ORIGINAL RESEARCH

Cohort Event Monitoring (CEM) of Newer Anti-anginal Drugs in Chronic Stable Angina Pectoris (CSAP) Patients in a Tertiary Care Hospital

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ABSTRACT

Introduction: To actively monitor the adverse events caused by newer anti-anginaldrugs(Ranolazine, NicorandilandIvabradine) in case of Chronic Stable Angina Pectoris(CSAP) Patients in Basveswar Teaching and General Hospital (BTGH), Kalaburagi.

Materials and Methods: The present work was an open label, prospective, non-comparative, observationalactivePharmacovigilance study conducted on CSAP Patients attending Medicine OPD of BTGH from March'14 to April'15. 30 CSAP Patients in each group taking either 500 mg Ranolazine twice daily or 10 mg Nicorandil twice daily or 5 mg Ivabradine twice daily as add on therapy, was interviewed and recorded the data on pretested questionnaire form at baseline and after 8 weeks. Their Hemodynamic parameter, Routine Hematological and biochemical investigations were also actively monitored along with adverse Drug Reactions (ADR).

Results: ADR in patients with Ranolazine were Dizziness (25%), Nausea (17.8%), Vertigo (7.1%), Vomiting (3.6%), Constipation (3.6%) and Fever (3.6%). ADR in patients with Nicorandil were Headache (25%), Flushing (17.8%),Weakness (14.2&), Dizziness (10.7%), Nausea (10.7%), muscle cramp (7.1%), Rectal Bleeding (7.1%) and Peptic Ulcer (3.6%). ADR in patients with Ivabradine were Dizziness (29.6%), Headache (18.5%), Flushing (14.8%), weakness (11.1%), Nausea (7.4%), Blurred vision (7.4%), Fever (7.4%) and Cough (3.7%).Blood Pressure, Heart rate and routine hematological and biochemical marker didn't show any significant differences at baseline and after 8 weeks. Only Ivabradine significantly decrease the heart rate after 8 weeks of intervention.

Conclusion: The present active Pharmacovigilance study represents the ADR Profile of presently used newer anti-anginal drugs in our hospital. The above finding would be helpful for the physician in rational prescribing.

Keywords: Cohort event monitoring (CEM), Ranolazine, Nicorandil, Ivabradine, Dizziness, Headache

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INTRODUCTION

It has been anticipated that by 2020, ischemic heart diseases (IHD) will be the leading cause of global disease burden.[1] In the last few decades, its incidence has increased in the economically developing countries like india. Current management paradigms focus on medications directed toward optimizing cardiac hemodynamic effects. In addition to hemodynamic treatments, a novel group of agents that work via other mechanisms are available for the treatment of myocardial ischemia. These agents improve cardiac metabolism and cardiac energy availability and are termed metabolicmodulators.

Currently available antianginal agents include beta-blockers, calcium-channel blockers, and long-acting nitrates (LANs).[2] However, these have some side-effects like negative inotropic effect with β blockers and hypotensive effect with CCBs and tolerance development in Long acting nitrates, which could have serious consequences.

New medicines in the management of coronary artery disease (CAD) include mainly metabolic modulator ranolazine, sinus node inhibitor ivabradine and Potassium channel opener Nicorandil. The antianginal action of RAN is due to blockade of the β oxidation of fatty acids and shifting the heart's metabolism to pro-

duce more energy as ATP from glucose. Because glucose needs less oxygen to generate the same amount of energy as fatty acids, this can be advantageous in the presence of IHD.It also blocks the late sodium current.[3]

Nicorandil, a nicotinamide ester produces antianginal effect by a two pronged mechanism of action. The unique action of opening ATP-sensitive potassium channels leads to dilatation of peripheral and coronary resistance arterioles, while its nitrate moiety dilates systemic veins and epicardial coronary arteries. Overall it increases the coronary blood flow, reduced preload and afterload.[4] Ivabradine is a specific heart rate (HR) decreasing agent acting on the sino-atrial node by selectively inhibiting the pacemaker I_f current in a dose-dependent manner and reducing HR with minimal effect on other hemodynamic parameter.[5,6]

The focus of the international health community has shifted from just efficacy to risk-benefit analysis partly due to the thalidomide tragedy and an publication by the US institute of Medicine report "To err is human: building a safer health system".[7,8] According to WHO, ADR are the fourth leading cause of death[9] ADR monitoring is a continuous and ceaseless process. Indian pharmacovigilance is still in its infancy and will likely expand in the time to come. With every new drug launch, the need for ADR monitoring will grow further. It is important to remember that most ADRs would subside if patients are actively monitored. Therefore, it is important to monitor actively the side effect profile of newer anti-anginal agents used in patients of Chronic Stable Angina Pectoris.Study was aimed to actively monitor the adverse event profile of newer Anti-anginal drugs and to assess the frequency of side effects of Ranolazine, Nicorandil and Ivabradine in patients of CSAP individualy.

MATERIALS AND METHODS

An open label,prospective,non-comparative, observational active Pharmacovigilance study conducted from April 2014 to March 2015 in a tertiary care hospital of Kalaburagi, with permission from the institutional ethics committee. Patients of either gender, >18 years and < 70 years of age, diagnosed to be suffering from CSAP, attending the Medicine outpatient department of the hospital, taking either Ranolazine or Nicorandil or Ivabradine as add on therapy are enrolled in this prospective study, Those who showed interest in joining and fulfilled the inclusion criteria were supplied with a detailed information sheet and briefed about the possible ADRs with newer anti-anginal medicines in vernacular language. Patients with BP > 170/100 mm, systolic BP < 100 mm, renal or hepatic impairment, pregnancy, lactation, severe bradycardia, moderate to severe heart failure, severe hypotension, second- to third-degree heart block, arrhythmias or anemia (Hb< 7 g/dL) were excluded. One hundred and fifty patients were assessed for eligibility, 60 were excluded and twopatient each was lost to follow-up in both the ranolazine and nicorandil group and three were lost in Ivabradine group.

After seeking permission from the attending physician, the 30 patients were started either Ranolazine 500 mg twice daily or 10 mg Nicorandil twice daily or 5 mg Ivabradine twice daily along with other antiplatelet, statin, antihypertensive and antianginal therapy on which they were already stabilized. Dosage of the medicines was based on previous studies. Patients ADR profile of all the three cohort groups were actively monitored at baseline and 2nd, 4th and 8th week. Hemodynamic parameter, routine hematological (Hb%, serum electrolytes) and biochemical evaluations (LFTs, RFTs, RBS) were also done at baseline and after 8week.

STATISTICAL ANALYSIS

Data was analyzed based on descriptive statistics. SPSS version 21 was used for generating tables.

RESULTS

Patients included in this CEM were farmers (40%, 25%,30%), retired personal (15%, 10%, 20%), business men (20%, 30%,25%), teachers (10%, 25%,10%) and housewives (15%, 20%, 15%) in the Ranolazine, Nicorandil and Ivabradine group respectively. Mean age and sex ratio is given in Table 1 & 2.

	Mean age	SEM
Ranolazine	60.68	1.66
Nicorandil	58.64	1.69
Ivabradine	55.78	1.20

Table-1: Mean age of three group

	Male	Female	Total
Ranolazine	17	11	28
Nicorandil	15	13	28
Ivabradine	18	9	27

Table-2: sex ratio of three group

Hemodynamic parameters of three group after 8 week of cohort monitoring

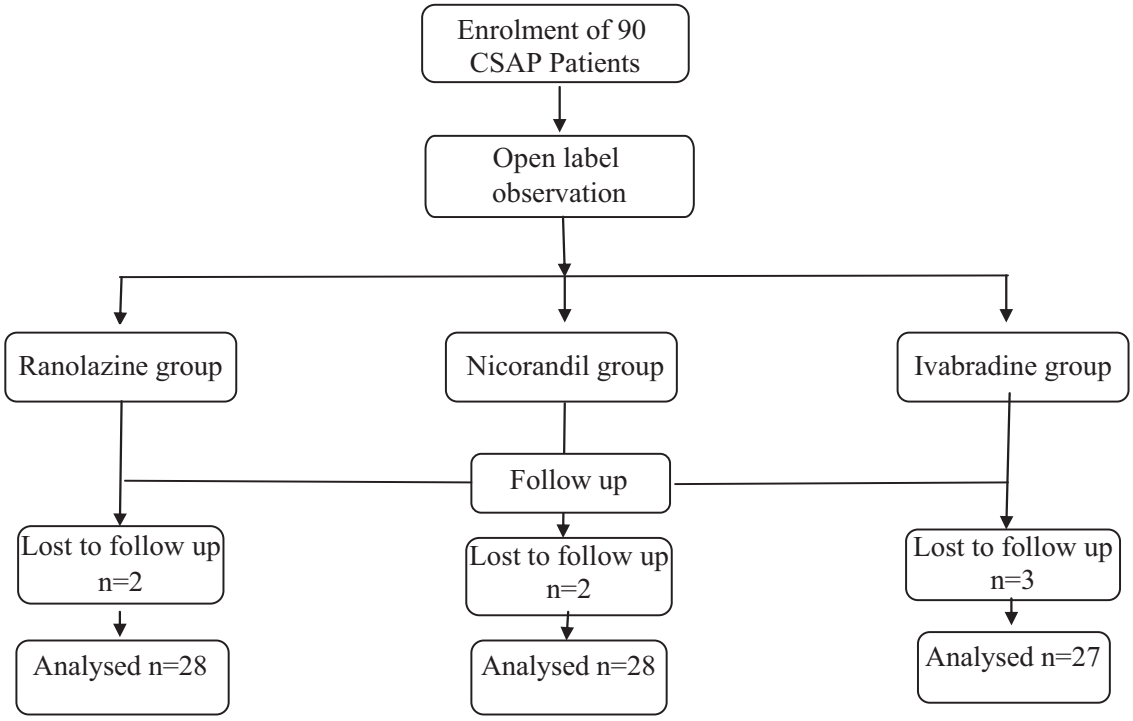
There was no significant difference in systolic BP, diastolic BP and HR in the Ranolazine group and Nicorandil group at baseline and 8 weeks of cohort monitoring, whereas Ivabradine decreased the resting HR but did not have a significant effect on the systolic and diastolic BP(Table 3).

Investigations of patients at baseline and 8 weeks of treatment(Mean±SEM)

Hb, LFTs, RFTs, serum electrolytes and RBS done at baseline and after 8 weeks of cohort monitoring did not show any significant difference(Table-4).

Assessment of the adverse drug reactions

Assessment of ADRs reported in three cohort groups



Flowchart: Consort flow chart of Cohort Event Monitoring

	Ranolazine group		Nicorandil group		Ivabradine group	
	Baseline	**After 8 wk**	**Baseline**	**After 8 wk**	**Baseline**	**After 8 wk**
Systolic BP	127.8±2.01	124.8±1.68	126±2.70	124±1.99	127.48±1.61	128.6±1.63
Diastolic BP	79.85±1.22	78±0.96	78.93±1.61	76.78±1.32	79.4±1.02	81.11±0.74
Heart Rate	74.71±1.13	72±1.01	78.29±1.44	78.29±1.28	74.37±0.83	66.74±0.83

Table-3: Hemodynamic parameter of three cohort group at baseline and after 8 week

	Ranolazine group		Nicorandil group		Ivabradine group	
	Baseline	**After 8 wk**	**Baseline**	**After 8 wk**	**Baseline**	**After 8 wk**
Hb%(mg%)	12.85±0.47	12.63±0.38	12.82±0.42	12.86±0.35	12.92±0.4	12.98±0.37
AST(IU)	37.68±1.66	36.07±1.16	45.89±2.39	37.78±1.39	39.33±1.8	34.6±1.21
ALT(IU)	26.75±1.71	27.93±1.05	36.82±2.02	31.14±1.59	34.89±1.5	32.67±1.56
Na^+(mmol/L)	132.68±0.79	131.39±0.62	133.14±0.86	133.11±0.75	130.5±0.44	130.4±0.56
K^+(mmol/L)	4.0±0.1	4.17±0.07	4.10±0.07	4.0±0.06	3.96±0.08	3.99±0.06
Urea(mg/dl)	17.61±0.87	18.78±0.77	21.21±0.79	20.57±0.79	20.78±0.8	20.67±0.62
Creatinine(mg%)	0.99±0.03	0.97±0.02	0.92±0.03	0.92±0.03	0.92±0.03	0.91±0.03
RBS(mg%)	114.18±6.15	117.89±6.51	126.6±6.76	122.57±6.11	121.3±8.69	116±6.86

Table-4: Biochemical and hematological parameter of three cohort group at baseline and after 8 week

was done within 8 week of observation period. 9 of 28 patients from the Ranolazine group, 17 of 28 patients from the Nicorandil group and 15 of 27 Ivabradine group were reported ADR at some point of the study period. In the Ranolazine group most common ADR was dizziness (25%) followed by nausea (17.8%). In the Nicorandil group most common ADR was headache (25%) followed by flushing (17.8%). Weakness (14.3%), nausea (10.7%), dizziness (10.7%), peptic ulcer (3.6%) was also reported. In the Ivabradine group most common ADR was Dizziness (29.8%) followed by headache (17.8%). Flushing and weakness was also reported. Individual frequency of ADRs of these three drugs have been listed hereunder in Table-5

	Drugs		
ADR	**Ranolazinegroup (%)**	**Nicorandil-group (%)**	**Iv-abradine-group(%)**
Flushing	-	17.8(5)	14.8(4)
Nausea	17.8(5)	10.7(3)	7.4(2)
Vimiting	3.6(1)	-	-
Constipation	3.6(1)	-	-
Headache	-	25(7)	18.5(5)
Dizziness	25(7)	10.7(3)	29.6(8)
Blurred Vision	-	-	7.4(2)
Muscle cramp	-	7.2(2)	3.6(1)
Arthralgia	-	3.6(1)	-
Vertigo	7.2(2)	3.6(1)	7.2(2)
Cough	-	-	3.6(1)
Fever	3.6(1)	-	7.2(2)
Rectal bleeding	-	7.2(2)	-
Weakness	-	14.3(4)	11.1(3)
Peptic ulcer	-	3.6(1)	-

Table-5: Percentage distribution of patients reporting ADR

DISCUSSION

Cohort event monitoring (CEM) is one of the standard methods of active PV and which has been best defined. It is used to monitor adverse events in patients who receive a particular Pharmacovigilance. A defined cohort (group) of patients is followed up prospectively and all adverse events occurring during treatment. Adverse events monitored in CEM do not necessarily have a causal relationship with the treatment, in contrast to established adverse drug reactions.

The demographic details of our study population showed male gender predominance over females, which was similar to that reported in other studies found in the literature.[10-12]

Most of the reactions were mild in nature which needs minimal intervention for treatment and it does hinder their normal activity.

Causality assessment showed that most of them were in the possible category according to Naranjo scale.

Most common system affected by newer anti-anginal drugs are Central nervous system (48%) which includes headache, dizziness, vertigo etc. followed by Gastro-intestinal system (18%) which includes nausea, Vomiting, peptic ulcer etc. Cardiovascular system and musculoskeletal system was also affected significantly. Few incidence of rectal bleeding and peptic ulcer is also seen in nicorandil group.

Nausea by Ranolazine was due to CTZ stimulation, vestibular disturbance or GIT dysfunction needs investigation. Others have reported dizziness, nausea, asthenia and constipation as being the frequent ADRs with Ranolazine.[13]

25% of the patients in the Nicorandil group18.5% in ivabradine group and none from the Ranolazinegroup reported headache after 8 weeks (Table 5). Headache may have been due to blurred vision, phosphenes, inflammatory mediators, dizziness, bradycardia and postural hypotension. As Ivabradine does not cross the blood–brain barrier, headache could not have occurred due to direct action of Ivabradine on the brain.[14] The reasoning is hypothetical and needs further investigation. Phosphenes are luminous phenomena, described as a transient enhanced brightness in a limited area of the visual field. It has been hypothesized that Ivabradine interacts with the visual system by inhibiting hyperpolarization-activated current in retinal cells (I_h).[15] Thirteen percent of the patients from our trial complained of blurred vision.Nicorandil dephosphorylate myosin and so hinders the actin filament contraction that is necessary for cell migration, as would be required to repair mucosal microtrauma which hinders early inflammatory phase of wound healing which leads to peri-anal and peri-stomal ulceration.[16] 7.2% and 3.6% patients from Nicorandil group shows rectal bleeding and peptic ulcer respectively (Table-5).

CONCLUSION

The above study is a part of ongoing pharmacovigilance program conducted in our teaching hospital. During this pharmacovigilance study, Nicorandil were found to be most frequently associated drug with ADR followed by Ivabradine.As the present study represents

the ADR Profile of presently used newer anti-anginal drugs in our hospital. The above finding would be helpful for the physician in rational prescribing, enhancing patient adhearence with the therapy by selecting medicines with lesser ADR profile, reducing unnecessary economic burden due to unwanted effects of the therapy.

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