OBSERVATIONS ON THE EFFECT OF β -ADRENOCEPTOR BLOCKING DRUGS ON GLYCERYL TRINITRATE TACHYCARDIA

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- 1 The administration of 0.5 mg glyceryl trinitrate by chewing and keeping under the tongue increased heart rate in normal subjects in the supine and erect posture.
- 2 There was no significant difference between the responses in the same subject on repeated administration of glyceryl trinitrate on different days but there was a significant difference between the responses in different subjects.
- 3 The oral administration of practolol and propranolol reduced the responses to glyceryl trinitrate. The two drugs progressively reduced the increase in heart rate produced by glyceryl trinitrate; there was no significant difference between their effects. Propranolol produced a significantly greater reduction than practolol in the maximum heart rate that was produced by glyceryl trinitrate.
- 4 The administration of practolol (300 mg) twice daily by mouth to patients after an acute episode of ischaemic heart disease significantly reduced the increases in heart rate produced by standing and by glyceryl trinitrate in comparison to the responses in similar patients receiving a placebo.

Introduction

The activity of β -adrenoceptor blocking drugs can be easily demonstrated in man. Inhibition of the increase in heart rate produced by the intravenous infusion or inhalation of isoprenaline has been widely used. Initially studies were made with single doses of isoprenaline, the effects of which could be blocked completely by appropriate doses of propranolol (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968), although much larger doses of practolol reduced but did not abolish the response. The competitive nature of this blockade has been demonstrated by completing dose response curves to isoprenaline before and after propranolol (Dollery, Paterson & Conolly, 1969) and practolol (Aellig & Prichard, 1970). Although such studies may indicate the potency ratio of different β -adrenoceptor blocking drugs they are of no value in determining the activity of these drugs in blocking endogenously released catecholamines. As the increase in heart rate which occurs on exercise results from an increase in sympathetic drive to the heart (Robinson, Epstein, Beiser & Braunwald, 1966), the effect of β -adrenergic blocking drugs on this response has been used to assess their activity (Brick *et al.*, 1968; Coltard & Shand, 1970). Both of these reports showed that a progressive reduction in an exercise tachycardia occurred with increasing doses of practolol and

propranolol. Such observations are readily made in normal subjects but may not be possible in patients who are ill.

Recently Fitzgerald (1970) has introduced a new test for assessment of the activity of β -adrenoceptor blocking drugs. He has shown that the increase in heart rate produced by the sublingual administration of glyceryl trinitrate to normal subjects in the erect posture was unaffected by atropine but reduced by propranolol and practolol. He suggested that this test might be of value in assessing the activity of β -adrenergic blocking drugs in normal subjects and in patients who were unable to exercise or to whom one did not wish to administer isoprenaline.

The present observations were carried out to investigate the value of inhibition of the tachycardia produced by glyceryl trinitrate in the assessment of the activity of β -adrenergic blocking drugs. Observations have been made in normal volunteers and in patients with ischaemic heart disease.

Methods

Observations were made in healthy male colleagues who volunteered for the experiments. Lead II of

the electrocardiogram was used to drive a Nielsen Cardiotachometer (Devices Ltd.) to provide a continuous and instantaneous reading of heart rate.

Observations were made with the subjects either lying quietly on a couch or standing. Heart rate was observed continuously on the ratemeter and when it has been steady for at least 5 min, the subject was given 0.5 mg glyceryl trinitrate which was chewed and kept under the tongue. Heart rate was continuously observed until the maximum increase was recorded. This always occurred within 6 minutes. Occasionally a subject in the erect position felt light-headed and faint after taking glyceryl trinitrate. When this occurred he was placed in the supine position and the heart rate immediately prior to this episode recorded.

Observations in patients

Observations were made in 63 patients with acute ischaemic heart disease who had been admitted to the coronary care unit in the Ulster Hospital, Belfast, with suspected acute myocardial infarction. These formed part of a trial (Barber, Boyle, Chaturvedi, Shanks & Walsh, 1973) in which 500 consecutive admissions to a coronary care unit with suspected acute myocardial infarction received either practolol, 300 mg, or placebo twice daily by mouth from admission to hospital for

three months. Lead II of the electrocardiogram was continuously recorded on a Mingograph ink recorder at a paper speed of 25 mm/s during the period of observations. Heart rate was obtained by determining the time taken for five complete cardiac cycles. Observations were made 4 h after administration of practolol or placebo on the morning before discharge from hospital. Heart rate was recorded with the patient lying supine in bed until a constant value had been obtained when the patient stood upright. After 3 min heart rate was again recorded. The patients lay supine during the remainder of the period of observation. After heart rate had become steady, the patients were given 0.5 mg glyceryl trinitrate which was chewed and kept under the tongue and the maximum increase in heart rate recorded. The maximum heart rate produced by glyceryl trinitrate is referred to as the glyceryl trinitrate tachycardia. The significance of differences between values has been determined either by analysis of variance or paired *t* tests.

Results

Heart rate response to glyceryl trinitrate

Observations were made on five separate occasions on each of the five subjects who were in the supine

Fig. 1 Effect on heart rate of the administration of glyceryl trinitrate on five occasions to five subjects in the supine position. Left hand panel: the lower of each pair of symbols is the value for resting heart rate and the upper symbol is the maximum value after glyceryl trinitrate. Right hand panel: the upper of each pair of symbols is the increase in heart rate produced by glyceryl trinitrate determined as the difference between resting heart rate and the maximum value after glyceryl trinitrate. The lower of each pair of symbols is the zero value.

position. Heart rate was recorded before and after the administration of 0.5 mg glyceryl trinitrate. The results from each subject are given in Fig. 1 which shows the heart rate before and after the administration of glyceryl trinitrate and the increases in rate produced by trinitrate. The mean values for each subject are given in Table 1. There was little variation in the values for resting heart rate in each subject on the five occasions. The differences were not significant. Greater variation occurred between the mean values for resting heart rates in the five subjects. These differences between subjects were significant ($P < 0.05$). Glyceryl trinitrate increased heart rate in all subjects on all occasions. The mean increase in all subjects produced by five separate administrations of glyceryl trinitrate was 14.1 ± 1.7 beats/min; this increase is significant ($0.01 > P > 0.001$). The increases in heart rate in each subject were similar on the five occasions and did not differ significantly ($P > 0.05$). There was greater variation between the increases in different subjects; this was not related to differences in the initial resting heart rate. There was a significant difference ($P < 0.05$) between the mean increases in rate in the five subjects. Variations occurred in the maximum heart rate produced by the five separate administrations of glyceryl trinitrate in each subject; these differences were not significant in any subject. Much greater variations occurred in the glyceryl trinitrate tachycardia in the five different subjects. These were not related to different values for resting heart rate. There was a significant difference between the mean values for the glyceryl trinitrate tachycardia in different subjects ($P < 0.05$).

Similar observations were made in six different subjects who received glyceryl trinitrate when in the erect position (Fig. 2 and Table 1). In four of the subjects there was little variation (< 10 beats/min) in the five separate values for resting heart rate. In one subject there was a difference of 27 beats between two values and in another a

difference of 12 beats/minute. There was no significant difference between the values for resting heart rate in the six subjects ($P > 0.05$). The administration of glyceryl trinitrate increased heart rate in all subjects on each occasion. The increases in rate were not related to the resting values although the greatest increases occurred in the subject with the lowest resting heart rate. The maximum heart rate after glyceryl trinitrate varied for each subject on the five occasions but the differences were not significant. There was a significant difference ($P < 0.01$) between the mean values for the glyceryl trinitrate tachycardia in different subjects. There was less variation in the increases in heart rate produced by glyceryl trinitrate on five occasions in each subject than in the increases between subjects which were significantly different ($P < 0.01$). The mean increase in all subjects on all occasions was 34.5 ± 5.1 beats/minute.

Some subjects complained of a throbbing headache which lasted for up to 2 h and of facial flushing after the administration of glyceryl trinitrate. Three of the six subjects given the drug when standing felt lightheaded on at least one occasion.

Effect of propranolol and practolol on the response to glyceryl trinitrate

Observations were made on five subjects who received, by mouth, in random order on seven occasions placebo, propranolol, 20, 80 or 320 mg and practolol 50, 200 or 800 mg. There was at least five days between two sets of observations. Two hours after drug administration heart rate was recorded with the subject standing before and after taking 0.5 mg glyceryl trinitrate. The averaged values for heart rate before and after glyceryl trinitrate and the increase produced by glyceryl trinitrate for all groups are given in Table 2 and some of the results are shown in Figure 3. The three doses of practolol had no consistent or

Table 1 Values for heart rate in six subjects in the erect position and five in the supine position before and after the administration of glyceryl trinitrate and for heart rate increase produced by the drug. Each value is the mean ($\pm$ S.E.M.) of observations on five separate occasions when glyceryl trinitrate was given.

<i>Erect</i>				<i>Supine</i>			
<i>Subject</i>	<i>Rest</i>	<i>GTN</i>	<i>Increase</i>	<i>Subject</i>	<i>Rest</i>	<i>GTN</i>	<i>Increase</i>
1	82.2 $\pm$ 2.1	110.8 $\pm$ 3.2	28.0 $\pm$ 2.6	A	87.8 $\pm$ 1.4	103.6 $\pm$ 2.2	15.8 $\pm$ 1.1
2	87.6 $\pm$ 1.7	108.4 $\pm$ 3.5	20.8 $\pm$ 2.5	B	72.8 $\pm$ 2.1	91.2 $\pm$ 3.6	18.4 $\pm$ 1.4
3	76.8 $\pm$ 1.5	129.4 $\pm$ 2.7	52.6 $\pm$ 2.8	C	81.4 $\pm$ 2.4	96.8 $\pm$ 2.3	15.4 $\pm$ 0.8
4	98.8 $\pm$ 1.1	132.0 $\pm$ 2.5	33.2 $\pm$ 2.0	D	62.2 $\pm$ 1.0	73.6 $\pm$ 1.6	11.4 $\pm$ 1.9
5	98.6 $\pm$ 0.7	124.6 $\pm$ 2.1	26.0 $\pm$ 2.3	E	58.0 $\pm$ 1.8	67.2 $\pm$ 2.3	9.2 $\pm$ 0.8
6	92.4 $\pm$ 5.1	139.0 $\pm$ 4.2	46.6 $\pm$ 2.1

Fig. 2 Effect on heart rate of the administration of glyceryl trinitrate on five occasions to six subjects in the standing position. The symbols in the two panels are as in Figure 1.

significant effect on resting heart rate but the three doses of propranolol produced a significant reduction that was not dose dependent. The three doses of both drugs produced significant reductions in the glyceryl trinitrate tachycardia. There was no significant difference between the effects of the three doses of practolol although the tachycardia was less after the smallest dose. A progressive reduction in the tachycardia was pro-

duced by the three doses of propranolol. The effects of 80 or 320 mg were not significantly different but were significantly greater than the effect of 20 mg propranolol and the effect of all three doses of practolol ($P < 0.05$). All doses of practolol produced significant reductions ($P < 0.01$) in the increases in heart rate produced by glyceryl trinitrate. The greatest reduction was produced by the first dose (50 mg) with further

Table 2 Effects of the administration of glyceryl trinitrate to five subjects on seven separate occasions 2 h after the oral administration of placebo, practolol, 50, 200 or 800 mg and propranolol, 20, 80 or 320 mg. Mean values ($\pm$ S.E.M.) for heart rate before and after glyceryl trinitrate and the increase in rate produced by the drug. The increase in heart rate has also been calculated on the basis that (a) resting heart rate did not change after practolol and propranolol and (b) that it was reduced by 10 beats/min by all doses of both drugs.

	Practolol				Propranolol		
	Placebo	50	200	800	20	80	320
Resting	80.0 ± 3.2	73.8 ± 2.8	78.6 ± 2.1	82.8 ± 2.4	71.0* ± 1.5	67.6* ± 1.7	71.2* ± 2.3
After GTN	124.0 ± 6.4	97.4* ± 5.7	100.2* ± 2.8	98.4* ± 3.5	97.0* ± 4.3	85.6* ± 3.7	84.4* ± 3.0
Increase	44.0 ± 7.6	23.6** ± 4.4	21.6** ± 3.9	15.6**	26.0** ± 4.6	16.0** ± 2.9	13.2* ± 2.2
Increase a	—	17.4	20.2	18.4	17.0	5.6	4.4
Increase b	—	27.4	30.2	28.4	27.0	15.6	14.4

* $P < 0.05$; ** $P < 0.01$.

Fig. 3 The effect of the oral administration of a placebo (Plac) and of a series of doses of practolol (○) and propranolol (●) on the increase in heart rate produced by the administration of glyceryl trinitrate to five subjects in the standing position. Each point is the mean ($\pm$ S.E.M.) of observations in five subjects. Upper panel: maximum heart rate after the administration of glyceryl trinitrate. Lower panel: increase in heart rate produced by glyceryl trinitrate.

Table 3 Heart rate supine, after 0 and 3 min standing, and after glyceryl trinitrate. Mean ($\pm$ S.E.M.) of observations in 36 patients receiving practolol, 300 mg, twice daily and in 27 patients receiving placebo.

Position	Placebo		Practolol	
	Mean	S.E.M.	Mean	S.E.M.
Supine	77.4	± 2.5	66.6	± 1.1
Standing 0	89.2	± 2.9	71.8	± 1.4
3	89.0	± 2.9	69.7	± 1.2
Supine	76.7	± 2.5	66.0	± 1.1
GTN	88.9	± 2.5	71.1	± 1.2

small reductions after 200 and 800 mg, but there was not a significant difference between the effects of the three doses. All doses of propranolol produced a significant ($P < 0.01$) reduction in the increases in heart rate produced by glyceryl trinitrate. The reductions were dose dependent. There was no significant difference between the effects of propranolol, 20 and 80 mg, and 80 and 320 mg but a significant difference between the effects of 20 and 320 mg ($P < 0.01$). There was no significant difference between the effects of the lowest doses, middle and highest doses of the two drugs.

Effects of practolol on heart rate responses to standing and glyceryl trinitrate in patients

Observations were made on 63 patients of whom 27 were receiving practolol, 300 mg twice daily, and 36 placebo. The mean values for heart rate in the two groups of patients are shown in Table 3 and Figure 3. There was no significant difference in heart rate with the patients in the supine position before standing and before glyceryl trinitrate in the placebo-treated group and in the practolol-treated group. Mean heart rates in the supine position before standing and before glyceryl trinitrate were significantly lower ($P < 0.01$) in the practolol-treated group than in the placebo group. There was no difference in heart rate recorded at 0 and 3 min after standing in each group; the value at 3 min has been taken in all further calculations. Heart rate increased significantly ($P < 0.001$) in both groups on standing but the absolute heart rate on standing and the increase produced by standing were significantly less ($P < 0.001$) in the practolol-treated group. Glyceryl trinitrate significantly ($P < 0.001$) increased heart rate in both groups. The absolute heart rate after glyceryl trinitrate and the increase in rate produced by glyceryl trinitrate were significantly less in the practolol-treated group ($P < 0.001$). There was no significant difference between the heart rate on standing and after glyceryl trinitrate or in the increases in rate produced by these two procedures in the placebo group and in the practolol group. No unwanted effects were produced by standing or by glyceryl trinitrate in the two groups of patients.

Discussion

The present observations confirm those of Fitzgerald (1970) who showed that the administration of glyceryl trinitrate to normal subjects in the erect position produced an increase in heart rate that was reduced by propranolol and by practolol.

Glyceryl trinitrate also increased heart rate in subjects in the supine position but the response was significantly less than that which occurred in the erect position ($P < 0.01$). The response to glyceryl trinitrate can be defined as either the maximum heart rate that is produced by trinitrate or as the maximum increase in rate from the initial resting heart rate. Fitzgerald (1970) in his studies used the latter value but in the present observations the results have been analysed using both values. The heart rate responses to glyceryl trinitrate using both methods of assessment were consistent in the same subject on different days but there were significant differences between responses in different subjects. These differences in response between subjects were not related to variations in resting heart rate.

The tachycardia produced by glyceryl trinitrate in normal people in the erect position was reduced by practolol and propranolol. The dose response curves were different as there was a progressive reduction with increasing doses of propranolol but the effect of practolol was maximal after its first dose. As increasing the dose of propranolol from 80-320 mg only reduced the tachycardia by 1.2 beats/min, which change was not significant, it would appear that maximum reduction in the response was produced by 80 mg propranolol after which the tachycardia was 85.6 beats/minute. The practolol dose response curve flattened at a value of 98 beats/minute. There is a significant difference between these values. A similar phenomenon was observed when the effects of the intravenous administration of practolol and propranolol on an exercise tachycardia were compared (Brick *et al.*, 1968). The reason for this difference in the effects of the two drugs was unexplained.

Comparison of the effects of the two drugs on the increase in heart rate produced by glyceryl trinitrate showed less difference in their effects. Increasing the dose of both drugs produced a progressive reduction in this response. The effect of propranolol was slightly greater but an accurate potency ratio could not be determined as different doses of the two drugs were used. The largest reduction in the response was produced by the first dose of the two drugs and the dose response curves flattened with the larger doses so that even after the largest dose there was still an increase in heart rate of 13-15 beats per minute. This flattening of the dose response curve with these two drugs was also described but not commented on by Fitzgerald (1970) whose largest dose was greater than that in the present study (practolol 1200 mg and propranolol 640 mg). He attributed the residual increase in rate, which in the present experiments was 13-15 beats/min and in his observations about 10 beats/min, to incomplete

blockade of the sympathetic drive to the heart. This seems unlikely as in the present experiments there was no significant difference in the effects of the last two doses of the two drugs and in Fitzgerald's study there was no difference in the effects of the last two doses of propranolol in two of three subjects and in the effects of the last two doses of practolol in three of the four subjects. Observations in normal subjects have shown that 100-200 mg practolol is required on oral administration to produce maximum reduction of an exercise tachycardia (Carruthers, Kelly, McDevitt & Shanks, unpublished observations). As the exercise tachycardia was greater than 150 beats/min, the sympathetic drive to the heart was greater than in the response to glyceryl trinitrate in the present experiments. Thus the largest dose of practolol used in the present experiments and by Fitzgerald (1970) in his experiments should have produced almost complete blockade of the increased sympathetic drive to the heart. The residual increase in heart rate may result from a reduction in parasympathetic activity and although Fitzgerald (1970) showed that atropine did not affect the increase in rate produced by glyceryl trinitrate, this does not exclude the possibility that such a mechanism does exist after the administration of β -receptor blocking drugs. The effects of combined blockade of sympathetic and parasympathetic nervous systems would be required to settle this point. The present observations confirm the suggestion of Fitzgerald (1970) that the increase in heart rate produced by glyceryl trinitrate can be used to demonstrate the activity of β -adrenoceptor blocking drugs in man, but suggest that the increase in rate probably does not result entirely from increased sympathetic activity.

As a number of normal subjects felt light-headed and one fainted after the administration of glyceryl trinitrate in the erect posture, it was decided to study the effects of glyceryl trinitrate in patients after an acute episode of ischaemic heart disease in the supine position. The mean increase in heart rate in 27 patients receiving the placebo was 12.2 ± 1.2 beats/min as compared to 14.1 ± 1.7 beats/min in the normal subjects in the supine position. No side effects were produced by the administration of glyceryl trinitrate in these patients. Glyceryl trinitrate increased heart rate in the 36 patients receiving practolol by 5.1 ± 0.7 beats/min, which is significantly less ($P < 0.001$) than the increase in the placebo treated group. Changing from the supine position in bed to free standing increased heart rate in these two groups of patients. The increases in each group were similar to those which occurred after the administration of glyceryl trinitrate. The increase in heart rate on standing was significantly less in the

practolol treated group than in the placebo group. These studies indicate that the increases in heart rate produced by standing and by glyceryl trinitrate can be used for the demonstration of the activity of β -adrenoceptor blocking drugs in patients but as the response to standing can be repeated at frequent intervals, it may be of more practical value.

A number of problems exist when inhibition of a glyceryl trinitrate tachycardia is used to assess activity of β -adrenergic blocking drugs. One of these concerns whether reduction in the absolute tachycardia or in the increase in rate produced by glyceryl trinitrate should be taken for the assessment of activity. The increase in heart rate is the difference between two values which may not be affected in the same way by all β -adrenoceptor blocking drugs. If all these drugs had the same effect on resting heart rate there would be no difference in their effects on glyceryl trinitrate tachycardia and on the increase in rate. This does not occur as indicated in the diagrammatic representation of the effects of two β -adrenergic blocking drugs in Figure 4. Both drugs reduce the glyceryl trinitrate tachycardia by 30 beats/min, but drug A reduced resting heart rate by 15 beats/min and drug B, which had intrinsic sympathomimetic activity, had no effect on resting heart rate. Thus the drugs were equi-active in reducing the glyceryl trinitrate tachycardia by 20%. Drug B reduced the increase in heart rate produced by glyceryl trinitrate by 50% but drug A only reduced it by 25%, indicating that B was twice as active as A. Clearly only the former method gives accurate comparison of the activity of the two drugs in inhibiting the increase in sympathetic activity which is produced by glyceryl trinitrate. This difference is seen when applied to the observations in this paper in normal subjects. The three doses of propranolol reduced resting heart rate to the same extent. The reductions in the glyceryl trinitrate tachycardia and in the increase in rate produced by trinitrate were directly related. The smallest dose of practolol produced the largest fall in resting heart rate with a progressive increase in rate with the two larger doses. The glyceryl trinitrate tachycardia was reduced to the greatest extent by the first dose of practolol, but the greatest reduction in the increase in heart rate occurred after the largest dose and was 8.0 beats/min greater than the reduction after the smallest dose. This difference resulted from the fact that resting heart rate was higher after the largest dose. The increases in heart rate produced by glyceryl trinitrate after each dose of the two drugs have been recalculated on the basis that resting heart rate was not changed by practolol and propranolol and also on the basis that it was reduced by 10

Fig. 4 Theoretical consideration of the effect of two drugs A and B on the increase in heart rate produced by glyceryl trinitrate. The lower of each pair of symbols is resting heart rate and the upper the maximum response to glyceryl trinitrate: response before drug (●); response after drug (○).

beats/min by all doses of both drugs. These results are given in Table 2. When resting heart rate did not change, the increase in rate was reduced to the same extent by the three doses of practolol. A much greater reduction was produced by the two greater doses of propranolol. When resting heart rate was considered to have fallen by 10 beats/min, a difference in the effects of the two drugs is still present. On the other hand if propranolol reduced resting heart rate by 10 beats/min and practolol did not alter it, there would be little difference between the effects of the two drugs. It would appear that the more accurate method for the assessment of the effects of β -blocking drugs is to compare their effects on the maximum heart rate that is produced rather than on the increase in rate. These considerations, however, throw no further light on the mechanisms of the difference in the effects of the two drugs on the glyceryl trinitrate tachycardia.

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