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Clinical reviews about Overall Incidence of Adverse Effects in Amiodarone Treatment

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Abstract : Amiodarone is a effective agent for the treatment of many cardiac rhythm disturbances, ranging from paroxysmal atrial fibrillation to intractable ventricular tachyarrhythmias. However, amiodarone causes variable adverse effects from minor to life threatening. The aim of this study was to review general incidence of and associated factors with the adverse effects of amiodarone medication. Eight hundred seventy six patients who had taken amiodarone regularly over three months or who stopped medication due to any adverse effect between November 1996 and March 2005 at Keimyung University Dongsan medical center were included. Ninty six patients (11.0%) developed the amiodarone toxicity in any type. Among them, 60 patients showed hypothyroidism and held 62.5%. 10 patients showed pulmonary toxicity and held 10.4%, 20 patients and 20.8%, 6 patients and 6.3%. Patients with toxicity were older than patients without toxicity as 65.1±12.1 and 61.9±13.4 yr (p=0.026). Total dose and duration of amiodarone medication in the toxicity group were 1615.4±1414.6 gm and 734.9±677.1 days and 565.4±668.1 gm and 1249.7±1411.6 days in non-toxicity group respectively. The incidence of amiodarone induced toxicity was generally lower than established reports. If we had done regular protocol for checking up amiodarone adverse effects, we could detect amiodarone induced toxicity more exactly. It suggests that an incidence of amiodarone induced adverse effects can be lessened and the toxicity is prevented to some degree treating patients with amiodarone more carefully and performing a regular follow up protocol during medication.

Key Words : Adverse effects Amiodarone, Doses, Duration

Introduction

Amiodarone is a potent antiarrhythmic agent used to treat ventricular arrhythmias and atrial fibrillation. The drug prevents the recurrences of life threatening ventricular arrhythmias and produces a modest reduction of sudden cardiac deaths in high risk patients.

[1-4] Amiodarone is more effective than sotalol or propafenone in preventing recurrent atrial fibrillation in patients for whom a rhythm control strategy in chosen.[5]

The use of amiodarone in any clinical setting, however, has been associated with concerns about adverse effects and end organ toxicities that might be outweigh its potent beneficial antiarrhythmic effect.

[6] Amiodarone has been reported associated with toxicities involving the lungs, thyroid gland, liver, eyes, skin and nerves.

[7-9] Pulmonary toxicity is the most serious adverse effect which may result from direct drug induced phospholipidosis or immune mediated hypersensitivity.

[7] Thyroid dysfunction is the most common complication that requires intervention. Thyroid dysfunction has been described up to 10% of patients receiving a long term amiodarone medication.

[5] Liver toxicity, manifested by an elevation of hepatic transaminase level, is common in patients who are receiving the long term amiodarone medication.

[8] Gastrointestinal symptoms, optic neuropathy, photosensitivity, corneal microdeposition and skin pigmentation has been developed in various rates. Many studies reports that the amiodarone induced toxicity was more common in higher amiodarone doses, and an advanced age.

[6,10,11] However, other studies report that few serious adverse effect have occurred when amiodarone is administered in lower doses. Many studies have tried to confirm what causes amiodarone induced toxicity. Nonetheless, an object assessment of likelihood of experiencing amiodarone related adverse effects with exposure various degree of dose is lacking in published data, and little informations have been available on relation with adverse effect rates and patient's characteristics. The aim of this study was to demonstrate a practical frequency of amiodarone induced toxicity by analyzing the patients' medical record in retrospective methods.

Materials and Methods

1. Patients population

The 876 patients who had taken amiodarone regularly between November, 1996 and March , 2005 over 3 months or who has stopped medication due to any adverse effect under the care of the Division of Cardiology at Keimuyng University Dongsan medical center were included. Patients who had taken medication under 3 months or used transient such as controlling atrial fibrillation at post operation were excluded. This study was performed by reviewing medical records retrospectively.

2. Definition of Amiodarone toxicity

In this study, we classified four adverse effects. Pulmonary toxicity, thyroid dysfunction, occular toxicity and dermatolgic

adverse effect. This study was performed in retrospective methods, some adverse effect has not been in medical records.

The pulmonary toxicity was defined when patient receiving amiodarone medication complained the pulmonary symptoms such as coughing, sputum and fever with new onset infiltrations on the simple chest radiography or computed tomography. Because this study was performed in retrospectively, clinical parameters such as Pulmonary Function test (PFT) was not done in all patients even if the patients who manifest pulmonary adverse effects. The thyroid dysfunction including hypothyroidism and hyperthyroidism was defined the combination of clinical symptoms and abnormal results in thyroid function test. We defined Hypothyroidism as the elevation of TSH and excluded an isolated elevation of T3 or T4. The patients who were diagnosed as hyperthyroidism or hypothyroidism before medication were excluded. The ocular toxicity was defined when patients complaint blurred visions. The dermatologic adverse effect was defined when patients complaint photosensitivity or bluish skin pigmentations. Other manifestations of adverse effects did not be found in medical records,

3. Data analysis

Clinical and dermographic characteristics were examined for possible association with the occurrence of amiodarone toxicity. Parameters specifically sought in each case were included the patient's age and sex, the dose and duration of amiodarone therapy, clinical evidence of amiodarone induced organ toxicity (especially pulmonary, thyroid, opthalmologic, dermatologic and hepatic injury). The duration of medication (day) was computed as the length of time from the start of amiodarone therapy until either the end of therapy, loss of follow up (last date for which reliable information was available) or the development of pulmonary toxicity. Total doses (gm) were calculated as the commucated amount of amiodarone taken during total duration (day). Mean dose was calculated as dividing total dose by duration of therapy.

4. Statistical analysis

Statistical analysis was done using SPSS statistical software, version 12 for Windows(SPSS Inc., Chicago, Illinois, USA). Comparison between patients with and without amiodarone pulmonary toxicity were made using t test for continuous variables. A p value of less than 0.05 was considered significant.

Results

1. Baseline characteristics

Among 876 patients enrolled in the study were 62.2 yr old in average and 505 patients (57.6%) were male. 598 patients had started to take amiodarone due to atrial fibrillation or atrial flutter. And 50 and 228 patients had started to take amiodarone due to supraventricular tachycardia (SVT) and ventricular tachycardia (VT) respectively. Total duration means the sum of all prescription day. Total doses was calculated by multiplying total prescription day and daily dose. Mean doses were calculated by dividing

total dose by total prescription day. Total duration, total doses and mean doses of all patients were 575.9±67.9 day, 1289.7±1415.8 and 266.9±101.5 mg, respectively.

2. The frequency of overall toxicity

Among 876 patients, 96 patients has showed toxicity in any form and held 11%. 780 (89%) patients has not showed any side effect. In the group which shows any adverse effect, total duration of medication were 734.9±677.1 days. Total dose and mean doses were 1615.4±1414.6 and 245.2±82.1 mg, respectively (Table 1).

In this study, we had found four category of amiodarone toxicity. These were pulmonary toxicity, thyroid dysfunction, opthalmologic adverse effect and dermatologic adverse effect. Hyperthyroidism and hepatic adverse effect has not been found in medical record.

Of 96 patients, 60 patients has showed hypothyroidism and held 62.5%. 10 patients showed pulmonary toxicity and held 10.4%, 20 patients and 20.8%, 6 patients and 6.3%. 52 patients were male and mean age of all patients was 65.1 yr. 67 patients had started to take amiodarone due to atrial fibrillation or atrial flutter. And 4 and 25 patients had started to take amiodarone due to supraventricular tachycardia (SVT) and ventricular tachycardia (VT) respectively (Table 2).

3. Thyroid dysfunction

60 patients showed thyroid dysfunction during treatment with amiodarone. The case of amiodarone induced hyperthyroidism has

Table 1. Clinical demaographic findinge of amiodarone induced toxicity in 876 patient

	Normal	Toxicity
Number of patient	780 (89%)	96 (11%)
Gender (M/F)	453/327	
Age(yr)*	61.9±13.4	65.1±12.1
Type of Pretreatment arrhythmia (n)		
AF of AFL	531 (68%)	67 (69.8%)
SVT	46 (5.9%)	4 (4.2%)
VT of VF	203 (26.1%)	25 (26%)
Total duration of medication (day)*	565.4±668.1	734.9±677.1
Total dose of medication (g)*	124.97±141.16	161.54±141.46
Mean dose of medication (mg/day)*	269.5±103.3	245.2±82.1

* $p<0.05$, AF; Atrial fibrillation, AFL; Atrial flutter, SVT; Supreventricular tachycardia, VT; Ventricular tachycardia, VF; Ventricular fibrillation.

Table 2. Overall incidence of amiodarone induced toxicity

	Hypothyroidism	Pulmonary toxicity	Ocular toxicity	Dermatologic toxicity
No. of patient	60 (6.9%)	10 (1.1%)	20 (2.3%)	6 (0.7%)
Gender (M/F)	28/32	7/3	12/8	5/1
Age (yr)	66.2± 11.2	73.8± 7.3	58.9± 13.9	60.2± 11.0
TP (day)	733.6±659.6	866.2±596.3	498.9±425.1	1316.8±1259.5
TD (g)	151.0±134.0	212.2±154.9	153.6±149.1	208.8± 179.6
MD (mg/day)	225.8± 68.5	258.2± 87.7	312.6± 87.8	193.8± 55.9

TP; Total duration of medication, TD; Total dose of medication, MD; Mean dose of medication

not been found. Among 60 patients, 28 patients were male and mean age was 66.2± 11.2 yr. Total duration of medication in this group was 733.6±656.9 days, total dose and mean dose was 1510.3±1340.4 mg and 225.8 ±68.5 mg, respectively.

4. Pulmonary toxicity

10 patients developed pulmonary toxicity, resulting in am overall incidence of 5.8%. 7 patients were male and mean age was 73.8± 7.3 yr. Total duration of medication was 866.2 ±596.3 days and total dose, mean dose was 2122.2±1548.5 mg and 258.2±87.7 mg respectively.

5. Occular toxicity

Among twenty patients showing occular toxicity, 12 patients (60.0%) was male and mean age was 58.9±13.9 years. Total duration of medication was 498.9±425.1 days and total dose, mean dose was 1535.5.2± 1490.38 mg and 312.6±87.8 mg respectively.

6. Dermatologic adverse effect

6 patients showed dermatolgic adverse effect. 5 patients were male and mean age was 60.2±11.0 years. Total duration of medication was 1316.8±1259.5 days and total dose, mean dose was 2087.5±1795.7 mg and 193.8±55.9 mg respectively.

7. Comparison between groups.

In the below, the group which didn't show any adverse effect was named group 1 and show any adverse effect named group 2. Cumulative dose of medication between group 1 and 2 was 1249.7±1141.6 mg and 1615.1± 1414.6 mg respectively and shows statistically significant difference. (p=0.017) Total medication duration (day) between group 1 and 2 was 556.4±668.1 and 734.1± 677.1 and shows statistical significance. (p=0.014) Patients, who developed amiodarone toxicity, were older compared with those without amiodarone toxicity. Mean age (years) of group 1 and 2 was 61.9±13.4 and 65.1±12.1 respectively and showed

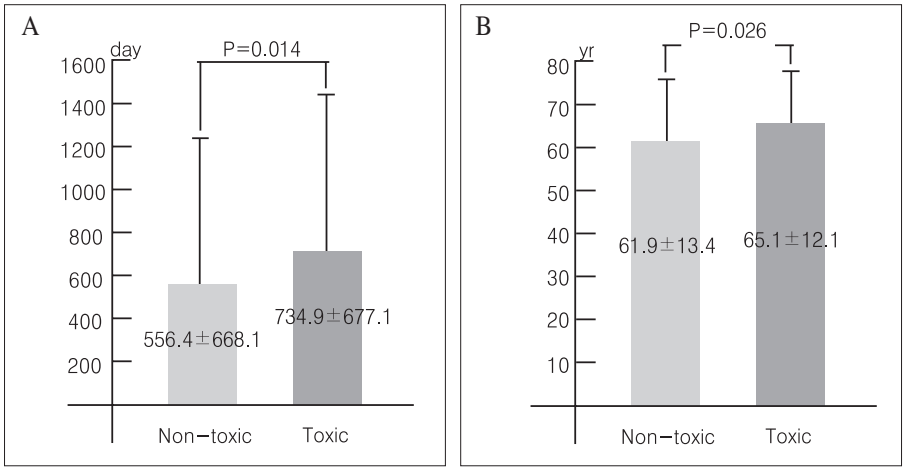

Fig. 1. Comparison between normal and toxicity group (A) Comparison total medication duration between 2 groups, (B) Comparison age between 2 groups

statistically significant difference. (p=0.026) (Fig. 1)

Discussion

1. Incidence of toxicity

Amiodarone is an iodine-containing compounds with some structural similarity to thyroxine[3] and highly effective agent for the prophylaxis and treatment of many cardiac rhythm disturbances, ranging from paroxysmal atrial fibrillation to life threatening ventricular tachyarrhythmia.[1-5] Unlike many other antiarrhythmic agents, amiodarone appears to be safe in patients with significant left ventricular dysfunction,[12-13] and may confer prognostic benefit in some patients subgroup.[14-15] Regardless of so many benefits, amiodarone has been limited in worldwide use because of adverse effects ranging from minor to life threatening event. There have been spontaneous case reports about amiodarone adverse effects and these reports maybe helpful in demonstrating diagnostic techniques, elucidating or suggesting mechanism or methods of management, or teaching and reminding. They can also give some idea of the range of amiodarone in unselected populations outside hospital during routine therapy. However, there has been little study about overall adverse effect in the large, unselected population in practice.

Many reports have been reported that relatively high incidence of thyroid dysfunction compared to other adverse toxicity. In general, many studies published reported an overall incidence of amiodarone induced thyrotoxicosis (AIT) ranging from 1% to 23% and Amiodarone Induced Hypothyroidism(AIH) ranging from 1% to 32%.[16] Lombardi *et al.*[17] reported that overall incidence of amiodrone induced thyroid dysfunction is in range of 14%-18%. Our data showed that 6.8% of the patients reveals thyroid dysfunction. However, we

could not found the case of hyperthyroidism induced by amiodarone in reviewing electrical medical records. Before we perform regular follow up monitoring program, thyroid function test had not been done until patient complaint consistent with thyroid dysfunction, real incidence of amiodarone induced thyroid dysfunction would be higher than our study. Physicians who treat patients with amiodarone have to be careful not to develop amiodarone induced thyroid dysfunction, so perform regular monitoring program which check up thyroid function regularly. The incidence of amiodarone pulmonary toxicity in the literature depends on the diagnostic criteria used. Initial reports by Dusman *et al.* in which patients were usually treated with amiodarone doses over 400mg/day noted as 5 to 15 percent incidence of pulmonary toxicity.[18] Smith *et al.*[19] and Hafajee *et al.*[11] have both reported a low incidence (1%) of pulmonary toxicity although the diagnosis in these studies relied mostly on radiographic abnormalities without histologic supports. A higher incidence (17%) of toxicity was reported by Magro *et al.*[20], who used similar clinical diagnostic criteria to those used in the present study but emphasized symptoms and radiographic abnormalities without the aid of DLCO abnormalities. Our incidence of 1.1% is lower than that of previously reported and was based on the appearance of new symptomatology, most frequently dyspnea and cough, and confirmed additional diagnostic testing including chest radiograph, pulmonary function test and computer tomography. Differences in the patient population studied and criteria used to make up the diagnosis of amiodarone pulmonary toxicity may account for the observed discrepancies between our findings and those of other reports. Most guidelines and reports classified amiodarone adverse effect as major including pulmonary, thyroid, liver and ocular adverse effect such as blurred vision and as minor including gastrointestinal symptom, photosensitivity, skin color discoloration and corneal microdeposition which didn't cause blurred vision. Connolly[8] reports that liver toxicity occurred at a rate of 0.6 % annually and Levis *et al.*[21] reported that asympotomatic elevation of aminotransferase levels was detected in approximately one-fourth of patients. However, we couldn't see liver toxicity that be defined to elevation of liver transaminase 3 times more than normal value because serial laboratory monitorings were not done until specific event has not occurred, so the actual incidence would be higher than our data, too. Pollak[7] reported that corneal microdeposits are visible on slit-lamp examination in nearly all patients treated with amiodarone and seldom affects vision and rarely necessitate discontinuation of the drug.[7] In our data, amomg 876 patients enrolled in these study, 20 patients complaints of blurred vision during follow up day and in the opthalmologic exam, showed corneal microdeposition. We have to perform regular opthalmologic examination on patients who take amiodarone before they complaint to symptom related to occular toxicity.

2. Dermographic factors predisposing to toxicity

When dermographic parameters were analyzed, a higher occurrence of amiodarone toxicity was found in the older patients.

Patients who received amiodarone in high dose and long time, higher occurrence of amiodarone induced toxicity developed. We have to be more careful when we treat patients who received amiodarone in higher dose in a long time and elderly patients.

3. The importance of follow-up protocol

Amiodarone used world wide agent to treat life threatening ventricular tachyarrhythmia. However, substantial adverse effect has been reported in variable incidence from minor adverse effect to fatal toxicity. In our study, overall incidence of amiodarone induced toxicity was lower than previous reports. It depends on diagnostic criteria, analyzing methods, population characteristics largely. Among previous reports, higher incidence of amiodarone toxicity was developed in studies which have strict, variable diagnostic criteria and performed in prospective methods that apply regular follow up protocols. It is suggesed that we have missed many adverse effect of various range until fatal toxicity has occurred. We have to perform regular follow up program including thyroid studies, liver tranminase levels, chest radiographs, PFT, eye examination and be careful the sign and symptoms suggesting amiodarone adverse effect.

Summary

Amiodarone is one of the most commonly used agent to treat ventricular tachyarrhythmia and atrial fibrillation, however, has the potential for a wide range of adverse effects. Major adverse effects have been reported at various rates, according to the difference patient population, criteria to make up diagnosis, and method to study. In our study, the incidence of amiodarone induced toxicity was generally lower than established reports. We investigated that clinical data in retrograde methods and which might be one of the most important reason of lower incidence. If we had done regular follow up protocol for checking up thyroid function, pulmonary function, hepatic transminase level, opthalmologic toxicity, could detect amiodarone induced toxicity before full brown clinical manifestation had occurred. That s why we think real incidence of amiodarone induced toxicity would be higher than these results. It suggests that amiodarone induced toxicity can be lessened and prevented to some degree. All physicians must be aware of the potential for amiodarone related toxicity of many organs, even with a short duration of treatment and perform regular follow up protocols for checking up amiodarone induced toxicity.

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References

1. Newman C M, Davies D W, Gray T A and Weetman A P. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;**79**:121-7.
2. Guarnieri T, Nolan S, Gottlieb SO, Dudek A, Lowry

DR. Intravenous amiodarone for the prevention of atrial fibrillation after open heart surgery: the Amiodarone Reduction in Coronary Heart (ARCH) trial. *J Am Coll Cardiol* 1999:**34**:343-7.

3. Maras D, Boskovic SD, Popovic Z, Neskovic AN, Kovacevic S, Otasevic P, Marinkovic J, Vuk L, Borzanovic M, Nastasis S, *et al*. Single-day loading dose of oral amiodarone for the prevention of new onset atrial fibrillation after coronary bypass surgery. *Am Heart J* 2001;**141**:E8.
4. Goldschlager N, Epstein AE, Naccrelli G, Olshansky B, Singh B. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelins subcommittee, North American Society of Pacing and Electrophysiology. *Arch Intern Med* 2000;**160**:1741-8.
5. Lyle A. Siddoway, M.D., York Hospital, york, Phennsylvania. Amiodarone : Guideline for Use and Monitoring. *Am Fam Physician* 2003;**68**:2189-96.
6. Vicken R. Vorpepian, MD, FACC, Thomas C. Havighurst, MS, Stephen Miller, M.D., Craig T.January, M.D.,Ph.d., FACC. Adverse effect of Low Dose Amiodarone; A meta analysis. *J Am Coll Caridol* 1997:**30**:791-8.
7. Pollak PT. Clinical organ toxicity of antiarrhythmic compounds; ocular and pulmonary manifestations. *Am J Cardiol* 1999;**84**:37R-45R.
8. Connolly SJ. Evidence based analysis of amiodarone efficacy and safety. *Circulation* 1999;**100**:2025-34.
9. Amiodarone Trials Meta-Analysis Investigators Effect of prophylactic amidarone on mortality after myocardial infarction and in congestive heart failure: Meta analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997;**350**:1417-24.
10. Nademanne K, Singh BN, Hendrickson J. Amioraone in refractory life threatening arrhythmias. *Ann Intern Med* 1983;**98**:577-84.
11. Hafajee CI, Love JC, Alperts JS, Asdourian GK, Solan KC. Efficacy and safrty of long term amiodarone in treatment of cardiac arrhythmias; dosage experience. *Am Heart J* 1983;**106**:935-43.
12. Doval HC, Nul DR, Grancelli HO, *et al*. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;**344**:493-8.
13. Cairns JA, Connolly SJ, Roberts R, *et al*. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature repolarizations. CAMIAT. *Lancet* 1997;**349**:675-82.
14. Hammill SC, Packer DL. Amiodarone in comgestive haert failure; unravelling the GESICA and GESICA-STAT differences. *Heart* 1996;**75**:6-7.
15. Gottlieb SS. Dead is dead-artificial definition are no substitute. *Lancet* 1997;**349**:662-3.
16. Harjai KJ, Licata AA. 1997 Effects of amiodarone on thyroid function. *Ann Intern Med* **126**:63-73.
17. Lombardi A, Martino E, Braverman LE. 1990 Amiodarone and the thyroid. *Thyroid Today* **13**:1-7.
18. Dusman, RE, Stanton, MS, Miles, WM, *et al*. Clinical features of amiodarone indueced pulmonary toxicity. *Circulation* 1990;**82**:51
19. Smith WM, Lubbe WF, Whitlock RM, Mercer J, Rutherford JD, Roche AH: Long-term tolerance of amiodarone treatment for cardiac arrhythmia. *Am H Cardiol* 1986;**57**:1288-93.
20. Margo SA, Lawrence EC, Wheeler SH, Krafchek J, Lin HT, Wyndham CRC. Amiodarone pulmonary toxicity: Prospective evaluation of serial pulmonary function tests. *J Am Coll Cardiol* 1988;**12**:781-8.
21. James HL, Richard CR, Anthony C, Lawrence KJ, Jackson FM, Kamal GI, Leonard BS, Hyman JZ. Amiodarone hepatotoxicity; Prevalence and clinicopatholgic correlation among 104 patients. *Hepatology* 1989;**9**:679-85.