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Side effects with amiodarone therapy

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Summary: Amiodarone hydrochloride is increasingly being used in the treatment of ventricular and supraventricular arrhythmias. Although a highly effective anti-arrhythmic agent, its use is restricted by the high incidence of side effects. To elucidate the value of monitoring serum level of both the parent drug and its active metabolite in predicting the occurrence of side effects, the investigators examined 109 patients from a register of patients treated with amiodarone for the prevalence of known side effects of the drug. The register contained over 90% of patients treated with amiodarone at the Leicester General Hospital during the period of the study.

The findings suggest cutaneous side effects and abnormal thyroid function tests (without overt gland dysfunction) are more likely to occur with increasing duration of treatment and cumulative dosage. However, neither the serum amiodarone level nor the serum metabolite level had any predictive power for the occurrence of side effects.

In view of this finding, it is recommended that close attention be paid to the continued clinical monitoring of side effects and that there is utility in measuring the serum amiodarone level in each patient to avoid the prescription of unnecessarily high doses. This is necessary not only to lessen the occurrence of cumulative dose-related side effects, but also because the variable but very long half-life of the drug leads to difficulties in relating spot drug levels to long-term effects.

Introduction

Amiodarone hydrochloride, an iodinated benzofuran derivative, is recognized for its anti-arrhythmic properties in treating both ventricular and supraventricular arrhythmias,[1,2] and for converting atrial fibrillation to sinus rhythm and maintaining sinus rhythm.[3]

Amiodarone has unusual and complicated pharmacokinetics: it is incompletely absorbed from the gastrointestinal tract and bioavailability is very variable, around 20–80%.[4–7] Its major metabolite is desethylamiodarone which is pharmacologically active. As use of amiodarone has increased, numerous side effects have been reported, though their prevalence in any particular patient population is variable.[8–15]

This study reports one centre's experience of the profile of side effects of patients taking amiodarone in relation to mean serum amiodarone level, mean serum desethylamiodarone level, mean maintenance dose, total cumulative dosage and duration of treatment.

Methods

One hundred and nine (69 male and 40 female) patients on the amiodarone register of the Department of Medicine, Leicester General Hospital, were studied. It is estimated that more than 90% of patients receiving amiodarone on a chronic basis during the time of the duration of the study were included in the register. They were currently or had been receiving treatment with amiodarone for ventricular or supraventricular tachycardia. Although this is not a prospective study, the register was compiled with a view to subsequent evaluation and data collection. Only a small number of staff were involved in maintaining the register. The case notes of each patient were reviewed by one of the authors (RS) for the occurrence of rashes, hair loss, thyroid function abnormalities, neurological effects and biochemical liver function abnormalities.

Liver function tests were performed routinely as part of the usual biochemical work-up of the patients. Thyroid function tests were performed at the time of initiating amiodarone therapy and were repeated on most occasions when an amiodarone serum level was measured. Every patient had at least one set of thyroid and liver function tests, and most patients had several.

Dosage regimen

Forty-four (40%) patients had only loading doses, the majority of the others had received a regimen of 600 mg/day for the first week followed by 400 mg/

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day for a month. A serum amiodarone level was measured at this stage and formed the basis for further dosing. In view of the very long half-life (20–107 days)[4] of amiodarone, no attention was paid to the time interval from the previously administered dose. We aimed at a serum amiodarone level of 1.6–4 μmol/l which is our laboratory's recommended therapeutic range[16] and a desethylamiodarone level below 3.2 μmol/l, which is also recommended by our laboratory. The remaining patients had a similar regimen but preceded by an intravenous dose either as a single bolus of 300 mg amiodarone, repeated bolus injections to a maximum of 1,200 mg/24 hours or as an infusion over 24 hours, dose ranging from 900 to 1,200 mg (although one patient received 1,800 mg over 24 hours).

The maintenance dose for all patients was determined by serum amiodarone level and serum desethylamiodarone level balanced against clinical efficacy and side effects. Apart from one patient (see Table VI), none of the other 108 patients had intravenous amiodarone dosing only. The side effects monitored included hepatic, gastrointestinal, cutaneous, pulmonary and thyroid gland effects, and any others volunteered by the patient.

The contribution of serum amiodarone and desethylamiodarone measurement to determining the maintenance dose of a patient was as follows. The patients arrhythmias were controlled with the usual empirical amiodarone dosage schedule and the dose was then reduced in a step-wise manner to keep the measured desethylamiodarone level below 3.2 μmol/l and the measured amiodarone level as near to 1.6 μmol/l as was compatible with continued rhythm control. The time between dosage adjustments was 2–4 months, which was extended to 6 months once stability had been reached.

Statistical analysis

Statistical analysis was performed using non-parametric tests: Fisher's exact probability test (two-tailed) and the Mantel–Haenszel chi-squared test. Simple correlation coefficients and rank correlation coefficients were also calculated.

Results

The mean age of the patients was 66.4 (s.d. ± 21.2) years. The mean duration of treatment was 25.0 (s.d. ± 19.4) months. Eighty-seven (76%) of the 115 amiodarone episodes had >12 months of treatment with amiodarone (including six patients with two periods of treatment at least 6 months apart). Eighty-three (76%) patients had an underlying cardiac condition (Table I). The range of arrhythmias the patients were treated for is shown in Table II. Two patients had no documented arrhythmia: a man with hypertrophic cardiomyopathy and a woman with severe heart failure, both of whom complained of palpitations. Six patients underwent two periods of treatment but only the data relating to the first period are included in the analysis. Table III shows the summary statistics for all 109 patients.

Table I Associated cardiac diagnoses

Underlying cardiac condition	n
Ischaemic heart disease	53
Hypertension	19
Valvular disease	4
Congestive cardiomyopathy	2
Wolff–Parkinson–White syndrome	2
Lown–Ganong–Levine syndrome	1
Mitral valve prolapse	1
Hypertrophic cardiomyopathy	1
Total	83

Side effects

Ninety-six patients reported side effects, of whom 63 patients reported two or more. The number and percentage of the 109 patients reporting each side effect are shown in Table IV.

Fifteen (38%) of the 40 female patients had abnormal thyroid function tests, compared to 12 (17%) of the 69 males, and this difference is statistically significant (Mantel–Haenszel test, $P = 0.014$).

The incidence of cutaneous and neurological effects, and abnormal liver and thyroid function tests were correlated with the duration of therapy, total dose of amiodarone, daily dose and age using rank correlation coefficients. The occurrence of the remaining side effects was too small for meaningful statistical analysis. No statistically significant correlation was found between the occurrence of any of the side effects and mean amiodarone level or mean desethylamiodarone level. There was no correlation between abnormal liver function tests and total cumulative dosage, mean daily dose or age.

Table V shows the adverse effects in relation to mean duration of treatment, total dose, daily dose and age. Although liver function test abnormalities were frequent, occurring in 53 (46.8%) patients, there was no correlation with mean length of treatment, total dose, daily dose and age of patient.

Table VI shows the number of patients in whom amiodarone was discontinued and lists the reasons. The policy regarding raised serum amiodarone levels or serum metabolite levels was to adjust the

Table II Types of arrhythmias treated

Underlying arrhythmia	n
Atrial fibrillation	71
Paroxysmal supraventricular tachycardia	9
Atrial flutter	8
Paroxysmal atrial tachycardia	2
Wolff–Parkinson–White syndrome with atrial fibrillation	1
Wolff–Parkinson–White syndrome with supraventricular tachycardia	1
Lown–Ganong–Levine syndrome with atrial fibrillation	1
Ventricular tachycardia	10
Ventricular tachycardia with ventricular fibrillation	2
Multifocal ventricular ectopics	1
Ventricular bigeminy/trigeminy	1
Total	107

Table III Amiodarone treatment details ($n = 109$)

	Mean	*s.d.*
Duration of treatment (months)	25.0	19.0
Total dose (g)	206	183
Mean daily dose (mg)*	266.4	71.3
Mean serum amiodarone level ($\mu mol/l^{-1}$)*	2.26	1.02
Mean serum metabolite level ($\mu mol/l^{-1}$)†	2.01	0.75

*No data available on one patient; †no data available on three patients.

Table IV Side effects

Side effect	n	%
Asymptomatic abnormal liver function tests	53	48.6
Clinical hypothyroidism	15	13.7
Clinical thyrotoxicosis	2	1.8
Cutaneous side effects	34	31.2
Photosensitivity	25*	22.9
Alopecia	9*	8.3
Slate-grey discoloration of the face	4*	3.7
Asymptomatic abnormal thyroid function tests†	27	24.8
Neurological effects (peripheral neuropathy and giddiness)	26	23.9
No side effects reported	13	11.9

*These numbers do not add up to 34 because a few patients had alopecia and photosensitivity or photosensitivity and slate-grey discoloration; †Excludes patients requiring treatment for hypothyroidism or thyrotoxicosis occurring as a direct consequence of amiodarone therapy.

dose in a downward direction. The three patients listed in Table VI had their treatment discontinued by junior medical staff in contradiction to the policy and without there being a clinical indication.

Potentially life-threatening effects occurred in four (3.7%) patients. Three of these were cardiac. One patient had atrioventricular nodal block (Mobitz type I), requiring insertion of a temporary pacemaker, after acute administration of intravenous admiodarone. After stopping the amiodarone, the block recovered within 24 hours and the temporary pacemaker was removed. Another patient had prolonged QT interval which recovered on cessation of therapy and the third had reversible postural hypotension severe enough to necessitate withdrawal of amiodarone. The remaining patient developed pulmonary fibrosis which regressed on cessation of amiodarone and did not require systemic steroid therapy. In two of the patients, raised metabolite levels led to the discontinuation

Table V Side effect in relation to mean duration of treatment, total dose, mean daily dose and age

Side effect	*Mean duration of treatment (months)*	*Mean total dose (mg)*	*Mean daily dose (mg)*	*Mean age (years)*
Photosensitivity				
Present ($n = 25$)	35.6	317,111	276.8	62.3
Absent ($n = 84$)	21.8	172,687	263.3	67.6
P	0.363	0.021	0.364	0.178
All cutaneous effects				
Present ($n = 34$)	32.9	297,392	283.8	62.2
Absent ($n = 75$)	21.4	164,182	258.4	68.3
P	0.063	0.002	0.064	0.063
Neurological effects				
Present ($n = 26$)	33.3	269,940	260.3	64.9
Absent ($n = 83$)	22.4	185,883	268.3	66.8
P	0.042	0.500	0.503	0.507
Abnormal thyroid function tests				
Present ($n = 27$)	32.4	242,154	246.8	67.6
Absent ($n = 82$)*	22.5	194,107	272.9	66.0
P	0.075	0.074	0.508	0.825

*No data on one patient in this group with respect to total or daily maintenance dose. *P* values are for a 2 × 2 contingency table using Fisher's exact test.

Table VI Reasons for discontinuation of therapy

	n
Patient now asymptomatic	6
Cardiac side effects	3
Failure of control of arrhythmia	2
High metabolite level	2
High amiodarone level	1
Non-compliance	1
Alopecia	1
Pulmonary disease	1
Abnormal liver function tests	1
Other	1
Total	19

of amiodarone. Neither of these had any serious side effects: one complained of facial flushing and the other had transiently abnormal liver function tests. The patient with a high amiodarone level (6 μmol/l) reported no side effects.

Discussion

This study was planned and the amiodarone register was set up expressly to capture serum amiodarone level data and investigate their relationship to a complete record of side effects encountered. It differs from a strictly controlled prospective study by not formally setting out inclusion and exclusion criteria. It was borne of a disciplined approach to the use of a new (to us) anti-arrhythmic drug in a cardiological service in a teaching hospital setting. In the event more than 90% of the amiodarone treatment population were included in the study. A bias is much more likely to have led to an overestimate of the side effects observed than an underestimate.

The study demonstrates some important statistically significant results. In general, patients are more likely to be found to have side effects the longer the duration of treatment with amiodarone and consequently the higher the total cumulative dosage. This has been well described for corneal microdeposits and slate-grey discoloration of the skin.[12] Side effects from amiodarone had been extensively reviewed.[9,10] If one excludes accentuation of the intrinsic pharmacological properties of the drug, for example, the tendency to induce sinus bradycardia, then cardiovascular toxicity is uncommon.[9,10] We describe three patients with acute cardiovascular toxicity which proved reversible in every case on discontinuation of the drug. There exist data supporting a negative inotropic effect of the drug when administered by the intravenous route,[17] but clinically significant haemodynamic deterioration is uncommon and was not seen in our patients. The data on patients receiving oral amiodarone are conflicting but the majority of studies report little or no worsening of congestive heart failure.[9] Significant sinus bradycardia may be due to interaction with concomitant beta-adrenergic or calcium channel blockage.[9] Long-term oral amiodarone is associated with a significant decrease in resting and exercise heart rate, but only

in extreme cases does the bradycardia become symptomatic or sinus arrest require ventricular pacing. Aggravation of arrhythmias has been reported only in up to 5% of patients.[9] Amiodarone prolongs the QT interval and, especially in the presence of hypokalaemia, the drug has been associated with polymorphic ventricular tachycardia.

Pulmonary complications, especially pneumonitis, are of major concern.[18,19] From several larger series of patients, a prevalence estimate of 5–10% has been described.[9] This contrasts with our single case of this complication. Our case proved reversible on discontinuing the amiodarone and required no other treatment. Against a background of chronic bronchitis and asthma we cannot completely exclude the possibility of minor pulmonary toxicity in some of these patients, but pulmonary function tests have not shown worsening function in any case despite continuing amiodarone administration. Pulmonary toxicity may be dose-dependent but it has been found to be rare in patients receiving less than 400 mg/day of amiodarone.[20] It is possible that the total cumulative dose or duration of exposure may be more important than the daily dose.

An increase in hepatic transaminases of up to four times the baseline levels is seen in 15–20% of patients receiving amiodarone therapy.[9] Our own experience mirrors that of one study[21] recording an incidence of 50%. The increase in transaminase levels is generally not dose-dependent, and the patients are generally asymptomatic and the elevated values are often transient. Our own analysis failed to find any relationship with serum levels, total dosage, length of exposure and age of the patient, and this side effect did not lead to any clinical action.

Neurological toxicity is reported infrequently. The most common side effects are tremor, ataxia and peripheral neuropathy. The tremor is often a manifestation of thyrotoxicosis and not of primary neurological toxicity. We had to discontinue amiodarone because of peripheral neuropathy, proven by nerve conduction studies. It is likely that minor neurological side effects, in particular ataxia, which has been described to be present in up to 37% of patients[22] and to be notable for the absence of long-tract physical signs, may have been overlooked.

Ocular changes during treatment with amiodarone are almost universal,[23] but the development of corneal microdeposits is rarely symptomatic and the development of photophobia, blurred vision and blue/green halos around objects is only exceptionally the reason for discontinuing the drug.[9,10] Ophthalmologists also report bilateral symmetrical microdeposits in the granular corneal epithelium, just anterior to Bowman's membrane, which occurs early in treatment and the deposits are found in nearly 100% of patients by 1–2 months.[9,12] The development of the lesions and their rate of progression is dose-dependent, but discontinuation of amiodarone because of microdeposits is usually not necessary and in cases where amiodarone is withdrawn the ocular changes regress completely in 3–4 months. This coincides with our experience.

Because of its large iodine content, amiodarone has several well-established effects on thyroid function and metabolism, and can produce significant abnormalities in thyroid function tests as well as clinically important hypo- or hyperthyroidism.[9] It has been shown[24] that amiodarone produces a significant increase in serum thyroxine (T4), free T4 and a small decrease in tri-iodothyronine (T3) and a large increase in reverse T3. The mechanism is considered to be inhibition of the conversion of peripheral T4 to T3 as well as a preference for conversion of T4 to reverse T3.[24] Thyroid-binding globulin is unchanged whilst a transient elevation of thyroid-stimulating hormone (TSH) is thought to be secondary to inhibition of nuclear binding of T3.[25] There is also evidence of an increased response of TSH to thyrotrophin-releasing hormone.[26] These changes in thyroid function have been more apparent in patients receiving higher doses of amiodarone. In our patients, abnormal thyroid function tests were much more common than clinically apparent thyrotoxicosis or hypothyroidism. Amiodarone-induced thyrotoxicosis occurs in 1–4% of patients[9] and this fits in with our experience. We did not find treatment of hyperthyroidism difficult and did not routinely withdraw amiodarone. Like other authors,[26] treatment with anti-thyroid drugs, radioidine or surgical ablation, was deemed to be appropriate. Treatment of hypothyroidism was by thyroid replacement therapy and its development was not considered a reason for discontinuing amiodarone.

Dermatological side effects from amiodarone therapy are common and may lead to termination of treatment. Photosensitivity is common and, although the reporting incidence varies between 5% and 57%,[9] minor erythema and swelling in sun-exposed areas is probably at some stage experienced by every patient. The relationship to dosage of amiodarone is uncertain.[27] In our patients the symptoms are more clearly related to the actinic dose, although it is rarely quantified. The avoidance of unnecessary sun exposure and the liberal use of commercially available sunscreens help to contain this side effect. The development of blue–grey discoloration of the skin is unacceptable and the reported prevalence of 1–7% of patients[9] is probably an underestimate for any group of patients whose treatment has been continued for years.

It is not surprising that spot amiodarone levels and averages computed from variable numbers of such levels contributing to mean levels did not correlate with the incidence of newly observed side effects. From the slow pharmacokinetics of amiodarone one would infer the likelihood of slow serum level and metabolite serum level changes, and a long delay between effect and measured serum level change. In any case the numbers of patients included in the various subgroups were too small to make such an analysis fruitful.

As expected, the data supported the well-documented near-linear relationship between serum amiodarone level and serum desethyl-amiodarone level. The serum levels did not correlate with mean daily dose. This is a reflection of the variable absorption of amiodarone from the gastrointestinal tract and the wide range of elimination amiodarone half-lives well recorded in the literature.[6,7] Systemic bioavailability is extremely variable and ranges from 20 to 89%,[5,7] primarily due to poor absorption and possibly high first pass metabolism.

Though raised amiodarone and desethylamiodarone levels are in individual cases not predictive of the occurrence of side effects, one may nontheless defend measuring them as they are helpful in judging a minimum effective anti-arrhythmic level. Knowledge of a particular patient's serum level aids in maintaining the patients on the lowest possible dose of amiodarone. This is a sensible strategy since treatment is usually long term and the occurrences of side effects appears at least in some cases to be related to total dose consumed. The high incidence of amiodarone side effects makes it highly desirable to minimize the exposure of an individual patient to the drug whilst maintaining effectiveness of therapy. Fortunately, most of these side effects are relatively well tolerated and only in a small minority of patients are these effects serious enough to necessitate withdrawal of therapy. With close monitoring, serious side effects can be kept at a low and acceptable level by taking the appropriate action whenever the serum level rises above the minimum value associated with rhythm control in a particular patient and an elevated metabolite level is treated as an early warning system.

The long-term use of amiodarone is beset with highly significant side effects which become more common and less likely to be tolerated with increasing total amiodarone dosage. The drug remains attractive because it is tolerated by patients with severe left ventricular dysfunction, is generally highly effective, and the role of class I anti-arrhythmic agents with more acceptable side effect profiles is under re-evaluation because of adverse effects on survival.[28]

We advocate and provide a case in favour of achieving adequate control of arrhythmias by the use of amiodarone doses limited by routine serum level control. Treatment with amiodarone is usually continued for years, even for the remainder of the patient's life. It would therefore be useful to supplement the post marketing surveillance data by incorporating serum level surveillance into further studies. It would in particular be interesting to obtain information whether the strategy of minimizing dosage but adhering to a predetermined therapeutic serum level range just postpones the appearance of long-term side effects or whether thresholds operate which limit the appearance of such side effects during the life of the patient.

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