Journal of Neurology, Neurosurgery, and Psychiatry 1994;57:340–343

Antiarrhythmic drugs and polyneuropathy

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Received 31 December 1992 and in revised form 8 June 1993.
Accepted 21 June 1993

Abstract

A total of 151 patients on chronic treatment with amiodarone and other antiarrhythmic drugs were subjected to standard clinical and electrophysiological investigation to assess the prevalence and specificity of polyneuropathy. Twenty two untreated patients with cardiac disorders and 246 normal subjects served as controls. Abnormal electrophysiological findings supporting the diagnosis of polyneuropathy were present in 38 subjects (25%) given antiarrhythmic drugs, with even distribution among drugs, and four untreated patients (18%). Concurrent clinical abnormalities were present in five treated patients (one each with amiodarone, propafenone, and flecainide, and two with multiple drugs). Therefore, electrophysiological abnormalities are a common, although non-specific, feature in patients taking antiarrhythmic drugs. Amiodarone users do not seem at higher risk of polyneuropathy than subjects treated with other drugs or even untreated patients with cardiac disorders.

(*J Neurol Neurosurg Psychiatry* 1994;57:340–343)

Several adverse effects of amiodarone have been reported, including neurological toxicity.[1 2] The commonest neurological symptoms and signs include tremor, ataxia, and polyneuropathy with or without spinal cord involvement.[3 4] Clinical and electrophysiological data supporting polyneuropathy have been confirmed by pathological findings in animals and humans, showing demyelination or axonal loss with lysosomal inclusions in different cell types.[5–8] Most data refer to case reports and selected clinical series, of which only two screened as many as 50 to 54 patients.[3 9]

Despite the recognition of common electrophysiological effects of the antiarrhythmic drugs,[10 11] only a few reports have been published on the potential neurotoxicity of agents other than amiodarone.[12–14] It is therefore not possible to estimate the risk of polyneuropathy in patients on chronic amiodarone treatment, the specificity of that risk, or the factors that may be accompanied by a higher risk.

We screened a fairly unselected group of patients treated with different antiarrhythmic drugs, including amiodarone, to assess the prevalence and risk factors of polyneuropathy, using standard clinical and electrophysiological techniques.

Materials and methods

Subjects aged 15 to 70 years and seen consecutively in four cardiological outpatient services in Italy (Monza, Turin, Rome, and San Giovanni Rotondo) were considered for inclusion if they had been first treated for no less than six months with the following drugs, singly or in combination: amiodarone, propafenone, atenolol, flecainide, mexiletine, propanolol, verapamil, quinidine. A small sample of patients who were considered candidates for antiarrhythmic treatment, but had not yet been treated, was included as a reference group.

A preliminary screening investigation was made by the consultant cardiologist during routine ambulatory practice. The cardiologist retained the patients fulfilling the inclusion criteria and excluded those with other concurrent factors or disorders causing polyneuropathy (indicated on a check list). The reasons for exclusion were: diabetes, liver disease, porphyria, amyloidosis, uraemia, thyroid disorders, paraproteinaemia, collagen disease, neoplasms (checked by history, reports of abnormal biochemical assays, or specific treatments). Patients treated with potentially neurotoxic agents[15] were also excluded. All the eligible patients were invited by appointment to undergo a detailed neurological evaluation, which included a standardised active search for symptoms of polyneuropathy and a formal clinical and electrophysiological assessment. A clinical diagnosis of polyneuropathy was made when there was evidence of bilateral impairment of strength, or sensation, or deep tendon reflexes, or a combination in the upper, or lower, or both extremities with fairly symmetrical distribution.

The electrophysiological screening was done on the right limbs according to a standard procedure.[16] Briefly, motor and sensory nerve conduction velocity, distal latency, and potential amplitude of median, ulnar, common peroneal, and sural nerves were measured with surface stimulating and recording techniques. Room temperature was maintained at 22–24°C. Skin temperature was measured in the presence of cool limbs. Limb warming was performed when specifically indicated. All the electrophysiological variables were compared with normal reference

values obtained from each centre separately and measured according to the same procedure.

In Monza there were 54 normal subjects (27 men, 27 women) aged 18 to 69 (mean 42 years). In Rome there were 60 patients (35 men, 25 women) aged 22 to 67 (mean 44 years), in Turin 60 (31 men, 29 women) aged 20 to 69 (mean 44 years), and in San Giovanni Rotondo 72 (47 men, 25 women) aged 17 to 69 (mean 47 years). No significant differences or age trends were detected within centres for any of the values. The normal limits for conduction velocity and distal latency were set at 2·5 SD from the mean for the controls. The action potential was abnormal if the amplitude was below the lowest value found in the controls. An electrophysiological diagnosis of polyneuropathy was made when conduction velocity, or distal latency, or potential amplitude, or a combination were abnormal in at least two nerves. Specific strategies were adopted to exclude mononeuropathies or multineuritides of diverse origin: (1) Patients with clinical findings suggesting mononeuropathy or profoundly asymmetric polyneuropathy were excluded; (2) abnormal electrophysiological variables were to be recorded from different nerves; (3) when entrapment neuropathies (for example, carpal tunnel syndrome) were suspected, the contralateral (left) limbs were examined; (4) mixed (sensory-motor) nerves (median, ulnar) were considered a single entity.

Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS). The prevalence of clinical and electrophysiological polyneuropathy was estimated in the whole sample, in different treatment groups, and in the untreated subjects. The presence of polyneuropathy was correlated with age, sex, and treatment modalities.

Results

From October 1990 to the end of December 1991 a total of 187 patients (117 men and 70 women) fulfilled the inclusion criteria. Patients' ages ranged from 21 to 69 (mean 55 (SE 12) years). Age and sex distribution of the cases within centres were fairly similar.

One hundred and seventy five patients were given one drug only. Amiodarone was the commonest drug (55 cases) then propafenone (41), verapamil and flecainide (25), atenolol (18), quinidine (seven), and mexiletine (four).

Thirty six patients (19%) were not given neurological assessment. The commonest reasons for exclusion were refusal and residence far from the hospital. These patients were similar to those completing the neurological assessment in terms of age, sex, and centre. Ninety six men and 55 women underwent complete neurological assessment. In these cases the underlying cardiac disorders were atrial arrhythmia (74 cases), Wolff-Parkinson-White disease (22), coronary artery disease (21), ventricular arrhythmia (19), arterial hypertension (five), sinus tachycardia (four), and miscellaneous cardiac disorders (six). The distribution of treated patients and the commonest drugs by centre were: Monza 54 (amiodarone 30, polytherapy six); Turin 47 (propafenone 15, verapamil and flecainide 10); Rome 36 (propafenone 10, amiodarone eight); San Giovanni Rotondo 14 (flecainide four, amiodarone and atenolol three). Untreated patients were evenly distributed among centres. Table 1 shows the general characteristics of the sample by treatment group. Untreated patients and subjects receiving flecainide were generally younger and those receiving mexiletine were older. Treatment duration ranged from 6 months to 10 years and was more than 3 years in 38% of the cases. Mean treatment duration varied for the different drugs. The daily doses of the drugs were within the standard therapeutic range for all the patients. Plasma concentrations of the antiarrhythmic drugs were not routinely measured.

Forty six patients (30%) complained of one or more symptoms of polyneuropathy, the commonest being paresthesiae (27 cases), followed by muscle cramps (18), restless legs (nine), standing or gait disturbances (five), burning feet, muscle pain, and troubles with object handling (four cases each). Abnormal clinical findings were present in 12 cases (amiodarone three, flecainide and verapamil two, propafenone and atenolol one, polytherapy three). They were mostly impairment of tendon reflexes (11 cases), then autonomic dysfunction (eight), hypotrophic muscles (three), muscle weakness, hypotonia, and sensation impairment (one case each). Electrophysiological polyneuropathy was present in 38 cases (25%) with similar distribution for the commonest drugs. Of these, five (3% of the entire sample) had concurrent clinical abnormalities (amiodarone, propafenone and flecainide one, polytherapy two). In none of the patients was treatment withdrawn because of symptoms or signs of

Table 1 Antiarrhythmic drugs and polyneuropathy: general characteristics of the sample by treatment group

	Drug treatment								
Variable	*None*	*Amiodarone*	*Propafenone*	*Atenolol*	*Verapamil*	*Mexiletine*	*Flecainide*	*Quinidine*	*Multiple drugs*
Total	22	46	32	14	19	3	20	5	12
Age (mean (SE))(y)	45(4)	57(1)	54(2)	58(2)	56(3)	62(3)	45(3)	54(4)	56(2)
Sex:									
Men	16	31	19	10	11	3	11	3	10
Women	6	16	14	4	8	—	9	2	2
Treatment duration (mean (SE))(months)	—	50(8)	31(4)	30(7)	43(8)	24(12)	30(5)	63(30)	—
Daily dose (mean (SE))(mg)		196(6)	474(33)	80(15)	217(23)	800(53)	190(17)	695(118)	—

Table 2 Antiarrhythmic drugs and polyneuropathy: electrophysiological (EP) and clinical (CP) polyneuropathy by patient, treatment, and disease characteristics

		EP		CP	
Variable	*No of cases*	*No*	*(%)*	*No*	*(%)*
Sex:					
Men	96	25	26·0	4	4·2
Women	55	13	23·6	1	1·8
Age (y)					
⩽ 45	30	7	23·3	—	—
46–55	37	7	18·9	2	5·4
56–65	58	15	25·9	1	1·7
> 65	26	9	34·6	2	7·7
Treatment duration (months):					
⩽ 12	36	6	16·7	2	5·6
13–36	57	15	26·3	1	1·8
> 36	58	17	29·3	2	3·4
Drugs:					
Amiodarone	46	10	21·7	1	2·2
Propafenone	32	7	21·9	1	3·1
Atenolol	14	3	21·4	—	—
Verapamil	19	7	36·8	—	—
Mexiletine	3	2	66·7	—	—
Flecainide	20	5	25·0	1	5·0
Quinidine	5	—	—	—	—
Multiple	12	4	33·3	2	16·7*
Untreated	22	4	18·2	—	—‡

*p < 0·05 *v* single drug treatment.
CP = electrophysiological *and* clinical polyneuropathy.
‡Clinical examination not done in 12 cases.

polyneuropathy. Clinical signs of peripheral nerve involvement were generally mild, and muscle weakness, when present, did not cause standing or gait difficulties.

The most commonly impaired nerve was the median (46 cases (30%)), then the ulnar nerve (35 cases (23%)), the peroneal nerve (30 cases (20%)), and the sural nerve (28 cases (19%)). Twenty three subjects had abnormal electrophysiological recordings in two nerves, 12 in three nerves, and three in four nerves.

Nerve potential amplitude was the most often impaired measure, maximally in the sural nerve (24 cases) followed by median motor (19 cases) and sensory (16 cases), ulnar motor (13 cases) and sensory (seven cases), and peroneal (10 cases). Impairment was more than 20% above normal in 27 cases and more than 40% in 22. All the cases with electrophysiological polyneuropathy presented impairment of potential amplitude. Distal latency was abnormal in the median nerve in 16 cases, in the ulnar nerve in 15, and in the peroneal nerve in 13. Abnormal nerve conduction velocity values were slightly less frequent and were detected in similar proportions in the nerves investigated: median sensory (12 cases) and motor (nine cases), peroneal and sural (11 cases each), ulnar motor (nine cases), and sensory (three cases). Severe (> 40%) impairment of nerve conduction velocity and distal latency was rare. No correlation was found between drugs and number of impaired nerves or between the extent of the electrophysiological impairment and age, presence of clinical abnormalities, or type of drug.

Table 2 gives the correlations between polyneuropathy and demographic and clinical features in the whole sample. Treatment with multiple drugs was the only variable that seemed correlated with the risk of polyneuropathy. Twenty two patients (16 men, six women) aged 17 to 69 years were considered candidates for antiarrhythmic treatment but were still untreated when assessed. Cardiac disorders included sinus tachycardia (eight cases), ventricular arrhythmia (five), coronary artery disease (four), Wolff-Parkinson-White disease (two), and miscellaneous disorders (three). Of these, four patients (18%) presented abnormalities confirming a diagnosis of electrophysiological polyneuropathy. One patient had electrophysiological abnormalities in three nerves; two had significant (> 40%) impairment of nerve potential amplitude (either sensory or motor). When performed, the clinical examination failed to detect abnormalities indicating peripheral nerve impairment.

Discussion

In this study 25% of the patients treated with amiodarone and other antiarrhythmic drugs presented electrophysiological findings in keeping with a diagnosis of polyneuropathy but only 3% also had clinical polyneuropathy. Impairment of deep tendon reflexes and symptoms of polyneuropathy were the most frequent features. The commonest antiarrhythmic drugs seemed involved to a similar extent.

Polyneuropathy among patients receiving antiarrhythmic drugs in clinical practice seems a common, but clinically irrelevant event. In fact, despite the frequent reports of paresthesiae here, which might be the result of the active search for the symptom, clinical polyneuropathy was generally mild and none of the patients needed treatment changes because of neurological toxicity. The use of low daily doses compared with other series may explain why no severe signs of neurotoxicity were detected, even among amiodarone users, despite prolonged treatment. Our data contrast with those of Charness and colleagues[3] who found neurological side effects in 54% of their patients taking amiodarone. In those patients, however, the mean daily maintenance dose of amiodarone was 580 mg as against 196 mg in the present study. In a recent experimental study a correlation was found between the amount of drug injected in the peripheral nerve and the extent of electrophysiological and pathological changes.[17]

Electrophysiological abnormalities in patients receiving antiarrhythmic drugs other than amiodarone may be explained by the partly overlapping mechanisms of action of these drugs, which contrast with the theoretical selectivity of their effects on the action potential of cardiac cells (sodium channel blockade, β-adrenergic blockade, prolonged repolarisation, calcium channel blockade).[11] Alternatively, abnormal folate metabolism, believed to predispose patients treated with the anticonvulsant phenytoin[18] to peripheral neuropathy, may be implicated here too. As phenytoin also has antiarrhythmic properties and most antiarrhythmic drugs undergo extensive hepatic metabolism[11] this may lead to folate deficiency. Tocainide and mexiletine increase the excitation threshold and reduce

sodium channel permeability in peripheral nerves.[19]

Another possible interpretation of our findings is that antiarrhythmic drugs at chronic maintenance dosages may induce functional impairment of the nerve with minimal or no anatomical damage. Indirect evidence tends to support this. Firstly, in our study the high frequency of electrophysiological abnormalities contrasts with a low prevalence of clinical signs of polyneuropathy. Secondly, in an ongoing prospective study of amiodarone neuropathy some patients receiving high doses presented abnormalities of nerve conduction that were detected after a few days of treatment (A Bono, personal communication). Thirdly, in several patients taking amiodarone the electrophysiological abnormalities were reversed by reduction of treatment or withdrawal.[9 20 21]

The electrophysiological polyneuropathy seen in 18% of untreated patients with cardiac disorders arouses the suspicion that peripheral nerve impairment may not always be related to antiarrhythmic treatment (electrophysiological assessment before treatment was not available in our patients). The disease may also be the complication of other known or less known factors, including the underlying heart disease. Given the prevalence of the disease in an untreated, otherwise similar, population the proportion of polyneuropathy attributable to drug treatment may thus be even lower than that reported in the whole sample.

Our patients presented diffuse electrophysiological signs of sensorimotor neuropathy. Previous reports provide conflicting results showing motor,[6] sensory,[7] or sensorimotor signs.[7 20] Our findings suggest a mixed polyneuropathy with axonal and demyelinating components. Predominant axonal damage was detected on nerve biopsy by some authors[7 22] whereas others found prevailing demyelination with only mild axonal loss,[6 23] and others found combined axonal and myelin involvement.[8] The different findings of the neuropathological studies may be explained by the different treatment schedules, which produce various electrophysiological and pathological changes, ranging from pure demyelination to complete axonal degeneration in the experimental animal.[17] The lack of pathological reports in our study prevents comparisons or definite conclusions on this issue and we could not establish why only some of the patients currently exposed to antiarrhythmic drugs develop signs of peripheral nerve impairment. Except for the use of drug combinations, which may imply a potentiation of the effect on nerve conduction on the basis of well-known drug interactions,[24] none of the more common characteristics of patients and treatment seemed to predispose to polyneuropathy. As there are anecdotal reports of lysosomal inclusions among patients treated with other drugs with pronounced lipophilic properties, such as perhexiline maleate[25] and chloroquine,[26] the toxic effects of amiodarone, like perhexiline and chloroquine, may act through an induction of enzyme deficiency in predisposed patients.[27] Such findings might not be present with other antiarrhythmic drugs, which thus merit further investigation.

Financial support from FIDIA Research Laboratories is gratefully acknowledged.

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