NIALAMID DURING ACUTE MYOCARDIAL INFARCTION

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The exhibition of MAO inhibitors causes an increase in urinary output of 5-hydroxytryptamine. This is a reflection of the effect that it exerts on the catecholamines in the body, and although it has been demonstrated that serotonin may adversely affect the tendency of intravascular thrombus formation, atheroma, and cardiac irritability, the use of Nialamid — a MAO inhibitor — in animal experiments unexpectedly showed a protective effect against thrombus formation (Shimamoto et al, 1960).

In myocardial infarction, the mortality is regarded as being due to a number of causes of which pulmonary embolism from thrombus formation either in the heart or the veins, and the extension of the thrombosis would appear to be most important. The use of anticoagulants has in most series reduced the mortality to approximately 10% but deaths from those two causes were not entirely prevented. It was thought that by using Nialamid in the first week, the risk of thrombus formation may be reduced, thereby producing a lower mortality. The theoretical danger of serotonin on an infarcted heart was appreciated, but in view of the unexpected effect of Nialamid in animals, it appeared that the risk might be more theoretical than real. Further, it is known that 90% of the mortality of cardiac infarction occurs in the first week of the disease. Hence the trial of Nialamid in the first week should produce sufficient data to permit a critical assessment of its effect on acute myocardial infarction. Accordingly, the following study was undertaken to evaluate the value of Nialamid during acute infarction.

Method :— A Modified double-blind trial was set up by dividing the patients into 3 lots serially according to the time of admission. The first patient was given tablet A, the second tablet B, and the third tablet C. 2 of these groups of tablets were Nialamid, and the other was placebo, but the nature of the tablet was not known to either the doctor in charge of the case, or to the patient until the end of the trial. The dosage was 50 mg. t.i.d. for 1 week from the time the diagnosis was made clinically, and each patient received the trial tablet and was placed on the usual regime for the treatment of cardiac infarction, namely rest, anti-coagulants and sedatives; and in addition oxygen, digitalis and other supportives were used where the need was present. Confirmation of the clinical diagnosis was made on electro-cardiographic changes and laboratory findings including serum transminase estimation. Examination of liver function and estimation of blood cholesterol were done as routine. The case was usually in hospital for 4 to 6 weeks prior to discharge. It was thought that 2 parallel Nialamid series could serve as a mutual check on reliability of the results and distribution, in addition to the comparison afforded by the control series receiving placebo. The observation went on as long as the stock of the tablets lasted.

Results :— Although the plan was to have 20 cases in each series, a number of cases had to be rejected at the end of the trial, because they proved to be suffering from other diseases, and a total of 50 cases were observed in this trial. The results were as shown in the ensuing tables :—

TABLE I

Groups	A (Nialamid)	B (Control)	C (Nialamid)
Dead	2*	1	2
Worse	1	3	1
Improved	14	11	11
Doubtful	0	1x	3
Total	17	16	17

*One case died after receiving one dose only. Necropsy showed advanced kidney, liver, and coronary disease, and probably should be excluded from the consideration of results.

xThis case could not be traced, and was presumably dead, but in view of the lack of certainty, it was not reckoned as a mortality.

TABLE II (AGE GROUPS)

Group	A		B		C	
Age	M	F	M	F	M	F
30 or less	0	0	0	0	1	0
30 - 35	1	0	1	0	2	0
35 - 40	0	1	1	1	1	0
40 - 45	4	1	0	1	2 D	0
45 - 50	2	0	4 *	1	2	0
50 - 55	3 D	0	3 D	0	2 D	1
55 - 60	2	0	3	0	3	1
60 & above	3 D	0	0	1	2	0
Total	15	2	12	4	15	2

D indicates one of the cases died.
* One of the cases could not be traced and was probably dead.

TABLE III (DISTRIBUTION ACCORDING TO ONSET)

Days of onset of infarction	A	B	C
1	5	8	6
2	7	6	4
3	0	1	0
4	2	1	2
5	0	0	0
6	1	0	1
7 and more	2	0	4
Total	17	16	17

TABLE IV — EFFECT OF ANTICOAGULANTS

Groups	Satisfactory Prothrombin Time Maintained.	Unsatisfactory
A	12 (D, D)	5
B	10 (D)	6
C	10 (D, D)	7
Total	32	18

Each D indicates a death in the group.

TABLE Va — RACIAL BREAKDOWN

Race	Case No. of Myocardial Infarction	Outpatient Attendance Government Clinics	General Hospital* Admissions	Population Ratio in %
Chinese	19	306,372	29,126(2162)	75.4
Indian	27	61,827	6,452(288)	8.6
Malay	2	30,149	2,411(167)	13.6
European & others	2	6,314	1,829(75)	2.4

* Deaths indicate within brackets.

TABLE Vb — EXPRESSED IN %

Race	Case No. as %	O.P. Attendance as %	General Hosp. Admn. %	Population Ratio %
Chinese	38	75.5	73.1	75.4
Indian	54	15.2	17.7	8.6
Malay	4	7.3	6.0	13.6
European & others	4	2.0	3.2	2.4

TABLE VI — BLOOD CHOLESTEROL

Serum Cholesterol mg. %	Number of cases
100	2
100 - 150	16
150 - 200	14
200 - 250	12
> 250	4

TABLE VII — ECG AND SGOT RESULTS

E.C.G.	Abnormal	47	49
	Normal	2	
SGOT	Positive	27	36
	Negative	9	

DISCUSSION

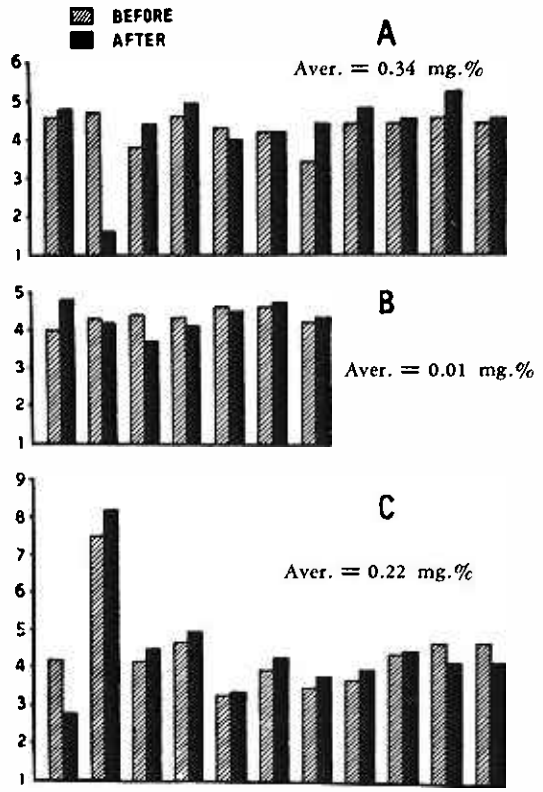
Locally, the death rate in coronary infarction has been estimated variously, but the general impression has been that pulmonary embolism is not an important cause of death in local cases. A visit to any ward in the hospital at any time will show that entities like deep vein thrombosis are extremely uncommon, and pulmonary embolism as a cause of death is hardly ever reported.

Ransome (1959) reported in his series of coronary thrombosis comprising 80 cases as 16% deaths with anticoagulants, and 32% in the control, although they were series treated at different periods of time, and might not be truly comparable. Further, the estimation of prothrombin time in these cases and other series suggested that many of the local cases on anticoagulants had in effect had inadequate dosage, and hence they could be more appropriately regarded as cases of control for the assessment of the value of anticoagulants. Danaraj et al (1959) in analysing cases that came to necropsy reported a preponderance of Indians, and Lloyd Davies (1961) reported some racial trends in blood cholesterol findings in the different races in Singapore. Pallister (1957) also reported a preponderance of Indians in myocardial infarction (44 out of 89 cases). These reports would suggest that locally coronary thrombosis occurred preponderantly in Indians, and that pulmonary embolism was not an important cause of death.

Bearing in mind that the value of anticoagulants in myocardial infarction has been mainly attributed to its prevention of intravascular thrombosis leading to pulmonary embolism, the rationale of anticoagulants in myocardial infarction locally with such a low incidence of pulmonary embolism may be open to doubt. However, it must be pointed out that other factors may account for the apparent difference in these reports. Thus, the figure of Danaraj et al shows the distribution in necropsies of cases that died in hospital and coroner's cases. This method is very likely to show a bias as the use of hospital services varies with the races as shown in the ratio of racial breakdown of hospital admission and outpatient attendance in Table Va, where the Indians constitute 8.6% of the population and Indian : Chinese bear a ratio of 1 :9, the outpatient attendance shows Indian : Chinese as 1 :5 approximately and the hospital admission as 1 :4.5 approximately, whereas cardiac infarction was 5 :4 approximately. The Malays, as a whole, refused postmortem examination completely, and the Indians more enlightened than the Chinese in this issue. The analysis of necropsy cases as regards incidence would have the further defect in that the figures were not necessarily in linear relationship to the total incidence, as the cases that survived could have a different distribution. However, taking the reports together, if necropsy analysis and clinical incidence were shown, the problem of Indian preponderance, whether a myth or a fact, could be determined more definitely.

In a previous paper (Gwee, 1960), it was noted that the serum albumin changed in some of the cases receiving Nialamid. The estimations of serum protein were done as routine in all these series before and at the end of one week as set out in Table VIII.

TABLE VIII. SERUM ALBUMIN.



Case 2 of series A and Case 1 of Series C were found to be due to technical error. It would be seen that whereas the average rise in serum albumin was 0.34 mg. % and 0.22 mg. % in the patient receiving Nialamid, the patient in the control series showed an average rise of 0.01 mg. %. Whether this is due to liver function disturbance or the effect of Nialamid on albumin metabolism remains to be elucidated.

It will be noted that the overall mortality for these 50 cases was 10% (5 cases) which appeared to be low, and also much below the improved figures, as reported by Ransome in cases receiving

anticoagulants (16%). What is even more unexpected was the finding that only 33 cases (66%) achieved a satisfactory prothrombin time during treatment (2½ times of normal), and also that all the 5 deaths that occurred were in the cases with satisfactory prothrombin time. Moreover, although it is generally accepted that the incidence of death is highest in the first 7 days, only one case as a matter of fact died on the 3rd day, and the rest on the 7th, 8th and 18th respectively. The case that died on the 3rd day had in addition granular kidneys and advanced liver cirrhosis which must have contributed to the death. He received only one dose of Nialamid before he died. Of those who died after 7 days, only one death was suspected to be due to pulmonary embolism, and that occurred in the control group. The use of Nialamid was stopped on the 8th day, and hence it would appear that barring one case, all the cases died whilst no MAO inhibitor was employed. This need not imply that MAO inhibitor is of value, as in the control group, no death occurred in the 1st week also, but it may indicate that a longer period of trial of Nialamid extending to beyond the 3rd week of attack would be worth considering.

The breakdown in Tables II and III would suggest that the series were reasonably but not very closely comparable. Bearing this in mind, it can be said that the study indicated that Nialamid did not favourably affect the survival rate in acute infarction, nor increase the risk during the first week. The occurrence of death in the group satisfactorily controlled with anticoagulants (Table IV) only appears disturbing, and seems to be contrary to the current view and also to the reported findings of Ransome (1957), an aspect which probably is worth exploring by a bigger control trial.

The racial breakdown in Table V lends further support to the reported findings locally that Indians appeared to be more liable locally to coronary thrombosis. The blood cholesterol findings would indicate that only 4 (8.3%) had a serum cholesterol of over 250 mgm. % With the exception of one case that died before E.C.G. could be done, only two had normal E.C.G. In comparison, 36 cases had one or more abnormal readings of serum transminase and 9 were within normal limits (< 100 units).

CONCLUSION

1. Locally, Indians appeared to be more liable to suffer from myocardial infarction.

2. Serum cholesterol is within normal limits in the majority of the cases.

3. Nialamid did not affect the survival of infarction in the first week one way or the other.

APPENDIX — Details of the 5 cases who died.

A 12:

Male Chinese, aged 60, admitted on 10.5.61 with a history of dyspnoea of sudden onset for 1 day. He had noted oedema of legs for last 3 days. There was no chest pain. He came for admission on the 3rd day of illness. On examination, he was ill with a pulse rate of 120/- regular and a blood pressure which was not registerable. The ECG showed generalised flattening of voltage and T inversion in II, III and V_7 and ST was not altered. SGOT 175 units. He was digitalised, given O_2 and put on noradrenaline and hydrocortisone drip and anticoagulant therapy was instituted. Tablet A was given but he died within 2 hours.

Postmortem examination showed gross arteriosclerosis with gross calcified occlusion of left coronary and same atheroma in the right. No acute cardiac muscle lesion was seen. The liver showed advanced cirrhosis and both kidneys were contracted and granular.

A 15:

Chinese male, aged 51, admitted 21.6.61 with history of retrosternal pain radiating to the left shoulder for one day.

On examination, he was ill, B.P. 150/106. He had a gallop rhythm and ECG showed T inversion in I, aVL, V_5 and V_7 and ST elevation in aVR, V_1 and V_3 and depression in V_5 and V_7 and aVF. SGOT was 48 units. He was given oxygen and anticoagulants and tablet A 50 mgm., t.i.d.

Next day, his condition worsened and noradrenaline drip had to be set up because his blood pressure was not registerable. He improved and 2 days later, his B.P. was 110/90 and generally he was better although still seriously ill.

The progress was steadily downhill until he died on the 7th day. Post-mortem examination was refused.

B 8:

Male Chinese, aged 52, admitted 25.4.61 with history of pain in the left side of the chest radiating to the left arm for 2½ hours prior to admission.

He was a diabetic receiving Rastinon (Tolbutamide) 0.5 mg. O.M. for the last 3 years. His general condition was poor. B.P. 90/90, pulse 86/- and regular. No evidence of cardiac decompensation was seen. ECG showed T inversion in I, aVR, aVL, V_3 and V_5 with ST elevation in I and aVL and V_5. Sedimentation rate 10 and SGOT 113 units.

He was put on Heparin 10,000 units statim and 6 hourly for 24 hours and Dindevan 150 mgm. stat and 50 mgm. O.M., and tablet B (control) 1, t.i.d. Next day, he brought out some blood-stained sputum, but his prothrombin was only twice that of normal. On the 5th day of admission, he complained of more dyspnoea, but his general condition remained much the same, until 2.5.61 when he suddenly had a mild haemoptysis, collapsed and died.

Post-mortem examination was refused and death was presumably due to pulmonary embolism.

C 11:

Male Australian, aged 53, admitted 7.5.61 with history of retrosternal pain lasting for 3 hours of sudden onset after a swim, and he was admitted 3 hours after attack.

On examination, he was very ill, B.P. 146/100. There was a gallop rhythm, and ECG showed QT in I, II, aVL and all the precordial leads. ST was elevated in I, II, aVL and all the precordial leads. SGOT 173 units.

He was given anticoagulants and the usual adjuncts of O_2 and morphia and tablet C, tab. T. t.i.d. Next day because of cardiac decompensation, he had to be digitalised.

On the 3rd day, he rallied round and appeared quite well, and the condition steadily improved until 19.5.61 when tablet C was stopped after 1 week of trial period was over.

On 25.5.61 he suddenly died when attempting to get up from bed.

Post-mortem examination showed a cardiac tamponade with 1,000 c.c. of free blood in the pericardial cavity. The left coronary was occluded and there was apical softening with superficial haemorrhages but not definite rupture of heart.

C 16:

Male Indian, aged 41, admitted on 16.7.61 with history of constrictive retrosternal pain of sudden onset in the morning of the day of admission.

On examination, he appeared satisfactory. B.P. 200/120, pulse 90/- and regular. ECG showed deep Q in II, III, aVF, V_5 V_6 and ST elevated in II, III, aVF and depressed in aVL, $V_{1, 2, 3}$ & $_4$. T inverted II, III, aVF, V_6 and $_7$. SGOT 130 units.

He was given anticoagulants with the usual regimen and tablet C, 0.05 gm., t.i.d.

He remained reasonably well but the BP fell to 130/80 and the systolic pressure remained throughout the period of observation below 140 mm. Hg. From the 3rd day onwards, he gradually deteriorated and died in cardiac failure on 24.7.61.

Post-mortem examination showed a fresh infarct in the posterior part of the heart extending to the inter-ventricular septum of the left coronary was obstructed.

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