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Clinical Investigations

Prevalence of Amiodarone-Related Hepatotoxicity in 720 Chinese Patients with or without Baseline Liver Dysfunction

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Summary

Background: The prevalence of hepatotoxicity after long-term oral amiodarone therapy in Chinese patients with or without elevated liver enzymes at baseline is unknown.

Hypothesis: Amiodarone may still be safely prescribed for Chinese patients who have baseline liver dysfunction.

Methods: This is a retrospective cross-sectional study. Significant liver dysfunction (SLD) was defined as alanine aminotransferase (ALT) > 2 times upper limit of normal range.

Results: Baseline liver function was checked in 628 of the 720 Chinese patients identified. The mean duration of amiodarone use was 615.9 ± 703.1 days. Ninety patients (14.3%) had elevated baseline ALT. The prevalence of SLD was 3.7% (confidence interval [CI] 2.1–5.3%) and 4.4% (CI 0.2–8.6%) in patients with normal (n = 538) and elevated (n = 90) baseline ALT, respectively (p = 0.765). Therapy was continued in 42 patients with elevated baseline ALT until final follow-up. Eight of these (19.0%) had elevated ALT upon final follow-up, but the derangement was mild (mean ALT 134.8 ± 145.9 IU/l, median 76 IU/l). During follow up, 24 patients developed SLD and half of these subsequently withdrew from therapy. The ALT levels at final follow-up had improved over time in both groups, but the mean difference was not significant (255.1 ± 706.4 vs. 131.0 ± 207.5 IU/l, p = 0.312).

Conclusion: The prevalence of SLD in Chinese patients taking oral amiodarone with or without elevated baseline ALT was similar (4.4 vs. 3.7%). It seems that amiodarone may be safely prescribed in patients with elevated baseline ALT.

Key words: amiodarone, hepatotoxicity, Chinese

Introduction

Amiodarone currently is a commonly used antiarrhythmic agent.[1] It has been reported that amiodarone can be associated with serious liver complications.[2–7] In one meta-analysis of the efficacy and safety of amiodarone after myocardial infarction (MI) and congestive heart failure (CHF), amiodarone was associated with more liver complications than placebo, with a prevalence of 1.0% per-patient-year.[8] However, this meta-analysis recruited only patients with MI and CHF who were taking amiodarone. The outcome in patients who developed amiodarone-related hepatotoxicity is not clearly defined in the literature. It is also unclear whether amiodarone can be safely used in patients with elevated baseline alanine aminotransferase (ALT). Our study aimed to investigate the prevalence of significant liver dysfunction (SLD) during amiodarone therapy in Chinese patients with or without baseline elevated liver enzyme. The subsequent outcome of patients who developed SLD is also assessed.

Methods

Patients

This is a cross-sectional retrospective analysis of Chinese patients taking maintenance oral amiodarone therapy at two hospitals. Prince of Wales Hospital (PWH) is a tertiary referral center and Alice HML Nethersole Hospital (AHNH) is a regional hospital in Hong Kong. According to our computerized dispensary records, we identified all patients who were taking oral amiodarone in PWH and AHNH from January 1998 to December 2000. Only adult Chinese patients (aged > 18 years)

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who had taken maintenance doses of oral amiodarone were included in the study; patients who were given only intravenous amiodarone were excluded. Case records were retrieved and data including indication of amiodarone, total dose taken, and serial liver function tests during follow-up were recorded. There were no specific follow-up intervals among these patients, but usually they were followed up in medical specialist clinics every 3 to 6 months.

Measurements

Alanine aminotransferase was the only liver enzyme used for assessment of liver function in this study; measurements < 58 IU/l were regarded as normal in our laboratory. Significant liver dysfunction was defined as ALT > 2× upper limit of normal range (i.e., ALT > 116 IU/l). Total cumulative dose was calculated by multiplying the daily dose by the duration of amiodarone therapy in days.

Statistical Analysis

Distribution of ALT and total cumulative dose was skewed to the right; therefore, nonparametric tests (e.g., Mann-Whitney U-test) were used for comparison. Student's *t*-test was used to compare the mean difference between the two groups believed to have normal distribution (e.g., duration of amiodarone use in days). Differences were considered significant at $p < 0.05$. Statistical Package for Social Sciences (version 10.0) computer software (SPSS Inc., Chicago, Ill., USA) was used to perform statistical analysis. Values were expressed as mean ± standard deviation. Categorical variables were compared using chi-square test or Fisher's exact test with an appropriate degree of freedom.

Results

In all, 720 Chinese patients were recruited for analysis. The demographic characteristics, maintenance dose of oral amiodarone, and indications for oral amiodarone are shown in Table I. Mean duration of oral amiodarone intake was 615.9 ± 703.1 days. A total of 318 patients (44.2%) stopped taking amiodarone during the follow-up period; the reasons for withdrawal are shown in Table II. Only four patients (0.6%) discontinued amiodarone because of liver dysfunction. No patient developed fulminant liver failure or had amiodarone-related death.

Baseline liver function was evaluated in 628 patients (87.2%) before oral amiodarone therapy. Of these, 538 patients had normal baseline liver function and 90 had elevated baseline ALT (mean 112.9 ± 222.3 IU/l). Serial liver function tests of the two groups of patients are shown in Figure 1. In those with normal baseline liver function, the prevalence of SLD was 3.7% (confidence interval [CI] 2.1–5.3%); for those with elevated baseline ALT, it was 4.4% (CI 0.2–8.6%). The difference was not statistically significant ($p = 0.765$, Fisher's exact test).

The evaluation of liver function in patients with elevated baseline ALT is shown in Figure 1. Of patients with elevated baseline ALT who developed SLD after amiodarone (n = 4), two subsequently withdrew from amiodarone therapy; the other two patients continued taking amiodarone in spite of the development of SLD. Their ALT on last follow-up ranged from 18 to 73 IU/l. The remaining 86 patients with elevated baseline

TABLE I Patient demographics (n = 720) and indication for amiodarone

Variable	Number (%)
Total number of patients	720
Prince of Wales Hospital	601 (83.5)
Alice HML Nethersole Hospital	119 (16.5)
Male	363 (50.4)
Female	357 (49.6)
Daily dose (mg)	
100	114 (15.8)
200	596 (82.8)
300	10 (1.4)
Mean ± SD daily dose (mg)	185.92 ± 38.65
Indications (%)	
Atrial fibrillation	541 (75.1)
Atrial flutter	68 (9.4)
Ventricular tachycardia	54 (7.5)
Ventricular fibrillation	5 (0.7)
Supraventricular tachycardia	43 (6.0)
Unknown	9 (1.2)

Abbreviation: SD = standard deviation.

TABLE II Reasons for amiodarone withdrawal (n = 720)

Reasons	Number (%)
Thyroid dysfunction	85 (11.8)
Pulmonary fibrosis	11 (1.5)
Hepatotoxicity	4 (0.6)
Ocular complication	8 (1.1)
Bradycardia	17 (2.4)
Torsade de pointes	2 (0.3)
Other side effects [a]	12 (1.7)
Patient's own decision	13 (1.8)
Unspecified	55 (7.6)
Others [b]	43 (6.0)
Amiodarone no longer necessary	74 (10.3)
Total	324 [c] (45.0)

[a] Included skin or mucosal discoloration, minor neurological complications, vomiting, and diarrhea.

[b] Included treatment failure, interaction between amiodarone and warfarin, switching of amiodarone to other drugs, and amiodarone already stopped in other hospitals.

[c] The total number of incidence was 324 instead of 318 because 4 patients experienced two and 1 patient experienced three adverse effects induced by amiodarone.

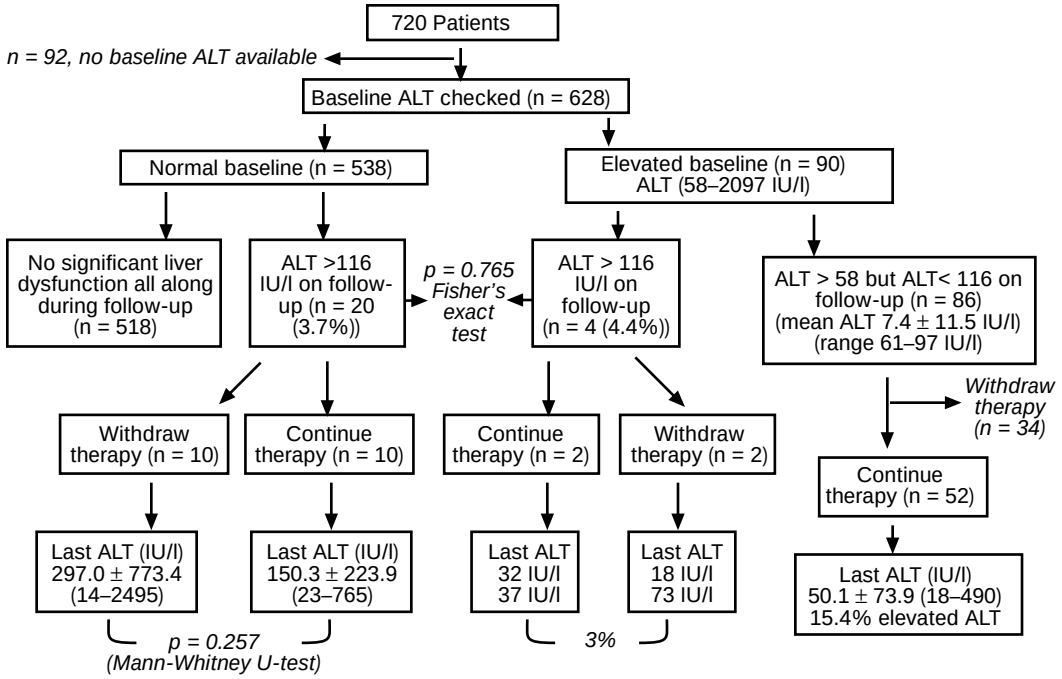

FIG. 1 Progress of patients during follow-up. ALT = alanine aminotransferase.

ALT did not develop SLD after amiodarone; of these, 52 (60.5%) continued taking amiodarone until final follow-up and 42 had liver function tests performed at last follow-up. Their mean ALT level on final follow-up was 50.1 ± 73.9 IU/l. Of these 42 patients, 8 (19.0%) had mildly elevated ALT on final follow-up (mean ALT 134.8 ± 145.9 IU/l, median 76 IU/l).

Twenty-four patients in our cohort were found to have SLD after amiodarone therapy (Fig. 2). Twelve patients (50%) subsequently withdrew from amiodarone therapy and 12 (50%) continued amiodarone therapy in spite of liver impairment. The ALT levels on final follow-up for most of these patients, whether or not they withdrew from amiodarone therapy, were

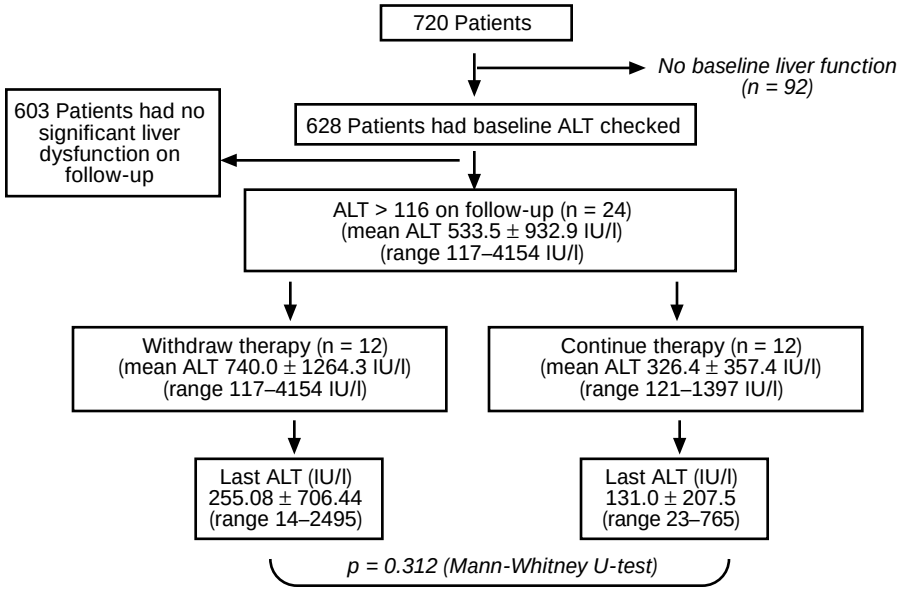

FIG. 2 Outcome of patients with significant liver dysfunction during amiodarone therapy. ALT = alanine aminotransferase.

TABLE III Liver test outcome in the 24 patients who had significant liver dysfunction after oral amiodarone therapy (all ALT values expressed in IU/l)

Baseline ALT	ALT after amiodarone	Withdrew or continued	ALT on last FU	Mean ALT on last FU	Proportion of elevated ALT on last FU	Duration to last follow-up (days) [a]	Cumulative dose of amiodarone taken (g)
84	138	Withdrew	18			1.274	13.8
27	155	Withdrew	131			1.129	31.8
20	213	Withdrew	114			1.093	14.4
28	155	Withdrew	19			1.042	255.0
21	184	Withdrew	69			973	8.4
29	117	Withdrew	22	255.1 ± 706.4	5/12	894	145.0
14	2,495	Withdrew	2,495		= 41.67%	266	176.4
39	125	Withdrew	32			148	4.6
34	203	Withdrew	14			145	212.6
48	4,154	Withdrew	41			112	2.6
14	380	Withdrew	33			91	30.4
98	567	Withdrew	73			19	31.1
						Mean	Mean
						598.8 ± 500.5	77.2 ± 92.6
45	1,397	Continued	765			112	22.4
16	519	Continued	183			590	118.0
29	157	Continued	157			353	70.6
17	238	Continued	147			48	9.6
29	228	Continued	64			746	149.0
52	242	Continued	61	131.0 ± 207.5	6/12	71	14.2
23	169	Continued	43		= 50%	1.147	118.0
19	151	Continued	34			432	86.4
18	133	Continued	26			500	100.0
25	160	Continued	23			1.255	377.0
465	402	Continued	37			678	136.0
128	121	Continued	32			848	170.0
						Mean	Mean
						565.0 ± 395.9	113.9 ± 98.1
				NS, p = 0.312	NS, p = 1	NS, p = 0.856	NS, p = 0.319

[a] For those who withdrew, it was the duration from the date of withdrawal to last follow-up; for those who continued therapy, it was the total duration of amiodarone intake up to last follow-up.

Abbreviations: ALT = alanine aminotransferase, FU = follow-up, NS = not significant.

found to have improved over time (Table III). The mean ALT on final follow-up in those patients who withdrew and those who continued therapy was 255.1 ± 706.4 IU/l and 131.0 ± 207.5 IU/l, respectively. The difference was not statistically significant (p = 0.312). Five of the 12 patients (41.67%) who withdrew from therapy still had elevated ALT over a long period of time (598.8 ± 500.5 days).

Discussion

Amiodarone-related hepatotoxicity has been described in many case reports, the majority of which describe severe or even fatal liver consequences associated with amiodarone.[9–19] However, these reports cannot provide information about the magnitude of the problem. Vorperian *et al.*[20] reported a meta-analysis of controlled trials using amiodarone and found that the odds of experiencing adverse liver effects in patients taking amiodarone were similar to those of taking placebo. Lewis *et al.*[5] reported the prevalence of amiodarone hepatotoxicity among 104 patients and found that the prevalence of symptomatic "hepatitis" was 3%. In our series of 720 patients, the prevalence of amiodarone-related hepatotoxicity in those with normal baseline liver function was 3.7%, which was consistent with previous studies.

The outcome of patients taking amiodarone who had elevated baseline ALT was also addressed in our study. Contrary to the serious complications described in isolated case reports, the prevalence of SLD among those with elevated baseline ALT was 4.4%, with no significant difference from those with normal baseline liver function. Among our patients with elevated baseline ALT who continued to take amiodarone up to the final follow-up, 44 had ALT checked at that time. The mean ALT then was 49.7 ± 72.2 IU/l. Only 8 of 44 patients

(18.2%) had mildly elevated ALT on final follow-up (mean ALT 134.8 ± 145.9 IU/l). No patient developed fulminant hepatitis, and there was no death related to liver complications. It seemed that mildly elevated baseline ALT is not an absolute contraindication for oral amiodarone therapy, as the outcome in this group of patients was not particularly worse. Close monitoring of liver function during amiodarone therapy may be all that is needed for patients with elevated baseline liver enzymes.

The effect of continuing amiodarone therapy in patients who developed SLD after taking it was examined in this retrospective analysis (Fig. 2, Table III). Among these patients, the mean ALT on final follow-up was similar whether or not amiodarone was withdrawn. Liver function remained impaired in 42–50% of patients irrespective of amiodarone withdrawal after an approximately 1.5-year follow-up. Although the half-life of amiodarone is up to 3 months, patients with persistent liver dysfunction despite drug withdrawal possibly have liver pathology other than amiodarone toxicity, considering that amiodarone therapy had been stopped for such a long period of time. It is interesting that continued amiodarone use in patients with SLD appeared not to be hazardous; only 1 of 12 patients continued to have a very high ALT level. It seems that amiodarone can still be continued in patients with mild liver dysfunction provided it is closely monitored. However, the exact cause of liver dysfunction among these patients could not be delineated in this study, which is a major limitation for retrospective analysis.

Study Limitations

This was a retrospective historical cohort study and it had certain limitations. First, documentation in case records may be incomplete, making it difficult to delineate the causes for abnormal baseline liver function. Second, viral hepatitis markers were checked in only a few patients, and we were not able to assess the relationship between chronic hepatitis and amiodarone-related hepatotoxicity. Third, symptoms related to elevated ALT were not known because of incomplete documentation in case records. Fourth, since it was a retrospective study, liver function tests were not performed on a regular basis. Therefore it was possible that some patients who developed SLD were missed.

Conclusion

The prevalence of significant liver dysfunction after oral amiodarone in our patients with normal or elevated baseline ALT was 3.7 or 4.4%, respectively. Liver dysfunction after oral amiodarone in patients who had elevated baseline ALT or who developed SLD during amiodarone therapy seemed not to be severe and may not warrant immediate withdrawal. Close monitoring of liver function is recommended.

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