Clinical pharmacology of chronic atrial fibrillation

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Atrial fibrillation is a common disorder which is particularly prevalent among the elderly [1,2] (Fig. 1). Long-term drug treatment is widely prescribed for patients with chronic atrial fibrillation and, whilst digoxin is traditionally regarded as the cornerstone of therapy, doubt has been cast upon its efficacy and its safety. Other classes of drugs, including the beta-blockers and the calcium antagonists, may have certain advantages over the cardiac glycosides and can be used alone and in combination with digoxin. This article reviews the therapeutic options currently available for the treatment of patients with chronic, stable atrial fibrillation.

General considerations

Haemodynamic disturbances

Atrial fibrillation represents a major disturbance of cardiac function and the main haemodynamic consequences result both from absence of atrial systole and from the rapidity and irregularity of the ventricular response.

1. *Absence of atrial systole.* It is difficult to establish the precise contribution of atrial systole to ventricular function because this depends, in part, upon filling pressures. In a group aof patients with complete heart block, the mean cardiac index decreased from 2.7 l/min per square metre during correct atrio-ventricular sequencing to 2.3 l/min during ventricular pacing [3]. Thus, absence of atrial systole reduces cardiac output although this alone does not appear to explain the full extent of impairment of cardiac function seen in atrial fibrillation. This suggests that both the rate and the irregularity of the ventricular response also contribute to the haemodynamic changes seen in atrial fibrillation [4].

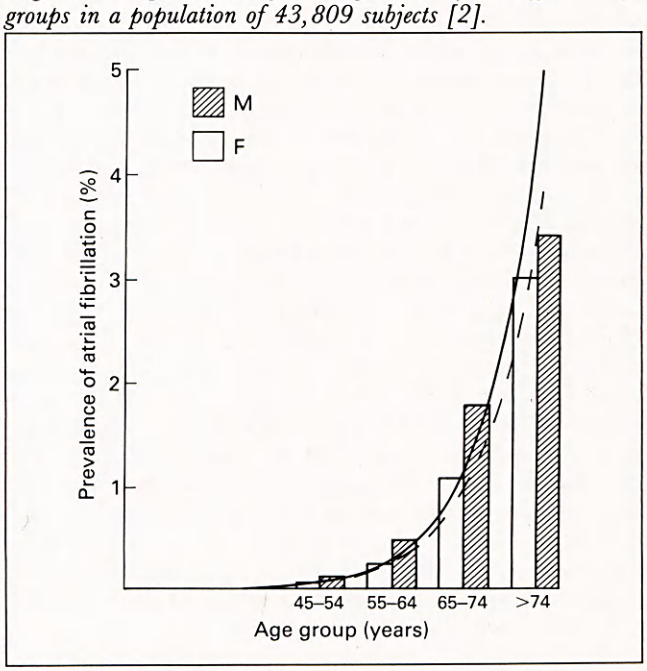
2. *Rapidity of the ventricular response rate.* In the presence of mitral stenosis, increases in diastolic dimensions are related to the duration of diastole (Fig. 2). Thus, when the ventricular rate is rapid, ventricular filling is incomplete and this may lead to a decrease in cardiac output according to the Frank-Starling mechanism. However, in patients with atrial fibrillation and normal mitral valves, left ventricular end-diastolic dimensions are reached early in diastole and remain constant thereafter (Fig. 2). Thus, the Frank-Starling mechanism is unlikely to be an important factor in this situation. When R-R intervals are extremely short, mechanical alternans may be seen and this phenomenon may contribute further to the deterioration of cardiac haemodynamics [5].

3. *Irregularity of the ventricular response.* In some patients, atrial fibrillation is associated with mitral regurgitation but this appears to be a consequence of irregular cycle lengths, rather than atrial fibrillation itself [6].

Clinical consequences of atrial fibrillation

The sudden onset of fast atrial fibrillation may precipitate overt cardiac failure, particularly if left ventricular function is already compromised by co-existing valvular or

Fig. 1. *The prevalence of atrial fibrillation in different age groups in a population of 43,809 subjects [2].*



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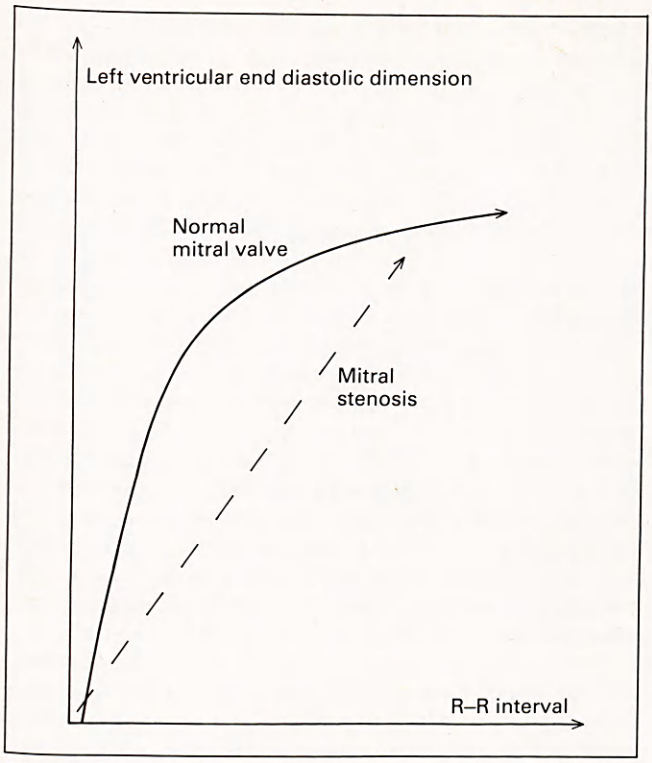

Fig. 2. *The relationship between left ventricular end-diastolic dimension and duration of R-R interval in patients with normal mitral valves and in mitral stenosis [25].*

ischaemic heart disease. More often, however, atrial fibrillation presents with less dramatic symptoms including palpitation, exertional dyspnoea, ischaemic cardiac pain or general fatigue and lethargy.

It is likely that haemodynamic disturbances in atrial fibrillation become more marked on exercise as a disproportionate rise in the ventricular response rate may occur during mild to moderate exertion. Symptoms such as dyspnoea, muscle fatigue or anginal pain (in patients with coronary artery disease) may limit maximum exercise tolerance and there is evidence to suggest that reversion to sinus rhythm is associated with improved exercise tolerance in some individuals. However, more subjective symptoms may occur at rest or during mild exercise and it is possible that awareness of cardiac irregularity itself may affect the perceived sense of well-being. Thus, in assessing patients with atrial fibrillation, attention should be directed towards subjective, as well as objective, parameters. Whilst measurement of heart rate, exercise tolerance and cardiac output may reflect changes in cardiac function, these variables may not be direct determinants of how well or unwell patients actually feel. For example, one study has shown that increasing doses of digoxin were associated with an improved sense of general well-being although only small changes in effort tolerance were reported [7].

Systemic embolisation is a recognised risk of atrial fibrillation, particularly in the presence of mitral stenosis. Long term anticoagulation appears to reduce the incidence of stroke in patients with atrial fibrillation associated with rheumatic heart disease. In patients with atrial fibrillation due to other causes the benefits of anticoagulation appear to be smaller and may not justify the potential risks.

Principles of drug treatment

In the majority of patients with chronic atrial fibrillation, restoration and maintenance of sinus rhythm is not possible unless a remediable cause such as thyrotoxicosis or valvular disease can be identified and corrected. However, in patients with atrial fibrillation of recent onset, cardioversion should probably be attempted at least once. Pre-treatment with amiodarone or quinidine may improve the success rate and may be continued after cardioversion to reduce the risks of relapse. However, in most patients, atrial fibrillation is likely to persist and treatment is then directed towards maintaining optimum cardiac function and controlling symptoms.

Drug treatment may reduce both the rate and the regularity of the ventricular response. The ventricular rate can readily be reduced by giving drugs which increase the extent of the atrio-ventricular (AV) nodal conduction block; this improves ventricular filling by increasing diastolic filling times. A rising heart rate is associated with increases in cardiac output until a critical value is reached after which ventricular filling becomes a limiting factor. Once this point is reached, cardiac output will tend to decline with further increases in the heart rate. One might expect that rate-reduction would be of particular value in patients with mitral stenosis, as increases in end-diastolic dimensions are related, over a certain range, to the duration to diastole. However, there is little evidence to suggest that patients with mitral stenosis do derive any particular benefit from the 'better' rate control which can be achieved with combinations of digoxin plus either calcium antagonsist or beta-blockers [8].

Finally, it is likely that some patients do not have symptoms which are directly related to their atrial fibrillation and, as treatment is primarily directed towards symptom control, drug therapy may well be inappropriate in such individuals.

Drugs used in the treatment of atrial fibrillation

Digoxin

Digoxin, which has now been in clinical use for over 200 years, is widely regarded as the drug of choice for the long-term treatment of chronic atrial fibrillation. In this context, the therapeutic effects of the cardiac glycosides are generally thought to be due primarily to their rate-limiting effects rather than their inotropic actions. Nevertheless, it has been known for many years that digoxin fails to control exercise-induced tachycardia, even when plasma drug concentrations are near the upper end of the accepted 'therapeutic' range [9]. This is predictable from the basic pharmacology of the cardiac glycosides, as they have little direct effect upon AV nodal conduction and their effects are mediated primarily via potentiation of vagal tone and inhibition of sympathetic stimulation [10].

During exercise, intrinsic vagal tone is withdrawn and sympathetic activity increases so that digoxin appears to have relatively little effect upon post-exercise heart rate when compared with placebo [11,12]. The reductions in heart rate observed during early experience with digoxin in severe congestive cardiac failure may, in fact, have been a secondary phenomenon reflecting an improvement in cardiac function brought about by some other mechanism.

Nevertheless, it is our impression (and that of many others) that digoxin does have a beneficial effect in patients with atrial fibrillation, and this raises the possibility that the therapeutic effects of the cardiac glycosides may not, in fact, be attributable solely to their rate-limiting effects. It is possible, despite considerable evidence to the contrary, that an inotropic effect may be maintained during chronic dosing. There is also evidence to suggest that digoxin may affect neuroendocrine systems and that it may partially inhibit renin release. It is also possible that digoxin may have central effects and that these may account for some of the subjective improvements reported by patients taking digoxin.

Whilst the cardiac glycosides fail to control exercise-induced tachycardia, it is clear that digoxin can achieve marked reductions in the resting heart rate. This may predispose to periods of quite marked nocturnal bradycardia, because a diurnal variation in heart rate is frequently seen in subjects with atrial fibrillation [13]. Digoxin has a narrow therapeutic ratio and toxicity may be associated with potentially lethal arrhythmias. The threshold for glycoside toxicity shows considerable inter-individual variability and both hypokalaemia and hypomagnesaemia predispose to cardiac toxicity. Conversely, serum concentrations of less than about 1 nmol/l are thought to be largely ineffectual. Within the accepted 'therapeutic' range (1.3 to 2.6 nmol/l) there is evidence of a weak relationship between plasma drug concentration and pharmacological effect [9].

Digoxin is generally well tolerated and the more common side effects such as nausea or sickness may respond to a decrease in drug dosage. However, there is some concern that even 'therapeutic' plasma concentrations of digoxin may increase the prevalence of ventricular arrhythmias [14]. There is also evidence to suggest that digoxin might have central effects which could interfere with memory or mood. Such effects would be of particular concern in the elderly who might be taking a variety of other drugs.

Verapamil and diltiazem

Rate-limiting calcium antagonists such as verapamil and diltiazem inhibit calcium influx at the atrio-ventricular (AV) node, thereby increasing the extent of the AV block and reducing the ventricular response rate [10]. In contrast to digoxin, verapamil and diltiazem act directly upon the heart and their efficacy is not attenuated by changes in intrinsic vagal and sympathetic tone. Both verapamil [15] and diltiazem [16] achieve better control of exercise-induced tachycardia than digoxin, and the magnitude of their effect appears to be related to the rapidity of the ventricular rate. They may be given either alone, or in combination with digoxin which appears to be particularly effective. But there is some concern that such combinations might predispose to periods of nocturnal bradycardia, and ambulatory ECG monitoring has shown that ventricular rates may fall at times to 30–40 beats per minute during the night. However, ambulatory monitoring frequently showed that periods of marked bradycardia occur also in normal subjects [17] and therefore the relevance of this finding is unclear. Nevertheless, some subjects with atrial fibrillation have a predisposition to heart block, and aggressive treatment might be expected to lead to problems in such patients. Apart from improving control of exercise-induced tachycardia, calcium antagonists may also reduce the irregularity of the ventricular response. This reduction may be due either to the formation of a total AV nodal block with the development of a nodal escape rhythm, or to synchronisation of nodal conduction; the former is thought to be the more likely of the two possibilities [18]. 'Regularisation' of ventricular response is theoretically desirable as mitral regurgitation seems to be a function of irregular cycle lengths.

Despite these theoretical benefits, it is really not clear whether calcium antagonists have important advantages over digoxin in clinical practice. Some workers have reported that verapamil, either alone or in combination with digoxin, might improve effort tolerance in particular subjects [19] but these findings have not been confirmed by others [15]. Similarly, there is little evidence to suggest that 'improved' rate control leads to a significant increase in cardiac output [12]. This may be because both verapamil and diltiazem are negative inotropes and any benefits brought about by improved ventricular filling are offset by their effect upon myocardial contractility. Both verapamil and diltiazem have a dual effect upon cardiac function; the depression of myocardial contractility after the first administration of either drug may be partially negated by subsequent peripheral vasodilation with a decrease in afterload and an increase in cardiac output. Nevertheless, it seems reasonable to suggest that drugs such as verapamil and diltiazem should be used only with caution in patients with atrial fibrillation complicated by cardiac failure, unless the latter is primarily a rate-related phenomenon. In contrast to patients with atrial fibrillation of ischaemic or rheumatic origin, patients with 'lone' atrial fibrillation (and the majority of those with thyrotoxic heart disease) are likely to have intrinsically good myocardial function and the risk of precipitating overt failure with calcium antagonists is probably small.

Both verapamil and diltiazem cause side effects [15, 16] which may outweigh any benefits that might accrue from tighter rate control. However, despite these side effects, rate-limiting calcium antagonists may be intrinsically 'safer' drugs than digoxin and might therefore have advantages in patients who are at risk of ventricular arrhythmias.

Beta-adrenoceptor antagonists

Like the rate-limiting calcium antagonists, beta-adrenoceptor antagonists (beta-blockers) may be used to im-

prove control of exercise-induced tachycardia in digitalised patients with chronic atrial fibrillation. However, treatment with beta-blockers is associated with impairment of maximum effort tolerance, reduced oxygen uptake during exercise, and a heightened perception of the severity of a given exercise workload [20, 21]. Moreover, beta-blockers have negative inotropic effects and may precipitate cardiac failure in susceptible individuals. Unlike the calcium antagonists, the beta-blockers do not have favourable effects upon the peripheral vasculature and the decrease in left ventricular workload obtained with verapamil and diltiazem would not be expected to occur during treatment with beta-blockers. Thus, beta-blockers are more likely to cause acute heart failure than calcium antagonists in individuals with atrial fibrillation associated with cardiac decompensation.

Moreover, treatment with beta-blockers may be associated with a range of side effects including peripheral coldness and certain central nervous system symptoms [22]. Beta-blockers without partial agonist activity (PAA) may predispose to periods of nocturnal bradycardia, but drugs with PAA, like pindolol and xamoterol, can control exercise-induced tachycardia without causing excessive slowing of the resting heart rate.

Amiodarone [23]

Amiodarone is a potent anti-arrhythmic agent which has two distinct roles in the treatment of atrial fibrillation. It has a blocking effect upon AV nodal conduction and can therefore reduce the ventricular response rate in established atrial fibrillation. It can also be used as a prophylactic agent to prevent recurrences of atrial fibrillation after cardioversion. It may also bring about reversion to sinus rhythm in patients with established atrial fibrillation.

The main electrophysiological effects of amiodarone in man include prolongation of the refractory periods of atrial and ventricular myocardium, lengthening of atrioventricular nodal refractoriness and conduction, and prolongation of the refractory period of the accessory pathway. Additional effects include depression of sinus automaticity and lengthening of His-Purkinje refractoriness.

Unfortunately, amiodarone is potentially a toxic agent which may cause a range of serious adverse effects [24] (Table 1). Of these, pulmonary fibrosis is probably the most serious, although often reversible when the drug is withdrawn. The current trend is to use relatively low doses of amiodarone wherever possible and this policy appears to be associated with a lower incidence of side effects. Nevertheless, many authorities feel that amiodarone should be reserved for potentially life threatening arrhythmias; chronic, stable atrial fibrillation would clearly not fall into this category.

However, amiodarone should be considered in the treatment of paroxysmal atrial fibrillation, where it appears to reduce the frequency of episodes of fibrillation. Paroxysmal atrial fibrillation can be difficult to treat, and abrupt episodes of rapid fibrillation may cause much more distress to patients than chronic stable atrial fibrillation. Although digoxin is sometimes of value in the treatment of this disorder, many patients fail to respond to treatment with digoxin.

Table 1. Side effects seen in 230 patients during treatment with amiodarone (from Heger et al., 1986[26]).

Side effect	No of occurrences
Cardiac	
Aggravation of VT-VF	10
Bradyarrhythmia requiring permanent pacing	4
Aggravation of heart failure	1
Non-cardiac	
Nausea, anorexia, wgt loss	62
Tremor	28
Blue skin discoloration	26
Ataxic gait	20
Visual 'halos'	19
Photosensitivity	11
Pulmonary toxicity	9
Headache	7
Impotence	7
Insomnia	6
Constipation	5
Hypothyroidism	4
Dermatitis	3
Purpura	2
Hepatotoxicity	2
Hyperthyroidism	1

Conclusions

Atrial fibrillation is a common disorder for which long-term drug treatment is widely prescribed. Digoxin remains the treatment of choice for most patients with symptomatic atrial fibrillation irrespective of the nature of the underlying heart disease, except those with the Wolff-Parkinson-White syndrome. A minority of patients continue to complain of symptoms directly related to a rapid heart rate (eg palpitation), despite plasma digoxin concentrations of between 1.3 and 2.6 nmol/l. For such individuals, additional therapy with either verapamil or diltiazem is preferable to an increase in the dose of digoxin because the latter would increase the risk of toxicity without conferring a significantly greater pharmacological effect. Both verapamil and diltiazem may increase plasma digoxin concentrations and the dose of digoxin may therefore need to be reduced.

In most patients, however, there is little evidence to suggest that aggressive treatment with combinations of digoxin and either a rate-limiting calcium antagonist or a beta-blocker brings benefit despite 'better' control of exercise-induced tachycardia; moreover, such combinations may precipitate marked resting bradycardia. The balance of the available evidence indicates that beta-blockers are likely to impair maximum effort tolerance whereas calcium antagonists may achieve small improvements in some subjects. Both beta-blockers and calcium

antagonists cause subjective side effects in a significant number of patients and might well offset any small improvement brought about by increased ventricular filling. There is concern that both beta-blockers and calcium antagonists may precipitate cardiac failure in patients with severe rheumatic or ischaemic heart disease; on theoretical grounds one would expect this to be more likely to happen with the former than with the latter.

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