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AN OBSERVATIONAL STUDY ON SAFETY AND TOLERABILITY OF HIGH INTENSITY ATORVASTATIN IN CARDIOVASCULAR DISEASES

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ABSTRACT

Objective: The main objective of the study is to assess the safety and tolerability of high intensity atorvastatin in various cardiovascular diseases. **Methodology:** A prospecive observational study was conducted in the cardiology department (in patient) of a tertiary care hospital. The data was collected from the in-patient department after considering inclusion and exclusion criteria for a period of 6 months and a total of 120 patients were analyzed with data collection form by interviewing the patient's about the socio -demographic questionnaire , for every 3 months the patient's blood samples are collected to observe lipid values. Statistical tools like Chi-Square test and T-test were applied to the data by using SPSS software. **Result:** Among 120 patients, males are more predominant than females. Patient's between the age group of 40 and 60 years are more prone to CVD. According to our data, 12.5% of patients are smokers, 30% are alcoholics and 12.5% patients are both alcoholics and smokers 25% of patients had a family history of HTN, 10 % of patients had a family history of DM and Heart disease and 7.5% of patients had a family history of Hypertension with Heart disease, 7.5% 0f patients had a family history of Hypertension with DM. Among 120 patients, 72 (60%) patients had a past history of Hypertension and DM. Among 120 patients, 25% of patients have IWMI, 25% of patients have AWMI, 12.5% of patients have NSTEMI, 2.5% patients have RHD, 15% patients have AIS, 10% patients have TIA, 10% patients have unstable angina. Among these patients, patients with IWMI(30) AND AWMI(30)were more common.40mgdose has been given to 54(45%) patients and 80mg dose has been given to 66(55%) patients. **Conclusion:** High intensity atorvastatin therapy was given for a period of 6 months in120 patients. High intensity atorvastatin is generally well tolerated in adults in both the 40mg and 80mg doses who are diagnosed with various types of CVD. The ADR of atorvastatin are well managed and are not severe and no one has been withdrawn from the therapy. The overall survival rate of the therapy is 100%. Thus, high intensity atorvastatin is safe and well tolerated.

KEYWORDS: Atorvastatin, Highintensity, CVD, ADR'S, Safety, Tolerability, Lipidvalues, Inferior wall myocardial infarction, Anterior wall myocardial infarction, RHD, NSTEMI, Hypertension.

INTRODUCTION

Atorvastatin is a HMG-CoA reductase inhibitor belonging to the class of drugs called 'statins' used as a lipid lowering medication in prevention and treatment of cardiovascular diseases.[1]

Chemical Formulae

(3R,Nr)-7-{2-(4-flurophenyl)-3phenyl 4 –(phenyl carbamoyl)-5-propan 2-pyrrol-1-yl)-3,5-dihydroxy hepatonic acid.
Generic Name : Atorvastatin.
Brand Name : Atocor, Lipitor

Atorvastatin is used primarily in the treatment of dyslipidemia like hyperlipidemia, and mixed dyslipidemia, homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia.[4] It is also used to prevent cardiovascular events in patients with abnormal lipid profiles in combination with dietary modifications.[2] Atorvastatin is indicated in condition like MI, fatal and non-fatal stroke, patients with CHD and also for revascularization procedures. It is used as a preventive agent in transient Ischemic attack (TIA).[3] Atorvastatin is available in the form of tablets in strengths of 10mg, 20mg, 40mg ,&80mg. Daily administration of 40mg and 80mg shows improvement in serum lipid in at least 3months.[4]

Mechanism of action: Statins act by competitively inhibiting the HMG CoA Reductase, the rate limiting step in the process of cholesterol synthesis by blocking the conversion of HMG CoA to mevalonic acid, thereby reducing LDL-C in the bloodstream and reducing cardiovascular morbidity and mortality.[5] This causes increased production of microsomal HMG CoA reductase by reducing. hepatic cholesterol synthesis within the liver.[6] In addition to these Atorvastatin also shows pleiotropic effects like anti inflammatory, immunomodulatory, anti thrombotic effects.[7]

Cholesterol Synthesis: Cholesterol is considered as an essential component of cell membrane and acts as the mainprecursor for the synthesis of steroid hormones.[8]

PHARMACOKINETICS

Absorption- Rapid absorption when taken orally with a plasma concentration of 1-2 hrs

Bioavailability- absolute-14% ,systemic availability-30%

Distribution- mean volume of atorvastatin distribution is approximately 381 L

- Protein bound ≥98% (secreted in to humans breast milk)

Metabolism- metabolized through cytochrome p450 3 A4 hydroxylation to form ortho and para hydroxilated metabolites

Excretion- primarily excreated through hepatic biliary excretion

- Elimination half life- 14hrs

PHARMACODYNAMICS: Liver acts as a primary site of action for atorvastatin as it is the site of both cholesterol synthesis and LDL clearence.

USES

- Hypercholesterolemia and mixed dyslipidemia
- To reduce TC ,LDL, Apo-B, Triglyceride levels ,CRP
- Used in prevention of heart attack and stroke
- It is a primary need for revascularization procedures in patients with stroke and heart attack
- Secondary prevention of MI and unstable angina.

SIDE EFFECTS: Myalgia, Cough, Difficulty with swallowing, Itching, skin rashes, Tiredness or weakness, Fever and dizziness

CONTRAINDICATIONS: Pregnancy or breast feeding, History of liver disease, Thyroid disorder

DRUG INTERACTIONS: Cyclosporine, Gemfibrozil

MATERIALS AND METHODS

This is an observational study of the duration of 6 months in the cardiology department at Kamineni hospital. The data was collected from Inpatient department of a medication history of 3 months or more. The subjects were interviewed by collecting the lipid profiles as well as patient case profiles. The data collection format was verified and authenticated by the hospital preceptors for the study.

Inclusion criteria were the patient aged between 40-80 years diagnosed with MI, Stroke, CAD, DM, Hyperlipidaemia and available with lipid profile, pregnant, lactating women, patients aged <40 and >80years,HIV, HBsAg positive, Patients who are unwilling to participate are excluded from the study.

Statistical analysis

Descriptive statistics was done by using SPSS software to determine mean and standard deviation of collected data. The statistical tool Chi square test was performed to determine P-Value of the collected data. The p-value was set at <0.05 and confidence interval was 95.

RESULTS

A Total of 215 patients of Epilepsy were screened according to Inclusion Criteria. (5.1) SOCIO DEMOGRAPHIC DETAILS OF PATIENTS:

GENDER DISTRIBUTION

Table (5.1.1) indicates gender wise distribution of patients. Percentage of females known withepilepsy was more in number (60%) than male (40%) as mentioned in figure 5.1.1.

Table (5.1.1): Gender wise distribution of study population.

S.no	Gender	Number of patients	Percentage
1.	Male	85	40%
2.	Female	130	60%
Total		215	100%

AGE DISTRIBUTION

Table (5.1.2) indicates age wise distribution of patients, among different age groups 21-30 years were highest (20.9%) and 71-80 years were least (6.97%) as mentioned.

Table 5.1.2: Age Distribution of Patients.

Age Group	Male	Female	Percentage
1-10	-	-	-
11-20	10	15	11.6%
21-30	25	20	20.9%
31-40	15	20	16.27%
41-50	20	15	16.27%
51-60	5	20	11.6%
61-70	5	30	16.27%
71-80	5	10	6.97%
80+	-	-	-

5.1.3: MARITAL STATUS

Table (5.1.3) indicates marital status. Where highest

incidence of epilepsy was seen amongmarried (79%)

Table 5.1.3: Indicating the Marital status of Epileptic patients.

Category	Male	Female	Frequency
MARRIED	105	110	79%
UNMARRIED	25	190	21%

5.1.4(a): PAST HISTORY OF EPILEPTIC PATIENTS

Among 215 patients 70 were with past medical history in which Hypertension and Hypothyroidism were recorded high in females than males as mentioned in table 5.1.4 and figure 5.1.4

Table 5.1.4: Past medical history of patients.

CATEGORY	MALE	FEMALE	FREQUENCY
HTN	15	45	55
DM-2	15	20	35
CVA	10	5	15
CKD	5	0	5
NEUROPATHY	5	0	5
HYPOTHYROIDISM	0	25	25
ENCEPHALOPATHY	0	5	5
DEMENTIA	0	5	5
DROP ATTACKS	0	5	5
SEIZURES	5	0	5
TIA	5	0	5
CSVT	5	0	5
TRAUMA	0	5	5

5.1.4(b): PAST HISTORY OF SEIZURES

Among 215 patients, the frequency/duration of seizure attack as follows

Table 5.1.4(b): Indicates the History of Seizure Attack.

	>oneweek	1month	3months	6months	1 Year	3 Years	5 Years	10 Years
Male	25	15	10	10	10	10	5	0
Female	25	35	15	10	10	20	10	5

PAST MEDICATION HISTORY OF PATIENTS

Among 215 patients, 130 patients were with past medication history.

Table 5.1.5: Indicates the Medication History of Patients.

Category	Male	Female	Frequency
Amlodipine	5	10	15%
Thyronorm	0	30	30%
Metoprolol	5	5	10%
Telmisartan	5	30	35%
Rosuvastatin	5	15	20%
Insulin	10	0	10%
Glimepiride	0	10	10%
None	55	80	145%

SOCIAL HISTORY OF PATIENTS

Table (5.1.6) indicates social history. In which smokers-10, alcoholic-35, both 20 as mentionedin figure (5.1.6)

Table (5.1.6): Social History of Patients.

MALE FEMALE CATEGORY		
SMOKING	50	0
ALCOHOL	125	0
SMOKING/ALCOHOL	25	5

TYPES OF SEIZURES

Table (5.1.6) indicates types of Seizures and is categorized into 7 types in which Generalized Tonic-Clonic Seizures is the most common type of seizures observed in 30% of population followed by Simple partial seizures (21%), Complex Partial Seizures (21%), Focal Seizures (14%),Localized Repetive Epilepsy (10%), TIA and Status Epilepticus (2%).

Table 5.1.7: Indicates percentage of Types of Seizures.

Type of Seizures	No of Patients with %
Generalized Tonic-Clonic Seizures	70(32%)
Simple partial seizures	50(23%)
Complex Partial Seizures	45(20%)
Localized Related Epilepsy	40(19%)
Status Epilepticus	10(7%)

5.1.8: SYMPTOMS

Among 215 patients 42%were with LOC,40% with jerking movements,40% with up rolling of eyes,35%with headache,26% with altered sensorium,23% with fever,21% with dizziness,19%with deviation of mouth,11% with frothing, slurred speech,7% are associated withtongue bite, lip smacking, vomiting, 4% with head injuries

Table: 5.1.8: Symptoms of Epileptic Patients.

Symptom	Percentage
Loss of Consciousness	42%
Jerking Movements	40%
Uprolling of Eyes	40%
Altered Sensorium	26%
Fever	23%
Dizziness	21%
Deviation of Mouth	19%
Slurred Speech	11%
Frothing	11%
Tongue bite	7%
Vomiting	7%
Lips Smacking	7%
Head Injury	4%

Table 5.2.1: Indicates Monotherapy, Polytherapy and Combination Therapy.

DRUGS	MONOTHERAPY		COMBINATION		POLYTHERAPY		TOTAL
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	FREQUENCY
LEVETIRACETAM	10	40	40	30	15	40	185
CLOBAZAM	-	5	5	5	-	20	35
LORAZEPAM	-	-	-	-	5	15	20
LACOSAMIDE	-	-	5	10	10	15	40
PHENYTOIN	-	-	15	-	5	15	35
DIVALPROEX	-	10	15	5	5	20	55
CARBAMAZEPINE	-	-	-	-	-	10	10
LOBAZAM	-	-	10	5	10	5	30
CLONAZEPAM	-	-	5	5	-	5	15
OXACARBAZEPINE	5	-	-	-	-	-	5

Table: 5.2.2: Indicates the Medication Adherence of Subjects.

CATERGORY	No. of Patients	Frequency
Male	83	38.5%
Female	125	58.3%

Table 5.2.3: Indicates the Present Health Status.

CATERGORY	I have no problem	I have problem	I am unable to perform
Mobility	184 Pt	24 Pt	9 Pt
Self-Care	174 Pt	25 Pt	16 Pt
Usual Activities	174 Pt	33 Pt	8 Pt
Pain/Discomfort	165 Pt	41 Pt	8 Pt

Table 5.2.4: Indicates the therapeutic outcome of Seizures in Epileptic Subjects.

CATERGORY	No. Of Patients	Frequency
Major	58	26.9%
Mild	71	33%
Didn't Experience a Seizure in past 4 weeks	86	40.1%

Table 5.2.5: Indicates the Frequency of Seizures Attack.

CATERGORY	No. of Patients	Frequency
ONE	87	40.46%
TWO	27	12.55%
THREE	79	36.74%
FOUR	6	2.79%
FIVE	5	2.32%
SIX AND MORE	11	5.11%

Table 5.2.6: Indicates the Quality of Life in Epileptic Subjects.

CATERGORY	No. of Patients	Frequency
Very Good	50	23.1%
Pretty Good	66	30.8%
Good/Bad	83	38.5%
Pretty Bad	16	7.6%
Very Bad	0	0%

Table 5.2.7: Indicates Cognitive effects of therapy.

	Attention	Memory	Fluency	Language	Visuospatial
Male Not Affected	77%	74%	78%	86%	88%
Male Affected	23%	26%	22%	14%	12%
Female Affected	24%	78%	79%	88%	93%
Female not Affected	76%	78%	79%	88%	93%

Table 5.2.8: Indicates the Neurological Effects of Subjects.

Neurological Effects	Male	Female	Total
Nausea	10	16	26
Headache	17	17	34
Sedation	35	18	53
Tingling	8	4	12
Numbness	75	77	152
Dizziness	43	20	63

Table 5.2.9: Indicates the Analysis BPRS Scale.

CATEGORY	VERY MILD	MILD	MODERATE
ANXIETY	33.3%	33.3%	26.7%
DEPRESSION	37.5%	18.8%	26.7%
MOOD CHANGES	30.8%	46.2%	30.8%
BEHAVIORAL CHANGES	69.2%	-	23.1%
HALLUCINATIONS	84.6%	15.4%	-
SUICIDAL THOUGHTS	-	-	-

Table (5.3.1a): Chi square P-value table.

CHISQAURE VARIABLES	SIGNIFICANT VALUE
HISTORY Vs FREQUENCY	0.008
TYPES Vs QUALITY OF LIFE	0.043
TYPES Vs FREQUENCY	0.006
HISTORY Vs NEUROLOGICAL EFFECTS	0.049
HISTORY Vs COGNITIVE EFFECTS	0.004
HISTORY Vs PSYCHOLOGICALEFFECTS	0.0043
NEUROLOGICAL EFFECTS Vs DRUGS	0.0079
COGNITIVE EFFECTS Vs DRUGS	0.008
PSYCHOLOGICAL EFFECTS Vs DRUGS	0.007

The BELOW Table (5.3.1b) shows information regarding Mean, Standard-Deviation and p-value of a various variables

Table (5.3.1b): Mean, Standard deviation & P-value table.

CHARACTERISTICS	N	MEAN	STANDARDDEVIATION	P-VALUE
AGE	215	41.51	17.915	0.0052
GENDER	215	1.60	0.491	0.0073
MARITAL STATUS	215	1.23	0.420	0.0038
TYPES	215	2.34	1.253	0.0083
HISTORY	215	3.27	2.108	0.0024
FREQUENCY	215	2.12	1.354	0.0013
QUALITY OF LIFE	215	2.17	0.856	0.0067
NEUROLOGICALEFFECTS	215	3.92	1.686	0.0024
COGNITIVE EFFECTS	211	1.88	0.822	0.0051
PSYCHOLOGICAL EFFECTS	215	2.76	1.302	0.0079
MONOTHERAPY	80	1.00	0	-
COMBO THERAPY	75	1.00	0	-
POLYTHERAPY	60	1.00	0	-

DISCUSSION

" AN OBSERVATIONAL STUDY : TO ASSESS THE SAFETY AND TOLERABILITY OF HIGH INTENSITY ATORVASTATIN IN VARIOUS CARDIOVASCULAR DISEASES " was conducted in a tertiary care hospital considering in-patients. The data was collected for 120 patients using data collection forms.

In our study, among 120 patients, 62% were males and 38% were females. Our study has a relatively high number of patients(31.6%),of age group between 51-60 years. Whereas age groups 40-50, 61-70 and 7180 also hold high number of patients i.e.,31%, 16% and 17% respectively.

In our study 45% of the patients were given 40 mg dose and 55% of the patients were given 80 mg dose of atorvastatin. Out of which few side effects were observed but are not severe or life threatening. Past medical history shows that 36 patients had HTN, 6 patients had DM, 36 patients had HTN with DM and 15 patients had old CAD.

In our study, the social history of patients was also considered. Among 120 patients, 36 patients had alcohol, 15 patients had smoking and 15 patients had both smoking and alcohol consumption habits.

Our study also considered complaints of subjects. Among which 41.6% patients had chest pain, 25% had SOB, 12.5% had sweating and 20.9% had palpitations.

In our study, IWMI & AWMI cases were most commonly reported, accounting for 25% of total.

TIA and Unstable angina have equal share in diagnosis i.e., 10% each. NSREMI was seen in 12.5%, AIS in 15% and RHD in 2.5%. RHD was least diagnosed in our study(2.5%).

The study was majorly focused on safety and tolerability of high intensity atorvastatin that can be evaluated by monitoring side effects and lipid values.

The Chi-Square test and T-test was performed for our study using SPSS software. It showed that the P-value was clinically significant for side effects and lipid values.

It was observed from our study that, The patients taking high intensity atorvastatin therapy have control over reducing LDL-C and TC, and increasing HDL-C levels. It also showed that atorvastatin is used to reduce cholesterol to a greater level and is considered as a good choice of drug in preventing various CVDs with lesser side effects.

CONCLUSION

Atorvastatin is a HMG-CoA reductase inhibitor belonging to the class of drugs called 'statins', used as lipid lowering medications in prevention and treatment of cardiovascular diseases.

It is used primarily in the treatment of dyslipidemia like hyperlipidemia, and mixed dyslipidemia, homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia.

It is also used to prevent cardiovascular events in patients with abnormal lipid profiles in combination with dietary modifications.

Atorvastatin is indicated in conditions like MI, fatal and non-fatal stroke, patients with CHD and also for revascularization procedures. It is used as a preventive agent in transient Ischemic attack (TIA).

Our study concluded that High intensity atorvastatin was found to reduce LDL-C, TC and TG to a greater level

and also increases HDL-C level. The study also found that Atorvastatin in both the 40 mg and 80 mg doses was well tolerated with fewer side effects and no patient had a severe or life threatening condition during the therapy. Thus it shows that High intensity Atorvastatin is used in prevention of various CVDs and is found to be safe and well tolerated.

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