Recently it has been our practice, particularly with younger patients, to use the nalorphine test when it is required urgently to know whether the patient is or is not "hooked on" heroin. A positive test is one in which there is a paradoxical pupil response—that is, one in which the pupils enlarge significantly within half an hour of the injection of 4 mg. of nalorphine subcutaneously. For the purpose of objective measurement, the response is recorded by means of a Polaroid camera, fitted with a pupillometer adapter. Severe reactions to this dose of nalorphine are rare, but should one occur it can readily be relieved by intravenous methadone. Despite the advantage of speed, the nalorphine test is not altogether satisfactory in practice, largely because of its non-specificity and the high incidence of both false-positive and false-negative results.

It is our belief that, provided the work-load justifies the employment of adequate technical and capital resources, the results of a qualitative urine analysis which does not possess the disadvantages of the nalorphine test can be returned to clinicians within 24 hours of receipt of the specimen, and in special cases in as little as five hours.

(2) Possession of objective data by the clinician in place of his complete dependence on the patient's history helps strengthen the doctor–patient relationship. The strength of this bond depends largely on the respect the doctor is able to command from his patient. It is particularly important in the type of patient under discussion, who frequently looks on the doctor as a "dupe" or "square" whose main function is to dispense drugs on demand.

(3) Clinical interpretation of the results of urine analysis may be difficult. Currently there are no methods suitable for detecting morphine in blood routinely; and quantitative measurements of morphine in urine are tedious and for various reasons offer no advantage over qualitative determination (Marks, 1966).

Technically it may not always be possible to identify morphine in the urine when it is present in small amounts. Not only may the quantity present be less than the sensitivity of the method (about 1 μg./ml.), but the presence in the urine of other drugs, or more often their metabolites in high concentration, may serve to obscure what little there is. The phenothiazines and the substitute narcotic methadone are particularly important in this respect. It is largely because these drugs are so often used in the treatment of heroin addiction that we have not found simpler methods of urine analysis for morphine (Harms, 1965; Davidow *et al.*, 1966) satisfactory in our laboratory.

Clinically it is difficult or impossible to distinguish by urine analysis a large dose of heroin administered a long time previously from a small amount taken recently. Nor is it possible to distinguish heroin from morphine. Moreover, absence of morphine from the urine is not conclusive evidence that the subject has not taken heroin; only that, if taken, the dose was too small or too long ago to be detectable. In practice a negative result generally means that less than 10 mg. of heroin has been taken in the past 24 hours. Consequently, a negative result in a patient who does not exhibit abstinence syndrome is good evidence against physical (though not necessary psychic) dependence on the drug. It must be remembered that urine morphine may originate either from heroin or morphine, though currently only the former drug is affected by the recent restriction on prescribing narcotics for addicts. Morphine also occurs in the urine, though only in the bound or conjugated form, of persons taking codeine owing to partial metabolic conversion in the body. This should not give rise to confusion in practice, as codeine is also present in large amounts and is readily detectable on the thin-layer chromatographic plate.

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Trasicor in Angina Pectoris: a Double-blind Trial

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Summary: Eighteen patients entered a double-blind trial of the beta-adrenergic blocking drug Trasicor in the treatment of angina pectoris. Six patients had to be withdrawn from the trial when substitution of placebo for Trasicor caused severe exacerbation of angina attacks. In these cases the frequency and severity of angina attacks fell to a minimum when Trasicor was re-established. A further 10 patients were significantly improved by Trasicor. Two patients showed no significant improvement. No side-effects were observed in doses ranging up to 400 mg. daily.

Introduction

Trasicor is a beta-adrenergic blocking agent which has recently been introduced by Ciba. A haemodynamic investigation of its effects showed that rapid intravenous injection of 5 mg. produced negative chronotropic and negative inotropic effects. In contrast, prolonged oral therapy with Trasicor produced a negative chronotropic and a positive inotropic effect, with a

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marked increase in stroke volume (Wilson *et al.*, 1968). Studies showed that the beta-blocker propranolol produced similar results when given intravenously, but the effects of long-term oral therapy appeared to be due solely to a negative chronotropic action, there being no change in stroke volume (Frohlich *et al.*, 1968).

A single-blind trial with Trasicor in nine patients with angina pectoris showed that the drug significantly reduced the number of angina attacks and that there were few side-effects (Wilson and Turner, 1967). It was therefore decided to conduct a double-blind trial in patients with angina pectoris so that a more accurate assessment of the drug could be made.

Method

In the majority of clinical trials reported in the literature a "fixed" dose medication was used. As there are obvious limitations to this approach, the conduct of the present trial was based on the fact that patients with angina who entered the trial had already been taking Trasicor for periods of from 3 to 18 months and were well stabilized on doses best suited to their needs. This optimum dosage had been determined by a run-in period for each patient. Initially 20 mg. of Trasicor had been given thrice daily with an additional 20 mg. at night for nocturnal angina. The dose was increased weekly by 60 to 80 mg. until maximum benefit was obtained. The final dosage ranged from 60 to 400 mg. daily.

The trial was designed to compare the effectiveness of Trasicor with that of placebo in the relief of attacks of angina pectoris under double-blind conditions. The trial lasted for four weeks and consisted of four periods each of one week; during this time each patient received Trasicor for two weeks and placebo for two weeks. The four periods were randomized so that for every six patients in the trial there were six different orders of administration. Both Trasicor and placebo were given as 20-mg. tablets identical in taste and appearance.

The patients who were admitted to the trial had suffered at least two attacks of angina pectoris each week before the beginning of Trasicor therapy. The pains were typical in character and distribution and were relieved by glyceryl trinitrate tablets. Nineteen patients entered the trial, which was controlled by a single clinician. The general purpose of the trial was explained to patients and they were told that various "strengths" of the drug were being assessed. In addition, they were instructed to consult an independent medical referee—a physician not otherwise connected with the trial—should untoward symptoms arise. This precaution was taken following the experience in our single-blind trial in which three patients had to be admitted to hospital with acute coronary insufficiency when Trasicor was abruptly stopped.

Assessment

At the beginning of the trial each patient was allocated a trial number and a brief history was recorded. Each was given a known number of glyceryl trinitrate tablets and told to take them for actual pain and not as a prophylactic. For each period of the trial the patient was asked to record each day, on the sheet supplied, the daily number and severity of angina attacks, the number of glyceryl trinitrate tablets taken, any side-effects noted, and a subjective assessment of the treatment for that particular period. He was then given a prescription indicating the number of "Trasicor" tablets to be supplied. This was presented to the pharmacist involved in the trial, who supplied the requisite number of tablets for the next period.

The medical referee found it necessary to break the code in connexion with those patients he had to withdraw from the trial. The trial was so planned that, apart from this, no one knew whether the drug or placebo was being taken until after the trial series had been completed.

Results

The results are shown in the Table. Six patients (Cases 2, 3, 7, 16, 17, and 18) were withdrawn from the trial by the medical referee. When put on the placebo these patients immediately developed severe continual angina attacks which were not relieved by glyceryl trinitrate therapy (status anginosus in the Table). One patient required admission to the coronary care unit for four days' observation, while the remainder were managed at home. When these patients were withdrawn from the trial the placebo was replaced by their optimum daily dosage of Trasicor. The patients who had to be withdrawn during the first two weeks of the trial (Cases 2, 3, 7, 16, and 17) were followed up for the next week or two on Trasicor therapy and were asked to record the number of angina attacks and glyceryl trinitrate consumption during this period. In this way the results of two weeks' Trasicor therapy for every patient can be shown in the Table. The angina attacks in all six patients fell to a minimum when Trasicor therapy was resumed. The seventh patient (Case 10) was able to complete the trial, though he experienced continual angina attacks for two days while on placebo.

Table of Results

Case No.	Sex and Age	Total Daily Dose (mg.)	No. of Angina Attacks in Two Weeks		Glyceryl Trinitrate Consumption in Two Weeks	
			Drug	Placebo	Drug	Placebo
1	M 64	180	1	5	½	1½
2	F 68	320	4	Status anginosus	4	Withdrawn
3	M 44	300	18	Status anginosus	18	Withdrawn
4	M 71	120	0	4	0	5
5	M 54	180	8	12	7	11
6	F 50	400	2	2	2	2
7	F 56	240	4	Status anginosus	4	Withdrawn
8	F 55	180	1	11	1	10
9	F 65	160	0	16	0	4
10	M 44	240	4	Status anginosus	0	2
11	M 57	160	1	10	1	12
12	M 75	120	2	3	2	2
14	M 57	240	11	39	6	25
15	M 52	400	0	15	0	5
16	M 76	340	16	Status anginosus	8	Withdrawn
17	M 55	360	0	Status anginosus	0	Withdrawn
18	F 62	60	0	Status anginosus	0	Withdrawn
19	M 69	120	6	15	6	15

Twelve patients completed the trial. When on Trasicor 10 showed a significant reduction of angina attacks accompanied by a sense of well-being and improved exercise tolerance. Several commented during their Trasicor treatment period that, because of improved exercise tolerance, their angina attacks had been precipitated only by severe exertion. In contrast, when taking placebo physical exercise was markedly limited, and this was attributed to the reduced strength of the tablet. Five patients were completely free of angina attacks while taking Trasicor. Two patients (Cases 6 and 12) were not helped by Trasicor. Wolfson *et al.* (1966) observed that propranolol did not befit patients with a normal coronary angiogram but with pain indistinguishable from angina pectoris. One patient (Case 13) was not considered in the final assessment, as he proved to be an unreliable trial subject.

No side-effects whatever were reported during the trial. Case 19, a diabetic, found he required half his previous dose of chlorpropamide when taking Trasicor.

Discussion

It became apparent during the trial that the customary quantitative assessment of results was not going to give a true picture. A qualitative assessment would also be required if a reliable indication of the status of Trasicor in the treatment of angina pectoris was to be obtained.

Thus in this trial the number of glyceryl trinitrate tablets used frequently did not reflect the condition of the patient, either when on Trasicor or on placebo. Only five patients

resorted to glyceryl trinitrate for every attack of angina pectoris. Even in those cases that had to be withdrawn from the trial the consumption of glyceryl trinitrate tablets in 24 hours was often of the order of one to three tablets. Patients limited their intake of glyceryl trinitrate for two reasons: they objected to "taking too many tablets" and the headache following glyceryl trinitrate was often extremely unpleasant. Relief from pain was obtained by a restriction of activity.

These findings differ markedly from those of many similar trials of drugs in the treatment of angina pectoris. Gillman and Prichard (1965) found a close correlation between glyceryl trinitrate consumption and angina attacks when working with propranolol.

Case 5 illustrates another aspect of the importance of the qualitative approach. When taking placebo this patient was confined to the house, physical activity was severely limited, and the slightest exertion precipitated his angina. On Trasicor therapy effort tolerance was greatly improved, so that pains were experienced and glyceryl trinitrate was taken only after severe exertion. Such marked improvement when on Trasicor therapy is not apparent from the Table, which depicts quantitative results only.

It is our opinion that in a trial of this nature more emphasis should be placed on qualitative results than has been customary in the past, as quantitative results can be misleading.

The abrupt replacement of Trasicor with placebo resulted in severe exacerbation of angina in seven patients, six of whom had to be withdrawn from the trial. This did not appear to be related to the dosage of the drug, which varied from 60 to 340 mg. daily in these cases. Perhaps the patients had become accustomed to a higher level of effort tolerance which could not be maintained once the Trasicor was discontinued. However, this does not appear to be the complete answer, as three patients suffered frequent angina attacks at rest and on effort for several days before reporting to the medical referee. Perhaps, in addition, there is some form of protracted "rebound" release of sympathetic drive when Trasicor is stopped abruptly. This finding suggests that caution should be exercised when stopping Trasicor in angina patients and that probably a count-down method should be used.

Patients who completed the trial commented on their sense of well-being and improved exercise tolerance during the Trasicor treatment periods. This contrasts with the mental depression reported following the use of propranolol (Waal, 1967). This may be explained by the difference in the haemodynamic effects of the two drugs (Wilson *et al.*, 1968).

We found that old age was no contraindication to Trasicor therapy and that large doses were well tolerated. One 76-year-old man had an optimum dosage of 340 mg. daily.

Conclusion.—This double-blind trial shows Trasicor to be non-toxic and a very useful drug for use in the treatment of angina pectoris.

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Preliminary Communications

Pituitary Polypeptide with Hypoglycaemic Action in Diabetes Mellitus

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Summary: A polypeptide isolated by the hydrolysis of growth hormone, studied in five patients with diabetes mellitus, has been shown able to produce hypoglycaemia, presumably by modifying the anti-insulin action of pituitary growth hormone. Possibly this substance may be suitable for treating cases of insulin resistance or when a circulating inhibitor of glucose uptake is present.

INTRODUCTION

Previously reported work (Bornstein *et al.*, 1968a) showed that hydrolysis of growth hormone yielded two ultrafilterable polypeptides, which by virtue of their specific action on the triosephosphate dehydrogenases appeared capable of accounting for the early hypoglycaemic action of growth hormone (polypeptide ACG) and later the hyperglycaemic action of the hormone (polypeptide ING).

Further investigations (Bornstein *et al.*, 1969a) have shown that all actions of growth hormone on carbohydrate and fat metabolism may be accounted for by the actions of these two polypeptides, since polypeptide ING inhibits glycolysis and fat synthesis while accelerating lipolysis, and polypeptide ACG is hypoglycaemic and able to reverse all inhibitions produced by ING.

All this previous work had been carried out in animals, but in view of these findings we decided to investigate the effect of polypeptide ACG on the hyperglycaemia of patients suffering from diabetes mellitus.

PRESENT INVESTIGATION

Techniques.—Polypeptide ACG was prepared from ovine growth hormone according to the technique previously described (Bornstein *et al.*, 1968b) and sterilized for use by ultrafiltration. The yield was 5 mg. from 2 g. of growth hormone, representing 500 g. wet weight of ovine pituitaries. The activity of each preparation was assayed by its ability to reverse the inhibition of glyceraldehyde-3-phosphate dehydrogenase produced by a standard concentration of ING. Blood glucose estimations were done by Dr. J. Owen, of the Biochemistry Department, Alfred Hospital, using the standard AutoAnalyzer technique. Plasma insulin estimations were done by using a modification of the double antibody immunoassay technique of Morgan and Lazarow (1963). The coefficient of variation of the method of a plasma pool containing 24 μu./ml. was 8%.