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Research Article

WHY CARDIAC PATIENTS DISCONTINUED LIPID LOWERING AGENTS: VIEWS ON GASTROINTESTINAL ADVERSE REACTIONS AND THEIR RISK FACTORS

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ABSTRACT

High incidence of adverse drug reaction (ADRs) found during statin therapy. Gastrointestinal (GI) ADRs mentioned in previous studies and many patients discontinued statin therapy because of these ADRs. Objective is prediction the incidence of GI ADRs induced by statins and their risk factors. Also determination the incidence of patients discontinued their medications because of GI ADRs. Cross-sectional study conducted to 500 outpatients at general hospital in Northern part of Malaysia Peninsula. The severity levels of GI ADRs induced by statin classified into mild, moderate and severe. Statin information, dyslipidemia type and concurrent diseases and medications were collected from patients' progress file. Flatulence occupied the highest incidence of severe GI ADRs (4.2%). The highest predicted risk factor associated to flatulence, swallowing difficulty, dyspepsia, constipation, diarrhea, nausea/vomiting, swallowing difficulty, and abdominal cramps was Indian (p=0.001, OR= 1.68) and (p =0.014, OR=2.1), consumption of alcohol (p=0.011, OR=2.9) and (p=0.001, OR=2.95), 60 mg lovastatin dose (p=0.039, OR=1.80) and (p=0.003, OR=6.9), and diabetes mellitus (p =0.01, OR=4.79), respectively. Incidence of patients discontinued their statin therapy because of GI ADRs was 4.8%. In conclusion, the risks factors contributed GI ADRs were; female, Indian race, consumption of alcohol, lovastatin dose, secondary dyslipidemia, diabetes and beta-blockers. Recommendations of study are stopping consumption of alcohol, changing in dose of lovastatin and antihypertensive type to reduce GI ADRs and minimize discontinuation of therapy.

Keywords: Gastrointestinal adverse reactions, Statin, Risk factors, Discontinuation of therapy

INTRODUCTION

Statin is the drug of choice to control dyslipidemia and cardiovascular diseases, and reducing the incidence of mortalities and morbidities in cardiac patients[1-3]. The reported incidence of patients used statin ranged 62.5% to 91.7%, and annual rate of utilization is 0.5% to 6.7%[4]. In Malaysia, about 90% of coronary heart patients use statins[5]. Therefore high incidence of adverse drug reactions (ADRs) induced by statins found during therapy. Cardiac patients are more susceptible to these ADRs because probability of risks by multiple therapies such as medication errors and polypharmacy[6].

ADRs induced by statin were reported by many studies [7-9], and considered to be early symptoms of polyneuropathy, myopathy, or extrapyramidal disorders if they were not handled[10]. However, these ADRs also contributed in discontinuation of therapy without informing their doctors[11-13], causing poor patients' adherence and dyslipidemia control[12, 14].

Several previous studies showed that gastrointestinal (GI) symptoms were the common adverse reactions during statin therapy[15, 16]. Previous reports stated these ADRs during statin therapy are abdominal pain, flatulence, nausea and vomiting, diarrhea, constipation, dyspepsia (indigestion), and swallowing problems[8]. Objectives of this study were to assess the incidences, severity and risk factors of GI ADRs. As well as determining the incidence of patients discontinued statin therapy.

METHOD

Study design

Cross-sectional conducted to five hundred of 1800 cardiac outpatients. This study carried out at general hospital in Northern part of Malaysia Peninsula. Approval of this study was granted from ethical committee of the hospital.

Assessment of ADRs and data collection

Validated self-administered questionnaire used in patients' reporting for GI ADRs induced by statin. The severities of GI ADRs categorized into mild, moderate and severe. The GI ADRs included in this questionnaire were abdominal pain, nausea and vomiting, flatulence, diarrhea, constipation, dyspepsia (indigestion), and swallowing problems. All information of these ADRs depended the patients' self-reporting. While all the information of statin therapy, dyslipidemia type, concurrent medication and diseases were collected from patients' progress files.

Inclusion and exclusion criteria

Patients able to understand English or Bahasa Malaysia language, age more than 18 years old, and use statin were included in this study. Patients from other clinics, changed in type or dose of statin, and had gastrointestinal problems were excluded.

Statistical Analysis

SPSS version 18 used to analyze the collected data from questionnaire. The statistical tests used were descriptive analysis, chi-square, logistic regression and reporting odd ratio (OR). Results considered statistically significant when their p values were less than 0.05.

RESULTS

Majority of patients were males (70%), Chinese (37.6%) and had primary dyslipidemia (51.5%), with small proportions of smokers (12%) and alcohol consumers (9%). The mean age of these patients was 60 ± 10 years and geriatric occupied 30% of them. The most common type and dose was lovastatin (81%) and 20 mg doses (57.8%) with mean duration of therapy 3.5±3.0 and small percentage of combination therapy (7%). Most of patients suffered from the hypertension (68.8%), ischemic heart diseases (60.8%), and diabetes (44.2%). The common concurrent medications were beta-blockers (80.4%), aspirin (70.6%), and angiotensin converting enzymes inhibitors (64.8%), as shown in Table 1.

Flatulence occupied the highest incidence (50%) among GI ADRs, followed by dyspepsia (41.2%), constipation (25.2%), abdominal cramps (24%), diarrhea (20.8%), nausea/vomiting (15.8%), and swallowing problems (14.4%). The incidences of severe ADRs were; flatulence (4.2%), dyspepsia (3%), constipation (1.6%), swallowing problems (1%) abdominal cramps (0.8%), nausea/vomiting (0.8%), and diarrhea (0.2%), as shown in Table 2.

The predicted risk factors significantly associated to GI ADRs were gender, race, consumption of alcohol, statin dose, type of dyslipidemia, concurrent diseases and medications. Females had higher incidence of swallowing problems induced by statin therapy (19.5%, p=0.037, OR=1.73). Indian patients had the highest incidence of flatulence (53.4%, p=0.001, OR= 1.68), dyspepsia (47.4%, p=0.017, OR=1.74), constipation (33.1%, p=0.033, OR=1.72), and swallowing problems (20.3%, p=0.014, OR=2.1). (Table 3)

Table 1 Demographic information of cardiac outpatients

Demographics	Variables	%
Gender	Male	70%
	Female	30%
Race	Malay	34.4%
	Chinese	37.6%
	Indian	26.6%
	Foreign	1.4%
Age	28-50 yr	19%
(mean 60±10)yr	51-65 yr	51%
	66-92 yr	30%
Smoke	Yes	12%
	No	88%
Alcohol consumption	Yes	9%
	No	91%
Dyslpidiemia type	Primary	51.5%
	Secondary	48.5%
Primary dyslipidemia subtype	I	5.3%
	IIa	50.6%
	IIb	23.9%
	III	2.8%
	IV	13%
	V	4.5%
Secondary dyslipidemia subtype	Renal	7.3%
	Diabetes	86.3%
	Nephrotic syndrome	0.4%
	Liver	0.4%
	Drugs	0.9%
	Hypothyroidism	4.7%
Type of statin	Atorvastatin	8%
	Simvastatin	9.4%
	Lovastatin	81%
	others	1.6
Combination therapy	Yes	7%
	No	93%
Duration of therapy	≤ 3mo. or less	3.2%
Mean (3.5±3.0) yr.	> 3mo. -1 yr	26.7%
	> 1yr-5yr	52.5%
	> 5yr-20y	17.6%

Table 2: Incidence and severity of gastrointestinal ADRs

GI ADRs	Overall % (no)	Mild % (no)	Moderate % (no)	Severe % (no)
Flatulence	50 (250)	29.2 (146)	16.6 (83)	4.2 (21)
Dyspepsia (indigestion)	41.2 (206)	27.8 (139)	10.4 (52)	3.0 (15)
Constipation	25.2 (126)	15.6 (78)	8.0 (40)	1.6 (8)
Abdominal cramps	24 (120)	18.4 (92)	4.8 (24)	0.8 (4)
Diarrhea	20.8 (104)	16.2 (81)	4.4 (22)	0.2 (1)
Nausea and vomiting	15.8 (79)	11.0 (55)	4.0 (20)	0.8 (4)
Swallowing difficulty	14.4 (72)	10.4 (52)	3.0 (15)	1.0 (5)

Table 3: Risk factors of GI ADRs induced by statins in cardiac outpatients

Risk factor	ADRs (percentage, *p* value, OR, CI)						
	Flatulence	Dyspepsia	Constipation	Abdominal cramps	Diarrhea	Nausea and Vomiting	Swallowing problems
Gender (female)	NS	NS	NS	NS	NS	NS	19.5% *p*=0.037 OR=1.73 CI=1.0-2.9
Race (Indian)	53.4%, *p*=0.001, OR= 1.68, CI=1.3-3.2	47.4%, *p*=0.017 OR=1.74 CI= 1.1-2.8	33.1%, *p*=0.033 OR=1.72 CI= 1.0-2.8	NS	NS	NS	20.3% p=0.014 OR=2.1 CI=1.16-3.6
Smokers	NS	NS	NS	NS	NS	NS	NS
Alcoholic	NS	57.5%, *p*=0.011 OR=2.9 CI=1.3-6.5	46.9% *p*=0.001 OR=2.95 CI=1.6-5.5	36.2% *p*=0.043 OR=1.93 CI=1.0-3.6	NS	NS	NS
Age	NS	NS	NS	NS	NS	NS	NS

Continued Table 3

Risk factor	ADRs (percentage, *p* value, OR, CI)						
	Flatulence	Dyspepsia	Constipation	Abdominal cramps	Diarrhea	Nausea and Vomiting	Swallowing problems
Duration > 5 yr	NS	NS	NS	NS	NS	NS	NS
Statin types	NS	NS	NS	NS	NS	NS	NS
Atorvastatin doses (20mg)	NS	NS	NS	NS	NS	NS	NS
Simvastatin dose (40mg)	NS	NS	NS	NS	NS	NS	NS
Lovastatin doses (60mg)	NS	NS	NS	NS	54.6% *p*=0.039 OR=1.80 CI=1.0-3.2	51.2% *p*=0.003 OR=6.9 CI=1.9-25	NS
Type of dyslipidemia (secondary)	NS	NS	NS	NS	NS	21.5% *p*=0.005 OR=2.1 CI=1.2-3.4	NS
Combination therapy	NS	NS	NS	NS	NS	NS	NS
Hypertension	NS	NS	NS	NS	NS	NS	NS
Diabetes mellitus	NS	NS	NS	54.2% *p*=0.01 OR=4.79 CI=1.5-15.8	NS	NS	NS
Ischemic heart disease	NS	NS	NS	NS	NS	NS	NS
Beta blockers	NS	43.3% *p*=0.023 OR=2.02 CI=1.1- 3.7	NS	NS	NS	NS	NS
ACE-I	NS	NS	NS	NS	NS	NS	NS
Aspirin	NS	NS	NS	NS	NS	NS	NS
Gliclazide	NS	NS	NS	NS	NS	NS	NS
Metformine	NS	NS	NS	NS	NS	NS	NS

Consumption of alcohol contributed to increase the incidence of dyspepsia (57.5%, *p*=0.011, OR=2.9), constipation (46.9%, *p*=0.001, OR=2.95) and abdominal cramps (36.2%, *p*=0.043, OR=1.93). Lovastatin dose (60 mg) significantly associated to diarrhea (54.6%, *p*=0.039, OR=1.80), and nausea/vomiting (51.2%, *p*=0.003, OR=6.9). Dyslipidmia type also associated to high incidence of nausea/vomiting (21.5%, *p*=0.005, OR=2.1). Diabetes mellitus and beta-blockers were significantly associated to high incidence of abdominal cramps (54.2%, *p*=0.01, OR=4.79) and dyspepsia (43.3%, *p*=0.023, OR=2.02) respectively, as shown in Table 3.

There were 24 (4.8%) patients discontinued their therapy after asked about severe GI ADRs triggered them to stop taking of medications without telling their doctors. However, the serious GI ADRs were dyspepsia (1.2%) and nausea/vomiting (1%), as shown in Table 4.

Table 4: Incidence of patients discontinued their therapy induced by GI ADRs of statins

GI ADRs	No. (%)
Flatulence	2 (0.4%)
Dyspepsia (indigestion)	6 (1.2%)
Constipation	3 (0.6%)
Abdominal cramps	3 (0.6%)
Diarrhea	4 (0.8%)
Nausea and vomiting	5 (1%)
Swallowing difficulty	1 (0.2%)

DISCUSSION

All GI ADRs mentioned in this study were mentioned in many previous studies[17-28]. Patients' self-reporting was the suitable method in assessment of adverse reactions because first patients were more opened in describing their serious symptoms during therapy. Second, some doctors were either unfamiliar or not caring about adverse reactions of medications[29,30]. According to literatures the incidences of ADRs by patients' self-reporting were higher than done by doctors; however, there is lack in assessing the severity of these ADRs and their relation to discontinuation of therapy. The incidence depended the self-reporting in this study was higher than reported in previous study, for example the incidence of nausea was 15.8% which higher than Hildemann SK *et al* (0.06%) [31], Sienra-Pérez JC *et al* (3.9%)[32], in Thiery J *et al* (less than 10%) [33], and Galal MS *et al* (4.3%) [34].

Logistic regression and reporting odd ratio used to determine the risks factors contributed in GI ADRs induced by statins. Females significantly associated to swallowing problems than males because higher susceptibility to ADRs and differences in pharmacokinetic and pharmacodynamic properties between genders[35]. FDA stated differences among races in comparing of ADRs[36], Indian patients had highest incidence of flatulence, dyspepsia, constipation, and swallowing problems. But the degree of association, using odd ratio, between these ADRs and ethnicity showed significantly higher in swallowing problems, followed by dyspepsia, constipation and flatulence. Alcohol also interacts with drug activity and function of mitochondria causing increasing the incidence of ADRs[37]. However, patients consumed alcohols had higher odd ratio in constipation followed by dyspepsia and abdominal pain, as shown in Table 3.

World Health Organization (WHO) recommended checking dose in dispensing of medications[38]. Higher dose of lovastatin (60 mg) contributed to increase the incidence of GI ADRs, but it more associated to nausea/vomiting followed by diarrhea. Type and etiology of dyslipidemia also contributed in increase the incidence of GI ADRs, secondary dyslipidmia had significantly higher incidence of nausea/ vomiting than primary, as shown in Table 3.

Although no significant impact of diabetes mellitus to GI ADRs in previous study[39], but it significantly associated to abdominal pain in current study. Also, beta-blockers related to higher incidence of dyspepsia and this is consistent to Colivicchi's opinion that increasing number of medications causes increasing the incidence of ADRs and discontinuation of medications[40]. Although GI ADRs of statin mentioned in previous studies and all patients used statin, but demographic data like consumption of alcohol, concurrent diseases

like diabetes, or concurrent medications like beta-blockers also associated to these ADRs.

There were 24 patients (4.8%) discontinued therapy because the GI ADRs. However, this finding was lower than mentioned in D'Agostino *et al* (20.4%) [21], and Colivicchi *et al* (28.8%)[40], but higher than Sienra-Pérez JC *et al* (3.8%)[32], Flack *et al* (3.2%)[12], Bissonnette *et al* (0.2%)[11] and Wierzbicki A *et al* (3.7%)[15].This variation because all studies used different type and doses of statin. In conclusion, patients' self-reporting is the proper method in reporting of ADRs during statin therapy than physicians' reporting[41,42]. Females, Asian Indians, consumers of alcohol, lovastatin dose (60mg), dyslipidemia type, diabetes mellitus and beta-blockers are the main risk factors of GI ADRs. Recommendations of study are stopping consumption of alcohol, changing in dose of lovastatin and antihypertensive type to reduce GI ADRs and minimize discontinuation of therapy.

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