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EFFECT ON MORTALITY OF METOPROLOL IN ACUTE MYOCARDIAL INFARCTION

A Double-blind Randomised Trial

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Summary The effect of metoprolol on mortality was compared with that of placebo in a double-blind randomised trial in patients with definite or suspected acute myocardial infarction. Treatment with metoprolol or placebo started as soon as possible after the patient's arrival in hospital and was continued for 90 days. Metoprolol was given as a 15 mg intravenous dose followed by oral administration of 100 mg twice daily. 1395 patients (697 on placebo and 698 on metoprolol) were included in the trial. Definite acute myocardial infarction developed in 809 and probable infarction in 162. Patients were allocated to various risk groups and within each group patients were randomly assigned to treatment with metoprolol or placebo. There were 62 deaths in the placebo group (8·9%) and 40 deaths in the metoprolol group (5·7%), a reduction of 36% ($p<0·03$). Mortality rates are given according to the treatment group to which the patients were initially randomly allocated.

Introduction

IN 1965 Snow[1] reported that propranolol given during the first few weeks of myocardial infarction (MI) reduced the mortality. Many trials have evaluated the effect of beta-blockade on survival both during the early stage of MI and during long-term follow-up. None of the trials starting from the day of onset of MI have demonstrated a reduction in mortality within three months of MI.[2-10] The results of trials with a treatment period of 0·5–3 years have been conflicting.[6-9,11-16] The Norwegian multicentre study of timolol[17] demonstrated significantly reduced mortality in patients randomly allocated to beta-blockade.

In the present double-blind trial, metoprolol or placebo were given intravenously shortly after arrival in hospital to patients with suspected MI. The injection was followed by double-blind oral administration of metoprolol or placebo for 90 days. Thereafter most patients received metoprolol. The primary objective was to determine whether metoprolol would reduce 3 month mortality. We also wanted to investigate the effects on infarct size and arrhythmias. This report deals with total mortality during the 90 days of double-blind treatment.

Patients and Methods

Between June, 1976, and January, 1981, patients with suspected MI admitted to hospital in the city of Göteborg with a catchment population of 450 000 were assessed for eligibility for this study. When the trial started all patients were sent to Sahlgren's Hospital, the only city hospital, but in March, 1978, the study was extended to the newly opened Östra Hospital. The opening of a new hospital in Göteborg and inclusion of patients admitted during only 9 months of the year (not during holiday periods) delayed patient recruitment into the trial. Therefore the study was extended outside Göteborg to the nearby community hospital in Skövde in August, 1980 (67 patients from this hospital were included). Doctors at the hospitals later included in the trial had participated in the trial when it started at Sahlgren's Hospital in 1976. The eligibility of all patients to join the study was assessed as soon as possible after arrival in hospital according to the following criteria: (1) residence in the catchment area; (2) chest pain of acute onset and of 30 min duration, or electrocardiogram (ECG) signs of acute MI with estimated onset of infarction within the previous 48 h; (3) age between 40 and 74 years. The subgroup of patients aged 40–69 years was included in the study in August, 1976, and subgroup of 70–74 years in January, 1978 (except at Östra Hospital).

2619 patients fulfilled the entry criteria and were then evaluated with regard to possible exclusion (table I). The main reasons for exclusion from entry were contraindications to beta-blockade (28%), need for beta-blockade (21%), and administrative reasons (42%). After exclusions, 1395 patients were randomly allocated to double-blind treatment; 697 received placebo and 698 metoprolol. The patients were allocated to risk groups according to age (40–69 years and 70–74 years), previous MI, chronic beta-blockade at entry, and clinical findings on admission (pain alone; pain + ECG signs of MI; pain and one of the following—heart rate >90 beats/min, respiratory rate ≥28 min, lung râles heard no more than 10 cm above the base, or previous unconsciousness). Two additional groups of patients consisted of those with temporary adverse

TABLE I—SELECTION OF PATIENTS

Selection			No. (%)
Patients eligible for study			2802
Patients included in other studies			183
Patients evaluated for entry			2619
Patients excluded from entry because of contraindications			1224 (47)*
Contraindications to β-blockade:			353 (28)
Cardiovascular		311 (25)	
Hypotension (<100 mm Hg)	63 (5)		
Bradycardia (<45 beats/min)	21 (2)		
Heart failure (basal râles >10 cm, poor peripheral circulation, shock)	183 (15)		
AV-block	44 (3)		
Bronchial asthma		42 (3)	
Requiring β-blockade			257 (21)
Serious or multiple diseases			92 (8)
Administrative reasons:			510 (42)
Refusal to participate		131 (11)	
Psychiatric disease, alcoholism		126 (10)	
Chronic atrial fibrillation		67 (5)	
Pacemaker at entry		43 (4)	
Non-resident or language problems		43 (4)	
Planned or previous coronary bypass		38 (3)	
Minor non-cardiovascular adverse reactions to β-blockade		27 (2)	
Confused or unconscious		20 (2)	
On "Ca^{++}-antagonists" at entry		15 (1)	
Reasons unknown			12 (1)
Randomly allocated to blind treatment			1395 (53)†

*Percentage of 2619 patients excluded because of contraindications.
†Percentage randomly allocated to treatment. All other numbers in parentheses are percentages of patients excluded from entry.

characteristics with hypertension (systolic blood-pressure <100 mm Hg) or lung râles heard more than 10 cm above the base. These patients were re-evaluated after 2 h and not later than 4 h after first examination by research team doctor and were then found to fulfil the entry criteria. One group had chronic beta-blockade at entry, the other did not. Only 24 patients belonged to these two groups, 11 in the placebo group and 13 in the metroprolol group. Entry characteristics of all patients are given in table II.

Treatment was started as soon as possible after arrival in hospital. Metoprolol 15 mg (7·5 ml) or placebo (saline, 7·5 ml) was given intravenously (a rapid injection of 2·5 ml was given every 2 min). The patient was kept under clinical observation by a physician, with simultaneous monitoring of ECG, heart-rate, and blood-pressure by a special research assistant. If there was a fall in systolic blood-pressure below 90 mm Hg, a fall in heart-rate below 40 beats/min, or development of atrioventricular block (PQ-time ⩽0·26 s), or if serious adverse reactions which could probably be ascribed to beta-blockade occurred (e.g., dyspnoea, nausea, cold sweat), no further injections were given. If the full dose was tolerated, one half of a tablet was given 15 min after the injections were completed and then every 6 h for 48 h, and thereafter one tablet every 12 h (placebo or metoprolol 100 mg). If less than the full intravenous dose was given, one quarter of a tablet was given every 6 h during the first 48 h followed by one tablet every 12 h. All data were registered on a special computer record form by the research assistant. These record forms were not available to any of the physicians managing the patient during the treatment period. The full intravenous dose was given to 1363 patients; 32 patients could not tolerate the full dose (placebo 12 patients, metoprolol 20 patients). A 12-lead standard ECG was taken on admission and special precordial mapping was performed with 24 electrodes at a paper speed of 50 mm/s. Precordial mapping was repeated on day 4. A standard 12-lead ECG was taken every morning during the first 3 days. Blood-samples for determination of lactate dehydrogenase (LD) I+II were taken every 12 h for 3 days. Blood-samples for transaminases were taken each morning during the first 3 days.

Procedures for withdrawal from tablet treatment (metoprolol or placebo) and schedules for treatment of different complications were specified in a manual of operation. Criteria for withdrawals and number of patients withdrawn are given in table III. Except for continuous ventricular tachycardia or fibrillation, ventricular arrhythmias were not treated. Lignocaine was given to 32 patients in the metoprolol group and to 55 patients in the placebo group. The following criteria were used for classification of definite and probable MI. For definite MI two of the following three criteria had to be fulfilled: (1) chest pain of at least 15 min duration; (2) Q-wave or ST-segment elevation followed by T-wave inversion in at least two electrodes in a 12-lead standard ECG; (3) two serum aspartate aminotransferase (ASAT) values twice the normal value in combination with low or normal serum alanine aminotransferase (ALAT) values. ECG changes in only one electrode or only one raised ASAT value in combination with at least one LD I+II value above normal were also regarded as definite MI. For probable MI chest pain plus one of the following criteria was required: (1) T-wave inversions; (2) one raised ASAT in combination with low or normal ALAT; (3) one or more raised LD I+II values; (4) Q-wave or ST-segment elevation followed by T-wave inversion in only one electrode.

After discharge from hospital, all patients were seen by physicians of the project at a special outpatient clinic. A computer record form was filled in at two visits at about 4 weeks and 3 months from first arrival in hospital. All deaths within 90 days of the start of blind treatment were recorded and classified by an independent safety monitoring committee consisting of one statistician and three physicians not otherwise involved in the study.

The appropriate number of patients necessary for satisfactory statistical analysis was calculated by statistical methods based on estimation of mortality in the treatment and control groups and the probability of detecting this difference. It was estimated that the three-month mortality in the placebo group might be 15% for those who developed definite MI under the most favourable conditions and it could be reduced to 9% in the treatment group. For those not developing definite MI, 3-month mortality was assumed to be zero. It was estimated that 800 patients with definite MI were needed to detect such a difference with more than 80% probability at the 5% significance level. The statistical test of the 90-day mortality was done with Fisher's exact test in fourfold tables. Mantel-Haenszel's method[18] was used to test differences in survival curves and Cox' proportional hazards model[19] was used to adjust for baseline variables. A two-tailed test with a p value <0·05 was regarded as significant.

Results

Comparability

There were some small differences between the 697 patients in the placebo group and the 698 patients in the metoprolol group in respect of sex, age, clinical history, therapy before admission, clinical findings at entry, or acute treatment given in the hospital before the injection (table II). There were no differences between the two groups as regards the interval between onset of symptoms and injection. The interval between the onset of pain and the start of treatment in hospital was 11·3±0·3 h. 43·6% of all patients were started on blind treatment within 6 h, 69·0% within 12 h and 90·7% within 24 h. There was no difference in this delay between the placebo and the metoprolol groups.

Mortality

There were 62 deaths in the placebo group (697 patients) and 40 deaths in the metoprolol group (698 patients). This means that the cumulative mortality rate for the double-blind treatment period of 90 days was 8·9% in the placebo group and 5·7% in the metoprolol group. Thus, the administration of metoprolol reduced the total mortality by 36%. In a two-

TABLE II—CHARACTERISTICS OF PATIENTS ON PLACEBO OR METOPROLOL

Characteristics	Treatment group: Placebo (n=697) %	Metoprolol (n=698) %
Sex:		
Men	76·2	75·5
Women	23·8	24·4
Age:		
<64 years	65·0	66·5
65–74 years	35·0	33·5
Clinical history:		
Previous infarction	22·7	21·2
Angina pectoris (5)*	34·7	35·7
Hypertension	29·7	29·1
Therapy before admission:		
Digitalis (6)	12·9	12·5
Diuretics (5)	18·7	18·7
β-blockers	25·4	25·2
Clinical status at entry:		
Pulmonary râles	9·0	11·6
ECG signs of infarction (1)	47·8	49·9
Heart-rate >100 beats/min (1)	6·2	4·7
Systolic blood-pressure <100 mm Hg (2)	4·4	3·3
Dyspnoea at onset of pain (29)	30·8	28·8
Treatment in hospital before blind injection:		
Morphine (3)	53·9	53·6
Atropine (3)	3·5	2·9
Isoprenaline or analogues (2)	0·0	0·0
Diuretics (3)	9·8	10·8
Digitalis (3)	1·9	2·3
Lignocaine (3)	2·7	2·3
β-blocker or verapamil (5)	1·6	2·2
Mean age±SEM	60·0±0·3	60·0±0·3
Mean time from onset of symptoms to blind injection±SEM (16)	11·4±0·4	11·1±0·4

*Numbers in parentheses are numbers of patients for whom data were missing.

tailed test the p value for this difference is <0·03 (p=0·030, Fisher's exact test; p=0·024, Mantel-Haenszel). In a Cox analysis adjustment for the slight differences of the baseline characteristics, including previous MI, age, delay, lung râles, and ECG signs of MI, gives a p value of <0·015. The mortality rates are given according to the treatment group to which the patient was initially randomly allocated. Fig. 1 shows the cumulative number of total deaths in all patients randomly allocated to treatment with metoprolol and placebo during the 90-day period.

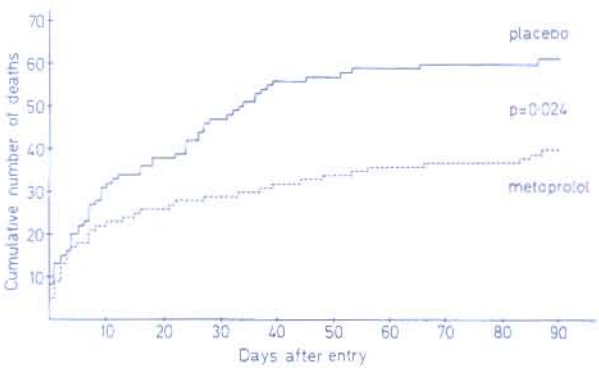

Fig. 1—Cumulative number of deaths in all patients randomly allocated to treatment with metoprolol and placebo.

p value is calculated according to Mantel-Haenszel.

TABLE III—NUMBERS OF PATIENTS WITHDRAWN FOR ALL REASONS EXCLUDING DEATH

Reasons for withdrawal	No. (%) withdrawn in groups on: Placebo (n=686)	Metoprolol (n=686)	Significance (p)
Cardiovascular:			
Hypotension (<90 mm Hg)	13 (1·9)	29 (4·2)	0·018
Bradycardia (<40 beats/min)	5 (0·7)	18 (2·6)	0·011
Heart failure	7 (1·0)	4 (0·6)	
AV-block II or III	11 (1·6)	16 (2·3)	>0·2
Need for β-blockade:			
Angina pectoris	28 (4·1)	14 (2·0)	0·04
Hypertension	4 (0·6)	2 (0·3)	
Arrhythmias	13 (1·9)	1 (0·1)	0·003
Other (subjective need, tremor &c.)	5 (0·7)	4 (0·6)	
Other:			
Side-effects	22 (3·2)	22 (3·2)	>0·2
Unwillingness	5 (0·7)	5 (0·7)	
Other causes	14 (2·0)	11 (1·6)	>0·2
Unknown	4 (0·6)	5 (0·7)	
Total number	131 (19·1)	131 (19·1)	>0·2
Missing data	11	12	>0·2

Total mortality in each risk group is given in table IV. Metoprolol significantly reduced 3-month mortality in the metoprolol group as a whole by 36%, in those aged 40–69 years by 37%, in those aged 65–74 years by 45% and by 34% in patients in whom definite MI developed. A similar reduction of mortality with metoprolol was found for the other subgroups.

In fig. 2, mortality is given for patients in the placebo and metoprolol groups who continued for 3 months on the treatment to which they had been allocated, those who stopped their allocated treatment during this period, and for patients with missing data on their blind tablet intake. For patients who continued treatment for the whole 3-month period, metoprolol treatment reduced mortality by 47%. There was no difference in mortality between the placebo and metoprolol groups in patients who prematurely withdrew from the allocated treatment. There were no deaths in the patients in whom tablet intake was uncertain. The patients who continued on allocated treatment in the two groups are not strictly comparable since there are different reasons for tablet withdrawal in those on metoprolol and on placebo (table III).

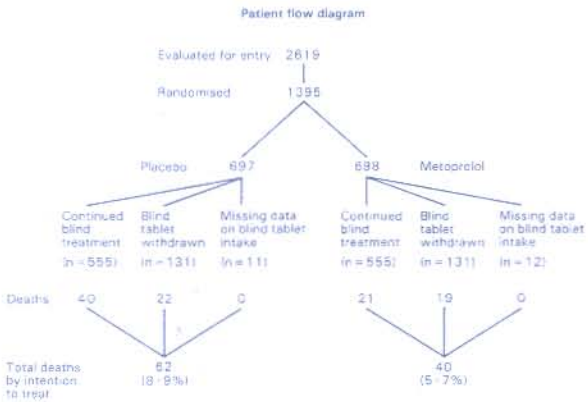

Fig. 2—Patient flow diagram for all patients evaluated for entry to the study and randomly allocated to treatment with placebo and metoprolol.

All deaths are total deaths by intention to treat.

TABLE IV—TOTAL NUMBER OF DEATHS IN ALL PATIENTS IN VARIOUS SUBGROUPS RANDOMLY ALLOCATED TO PLACEBO OR METOPROLOL

Group	No. of deaths/patients (%) in groups: Placebo	Metoprolol	Significance (p)	Effect* (%)
All patients	62/697 (8·9)	40/698 (5·7)	0·030	36
No history of previous infarction	44/539 (8·2)	30/550 (5·5)	0·101	33
History of previous infarction	18/158 (11·4)	10/148 (6·8)	>0·20	41
Not on chronic β-blockade at entry	46/520 (8·8)	30/522 (5·7)	0·071	35
On chronic beta-blockade at entry	16/177 (9·0)	10/176 (5·7)	>0·20	37
Ages 40–69 years	51/627 (8·1)	32/629 (5·1)	0·039	37
Ages 70–74 years	11/70 (15·7)	8/69 (11·6)	>0·20	26
Ages 40–64 years†	26/453 (5·7)	21/464 (4·5)	>0·20	21
Ages 65–74 years†	36/244 (14·8)	19/234 (8·1)	0·032	45
Definite MI†	56/410 (13·7)	36/399 (9·0)	0·046	34
No definite MI†	6/287 (2·1)	4/299 (1·3)	>0·20	36

*Percentage reduction in mortality = $\frac{\text{(mortality rate placebo} - \text{mortality rate metoprolol)} \times 100}{\text{mortality rate placebo}}$

†Analysis of retrospectively formed subgroups.

Compliance and Adverse Reactions

The patients' compliance with treatment was judged by tablet counts and assay of metoprolol in urine. Analysis from a random subgroup of 1094 patients showed that 78% of the patients had taken more than 90% of the prescribed doses.

Tablet treatment was withdrawn in 19% of both groups of patients during the total 90-day period of treatment (table III). More patients were withdrawn from treatment in the metoprolol group because of suspected adverse cardiovascular reactions. The need for beta-blockade because of recurrent chest pain and tachyarrhythmias was a more common reason for withdrawal of treatment in the placebo group.

Discussion

This study has demonstrated a reduction in total mortality in patients with definite or suspected MI by metoprolol treatment started on admission to hospital and given for 3 months. There were only very small differences in characteristics of the patients before entry to the trial. These differences tended to balance each other but were mainly prognostically unfavourable for the metoprolol group. When differences were adjusted according to Cox' proportional hazards model, the statistical significance was improved with a p value below 0·015. The reduction of mortality with metoprolol was significant also in the subgroups of patients aged 40–69 and 65–74 years and in patients in whom a definite MI developed. A similar reduction in mortality, was seen also in subgroups of patients with and without previous MI and in patients with and without chronic beta-blockade treatment before entry to the trial.

This study is the first to demonstrate a beneficial effect of beta-blockade on survival during the early phase of MI. Since the first optimistic report from Snow in 1965,[1] the only other study that has demonstrated a positive effect on survival when beta-blockade has been given from the day of admission is the Copenhagen study on alprenolol.[16] However, in that study a positive effect of alprenolol was reported only after one year of follow-up in patients younger than 65, while there was a negative trend on survival in patients older than 65 years. The Copenhagen study has been criticised because of conflicting results for the two age-groups.[20] In the Norwegian timolol study[17] there was a significant reduction in mortality in postinfarction patients below and above 65 years of age. The present study of metoprolol also accorded with the timolol study, by demonstrating a significant reduction in mortality in patients aged 65–74 years (45%) as well as in patients aged 40–69 years (37%). Data were analysed as three-year age-groups from 40 to 74 years. There were fewer deaths on metoprolol treatment in all groups with exception for the group 61–63 years (to be published). From the present material we cannot claim that metoprolol has a more beneficial effect on mortality in any particular age-group.

Compliance was good in the present study, as was the tolerance to metoprolol; this is reflected by the low number of treatment withdrawals compared with many other studies in acute infarction and also in postinfarction patients.[9,10,14,17] The number of treatment withdrawals was the same in patients given metoprolol and placebo. There was a higher number of adverse cardiovascular reactions in the metoprolol group, but this was balanced by a higher withdrawal in the placebo group because beta-blockade was needed to treat angina pectoris, hypertension, and arrhythmias.

The present study strongly supports the theory that beta-blockade of patients during the acute and postinfarction period can reduce mortality, as has been suggested earlier in studies on alprenolol,[12,13,16] practolol,[14] and timolol.[17] This study on metoprolol is the first to show a significant effect of a $beta_1$-selective blocker and also to show an effect on mortality in the early phase of MI. These results support the view that early administration of beta-blockade in acute MI is of value and that the important property and the only one common to all beta-blockers with a positive effect on survival, is $beta_1$-receptor blockade. Neither intrinsic stimulating activity, $beta_2$-receptor blockade, nor membrane-stabilising properties should be a prerequisite of the protective effect. This accords with observations of the protective effect of beta-blockade on ventricular fibrillation in animal models.[21]

The reasons for the reduction in mortality with metoprolol in the present study are not known. An analysis of the modes of deaths with regard to suddenness, symptoms, arrhythmias, and necropsy findings is in progress. We compared the reduction of mortality in this study with that of the timolol study from Norway.[17] During a mean follow-up time of 17 months in that study there were 152 deaths in the placebo group and 98 deaths in the timolol group, a 35·5% reduction. This resembles the reduction obtained within 3 months in the present study, with 62 deaths in the placebo group and 40 deaths in the metoprolol group, a reduction by 36%. The mortality from 12 days to 3 months was reduced by 42% with metoprolol and by 24% with timolol. This might be the result of starting treatment much earlier in the metoprolol study, of a difference in the patients, or a difference in efficacy between metoprolol and timolol. The fact that metoprolol caused a 15% reduction in enzyme-estimated infarct size among patients treated within 12 h after onset of pain (69% of all patients) suggests that the benefit is related to the early administration of metoprolol (unpublished). Only 32 patients in the metoprolol group, compared with 55 in the placebo group, were given lignocaine for the treatment of ventricular tachycardia and fibrillation. It therefore seems reasonable to believe that metoprolol has beneficial effects during the first days of acute MI as well as during later stages of the early infarct period.

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ACYCLOVIR IN HERPES ZOSTER

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Summary In a double-blind randomised trial patients with acute herpes zoster received either 5 mg/kg acyclovir (27) or placebo (29) intravenously three times daily. Acyclovir significantly improved the rate of healing of the skin lesions and shortened the period of pain in the acute phase of zoster. Particularly responsive patients were those above 67 years, those with fever, and those with less than four days of pain before treatment. No adverse effects were observed. Acyclovir seems to be active against varicella/zoster virus.

Introduction

FOR chemotherapy of systemic varicella/zoster and herpes simplex virus infections the options seem limited to vidarabine or acyclovir.[1] The guanine derivative acyclovir (9-[2-hydroxyethoxymethyl] guanine) is selectively monophosphorylated in herpes simplex virus infected cells by a virus-specific thymidine kinase, and the resultant triphosphate derivative specifically inhibits the DNA polymerase of herpes simplex virus.[2] Selby and co-workers[3] reported encouraging results with acyclovir in patients with disseminated or localised herpes simplex or varicella/zoster infections; and in herpes simplex infections controlled trials have borne these out. For instance, in a recently reported study in immunocompromised patients with herpes simplex virus infection, acyclovir shortened the period of virus shedding and pain.[4] In varicella/zoster virus infections, however, controlled studies of systemic acyclovir have been lacking. We report here a comparison of acyclovir and placebo in non-immunocompromised patients with herpes zoster.

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Patients and Methods

Our observations concern 56 consecutive patients admitted to hospital with herpes zoster who met the criteria of being over 30 years of age, free of malignant disease, and not on treatment with corticosteroids. In the period of recruitment 3 patients were excluded on these criteria; and 1 patient was removed from the study upon diagnosis of a lymphoma. All patients gave informed consent by signature.

Placebo (100 mg mannitol *BP* per vial) or acyclovir (5 mg/kg, 250 mg per vial) was given 8-hourly for 5 days as an intravenous bolus injection. The vials were coded and injections were given as if all vials contained active drug. A prearranged schedule for increasing the interval between doses in case of renal insufficiency did not come into use, since all patients had a serum creatinine below 1·5 mg/dl (133 μmol/l).

Previous experience in 222 patients with herpes zoster[5,6] indicated that the severity of the inflammatory reaction, the rate of healing, and the duration of pain are dependent on sex, age, the presence of fever, and the affected dermatome(s) and also that the period of pain before skin eruption is considerably longer in thoracic than in trigeminal zoster. The placebo group (29 patients) and the acyclovir group (27 patients) proved to be matched with respect to all of these variables, as well as with respect to the number and size of vesicles (table I). However, the patients in the placebo group were in hospital longer than those receiving active drug (placebo $\bar{x} = 7 \cdot 48$ days, $n = 29$, $SD = 2 \cdot 59$, skewness $0 \cdot 86$, $t = 2 \cdot 014$ ($p < 0 \cdot 05$); acyclovir $\bar{x} = 5 \cdot 88$ days, $n = 26$, $SD = 1 \cdot 48$, skewness $0 \cdot 23$, $t = 0 \cdot 50$). In the acyclovir group 1 patient remained in hospital for 6 weeks for reasons other than the acute eruption and has been excluded from the calculation.

The patients were examined daily for collapse of vesicles, formation of scabs, fever, and development of new vesicles. As previously,[5] one of us (V. E.) evaluated serial photographs of an early, $7 \cdot 1 \times 9 \cdot 9$ cm, lesion independently of the clinical examination. The time taken for collapse of all vesicles, for disappearance of inflammatory lividity, and for the appearance of the first scab and total scab formation was noted. Satisfactory series were present in 22 patients from the placebo group and 20 patients from the acyclovir group.

The presence of pain was recorded daily in hospital and also at follow-up one and three months after the dare of admission. The hospital stay was shorter in this study than in similar previous investigations, probably because the patients were aware of taking part in a research programme. The interval between discharge and follow-up examination one month after admission was therefore in some cases quite long and statements made after discharge about the day of disappearance of pain were not deemed valid.