Pentaerythritol tetranitrate (sustained action) in acute myocardial infarction

D. J. Newell¹ and Clinical Collaborators²

A multicentre trial of pentaerythritol tetranitrate (sustained action) 80 mg. b.i.d. in the 3 months after an acute myocardial infarction is described. Included in the trial were 346 patients, and at 6 months, the mortality rates in the treated and control group were almost identical at 23 per cent.

In young male patients, however, a favourable result to pentaerythritol tetranitrate (PETN) was obtained, supporting the finding of Oscharoff, who studied a somewhat differently defined group of young men. In women over 70, however, mortality in the treated group was significantly higher than in controls.

Mortality following acute myocardial infarctions remains high. Hyperbaric oxygen (Cameron *et al.*, 1965), glucose insulin and potassium (Paulley *et al.*, 1967; Medical Research Council, 1968), and propranolol (Snow, 1965; Balcon *et al.*, 1966; Multicentre Trial, 1966; Clausen *et al.*, 1966; Norris, Caughey, and Scott, 1968) have their proponents, but controlled trials in the references cited have not indicated an unequivocal reduction in mortality. The role of anticoagulants in the immediate post-infarction period is established (Lancet, 1967; Merskey and Drapkin, 1965; Estes and Smith, 1966). Lumb, Singletary, and Hardy (1962) and Lumb and Hardy (1963) have described the value of pentaerythritol tetranitrate in the establishment of collateral circulation after occlusion of the coronary artery in the pig. In the human, sustained action pentaerythritol tetranitrate provides a dosage of 80 mg. (20 mg. immediately, the remainder over 12 hours), and is administered twice daily. The sustained action form of presentation will be abbreviated to PETN in this paper. It has been used as an adjunct therapy in a controlled trial by Oscharoff (1964) in the post-infarction period in male patients under the age of 65, suffering their first infarction. The mortality within three weeks was only 4 per

cent in 50 men treated with PETN, compared with 22 per cent in 50 controls. Such a remarkable result merits confirmation in a larger series.

Patients and methods

The present paper describes a multicentre controlled trial of PETN as an addition to the usual therapy in each co-operating hospital.

Ten clinicians in eight centres took part, contributing in all 346 patients with definite acute myocardial infarction.

Diagnosis The fundamental diagnostic question which the physician asked himself was, 'Is this a patient whom I would willingly expose to PETN or to placebo, along with the usual range of analgesics, sedatives, anticoagulants, and oxygen, according to my current practice?'

The essential feature was a fresh myocardial infarction. For inclusion in the trial, treatment with PETN or Dummy must have started within 48 hours of the infarct. In 74 per cent of the cases included it had started within 24 hours, but an additional 91 cases were included where a further day had passed before the patient had been admitted and treatment had begun. In 9 cases included, the exact time of the infarct was not known, but it was under 48 hours.

With this early treatment, the diagnosis could not be confirmed immediately, and a number of cases originally admitted to the trial were withdrawn because the diagnosis of an infarct could not be confirmed on serial electrocardiograms. A total of 346 cases with infarctions is included in this analysis, and a further 126 cases were withdrawn, mainly because the diagnosis was not confirmed. One case was withdrawn on account of severe side effects, a patient who had previously reacted against three other cardiovascular drugs acting on the vascular system. No restriction was made on the history of previous infarction, angina, or diabetes, and the frequency

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¹ Professor of Medical Statistics, The Medical School, Newcastle upon Tyne.

² Dr. J. Black (Warrington), Dr. C. Bremer (Sunderland), Dr. R. J. Calvert (Burnley), Dr. C. Davidson (Bradford), Dr. D. Freeman (Warrington), Dr. G. T. Gooding (Leeds), Dr. A. A. McI. Nicol (Sunderland), Dr. W. S. Suffern (Harrogate), Dr. R. H. Vasey (Sunderland), and Dr. A. A. Williams (Middlesbrough).

TABLE 1 Clinical findings on admission

Age (yr.) and sex	No. of patients	Per cent of total
<50 M	53	19.6
50-59 M	88	32.5
60-69 M	95	35.1
70+ M	35	12.9
Total	271	100
<60 F	21	28.0
60-69 F	33	44.0
70+ F	21	28.0
Total	75	100
Previous infarctions		
None	264	76.3
One	67	19.4
Two	13	3.8
Three	2	0.6
History		
Angina	224	64.7
Diabetes	17	4.9
'Clinical shock' on admission	102	29.5
	Mean	SD
Systolic BP (mm. Hg)	143	±26.7
Diastolic BP (mm. Hg)	97	±17.2
Pulse rate on admission (min.)	86	±22.7

of these items is also shown in Table 1 which gives the clinical findings on admission.

Treatments, and allocation to treatments

Each patient was allocated to either PETN or indistinguishable placebo tablets. The PETN tablets contained 80 mg. pentaerythritol tetranitrate, and the dosage for each patient was 1 tablet every 12 hours, for a total of 12 weeks. Treatment started as soon as the patient was admitted to hospital, and was continued on an out-patient basis after discharge.

The axes of stratification for the random allocation were hospital and 'history'. Three 'history' categories were defined for this purpose: first attack without history of angina, first attack with history of angina, and subsequent attack. For each of these categories in each hospital, a dispensary list was prepared on which the allocation to PETN or Dummy was indicated. As soon as a patient was selected as suitable for the trial, a 'blind' prescription was made out by the physician, which the dispensary then interpreted according to the list. Thus neither the patient nor the physician knew which treatment the patient was receiving. This randomization and the subsequent withdrawal of patients

TABLE 2 Other treatments used during hospital stay

	PETN	Dummy
(a) Analgesics		
None	51	55
Narcotics* alone	108	95
Narcotics with others	13	11
Other analgesics	9	4
$\chi^2 = 2.3$, d.f. = 3, $p > 0.5$ not sig.		
(b) Sedatives		
None	54	53
Barbiturates alone	82	74
Barbiturates with others	15	10
Non-barbiturate hypnotics	15	14
Phenothiazine derivatives	8	7
Morphia	5	6
Others	2	1
$\chi^2 = 0.75$, d.f. = 4, $p > 0.9$ not sig.		
(c) Anticoagulants		
None	43	39
Phenindione alone	32	40
Phenindione after heparin	48	42
Phenprocoumon after heparin	47	32
Warfarin after heparin	4	5
Heparin alone	3	3
Warfarin alone	3	3
Phenprocoumon alone	1	1
$\chi^2 = 3.6$, d.f. = 4, $p > 0.3$ not sig.		
(d) Oxygen		
Administered	23	17
None	158	148

* 'Narcotic' analgesics in this classification are morphine and its derivatives, pethidine, and other synthetic drugs of addiction: other analgesics included drugs classified as nonbarbiturate hypnotics, phenothiazine derivatives, antihistamines, antiemetics, coronary vasodilators, and 'other analgesics'.

in whom the diagnosis was not confirmed, led to 181 patients on PETN and 165 patients on Dummy being included in the trial.

Other treatments used during the patient's stay in hospital were also recorded, and are shown in Table 2, subdivided according to the trial treatment (PETN or Dummy), and to the nature of the other treatments: analgesic, sedative, or anticoagulant. To summarize the very large number of other drugs used, they have been classified on the basis of the headings in Medindex (Jan.-March 1966). No special monitoring or 'intensive care' was arranged for these patients.

The types of analgesics given were similar in the PETN and Dummy groups. In all, 227 (66%) of the patients received a narcotic (as defined in Table 2) occasionally with another analgesic. This proportion varied

widely from hospital to hospital. The hospital with the largest number of patients in the trial gave narcotics to 45 per cent of patients, but 82 per cent of patients received them at the next largest hospital.

There were no significant differences between the two treatment groups in the proportions of patients who received the different types of sedatives or anticoagulants, nor those who received oxygen.

Comparison of treatment groups before treatment

Statistical comparisons disclosed no significant differences between PETN and Dummy groups in the following respects: age and sex, blood pressure, pulse rate, incidence of shock, number of infarctions, and history of angina and diabetes. Among the non-significant differences was only one conspicuous feature: 34 men aged under 50 were included in the PETN group, and only 19 in the Dummy group. Since prognosis is better in young patients, this tends to bias the over-all result in favour of PETN. Since the other treatments given in hospital to the PETN and Dummy patients also did not differ significantly, the trial yielded two similar groups, in whom a fair comparison of the effects of PETN could be made.

Comparison of treatment groups while in hospital (first 21 days)

(a) **Mortality** Table 3 (a) shows that 13.8 per cent of the PETN cases, and 14.5 of the Dummy cases died within the first 21 days. These figures include 13 and 12 cases, respectively, who died within the first 3 days, and may not have had time to obtain any effect from PETN. The number and timing of the later deaths in the first 3 weeks are very similar for the two treatments.

(b) **Minimum systolic pressure in first 14 days** As an indication of the presence of shock during hospital stay, the minimum systolic pressure recorded at the routine morning blood pressure readings in the first 14 days was analysed, for all patients who survived 14 days. Table 3 (b) shows that almost identical proportions showed readings below 100 mm. Hg (18.6% PETN, and 18.3% Dummy), and that the distributions of minimum pressures for the two groups were very similar. For the patients who died between 4 and 14 days, the mean minimum systolic pressures recorded were PETN 104, Dummy 108; again not a significant difference.

Thus on the criteria of mortality, and minimum systolic pressure we are unable

TABLE 3 *Comparisons during hospital stay*

	PETN	Dummy
(a) <i>Mortality</i>		
Day 1	6	5
" 2	5	4
" 3	2	3
" 4-7	3	7
" 8-14	5	3
" 15-21	4	2
Survived 21 days	156 (86.2%)	141 (85.5%)
Mean survival of deaths under 21 days	6.3 days	5.3 days
Mortality under 21 days (%)	13.8	14.5
(b) <i>Minimum systolic pressure in first 14 days of survivors for 14 days</i>		
<i>Minimum systolic BP (mm. Hg)</i>		
60-79	2	2
80-99	27	24
100-119	85	73
120-139	34	31
140+	8	12
Not recorded	4	1
Per cent below 100 mm. Hg	18.6	18.3
Mean minimum systolic BP	112.5	113.7
$t = 0.61, \text{ d.f.} = 296, p > 0.5 \text{ not sig.}$		

to confirm the findings of Oscharoff (1964), who by 21 days after the infarct found a mortality difference of 4 per cent with PETN against 22 per cent with Dummy and a difference in shock occurring after admission of 8 per cent with PETN against 24 per cent with Dummy. His criterion of 'shock' was a minimum systolic pressure of under 90 mm. Hg, but such pressures were rarely recorded in the present trial, and were certainly not more frequently recorded on the Dummy treatment.

(c) **Side-effects** Patients were not specifically asked about side-effects, in order to avoid producing them by suggestion. Apart from one case withdrawn from the trial, side-effects were reported by only 20 patients, equally divided between the PETN and Dummy groups.

Comparison of treatment groups at 6-month follow-up

The most important criterion of success of treatment is survival. Table 4 (a) shows that 76.2 per cent of patients were alive at 6 months after PETN and 77.0 per cent were alive after Dummy. Only 5 patients included were not examined at the follow-up, but their

survival and general health at 6 months after the infarct have been ascertained from their general practitioners. The time to death in the quarter of patients who did not survive for 6 months was also similar in the PETN and Dummy groups.

Within the 6-month period, 9.4 per cent of PETN cases and 5.5 per cent of Dummy cases had a further infarct, a non-significant difference. The time distribution to a further infarct was also similar.

At the 6-month re-examination, every surviving patient was assessed by the clinician. Table 4 (c) shows that 44.8 per cent of PETN patients were recorded as 'well at 6 months', against 38.8 per cent of Dummy patients. When the two groups 'well' and 'fair' at 6 months are put together, 58 per cent of PETN patients, and 51 per cent of Dummy patients are included. This difference is not statistically significant. Angina at 6 months was reported for 17.1 per cent of those treated with PETN and 23.6 per cent of the Dummy patients.

Factors relating to mortality within six months

Since the PETN or Dummy treatment did not affect the over-all mortality of these patients, the two treatment groups can be combined to provide a larger sample, which can be examined for major factors related to mortality.

Mortality was closely related to age at onset, but there was no evidence of a sex difference in mortality, when age was taken into consideration. For each sex, death occurred within 6 months for about 10 per cent of the under 60's, 25 per cent of the 60-69's, and nearly 50 per cent of the patients aged 70 or over. These results are fairly similar to those achieved in an intensive care unit (Lawrie *et al.*, 1967), but as our patients were admitted on average longer after the infarction, strict comparison is not possible. For the same reason, we cannot claim that our mortality rate in hospital was better than that of 19 per cent at another intensive care unit (Thomas, Jewitt, and Shillingford, 1968).

A pulse rate of over 95 beats a minute is associated with a mortality of nearly 50 per cent; lower pulse rates have 15 per cent mortality.

First infarctions have a better prognosis (mortality of 20%) than subsequent infarctions (mortality of 33%).

No significant mortality associations were found with the hospital centre in the trial, with the time between infarction and treat-

TABLE 4 Comparison of longer term effects: follow-up to 6 months

	PETN	Dummy
(a) Mortality		
Died within 21 days (Table 3a)	25	24
Died 22-99 days	11	9
Died 100-193 days	7	5
Survived 6 months	138 (76.2%)	127 (77.0%)
Mortality under 6 months (%)	23.8	23.0
(b) Time to further infarct		
< 1 month	1	2
1 month	4	—
2 months	3	2
3 months	3	1
4 months	4	1
5 months-6 months	2	3
No further infarct in 6 months	164 (90.6%)	156 (94.5%)
$\chi^2 = 1.40$, d.f. = 1, $p > 0.2$ not sig.		
(c) Clinician's assessment at 6 months		
Died before 6 months	43 (23.8%)	38 (23.0%)
Well, no after effects mentioned	81 (44.8%)	64 (38.8%)
Fair	24 (13.3%)	20 (12.1%)
Angina	31 (17.1%)	39 (23.6%)
Other comments*	2	3
Seen, not assessed	0	1
$\chi^2 = 2.91$, d.f. = 3, $p > 0.3$ not sig.		

* Includes depression, arrhythmia, ischaemia.

TABLE 5 Effect of PETN on mortality in age-sex groups

Age (yr.) and sex		PETN		Dummy		
		Died	Total	Died	Total	
< 50	M	1 (3%)	34	5 (26%)	19	p=0.04
50-59	M	7 (17%)	41	7 (15%)	47	
60-69	M	13 (25%)	52	9 (21%)	43	
70+	M	10 (53%)	19	7 (44%)	16	
< 60	F	1 (8%)	12	1 (11%)	9	p=0.014
60-69	F	4 (27%)	15	6 (33%)	18	
70+	F	7 (86%)	8	3 (23%)	13	

ment, with blood pressures on admission, or with a history of angina or diabetes.

Analysis of the effect of PETN on subgroups of patients

Though the over-all result with PETN was no better than with Dummy, we wondered whether it had been effective in specific subgroups of the population. In searching for such subgroups, there is a risk of finding the 'chance' 1-in-20 significant result in 20 comparisons, and the exercise might be referred to as hypothesis forming, rather than hypothesis testing.

The main difference between the present study and that of Oscharoff (1964) is that his

patients were all male, suffering from their first infarct, and aged under 65. Our patients were of all ages, both sexes, and some had previous infarcts. This provided a broad-based study, and is fully justified, but it is not directly comparable to Oscharoff's results.

Among men under 60 suffering their first infarction in the present study, 6 out of 63 (10%) died after PETN and 6 out of 51 (12%) died after Dummy, clearly a non-significant difference.

Ignoring the factor of first or subsequent infarction, a further analysis (Table 5) was made of the relation between PETN and six-month survival in each of 7 age-sex groups. In 2 of these, statistically significant results were found, though the numbers were small.

In men aged under 50, 1 death in 34 PETN cases was significantly better than 5 deaths in 19 Dummy cases. On the other hand, in women aged 70 or over, 7 deaths in 8 PETN cases was significantly worse than only 3 deaths in 13 Dummy cases. In none of the other age-sex groups was there any hint of an association between PETN and mortality or survival.

We conclude, in the light of Oscharoff's (1964) findings and our own, that there may be some case for the use of PETN in younger men, and in the absence of further studies, a contraindication for its use in the oldest women.

Discussion

Several of the treatments for acute myocardial infarction listed in the introduction to this paper have at first shown remarkably satisfactory results, usually in uncontrolled trials, occasionally in controlled trials (e.g. Snow, 1965). PETN follows this pattern of a very significant reduction in mortality in one trial (Oscharoff, 1964), and relatively little effect in the present trial. The unusual feature of this trial is the apparent value to younger men, counterbalanced by the apparent lethality of PETN to older women. While it is tempting to dismiss one of these two results as a chance occurrence, there is no rational basis for deciding which should be so dismissed. When a group comparable with Oscharoff's (young men suffering their first infarction) is constructed from the present trial, there is again no apparent value of PETN in reducing mortality.

This trial suggests that further trials in young men – in whom there may possibly

be latent collateral channels in the myocardium – would be worth while, but old age in women appears to be a contraindication.

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