



DRUG INDUCED BRADYCARDIA; OUTCOME OF PATIENTS WITH BRADYCARDIA AFTER DISCONTINUATION OF RATE SLOWING DRUGS IN TERMS OF FREQUENCY OF PERSISTENT BRADYCARDIA.

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ABSTRACT... Background: Bradycardia in patients on rate slowing drugs i.e. beta blockers, digoxin and non dihydropyridine calcium channel blockers is common after discontinuation of rate slowing drugs. Bradycardia persists in majority of patients, so bradycardia is not truly drug induced but due to underlying conduction system disease. **Objectives:** To determine the outcome in patients with bradycardia after discontinuation of rate slowing drugs in terms of frequency of persistent bradycardia. **Study Design:** Descriptive cross-sectional. **Place and Duration of Study:** Cardiology Department, Faisalabad Institute of Cardiology, Faisalabad, from September 2015 to March, 2016. **Methodology:** After written informed consent 95 patients who fulfilled the inclusion and exclusion criteria were selected for this study. Patients with bradycardia (heart rate less than 60 beats per minute) identified by pulse and electrocardiography (ECG) were admitted and culprit drug was discontinued. All admitted patients were followed everyday by doing ECG and counting pulse twice. Patients, in whom bradycardia resolved, were discharged. Patients were monitored for persistent bradycardia after discontinuation of culprit drug for 5 days. **Results:** Out of 95 patients 46 (48%) were male and 49 (52%) female, age range was 25-85 years with mean age 61 ± 11 years. Heart rate ranged 25-45 beats per minute with mean value of 31.28 ± 6.08 , 72 (75.8%) patients were on beta blockers, 19 (20%) on calcium channel blockers and 4 (4.2%) patients were on digoxin. 73 (76.80%) patients had 3^o AV block, 19 (20%) 2^o AV block while 3 (3.20%) had sinus bradycardia. Bradycardia persisted in 69 (72.60%) patients out of which 32 (69.6%) were male and 37(75.5%) female. Bradycardia resolved in 26 (27.40%) patients in which 14 (30.4%) were male and 12(24.5%) were female. **Conclusion:** Persistent bradycardia is common in patients with drug induced bradycardia. Such bradycardia is not truly drug induced but is related to unmasking of subclinical conduction system disease by rate lowering drugs like beta blockers, calcium channel blockers and digoxin.

Key words: Drug Induced Bradycardia, Persistent Bradycardia, Rate Slowing Drugs (Beta-Blockers, Digoxin, Non Dihydropyridine Calcium Channel Blockers).

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INTRODUCTION

Bradycardia or bradyarrhythmia in adults is defined as heart rate slower than 60 beats per minute (bpm) in case of sinus rhythm, a variety of atrial rhythms including slow atrial flutter/fibrillation, junctional or idioventricular rhythm.¹ The normal conduction system of the heart is composed of sinus node (SA node), inter-nodal pathways, atrio-ventricular node (AV node), His bundle and its branches and sub-endocardial purkinje fibers.² SA node is located in upper part of the right atrium at its junction with superior vena cava. SA node is composed of specialized cells² called as pacemaker cells. SA node is

dominant pacemaker of the heart as it generates cardiac impulses ranging between 60-100 beats per minute. Severe Bradycardia with heart rate as low as 50 bpm can be seen during sleep, in well trained athletes and hypothermia. Bradycardia may result from intrinsic dysfunction or damage to the conduction system or by the response of conduction system tissue to extrinsic factors.³

Clinically important bradycardia can result from beta blockers, non-dihydropyridine calcium channel blockers (non-DHP CCBs), digoxin and antiarrhythmic drugs.⁴⁻¹⁰ Also in this list of drugs include sympatholytic antihypertensives,

tedisamil, carbamazepine, cimetidine, anti-depressants, lithium, opioid blockers and cocaine.^{6,11} Use of a honey called mad honey containing Grayanotoxins derived from nectar of rhododendrons can cause severe bradycardia.¹² Some anti-smoking remedies (herbs) and some anti cancer drugs like doxorubicin can cause bradycardia due to their toxic effect.¹³⁻¹⁴ Not all but few antiarrhythmic drugs also can lead to severe bradycardia related to their proarrhythmic effect. Drug related bradycardia can be divided into three types. Firstly, it can be the result of drug overdose or toxicity in patients with normal conduction system and this bradycardia is termed "Drug Induced" bradycardia". Secondly, it can be the result of some underlying latent disease of the cardiac conduction system and is related even to sub-therapeutic drug dose; such bradycardia is termed "Drug Provoked" bradycardia". Thirdly, it can be the result of brady effect of drugs in patients with underlying latent disease of conduction system and this variety is termed as "Drug Associated" bradycardia.

Varying degrees of temporary or permanent atrio-ventricular block (AV block) may develop in different clinical situations. Drugs are labeled as reversible causes of AV block that do not need pacemaker (PM) implantation.¹⁵⁻¹⁷ However drug induced AV block recurs in patients with drug induced AV block after discontinuation of the culprit drug as per reports of major clinical journals.^{5,18} Rationale of this study was that bradycardia in patients on rate slowing drugs i.e. beta blockers; digoxin and non-dihydropyridine calcium channel blockers is common and persists or recurs after discontinuation of rate slowing drugs, such bradycardia is not truly drug induced but due to underlying conductive system disease. The objective of this study was to determine the outcome of patients with drug induced bradycardia after discontinuation of rate slowing drugs in terms of frequency of persistent bradycardia.

MATERIALS AND METHODS

Place and Duration of Study

Faisalabad Institute of Cardiology, Faisalabad,

from September 2015 to March 2016.

Study Design

Descriptive cross-sectional study.

Sample Size

By using WHO sample size calculator:

- $P = 18.41\%$ ¹
- Absolute precision required = 8%
- Confidence Level = 95%
- Sample Size = 95

Sample Technique

Non-probability consecutive sampling

Inclusion Criteria

1. Age: 25 -80years
2. Sex: Either
3. Pulse rate: Less than 60bpm
4. Patients on rate slowing drugs i.e beta-blockers, non dihydropyridine calcium channel blockers, and digoxin.
5. Duration of intake of culprit drug: One or more than one day.

Exclusion Criteria

1. Acute MI
2. Digoxin toxicity
3. Bradycardia without rate slowing drugs beta blocker, non dihydropyridine calcium channel blocker, and digoxin.
4. Patient on chronic amiodarone therapy.
5. Hyperkalemia
6. Renal failure

Data Collection and Analysis

Ninety five (95) patients who fulfilled the inclusion and exclusion criteria were selected from emergency department after taking informed consent. All selected cases with bradycardia identified by pulse and ECG were admitted and culprit drug was discontinued. All admitted patients were followed everyday by doing ECG and counting pulse twice. Patients, in whom bradycardia resolved, were discharged. Patients were monitored for persistent bradycardia after discontinuation of culprit drug for 5days. Data was entered and analyzed by using SPSS-20.

RESULTS

During six months of study we found ninety five (95) patients with drug induced bradycardia. All patients were on either beta-blockers, non-dihydropyridine calcium channel blockers or digoxin either alone or in combination for different clinical indications.

Out of 95 patients, 48% (n=46) were male and 52% (n=49) were female. Patient’s age ranged between 25-85 years with mean age 61± 11 years (Table-I). Heart rate ranged between 20-45 beats per minute with a mean heart rate of 31.28 bpm ± 6.08 beats per minute.

Out of 95 patients, 75.8% (n=72) were using beta blockers, 20% were using non dihydropyridine calcium channel blockers (n=19) while 4.2% (n=4) were on digoxin (Table-I). Many patients were using these medications for hypertension.

On electrocardiographic analysis 76.8% (n=73) were found to have 3^o AV block, 20% (n=19) 2^oAV block while 3.2% (n=3) were found to have sinus bradycardia (Table-I).

Variable	Frequency	Percentage
Gender		
Male	46	48%
Female	49	52%
Total	95	100%
Age (In Years)		
		25-85 years
	Mean ± SD	61±11years
Drugs Used		
Beta Blockers	72	75.80%
Calcium Channel Blockers	19	20%
Digoxin	4	4.20%
Drug Induced Bradycardia		
Sinus Bradycardia	3	3.20%
2nd Degree AV block	19	20%
3rd Degree AV block	73	76.80%
Patient outcome		
Persistent Bradycardia	69	72.60%
Resolved Bradycardia	26	27.40%
Pulse Rate / Min Range		
		20-45 bpm
Mean ± SD		31.28±6.08

Table-I. Baseline patient characteristics.

All patients were monitored for 5 days after discontinuation of culprit drugs to look for resolution of bradycardia. On Chi-square analysis there was no gender difference regarding resolution of bradycardia. Bradycardia persisted in 72.6% (n=69) patients, out of these 75.5% (n=37) were female and 69.6% (n=32) were male. However bradycardia resolved in 27.4% (n=26) patients, out of these 30.4% (n=14) were male and 24.5% (n=12) were female (Table-II).

Table-III. Propensity of different degrees of AV block to persist after 5 days of offending drugs discontinuation.

Regarding percentage of electrocardiographic outcome after 5 days of discontinuation of heart rate slowing drugs, out of 3.2% (n=3) patients with sinus bradycardia at presentation and after 5 days of culprit drug discontinuation, sinus bradycardia persisted in 1 patient (33.3%) and resolved in 2 patients (66.7%), out of 19 patients ((20%) with 2^o AV block at presentation, after 05 days of drug discontinuation 2^o AV block persisted in 7 patients (36.8%) and resolved in 12 patients (63.2%) and for 3^oAV block at presentation it persisted in 61 patients (83.6%) and resolved in 12(16.45) patients after 05 days of culprit drug discontinuation (Table-III).

DISCUSSION

Bradycardia associated with rate slowing drugs is a common clinical entity; however little is known about its natural history and prognosis. This study was conducted in our institute to study the “resolution of drug induced bradycardia” in patients during their hospital stay. Heart rate slowing drugs were discontinued for five days for their complete elimination as it is well known that all the drugs are eliminated within their five half lives. Ninety five patients were identified with bradycardia during the six months study period. Patients were monitored during their hospital stay for resolution of bradycardia in the absence of drugs.

In Hospital Outcome		Gender		Total
		Male	Female	
Bradycardia persists after 5 days of drug discontinuation	Yes	32(69.6%)	37(71.5%)	69(72.6%)
	No	14(30.4%)	12(45%)	26(27.4%)
Total		46	49	95

Table-II. Frequency of bradycardia outcome 5 days after drug discontinuation

In Hospital Outcome		ECG Findings			Total
		Sinus Bradycardia	2nd Degree AV block	3rd Degree AV Block	
Bradycardia persists after 5 days of drug discontinuation	Yes	1(33.3%)	7(36.8%)	61(83.6%)	69(72.6%)
	No	2(66.7%)	12(63.2%)	12(16.4%)	26(27.4%)
Total		3	19	73	95

Table-III. Frequency of ECG findings after 5 days of drug discontinuation

In our study majority of patients were on beta blockers followed by non dihydropyridine calcium channel blockers (non -DHP CCBs) and digoxin. In our study bradycardia persisted in 69 (72.6%) patients and resolved in 26 (27.4%) patients after discontinuation of afore mentioned drugs. In a study by Zeltser D et al⁵ bradycardia persisted in 56% of the patients while it resolved in 41% patients after discontinuation of beta-blockers and non-DHP CCB. In study done by Sima Sayahet al¹⁹, AV block persisted in 57% of patients while it resolved in 43% of patients after discontinuation of beta blockers and non-DHP CCBs.

In our study, sinus bradycardia was found in 3 patients, 2nd degree AV block in 19 patients and 3rd degree AV block in 73 patients. It persisted in one patient with sinus bradycardia, in 7 patients with 2nd degree AV block and in 61 patients 3rd degree AV block after five days of drug discontinuation. In a study of 38 patients by Lee JH et al²⁰, who were on beta blockers and non-DHP CCBs either alone or in combination, documented sinus bradycardia in 13 patients, sinus bradycardia with junctional escape in 18 patients and complete heart block in 7 patients. Culprit drug discontinuation was followed by complete resolution of bradycardia 28 (73.7%) patients and persistent bradycardia persisted in 10 (26.3%) patients. The difference in results in both studies could be related to more advanced AV block in our study patients.

Cardiac conduction system disease is common with advancing age. In our study average age

was 61 years and both genders represented almost equally. Rate limiting drugs (like non-DHP CCBs, digoxin and beta blockers) slow down conduction and prolong refractory period in nodal tissue while they decrease conduction block at infra-nodal level; hence nodal conduction defect is more likely to resolve after discontinuation of these drugs; and this would have no effect in case of infra-nodal blocks. Patients having drug induced heart block could be related to unmasking of latent conduction system disease by rate slowing drugs as therapeutic doses of such drugs rarely cause heart blocks in patients with normal conduction system. In a study by Zeltser D et al⁵, in patients treated with beta-blockers and non-DHP CCBs, AV block truly caused by drugs was seen in only 15% (n=14) of the patients and in majority of patients the ‘culprit’ drugs were considered ‘innocent bystanders’. Thus drug induced bradycardia in patients with subclinical disease of nodal and infra-nodal tissue is most commonly produced by trigger effect even to the sub-therapeutic doses of rate slowing drugs.^{7,21}

ECG diagnosis of infra-nodal disease is likely with prolonged QRS (≥ 120 ms) and ventricular rate of less than 40 beats per minute.²² This finding in patients with drug induced bradycardia favors infra-nodal conduction system disease. In study by Lee JH et al²⁰ this finding was seen in 26.3% patients that persisted after discontinuation of culprit drug suggesting underlying infra-nodal conduction system disease. Similar to above study Kenneback G et al²³ stated in their findings that high-degree AV block and QRS width ≥ 120

ms were independent predictors of progression to a complete heart block requiring permanent pace maker implantation following culprit drug discontinuation, thus favoring infra-nodal etiology as this site is mostly associated with such an AV block. However we did not assessed this finding in our study.

Drug induced bradycardia related outcome has been reported in few studies.^{5,18,20} A study by Ovysyshcher IE and Barold SS⁴ reported an incidence of 1-15% persistent bradycardia after anti-arrhythmic drugs discontinuation, requiring permanent pace maker (PPM) implantation. A study by SimaSayah et al¹⁹ reported recurrence rate for 2nd and 3rd degree AV block of 50% after discontinuation of beta and non-DHP CCBs that required permanent pace maker implantation during follow up. A similar study by Osmanov D et al reported recurrence rate of 27% for AV block requiring PPM implantation in nearly half of patients who were on treatment with beta and calcium channel antagonists and digoxin.

Thus drug-induced bradycardia is a common clinical scenario with the heart rate slowing drugs. True bradycardia is rarely caused by therapeutic doses of such drugs and commonly happens with drug overdose or toxicity or if such drugs are given in combination that can lead to their synergistic effect with consequent conduction blocks in patients with normal conduction system. However in patients with underlying conduction system disease even sub-therapeutic doses of rate slowing drugs can lead to severe bradycardia due to trigger effect. In patients with symptomatic or clinically significant drug-induced bradycardia, one must decide whether to stop or reduce the drug therapy or to continue it if there is no acceptable alternative, in which case pacing therapy should be considered. In most cases, clinical difference between drug-induced, drug-provoked, and drug-associated bradycardia may be invisible and they may be poorly differentiated.

STUDY LIMITATIONS

Diagnosis of infra-nodal disease depends on the ECG criteria and EP study. We did not studied these patients electro physiologically. Due to

nature of study, patient's follow up was limited up to their hospital stay. This strategy left a large proportion of patients in whom the bradycardia resolved. Ideally these patients should have been studied by Holter monitoring at least two weeks after discharge for resolution or recurrence of bradycardia.

CONCLUSION

In majority of patient on rate slowing drug i.e. beta-blocker, non-dihydropyridine calcium channel blockers and digoxin, bradycardia persisted after discontinuation of these drugs. So bradycardia was not truly drug induced, but it was due to underlying conductive system disease which was unmasked by rate slowing drugs.



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