PROPHYLACTIC USE OF ANTIARRHYTHMIC DRUGS FOLLOWING MYOCARDIAL INFARCTION: OBSERVATIONS OVER 12 MONTHS

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BACKGROUND

Most patients who die after leaving hospital following admission with myocardial infarction die either after more chest pain or they die suddenly[1]. In controlled trials of long-term anticoagulant therapy reduced mortality in treated groups appears to have been due to reduction in deaths after chest pain, not in sudden deaths[2]. The death rate over 2 years after leaving hospital has been reported to be increased in patients who had arrhythmias or conduction defects recorded while in hospital and one study suggested the risk of late sudden death was greatest in those with positive record[3].

On the basis of these findings a controlled trial was undertaken of an antiarrhythmic drug, phenytoin, given to patients for 12 months after leaving hospital following admission with myocardial infarction. The aim was to find out if phenytoin reduced mortality, and particularly sudden deaths.

CONTROLLED TRIAL WITH PHENYTOIN

Five hundred and sixty eight patients in 6 hospitals were entered in the trial. There was no difference in the survival rates of patients treated with 300-400 mg/day compared with the comparative group[4].

Two further findings are worth mentioning. The variation in blood phenytoin levels between individuals prescribed the same dose was large and in the hospital in which blood levels were measured there were 10 deaths in the 64 patients whose plasma levels averaged <10 μg/ml and no deaths in the 32 patients whose levels averaged $\geqslant 10$ μg/ml. This was a post-hoc observation and could have reflected chance differences in risk factors between the patients who achieved different blood levels.

The other observation was made on 1-minute E.C.G. rhythm strips recorded at each visit in The Royal Melbourne Hospital patients. The incidence of frequent ventricular extrasystoles (V.E.S.) in these strips was less in the treatment group than in the controls. Evidently the ability of a drug to reduce the incidence of frequent V.E.S. is not necessarily paralleled by its ability to prevent sudden fatal arrhythmias.

PROGNOSTIC IMPLICATIONS OF INDIVIDUAL ARRHYTHMIAS

In the phenytoin trial data was recorded that might throw more light on the long-term prognostic implications of individual arrhythmias and conduction defects in the acute attack. Previous observations on the long-term implications of arrhythmias had been made before the era of E.C.G. monitoring in coronary care units (C.C.U.s), so they presumably related to severe or persistent rhythm disturbances[3, 5, 6, 7]. Also, in assessing the possible effect of arrhythmias, account was not always taken of other major determinants or prognosis such as age, prior ischaemia and the severity of the acute attack.

To examine the effect of arrhythmias **per se**, we have selected only the 226 patients (210 male, 16 female) in the phenytoin trial who had no previous history of myocardial infarction, all of whom were admitted to C.C.U.s and who, during their admission, were observed to have either no arrhythmia or one type of arrhythmia only.

RESULTS

The arrhythmias coded in hospital and those excluded from coding are shown in Table 1. Coded arrhythmias were recorded in 86 (39%) of the 226 patients. A check on a sample of patients with no records of coded arrhythmias showed that 90% had notes of arrhythmias of the sort that were excluded from our classification. This explains the apparently low recording rate and suggests that those arrhythmias we set out to examine were correctly recorded.

Table I shows that the commonest coded arrhythmias were V.E.S. $\geqslant 10\%$ of beats.

Table II shows that the survival rate at 12 months in the no-arrhythmia group was 95% which was significantly higher than the rate of 83% in the ventricular arrhythmia group ($p < 0.05$). In the A-V block group the survival rate was 84%.

In the ventricular arrhythmia group, 6 of the deaths were in patients with only frequent V.E.S., the other was in a patient with V.F. only.

Table III shows that the mean ages of the no-arrhythmia, ventricular arrhythmia and A-V block groups were almost the same. In each group the mean ages of those who died were also similar and higher than the means for their groups; the age ranges were similar. Thus differences in age did not determine the different survival rates between the groups.

A history of angina occurring for more than one month prior to the qualifying myocardial infarction provided an index of prior ischaemia. Table IV shows that overall a past history of angina was recorded in 32 patients (14%). It was recorded in 11 of 41 patients (27%) in the ventricular arrhythmia group compared with 15 of 139 patients (11%) in the no-arrhythmia group ($p < 0.05$); it was also recorded in 21% of the A-V block group.

Subdivision of these groups to examine survival rates resulted in numbers too small for statistical comparisons. As expected, the overall survival rate of patients with a past history of angina (87%) was lower than that of patients without such a past history (93%). The survival rates of patients in the ventricular arrhythmia group and A-V block group were lower than those of the no-arrhythmia group, whether or not they had a past history of angina.

A peak SGOT $\geqslant 300$ u. was recorded in 38 patients (17%). It was recorded significantly more often in the ventricular arrhythmia group (24%, $p<0.05$) and in the A-V block group (47%, $p<0.001$) than in the no-arrhythmia group (12%). Again, subdivision for comparisons of survival resulted in numbers too small for statistical analysis. Overall the survival rate of patients with the SGOT levels $\geqslant 300$ u. (86%) was lower than that of patients with lower levels (93%) and the survival rates of patients in the ventricular arrhythmia and A-V block groups were lower than those of the no-arrhythmia group whether their SGOT levels were high or low.

Information on modes of dying was available in all but 3 patients (Table V). There was no indication that patients died suddenly—within 24 hours or within minutes—more often in the arrhythmia as compared with the no-arrhythmia group.

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TABLE I

CLASSIFICATION OF ARRHYTHMIAS
ARRHYTHMIAS CODED

Ventricular (42)	33, V.E.S. >10% of beats only	**A-V Block** (19)	10, 3rd degree
	4, V.F.		4, 2nd degree
	2, V.F. and standstill		5, 1st degree
	3, V.T.		
Atrial (19)	15, fibrillation/flutter	**B.B.B.** (6)	2, L.B.B.
	3, nodal rhythm		2, R.B.B.
	1, tachycardia		2, mixed

ARRHYTHMIAS EXCLUDED

Sinus bradycardia, sinus tachycardia,
Atrial and ventricular extrasystoles if less than 10% of beats.

TABLE III

AGES OF THE PATIENTS

	Arrhythmia Classification				
	None	Ventricular	A-V block	Atrial	B.B.B.
Mean age (year) ± S.D.	52 ±8	53 ±9	52 ±8	58* ±6	55 ±10
Age of patients dying (and range)	58 (46-69)	57 (41-60)	56 (45-63)		

* For comparison with no-arrhythmia group, $p < 0.001$.

TABLE IV

SURVIVAL IN RELATION TO PAST HISTORY OF ANGINA

	Arrhythmia Classification					
	None	Ventricular	A-V block	Atrial	B.B.B.	Total
Total patients	139	41	19	19	6	224**
Prior Angina						
No. of patients	15	11*	4	0	2	32
% surviving 1 year	93	78	75	100	100	87
No Prior Angina						
No. of patients	124	30	15	19	4	192
% surviving 1 year	94	83	87	100	100	93

* proportion with prior angina was significantly higher than in no-arrhythmia group ($p < 0.05$).

**excludes 2 with angina history not recorded.

TABLE II

FATE OF THE PATIENTS

	Arrhythmia Classification					
	None	Ventricular	A-V block	Atrial	B.B.B.	Total
No. of patients	140	42	19	19	6	226
Lost	1	2				3
Died in 1st year	8	7	3			18
% survival at 1 year	95	83*	84	100	100	

* For comparison with no-arrhythmia group, $p < 0.05$.

TABLE V

MODES OF DYING

	Modes of dying				
Arrhythmia group	Total Number	Within 24 hr.	(Within minutes)	> 24 hr.	Not Known
None	8	6	(4)	1	1
Ventricular	7	4	(3)	1	2
A-V block	3	3	(0)		

DISCUSSION

These observations show that the recording of ventricular arrhythmias alone (in this series predominantly V.E.S. 10% of beats) during the acute phase of a first attack of myocardial infarction, is associated with diminished probability of surviving 12 months after leaving hospital. The same may be true of A-V block.

With regard to possible interactions with other major prognostic risk factors, age does not determine the association between ventricular arrhythmias and impaired prognosis.

Prior ischaemia, as judged by a past history of angina, is associated with ventricular arrhythmias and possibly A-V block. Our findings suggest however that ventricular arrhythmias have an adverse effect on prognosis which is additional to that of prior ischaemia, though the numbers of cases do not permit a firm conclusion.

An association also exists between high SGOT levels ($\geqslant 300$ units) and both ventricular arrhythmias and A-V block. High SGOT levels might be consequences of arrhythmias but we think it more probable that severe muscle injury is usually the primary factor and that arrhythmias are often the consequence of this.

CONCLUSION

In patients with first episodes of myocardial infarction, admitted to coronary care units, and experiencing only one type of arrhythmia, ventricular arrhythmias (mostly frequent V.E.S.) have an adverse effect on survival at 1 year; the same is probably true of A-V block.

The association between frequent V.E.S. and impaired prognosis is not dependent on age and probably not on prior ischaemia but it may be related to the extent of myocardial injury.

Long-term prophylactic therapy with antiarrhythmic drugs after myocardial infarction holds less promise than appeared to be the case a few years ago because:

(i) a controlled trial with one such drug (phenytoin) did not influence survival despite its ability to reduce the prevalence of frequent V.E.S.

(ii) in a more homogeneous group of patients than ones previously studied, an association between single arrhythmias in the acute attack and later sudden death has not been found so that the idea that such arrhythmias might identify patients particularly predisposed to later fatal arrhythmias is not supported.

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REFERENCES

1. Lovell, R. R. H., Denborough, M. A., Nestel, P. J. and Goble, A. J. Med. J. Aust., 2, 97, 1967.
2. Lovell, R. R. H. Med. J. Aust., 2, 425, 1969.
3. Denborough, M. A., Lovell, R. R. H., Nestel, P. J. and Goble, A. J. Lancet, 1, 386, 1968.
4. Collaborative Group, Lancet, 2, 1055, 1971.
5. Cole, D.R., Singian, E.B. and Katz, L.N. Circulation, 9, 321, 1954.
6. Honey, G. E. and Truelove, S. C. Lancet, i, 1209, 1957.
7. Beard, O. W., Hipp, H. R., Robins, M., Taylor, J. S., Ebert, R. V. and Beran, L. G. Am. J. Med., 28, 871, 1960.