used. The figures for myocardial infarction refer to the period when oral contraceptives containing less than 50 μg of oestrogen were more often in use. The present mortality from pulmonary and cerebral thromboembolism attributable to oral contraceptives may therefore be slightly lower than that given in the table. We assumed that oral contraceptives are 99% effective as a method of contraception and that the failure rate among users of the diaphragm is 10% a year for women aged 20-34 years and 5% a year for women aged 35-44 years. There is an excess of 1·4 deaths per 100 000 in the younger age group of women using oral contraceptives and of 9·5 per 100 000 among women aged 35-44 years. The excess number of deaths attributable to complications of oral contraceptive use would have been greater if the 40-44-year age group had been considered, but relevant data for pulmonary and cerebral thromboembolism[8] were not available.

These simple calculations did not include several other aspects that may be relevant. Surgery for gall-bladder disease—more common among users of oral contraceptives[9 10]—may be associated with a significant mortality, as may cerebral haemorrhage[11] and other, less common adverse reactions.[12] Furthermore, widespread use of legal abortion of unwanted pregnancies among users of the diaphragm might reduce the number of deaths in this group. These observations, and the fact that a pessimistic failure rate for the diaphragm was assumed,[13] suggest that the estimate of the excess deaths among oral contraceptive users may have been a conservative one. In England and Wales the increased risk of death from thromboembolism to users of oral contraceptives aged 20-34 years may still be less than half that of death from road-traffic accidents, but for those in the 35-44-year age group the increased risk may be double that from road-traffic accidents.[14] Whether this is an acceptable risk for so effective a method of contraception remains to be decided.

The risk estimates for death from thromboembolism in table II were made before the introduction of oral contraceptives containing less than 50 μg of oestrogen. Since a dose-response relationship has been shown between higher oestrogen doses and deaths from thromboembolism,[15] probably oral contraceptives containing smaller amounts of oestrogen may be associated with an appreciably reduced risk. The prescribing of alternative methods of contraception for women at risk of myocardial infarction for other reasons—for example, hypercholesterolaemia, heavy cigarette smoking, hypertension, and diabetes—could further reduce the number of deaths associated with oral contraceptive use.[6]

We thank the medical officers on the committee's staff who carried out the interviews; the many doctors who gave their time to provide us with information; Sir Richard Doll and Professor M P Vessey for advice; Dr A M Adelstein and Mr J G Gerrard, of the Office of Population Censuses and Surveys, who arranged for us to receive transcripts of the death certificates; and Mrs A Renauld, Mrs M Spellman, and Mrs A Read for secretarial help.

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Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia

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Summary

Metoprolol and acebutolol, two supposedly cardioselective beta-adrenergic receptor blocking agents, were tested in healthy volunteers against propranolol, a non-selective drug, for their effect on blood glucose levels during insulin-induced hypoglycaemia. There was no significant difference between propranolol and metoprolol, which both potentiated the initial hypoglycaemic action of the insulin and delayed the return to normoglycaemia. Acebutolol, even though potentiating the initial hypoglycaemia, did not possess a significant delaying effect. A similar trial should be undertaken in diabetics to determine with certainty the safety of such drugs in diabetes mellitus.

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Introduction

One of the body's most important responses to hypoglycaemia is the release of adrenaline from the adrenal medulla. This hormone stimulates glycogenolysis, and the subsequent release of glucose tends to restore the blood glucose level towards normal.[1]

The beta-adrenergic receptor blocking agents available are non-selective in their action and are thought to inhibit glycogenolysis. These drugs would therefore be expected to possess a hypoglycaemic effect, and indeed hypoglycaemia precipitated by propranolol has been reported.[2-4] After such reports it was suggested that drugs like propranolol should be used with extreme caution in insulin-treated diabetics and in patients prone to hypoglycaemia.[2 5-7]

The evidence published in the past decade on the effect of beta-adrenergic blockade on blood glucose levels has not, however, been unanimous in supporting this recommendation.

For example, a survey of about 80 000 diabetics carried out under the auspices of the British Diabetic Association showed that 152 patients were receiving propranolol. In none of these patients was a hypoglycaemic action of propranolol shown.[8] Similarly, Abramson *et al*[5] could not show that propranolol potentiated the hypoglycaemic action of insulin in man nor could Cowell and Hetenyi[9] show this in dogs.

Recently, some new beta-adrenergic receptor blocking drugs have been introduced into clinical practice. These are said to be selective in their effects, their action being maximal on cardiac beta-receptors and less definite on beta-receptors in other tissues.[10] No data have, however, been published on the selectivity of this type of drug on glucose metabolism and hence it was decided to compare the effects of the supposedly cardio-selective beta-blockers metoprolol and acebutolol with those of the non-selective drug propranolol on the recovery from insulin-induced hypoglycaemia.

Subjects and methods

Eleven healthy male medical students aged 20-23 years with no history of diabetes mellitus, ischaemic heart disease, or obstructive airways disease volunteered for this project. Each was instructed to take his usual diet and to avoid undue or violent exercise and alcoholic excess in the 48 hours before the test.

Each subject underwent four insulin-induced hypoglycaemic episodes: one control and one after a course of each of the three drugs. After the uneventful administration of a test dose of each drug propranolol (Inderal), metoprolol (Lopressor), and acebutolol (Sectral) in doses of 40, 50, and 100 mg twice daily respectively were taken for 48 hours in a single-blind manner before each test session, with the last dose two hours before the start of the test.

After a 12-hour overnight fast each subject rested in a recumbent position and a 19-gauge butterfly needle was inserted into an antecubital vein and kept patent by irrigation with 0.9% saline. After 30 minutes' stabilisation the first sample of blood was withdrawn followed by the rapid intravenous injection of insulin *BP* 0·1 U/kg body weight. Further samples were taken at 30, 45, 60, 90, and 120 minutes afterwards, and the heart rate was noted on each occasion. Each sample was collected into tubes containing fluoride-oxalate for the determination of glucose by the spectrophotometric GOD-Perid method,[11] using the Biochemica test combination (Boehringer). All analyses were performed in duplicate and the mean value taken for subsequent statistical analysis.

In all cases the first hypoglycaemic episode of each series of tests was the control. The order of the subsequent studies using the drugs under investigation was randomised and at least four days elapsed between tests.

Results

Blood glucose concentration and heart rate during the course of the insulin-induced hypoglycaemic episodes are summarised in Figs 1 and 2.

The results of the blood glucose determinations were examined statistically in two ways. Firstly, graphs of blood glucose concentrations versus time were plotted for each hypoglycaemic episode in each volunteer and the areas enclosed under the recovery phase of the curves computed. The areas obtained for each drug were then compared by Student's *t* test. Secondly, each point in fig 1 was compared by Student's *t* test for paired data. Significance was accepted at the 5% level of accuracy, and both statistical techniques gave the same results.

All three drugs significantly potentiated the initial hypoglycaemic effect of the insulin ($P < 0.05$ for acebutolol and $P < 0.02$ for propranolol and metoprolol). No significant difference was found between the control value and values on acebutolol during the recovery part of the experiment, but propranolol and metoprolol delayed the return to normoglycaemia ($P < 0.0025$ in both cases). No significant difference was found between propranolol and metoprolol.

All three drugs reduced the resting heart rate by the same amount and reduced or even abolished the tachycardia induced by the hypoglycaemia (fig 2). This was taken as evidence that the volunteers did in fact take the drugs as instructed and were all effectively beta-blockaded.

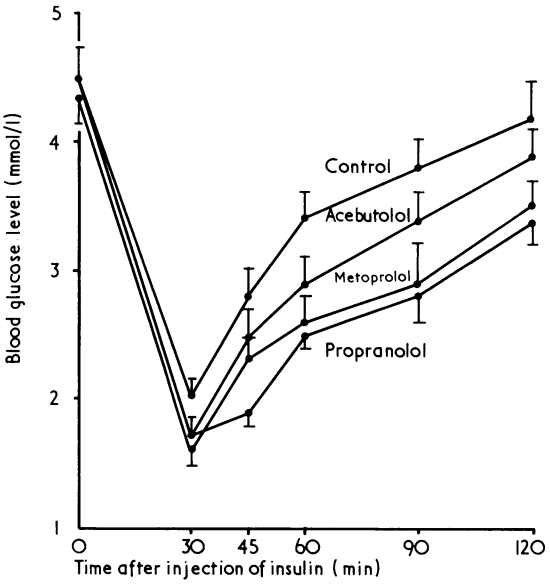

FIG 1—Effect of beta adrenergic blockade on blood glucose levels after insulin 0·1 U/kg body weight. Each point represents mean (±SE of mean) of at least seven values.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

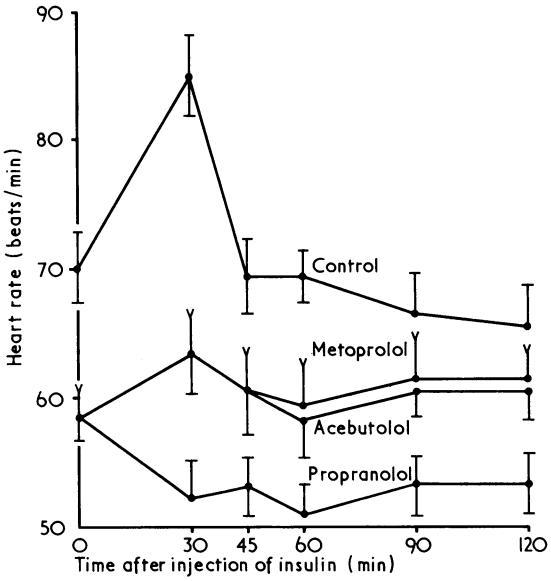

FIG 2—Effect of beta-adrenergic blockade on heart rate after insulin 0·1 U/kg body weight. Each point represents the mean (±SE of mean) of 11 values.

Side effects—One case of indigestion and one of nausea and sweating were noted during the administration of propranolol. One volunteer reported slight wheezing while taking acebutolol. All volunteers reported that the subjective feelings of hypoglycaemia were reduced by all the drugs under investigation. Indeed, no symptoms at all were reported by one subject taking propranolol, two taking metoprolol, and two taking acebutolol in spite of blood sugar levels of 1·3-2·2 mmol/l (23-40 mg/100 ml) 30 minutes after insulin administration.

Discussion

Propranolol potentiated the initial hypoglycaemic effect of the insulin and delayed the return to normoglycaemia. These findings agree with most published results after propranolol has been given before insulin administration.[12-14] They are also

compatible with the results of Brown and Riggilo[12] with the non-selective drug sotalol. The only published findings that totally disagree with these results are those of Walter *et al.*[15] They showed that propranolol had no significant effect on the blood glucose levels after insulin administration. This trial is not strictly comparable, however, since it was performed after a five-day fast, and by this time liver glycogen stores, a readily available source of glucose, would have been exhausted. Abramson *et al*[2] partly disagreed with the above results. They found that the initial hypoglycaemic effect of the insulin was not potentiated by propranolol but confirmed that the return to normoglycaemia was significantly delayed.

Both supposedly cardioselective beta-adrenergic receptor blocking agents used in this trial potentiated the initial hypoglycaemic effect of the insulin in the same way as propranolol, but only metoprolol significantly delayed the return to normoglycaemia. There are no other published results on the effect of these two drugs on blood glucose levels and comparison must therefore be made with the only other experiment in which selective beta-adrenergic receptor blockade was used. When Baird and Carter[14] gave oral practolol and tolamolol to rats these drugs did not significantly potentiate the hypoglycaemic effect of insulin one hour after administration. Only when given intraperitoneally in very high doses did practolol have a possible potentiating effect. Unfortunately, no information was given on the return of blood glucose levels towards normal, but Barnett,[16] using the same drug in man, did not show any delayed normoglycaemia after insulin. Recently both products have been almost completely withdrawn from clinical practice.

These results were obtained in healthy volunteers and are therefore not strictly applicable to patients with diabetes mellitus. A similar trial in diabetics should therefore be undertaken to determine with certainty the safety of such drugs in the condition.

I thank Dr D Barnett, consultant physician to this hospital, for placing the facilities of his metabolic laboratory at my disposal and for allowing his technician, Mrs Jill Unsworth, to perform the analyses. I am grateful to Geigy Pharmaceuticals Ltd for providing financial assistance and to my 11 volunteers without whose help this project would not have been possible.

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First electrocardiogram in recent myocardial infarction

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Summary

The admission electrocardiogram (ECG) was studied in 898 patients admitted to a coronary care unit over two years. The diagnosis made from this tracing was compared with that made at the end of the patient's stay. About half the cases of recent myocardial infarct were diagnosed from the admission ECG, but accuracy rose to 83% with serial ECGs in the unit. The ECG is important but not entirely reliable in the early detection of acute myocardial infarction, which should be largely a clinical diagnosis.

Introduction

Studies of myocardial infarction have shown that mortality is high at and immediately after its onset and rapidly decreases with time.[1 2] This observation has led to the formation of special units for the early care of these patients, and in some centres these have been logically extended to the patient's home as mobile coronary care units.

Implicit in this is the assumption that the condition can be diagnosed in the early stages, and many clinicians and even laymen believe that the value of the electrocardiogram (ECG) is paramount. The value of an early ECG has not yet been clearly defined, but its diagnostic limitations in a selected group of patients with mild myocardial infarction have been shown.[3]

We decided to study prospectively over two years every patient with suspected myocardial infarction admitted to a coronary care unit to assess the relation between the admission ECG diagnosis of acute myocardial infarction and the eventual diagnosis reached after clinical appraisal, serial ECGs, and enzyme studies, with necropsy findings when appropriate.

Patients and methods

Over two years 918 patients were admitted to a coronary care unit. As a rule only patients thought by their practitioners to have had a myocardial infarction within the previous 48 hours were admitted but there were no age or sex restrictions. An occasional exception was made to this rule for troublesome complications of an older myocardial infarct such as arrhythmia. A full 12-lead ECG was recorded on admission in 898 patients and on each successive morning until the patient left the monitoring unit. These 898 patients are the subjects of the

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