

# Conversion of paroxysmal atrial fibrillation to sinus rhythm by intravenous pirmenol

## *A placebo controlled study*

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**SUMMARY** The efficacy of pirmenol (a class I antiarrhythmic agent) as a converter of paroxysmal atrial fibrillation was investigated. Forty patients without congestive heart failure or a history of sinus node disorder were randomly allocated to receive either intravenous pirmenol (50-100 mg) or placebo in a double blind trial. In 12 of 20 patients sinus rhythm was restored 2-16 minutes after pirmenol, and in 3 of 20 patients in the control group it returned within one hour. A nodal escape rhythm was seen during sinus slowing in one patient, but in other patients there was no sinus arrest, atrioventricular conduction disturbance, or hypotension. The ventricular rate was slightly increased in patients in whom sinus rhythm was not restored by pirmenol. The results indicate that pirmenol has an antifibrillatory effect on the atria. Sinus rhythm was restored rapidly after intravenous administration. It was well tolerated in patients with atrial fibrillation of recent onset.

Pirmenol has class I antiarrhythmic effects in Purkinje fibres.<sup>1</sup> It suppresses premature ventricular complexes in patients<sup>2,3</sup> and terminates paroxysmal supraventricular tachycardia.<sup>4</sup> Depression of the fast inward current and a considerable increase in the duration of action potential in the rabbit atria have been reported,<sup>5</sup> which might suggest an antifibrillatory effect on the atria. Pirmenol converted atrial tachycardia and fibrillation to sinus rhythm in dogs.<sup>6</sup>

The present randomised double blind study was undertaken to examine the efficacy of intravenous pirmenol in the acute treatment of paroxysmal atrial fibrillation.

### **Patients and methods**

Forty patients admitted to a hospital emergency department with atrial fibrillation of recent onset ( $\leq 48$  hours) participated in the study. Patients known or suspected to have a sinus node or atrioventricular

conduction disorder, acute myocardial infarction, or other severe illness, or congestive heart failure leading to interstitial extravasation shown by chest radiography were excluded. Patients who had taken digitalis or beta blocking agents  $\geq 3$  hours before the study were included, but those patients on other antiarrhythmic agents were excluded. The appearance of symptoms was taken to indicate time of onset of fibrillation.

The patients were observed over 30 minutes for clinical evaluation and to allow their condition to stabilise. They were observed for 60 minutes after administration of pirmenol or placebo. A two lead electrocardiogram with a time track was continuously recorded at a paper speed of 50 mm/s for analysis of the rhythm, heart rate, and electrocardiographic intervals. Brachial cuff blood pressure was measured every five minutes. Patients were randomly allocated to receive either pirmenol or placebo (20 patients each) in a double blind trial. Pirmenol (a 50 mg bolus in 5 ml of physiological saline) or 5 ml of physiological saline were injected over 2 minutes and the dose was repeated after 10 minutes if sinus rhythm had not returned. Blood samples for the determination of plasma concentrations of pirmenol were drawn five minutes after the injections and at the end of the 60 minute observation period. Chest

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radiographs and M mode echocardiography for determination of left atrial end systolic diameter and left ventricular dimensions according to European standards<sup>7</sup> were obtained when in sinus rhythm. Pirmenol concentrations were measured by high performance liquid chromatography.<sup>8</sup>

#### STATISTICAL ANALYSIS

Analysis of variance was used to examine the significance of serial changes. We used Student's *t* tests for continuous variables and Fisher's exact test for discrete variables to compare differences between the treatment groups and between converters and non-converters. We used the Mann-Whitney rank sum test to examine differences in duration of fibrillation. Differences of  $p < 0.05$  were regarded as statistically significant.

### Results

Age, left atrial and ventricular echocardiographic diameter, radiological heart volume, initial heart rate, duration of fibrillation, and use of digitalis and beta blockers were similar in the groups given active drug or placebo. Because there was a slight decrease in diastolic blood pressure ( $p < 0.05$ ) and heart rate ( $p < 0.0001$ ) in the 30 minute period of baseline observation, we used only the values obtained during the last 15 minutes as the basis for the comparison of responses.

#### EFFECT ON RHYTHM

Sinus rhythm was restored in 12 (60%) of 20 patients on pirmenol and in three (15%) of 20 patients given placebo ( $p < 0.01$ ). Conversion occurred 2–16 minutes after the first bolus of the active drug, but conversion times were randomly distributed in the placebo group (Figure). Sinus rhythm appeared after 50 mg of pirmenol in seven patients and after a total dose of 100 mg in five patients.

A nodal rhythm at a rate of 60 beats per minute appeared for 15 seconds after the first three sinus beats in one patient. Bradycardia or conduction disorders did not occur and there were no sinus arrests or escape rhythms in other patients. One patient who received a placebo injection developed non-sustained ventricular tachycardia, but none of the pirmenol group did so.

Fibrillation before treatment tended to last longer in non-converters than in converters ( $0.05 < p < 0.1$ ; Table 1). More patients in the converter group than the non-converter group had used beta blockers (7/12 vs 1/8;  $p = 0.07$ ). No significant differences were found in any of the other baseline characteristics (Table 1).

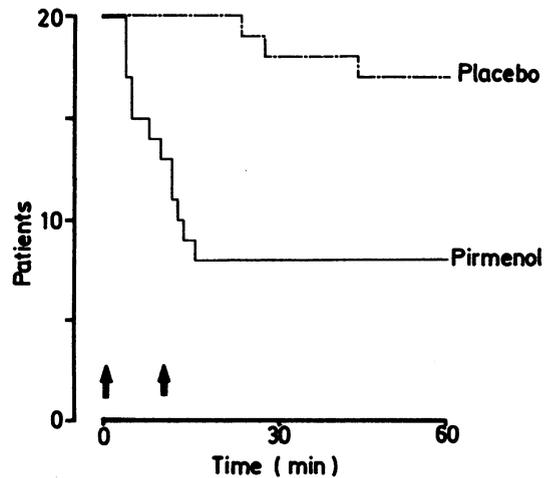


Figure Conversion of atrial fibrillation to sinus rhythm in the pirmenol and placebo groups. Vertical line shows patients remaining in atrial fibrillation. The injection times are indicated.

Table 1 Patient characteristics in the pirmenol group (mean (SD))

	Converters (n=12)	Non-converters (n=8)
Age (years)	51 (19)	49 (10)
Radiological heart volume (mm/m <sup>2</sup> )	410 (80)	520 (180)
Initial heart rate (beats/minute)	115 (19)	99 (24)
Left ventricular end diastolic diameter (mm)	51 (5)	49 (8)
Left atrial diameter (mm)	31 (6)	34 (6)
Left ventricular fractional shortening	0.32 (0.07)	0.33 (0.08)
Duration of atrial fibrillation (h)	8 (7)	18 (14)
Serum potassium ion concentration on admission (mmol/l)	3.8 (0.2)	4.1 (0.2)
Heart disease* (n)	6	4
Previously documented atrial fibrillation (n)	8	6
History of high alcohol consumption (n)	5	1
Digitalis used (n)	3	2
Beta blockers used (n)	7	1

\*Coronary artery disease (4 patients), cardiomyopathy (2), hypertensive heart disease (3), atrial septal defect (1).

#### RESPONSES IN HEART RATE AND BLOOD PRESSURE

Ventricular rate increased in eight non-converters by a mean of 19 beats/minute five minutes after the second bolus of pirmenol. The use of beta blocking agents influenced the changes in heart rate. The mean heart rate before conversion or after the second bolus in eight patients who took beta blockers did not increase, whereas in 12 patients who were not on beta

blockers the mean increase was 17 beats/minute (Table 2). Use of digitalis did not influence the change in heart rate in patients on pirmenol.

There were no significant drug induced changes in systolic or diastolic blood pressure in the converter and non-converter groups nor in those patients who used a beta blocking agent. The lowest systolic blood pressure recorded in any patient was 104 mm Hg. There were no significant changes in the blood pressure or heart rate in the placebo group.

#### ELECTROCARDIOGRAPHIC INTERVALS AND PLASMA CONCENTRATIONS OF PIRMENOL

There were mean increases in QRS duration and QT interval of 12 ms ( $p < 0.01$ ) and 33 ms ( $p < 0.001$ ) respectively 15 minutes after the first injection. The longest uncorrected and corrected (Bazett's formula) QT intervals in any patient were 440 ms and 490 ms respectively. No bundle branch block appeared. The mean (SD) plasma concentration of pirmenol five minutes after the first bolus was 1.3 (0.5) mg/litre. In patients who received a total dose of 100 mg, the concentration was 2.1 (0.8) mg/litre five minutes after the second bolus and 1.1 (0.3) mg/litre at the end of the 60 minute observation period.

No patient experienced any side effects and none had any chest pain or increased dyspnoea. Sinus rhythm was later achieved in all patients after a drug induced or electrical conversion.

#### Discussion

This is the first report of the effects of pirmenol in paroxysmal atrial fibrillation. Other antiarrhythmic drugs have been given intravenously to convert non-established atrial fibrillation. Halpern *et al* showed that intravenous procainamide restored sinus rhythm in nine of 21 patients (43%)<sup>9</sup> and Fenster *et al* reported that procainamide restored sinus rhythm in 58% of patients with atrial fibrillation.<sup>10</sup> In a study by Camm *et al* disopyramide terminated atrial fibrillation in 10 of 14 subjects (71%).<sup>11</sup> A single bolus of intravenous amiodarone restored sinus rhythm in 46% of patients in 30 minutes.<sup>12</sup>

Intravenous flecainide converted atrial fibrillation to sinus rhythm in 14 of 39 patients within 15 minutes.<sup>13</sup> Verapamil was successful in 8–15% of patients.<sup>14–16</sup>

Duration of fibrillation<sup>10</sup> and the size of the left atrium<sup>9,17</sup> influence the success of conversion. All the previously mentioned studies were largely performed in subjects with non-established paroxysmal or acute atrial fibrillation.<sup>9–16</sup> Although the duration of fibrillation varied between studies, making comparison of the therapeutic effects difficult, fibrillation had not lasted more than one day in most patients. The success rate (60%) of pirmenol resembles that of procainamide disopyramide, and amiodarone for short term intravenous use. All of these agents restore sinus rhythm rapidly.

Pirmenol increases the effective refractory period of the atria in man (unpublished). Increased refractoriness could result either from depression of the fast response channel or from prolongation of the action potential, both of which effects have been observed in rabbit atria.<sup>5</sup> A lengthening of the atrial effective refractory period theoretically reduces the number of disorganised activation wave fronts circulating in the fibrillating atria.<sup>18</sup> Defibrillation may be the result of the increased probability of a conduction block with extinction of re-entry due to prolonged refractoriness. Furthermore, experiments in rabbits indicate that synchronisation of atrial activation wave fronts or reduction in their number may enhance the effective conduction of the atrioventricular node and reduce the degree of concealed conduction in the atrioventricular node and hence increase the transmission of impulses to the ventricles.<sup>19,20</sup> The anticholinergic effect of pirmenol<sup>21</sup> probably also contributes to the increase in ventricular rate during atrial fibrillation.

A higher proportion of patients on beta blockers achieved sinus rhythm (7/8 *vs* 5/12;  $p = 0.07$ ), and there was no increase in heart rate in those patients who were on beta blockers. Whether beta blocking agents were causally related to the success of conversion by pirmenol cannot be definitely established. It is unlikely that their use merely selected those

Table 2 Heart rate responses (beats/minute) in patients in relation to conversion of atrial fibrillation and use of beta blockers. Values are mean (SD) at baseline and before termination of fibrillation or five minutes after the last bolus

	No	Baseline	Pirmenol	p value for	
				Change	Interaction between group and change
Converters	12	111 (20)	116 (18)	NS	
Non-converters	8	94 (21)	113 (19)	<0.01	<0.05
Beta blocker	8	102 (26)	103 (18)	NS	
No beta blocker	12	106 (20)	122 (14)	<0.01	<0.05

patients with a greater chance of conversion, because left atrial diameter or duration of fibrillation were no more favourable in those on beta blockers. Also, six of the eight patients had been on long term beta blockers treatment, and this indicates that these drugs were unable to prevent the paroxysm. Similar synergism between beta blockers and quinidine in atrial fibrillation has been suspected.<sup>22</sup>

The dosages of pirmenol tested and plasma concentrations obtained paralleled those which are effective in other arrhythmias. Similar doses (50 mg) given intravenously once or twice terminated paroxysmal supraventricular tachycardia,<sup>4</sup> and single short infusions of up to 150 mg abolished premature ventricular complexes.<sup>2</sup>

Rapid conversion of atrial fibrillation of recent onset by intravenous injection of a drug may avoid the need for electrical cardioversion and shorten hospital stay. A fall in blood pressure and depression of the sinus node and atrioventricular conduction system are potential adverse reactions of intravenous administration of drugs for conversion of atrial fibrillation.<sup>9-11,14</sup> Quinidine-like class I antiarrhythmics may also increase ventricular rate.<sup>11</sup> These untoward effects have prevented the use of intravenous conversion as a routine treatment. In the present study, from which patients with advanced cardiac diseases were excluded, restoration of sinus rhythm was uncomplicated except for a short period of nodal rhythm in one patient. Although the full electrophysiological effects of pirmenol are not known, by analogy with other fast inward current inhibitors<sup>23-25</sup> it is likely to depress impulse formation and conduction when it is used to treat arrhythmias associated with sinus and atrioventricular nodal disorders. None of our patients had a hypotensive reaction. Pirmenol is known to increase blood pressure slightly and has only a slight myocardial depressant effect.<sup>26</sup>

In conclusion, pirmenol has an antifibrillatory effect in the atria. Its efficacy seems comparable to that of the agents presently available for rapid conversion of atrial fibrillation. It is well tolerated by patients without congestive heart failure or a diseased sinus node.

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