienced by patients related to drug use using the Naranjo scale. The Naranjo scale is a scale developed to assist in the standardization of causality assessment for adverse drug events.
Probability is given through a particular score, may occur, is not specific to happen, or is doubtful. This naranjo scale can only be filled out by health professionals 30. Drug side effect categories based on the Naranjo scale can be divided into Highly probable categories with scale values ≥ 9, Probable is 5-8, Possible categories is 1-4, and Doubtful is 0.[31]

It is recommended that suspected ADR be reported to determine the incidence, so that there is no need to worry that ADR are minor or unimportant. At the same time, the current management and extraction of information related to side effects that occur in patients is still incomplete. There is a need for SOPs related to receiving adverse event reports from patients. Serious adverse drug events are those that can cause death, are life-threatening, result in extended or unexpected hospitalization, cause congenital abnormalities, lead to disability, and require medical or surgical intervention to prevent a worse condition.

The results of this article review are expected to provide information on the side effects of BDQ in MDR TB patients, as well as provide recommendations for monitoring patients undergoing treatment with the drug to help improve the quality of MDR TB treatment and reduce the risk of side effects caused by the use of BDQ. In addition, with a better understanding, pharmacists can play a more active role in monitoring patients undergoing treatment with the drug. They can also provide recommendations to clinicians regarding the

monitoring and management of side effects that may occur. In addition, pharmacists can also use the information obtained from this journal to report adverse drug events to the FDA reporting system, thus helping improve patient safety in using BDQ.

Conclusion

BDQ is used as part of combination therapy for MDR TB patients unresponsive to standard treatment. BDQ works by inhibiting ATP synthase on the microbial membrane. BDQ can cause various side effects, such as QT interval prolongation, cardiac arrhythmias, gastrointestinal disorders, joint and muscle pain, hearing loss, acne, and chest pain. Therefore, treatment of MDR TB with BDQ requires close monitoring and supervision. This aims to ensure patient compliance and early detection of side effects that may occur to ensure treatment safety and effectiveness.

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Conflict of Interest

None declare

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Table 1. Studies of Drug Side Effects in MDR TB Regimens

Author	Sample	Method	Result	MDR TB Therapy
(Farrukh, et.al., 2023) [11]	This multicenter prospective cohort study included patients with MDR TB who started treatment with new and reused drugs in routine care from April 2015 to September 2018 in 17 countries. Between April 1, 2015, and March 1, 2023, 1057 women of childbearing age (15-49 years) received treatment with BDQ and demand, and 48 pregnancies in 43 women were reported to the study. For both cohorts, all MDR/RR-TB patients who reported pregnancy during treatment or follow-up were included in the study.	A multicenter prospective cohort study	Among 43 pregnant women who received MDR/RR TB treatment with BDQ and Dlm, 98% had good treatment outcomes. Of the 31 pregnancies that continued, 81% delivered live babies without malformations, and 68% of neonates had average weight. Effective treatment of MDR/RR TB during pregnancy can improve pregnancy outcomes without jeopardizing the newborn. These data can be confirmed by comparison of other groups and identification of factors contributing to low birth weight in infants of mothers with MDR/RR TB.	Treated pregnant women received MDR/RR TB treatment with Linezolid, BDQ, Clofazimine, Dlm, Amikacin, Capreomycin, and Kanamycin.
(Hurgea, et.al., 2022) [12]	A prospective, multicenter observational study in 14 countries examined MDR TB/RR patients who received concomitant Bdq-Dlm between April 1, 2015, and September 30, 2018. All severe and adverse events that led to changes or were judged significant by clinicians were monitored and documented.	A multi-centric, prospective observational cohort study	472 patients received concurrent Bdq and Dlm. Most also received linezolid (89.6%) and clofazimine (84.5%). Almost all (90.3%) had severe disease, and most (74.2%) were fluoroquinolones resistant. The most common AESIs were peripheral neuropathy (28.4%) and electrolyte depletion (19.9%). Acute kidney injury and myelosuppression were seen in 8.5% and 5.1% of patients, respectively. QT prolongation occurred in 1.5% of patients. 78.0% had a successful outcome, 8.9% died, and 7.2% failed. Concurrent use of Bdq, Dlm, linezolid and clofazimine is safe and effective for severe MDR TB. It is an excellent therapeutic option for multidrug-resistant patients.	Of the 2731 patients in the final TB cohort, some received BDQ and Dlm concurrently at the initiation of MDR/RR TB treatment. Most patients also received linezolid and clofazimine in addition to BDQ and Dlm. Injectable drugs such as aminoglycosides or polypeptides were also given concurrently with BDQ and Dlm at treatment initiation, as were patients who later received a combination of these drugs.

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Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(Gao, et.al., 2021) [9]	This study data was prospectively collected with demographic, bacteriologic, radiologic, and clinical data from 54 sites across China at enrollment and during treatment between February 2018 - December 2019. This interim analysis included patients still in and having completed treatment. Descriptive analysis was performed on patients evaluated in the Cohort.	A multicenter prospective cohort study	As of December 31, 2019, 1162 patients received anti-TB treatment containing BDQ. A total of 1563 AEs were reported, 66.9% minor (Grade 1-2) and 33.1% serious (Grade 3-5). The mean duration of BDQ was 167.0 [interquartile range (IQR): 75-169] days. 86 patients (7.4%) received treatment for 36 weeks with BDQ. The incidence of AEs and serious AEs were 47.1% and 7.8%, respectively. The most commonly reported AEs were QT prolongation (24.7%) and hepatotoxicity (16.4%). There were 14 (1.2%) AEs that caused death. Based on Fridericia's formula-based corrected QT interval (QTcF) data, 3.1% (32/1044) had a post-baseline QTcF≥500 ms, and 15.7% (132/839) at least one QTcF change≥60 ms from baseline. 49 patients (4.2%) experienced QT prolongation AEs that led to BDQ discontinuation. Nineteen patients reported 361 AEs with second-order hepatotoxicity. Thirty-four patients reported 43 AEs of liver injury attributable to BDQ, much lower than prothionamide, pyrazinamide, and para-aminosalicylic acid individually.	The therapeutic regimen consists of a combination of various formulations of anti-TB drugs, such as BDQ, moxifloxacin, Levofloxacin, linezolid, clofazimine, amikacin, capreomycin, prothionamide, cycloserine, pyrazinamide, ethambutol, para-aminosalicylic acid, high-dose isoniazid, meropenem, and amoxicillin/clavulanate.
(Khan, et.al., 2019) [13]	The endTB observational study protocol enroll 2600 patients (April 2015 to September 2018) in 17 countries. Patients: essential subgroups (XDR and pre-XDR-TB patients, children, pregnant women, extra-pulmonary TB patients, and with comorbidities). The patients were on BDQ or Dlm active ingredient regimen treatment in routine care. Data collection: a customized open-source electronic medical record (EMR) system developed in 17 countries.	A multicenter prospective observational cohort study	The late TB observational study protocol and discussion should have presented specific results. However, the study aimed to generate evidence on the safety and efficacy of BDQ and demand-based regimens in a large, highly diverse cohort of MDR TB patients from 17 epidemiologically diverse countries. The study collected repeated effectiveness and safety data and analyzed the data to improve the quality of evidence available to inform MDR TB treatment and policy decisions.	This treatment refers to the national TB and MDR TB treatment guidelines, which reflect the guidelines for BDQ or Dlm regimens.

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Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(Lachenal, et.al., 2020) [14]	Launched with full support from UNITAID in April 2015, the endTB (Expanding Access to New Drugs for Tuberculosis Disease) initiative facilitated the treatment of 2600 patients with BDQ and Dlm in 17 countries. It contributed to the establishment of a universal patient safety database.	Narrative Review	Between April 1, 2015, and March 31, 2019, PVU received and assessed 626 cases of severe adverse events (ESBs) experienced by 417 patients on BDQ treatment. It reviewed unexpected ESBs that may be drug-related to detect safety signals. Experts discussed high-risk patient groups, especially polypharmacy, and the use of non-prescription drugs, which encouraged a patient-centered care approach. Setting up advanced PV in routine care is feasible but resource-intensive. It makes more sense for local/national programs to focus more on clinical management, reporting to the DSM system only for critical data such as ESB.	The study included MDR TB patients who received a BDQ-containing regimen. During treatment, patients were also given other drugs such as linezolid, clofazimine, levofloxacin/moxifloxacin, or Dlm.
(Koirala, et.al., 021) [15]	A 28-year-old man from Egypt, with previous history of TB treatment. Status: diabetes, HIV, or alcohol abuse are negative. Current diagnosis: MDR/RR pulmonary TB with cavitary lesions. A 45-year-old woman from Mexico, no previous TB treatment. Status: managed diabetes without complications and free from HIV or alcohol. Current diagnosis: pulmonary MDR/RR TB with cavitary lesions. A 20-year-old man from Vietnam, no history of TB. Status: diabetes and alcohol are negative, HIV positive. Current diagnosis: pulmonary MDR/RR TB without cavitary lesions. This illustrates the global impact of MDR TB across different demographics and health backgrounds.	A large global cohort	Geographical variations in success rates explained the diverse treatment outcomes. The study also highlighted the severity of drug resistance patterns, with a proportion experiencing multi-drug resistant TB. Finally, the duration of anti-TB treatment, BDQ, and Dlm was explained for patients with an outcome. The results of this study highlight the efficacy of regimens containing BDQ and Dlm in managing multidrug-resistant TB.	All patients treated with BDQ and Dlm (including children/adolescents) are first registered and managed according to WHO and national guidelines respectively.

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Table 1. Studies of Drug Side Effects in MDR TB Regimens (cont..)

Author	Sample	Method	Result	MDR TB Therapy
(van der Walt, et.al., 2020) [16]	This study investigated treatment, as well as pregnancy and infant birth outcomes, in a cohort of pregnant women with drug-resistant tuberculosis (DR-TB) from three MDR TB hospitals from 2010 to 2018.	Retrospective record review	The mean age was 29 years (standard deviation ± 5.1), ranging from 21 to 40 years. Eleven individuals (42.3%) had previously undergone treatment using first-line TB drugs, another eleven (42.3%) had not previously undergone treatment, and four individuals (15.4%) had been treated for drug-resistant tuberculosis (DR-TB). Of the total 26 women, 15 (57.7%) experienced at least one Adverse Drug Effect (ADE), but the majority experienced more than one ADE. 17 were successfully treated, and 22 live births were recorded. There was a significant association between live birth outcomes and the trimester in which DR-TB treatment was initiated (p = 0.036). The proportion of live births for the trimester of pregnancy at the start of DR-TB treatment was 60.0%, 90.9%, and 100.0% for the first, second, and third trimesters, respectively.	The drugs used in the treatment of MDR TB are P-aminosalicylic acid, Linezolid, Clofazimine, Levofloxacin, Ofloxacin, BDQ, Isoniazid, Kanamycin, Capreomycin, Ethambutol, Pyrazinamide, Terizidone, Moxifloxacin, and Ethionamide. Most pregnancy status was ascertained before the start of MDR TB treatment, during the intensive phase of treatment, and after the intensive phase.
(Hewison, et.al., 2022) [8]	This prospective, multicenter observational study (conducted in 16 countries) describes the incidence and frequency of adverse events of clinical relevance and concern (AEs) in patients undergoing treatment for drug-resistant tuberculosis (MDR TB). MDR TB/RT treatment includes the use of BDQ and Dlm. Serious adverse events (AESIs) were previously defined as significant events caused by the use of BDQ, Dlm, linezolid, injectable drugs, and other commonly used drugs. These AESIs were also reported when exposed to the causative agent.	A multicenter, prospective, observational cohort study	Of the 2,296 patients, the most clinically common adverse events were peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%). The incidence per 1000 persons per month of treatment for the three adverse events was 21.5 (95% confidence interval [CI]: 19.8-23.2), 20.7 (95% CI: 19.1-22.4), and 9.7 (95% CI: 8.6-10.8) respectively. The increase in QT interval occurred in 2.7% or 1.8 (95% CI: 1.4-2.3)/1000 person-months of treatment. Patients who received injections (N=925) and linezolid (N=1826) had the highest risk of experiencing adverse events during exposure. Hearing loss, acute renal failure, or electrolyte depletion occurred at a rate of 36.8% or 72.8 (95% CI: 66.0-80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis, and myelosuppression occurred at a rate of 27.8% or 22.8 (95% CI: 20.9-24.8) times/1000 patient months of linezolid exposure.	The drugs included in the baseline treatment regimen of the study were BDQ, Dlm, BDQ and Dlm, Linezolid, Clofazimine, Cycloserine, Moxifloxacin or Levofloxacin, Prothionamide/Ethionamide, Kanamycin, capreomycin, or amikacin, P-aminosalicylic acid, Imipenem/Cilastatin or meropenem, pyrazinamide.

Table 2. Bedaquiline Drug Information

	Drug Information	References
Goals	Diarylquinoline	(Chahine, et al., 2014) [25]
Indications	TB - MDR	(Indonesian Ministry of Health, 2020) [20]
Dosage	BDQ was administered at the recommended dose of 400 mg once daily for 14 days, followed by 200 mg thrice weekly for the remaining 22 weeks.	(Gao, et.al., 2021) [9]
Pharmacodynamics / Mechanism of Action	An adenosine triphosphate (ATP) synthase inhibitor that acts on the microbial membrane, disrupting the bacteria's energy metabolism.	(Guglielmetti, et.al., 2017) [26]
Pharmacokinetics	**Absorption**: BDQ is administered orally and absorbed rapidly, Tmax 4 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) increase proportionally with increasing doses of BDQ, which displays a linear pharmacokinetic profile up to a dose of 700 mg. **Distribution**: BDQ is widely distributed in tissues and can be bound to plasma proteins (>99%). **Metabolism**: BDQ is metabolized via cytochrome P450 (CYP) isoenzyme 3A4, which catalyzes N-demethylation to form metabolite M2. BDQ and M2 have high protein binding, >99.9% and >99.7%, respectively. **Excretion**: BDQ and its metabolites are excreted mainly through feces, with a small amount excreted through urine.	(Chahine, et.al., 2014; Svensson, et.al., 2016) [25,27]
Side effects	QT interval prolongation, cardiac arrhythmias, nausea, vomiting, headache, elevated liver enzyme levels, joint pain and muscle pain, joint and muscle inflammation, impaired liver function, gastrointestinal disorders, bilateral hearing loss, acne, and chest pain.	(Kemenkes RI, 2020; Chahine, et.al., 2014; Guglielmetti, et.al., 2017) [20,25,26]