Clinical Trial

CLINICAL EVALUATION OF ANTI-ANGINAL DRUGS WITH PARTICULAR REFERENCE TO BENZIODARONE, A NEW CORONARY VASODILATOR

GERALD SANDLER,* M.D., M.R.C.P.,

L. N. PATNEY, M.D.,

C. W. LAWSON, M.D., M.R.C.P.

from the Cardiac Department, Leicester Chest Hospital

ALTHOUGH many long-acting coronary vasodilators have been introduced for the prophylactic treatment of angina pectoris few have survived a controlled objective study in which the main criterion of effectiveness is an improvement in the degree of myocardial ischaemia and not solely an alteration in the frequency or severity of anginal attacks.

A new coronary vasodilator, benziodarone (Cardivix), a benzofuran derivative, has been found experimentally to produce a marked increase in coronary blood flow in healthy dogs (Charlier, 1959), and has also been claimed to produce considerable improvement clinically in anginal patients (Gillott, 1959). Gillott's study was based on an uncontrolled and subjective evaluation of the action of benziodarone. Assessment of any anti-anginal drug, however, must take into consideration the suggestibility of anginal patients, the limitations of subjective data provided by the patients themselves, and the lack of any direct relationship between the development and severity of anginal pain and the degree of coronary insufficiency (Russek, Zohman and Dorset, 1955).

It is with these considerations in mind that it was decided to carry out a controlled double-blind and objective evaluation of the use of benziodarone in the treatment of angina pectoris.

Patients and Methods

Twelve patients, aged from 41 to 67 years, with typical angina pectoris on exertion were studied. All the patients were males but this was not due to sex selection as suitable patients were included in the trial as they became available. The duration of angina ranged from 6 months to 4 years. The presumptive cause of the angina was coronary artery disease and 2 patients had electrocardiographic evidence of previous myocardial infarction. All the patients were taking glyceryl trinitrate freely for their anginal attacks.

A double-blind technique was employed. An initial control period of one month was allowed when the only coronary vasodilator permitted was glyceryl trinitrate sublingually. Over the next two months individual monthly supplies of tablets of identical appearance containing either benziodarone or an inert placebo were provided in random order, neither the patient nor the observer being aware of which drug was given. The

dosage of benziodarone was 200 mg. (2 tablets) three times daily. Each patient was also supplied with a specific number of glyceryl trinitrate tablets which were counted by the observer at each monthly visit, this ensuring a more objective estimate of the frequency of anginal attacks than would be obtained from the patient himself. The fourth and final month of the study was again a control period when glyceryl trinitrate alone was used.

Exercise tolerance tests were carried out at the beginning of the study and at monthly intervals until its conclusion. The type of test used has been described in detail in an earlier publication (Sandler, 1963) and briefly consists of exercise at the patient's own normal rate over 2 steps each 9 inches (23 cm.) high until he is stopped by anginal pain thus keeping within the limits of his own capacity. The total amount of exercise, recorded as number of circuits, and the total time taken are noted. A tablet of glyceryl trinitrate sublingually is given at the onset of angina and the duration of the pain accurately timed with a stop-watch. Electrocardiograms are recorded fully before starting the exercise and then chest lead V₅ is recorded immediately afterwards and at 30 second intervals until the electrocardiographic signs of ischaemia have disappeared (see Fig. 1). The position of V₅ is marked on the patient's chest before exercise so that it can be accurately replaced after exercise. Depression of the ST segment below the iso-electric line, either plane or sagging, of at least 0.08 second's duration is regarded as indicative of myocardial ischaemia (Lloyd-Thomas, 1961; Master and Rosenfeld, 1961); the degree and duration of depression are recorded for each patient. All 12 patients in the study developed ischaemic changes after exercise. The nature and purpose of the tests were explained to all patients.

The weight and resting blood pressure were also recorded monthly in all patients and any side-effects with the drugs noted.

Results

Since the patients were acting as their own controls, in addition to comparison of mean values in the various periods of study, the differences in each individual patient resulting from benziodarone or placebo were analysed statistically. In this way, variation between different subjects was eliminated and the changes produced by the drugs became more apparent.

Table 1 shows the weekly number of trinitrate tablets used during the control period (average of the 2 control periods at the beginning and

* Present address: The Royal Infirmary, Sheffield 6.

FIG. 1.—Typical ischaemic ST depression after exercise tolerance test (time in seconds).

end of the study) and while the patients were having benziodarone and placebo. Eight patients showed a reduction in trinitrin consumption with benziodarone but 6 of these showed a similar fall with the placebo also. Although the mean weekly consumption of glyceryl trinitrate when using benziodarone was not significantly different from that in the control period, the mean fall in trinitrate consumption was a significant one ($P < 0.05$). However, a similar significant reduction in trinitrate requirements was evident with the placebo also ($P < 0.05$) and comparison of the mean weekly consumption of trinitrate with benziodarone and the placebo showed no significant difference.

The results of the exercise tolerance tests are shown in Table 2. When using benziodarone neither the mean amount of exercise carried out before angina occurred, nor its rate of performance differed significantly from the control values. In addition there was no significant change in these parameters following use of the drug.

The degree of depression of the ST segment after exercise and the time required for it to return to the iso-electric line is shown in Table 3. There was no significant reduction in either the mean amount of ST depression or its duration after a course of benziodarone. Similarly the change in degree and duration of ST depression with benziodarone was not a significant one.

Finally, the duration of angina induced by the

exercise tolerance tests is recorded in Table 4 and once more benziodarone failed to influence significantly either the mean duration of angina or the mean change in its duration.

There was no alteration in either blood pressure or weight in the 12 patients during the course of the investigation.

The only untoward side-effect experienced with benziodarone was gastro-intestinal discomfort which occurred in two patients soon after taking each dose.

Discussion

It has been suggested that the only way to determine the clinical usefulness of an anti-anginal drug is to test its ability to relieve angina (Katz, 1956). However, there are a number of difficulties inherent in this approach. First is the suggestibility of anginal patients and the frequency of response to any new preparation irrespective of its active or inert properties (Greiner and co-workers, 1950). To some extent this can be overcome by using a placebo but here also relief of angina occurs in as many as 40% of patients (Evans and Hoyle, 1933). More important is the unreliability of observations made by anginal patients with regard to their response to treatment, and there are few experimental procedures in which it would be permissible to put so vital a part of an experiment as the collection, storage and interpretation of observations into the hands

TABLE 1
WEEKLY CONSUMPTION OF GLYCERYL TRINITRATE DURING CONTROL PERIOD AND DURING ADMINISTRATION OF BENZIODARONE AND PLACEBO

Case no.	Age in years	No. of glyceryl trinitrate tablets per week			Change in glyceryl trinitrate consumption per week	
		Control period (average of two)	Benziodarone	Placebo	Benziodarone	Placebo
1	56	23	28	4	+ 5	-19
2	57	28	20	42	- 8	+14
3	67	5	7	5	+ 2	0
4	50	29	24	33	- 5	+ 4
5	57	35	24	23	-11	-12
6	60	17	2	5	-15	-12
7	63	30	17	17	-13	-13
8	43	25	20	11	- 5	-14
9	56	16	18	11	+ 2	- 5
10	55	22	20	27	- 2	+ 5
11	41	49	44	23	- 5	-26
12	58	7	6	4	- 1	- 3
Mean		23.9	19.2	17.1	-4.7	-6.7
Standard error		3.5	3.2	3.6	1.8	3.3

TABLE 2
RESULTS OF EXERCISE TOLERANCE TESTS

Case no.	Amount of exercise					Rate of exercise				
	Total no. of circuits			Change in no. of circuits		Mean time per circuit (seconds)			Change in time per circuit (seconds)	
	Control period	Benzio-darone	Placebo	Benzio-darone	Placebo	Control period	Benzio-darone	Placebo	Benzio-darone	Placebo
1	43	51	42	+ 8	- 1	6.1	6.2	6.4	+0.1	+0.3
2	32	20	42	-12	+10	8.0	8.3	8.3	+0.3	-0.3
3	23	23	17	0	- 6	8.9	8.6	8.9	-0.3	0
4	45	54	57	+ 9	+12	6.2	6.3	6.0	+0.1	-0.2
5	30	25	26	- 5	- 4	6.0	6.4	5.6	+0.4	-0.4
6	28	36	28	+ 8	0	6.6	6.1	6.0	-0.5	-0.6
7	16	17	27	+ 1	+11	9.0	9.1	8.5	+0.1	-0.5
8	46	37	39	- 9	- 7	5.7	5.9	—	+0.2	—
9	26	24	19	- 2	- 7	6.6	6.5	6.5	-0.1	-0.1
10	27	31	41	+ 4	+14	6.8	6.5	6.4	-0.3	-0.4
11	43	20	35	-23	- 8	6.1	6.0	6.1	-0.1	0
12	58	100	47	+42	-11	8.3	7.3	8.1	-1.0	-0.2
Mean	34.7	36.5	35.0	+1.7	+0.25	7.0	6.9	7.0	-0.09	-0.16
Standard error	3.5	6.9	3.0	1.4	2.7	0.4	0.7	0.3	0.40	0.12

of an interested, biased and untrained assistant. In addition there are a number of drugs which may relieve anginal pain such as analgesics, placebos and coronary vaso-dilators. While the patient's concern is with the relief of the pain, it is the physician's responsibility to control this by a drug which eliminates the pain-producing myocardial anoxia and not by measures which interfere with either the anatomical pathways of pain sensation or its central perception. A drug which improves angina without producing a corresponding improvement in myocardial blood

supply may result in increased myocardial ischaemia by allowing excessive exertion (Sandler, 1961). Finally the lack of any direct relationship between the development and severity of anginal pain and the degree of coronary insufficiency (Russek, Zohman and Dorset, 1955) makes relief of anginal pain a poor criterion of the effect of a drug in improving myocardial ischaemia. The necessity therefore of a controlled double-blind and objective evaluation of an anti-anginal drug becomes apparent and assessment should be made by a method such as exercise tolerance with elec-

TABLE 3

ST CHANGES DURING THE CONTROL PERIOD AND DURING ADMINISTRATION OF BENZIODARONE AND PLACEBO

Case no.	Degree of ischaemia					Duration of ischaemia				
	ST depression (mm.)			Change in ST depression (mm.)		Duration ST depression (seconds)			Change in duration ST depression (seconds)	
	Control period	Benziodarone	Placebo	Benziodarone	Placebo	Control period	Benziodarone	Placebo	Benziodarone	Placebo
1	3.5	3.0	3.0	-0.5	-0.5	540	450	1020	-90	+480
2	1.0	2.0	1.0	+1.0	0	180	300	600	+120	+420
3	1.0	0.5	1.0	-0.5	0	270	240	240	-30	-30
4	0.75	0.5	0.5	-0.25	-0.25	470	600	600	+130	+130
5	1.5	1.5	1.0	0	-0.5	600	480	360	-120	-240
6	1.5	1.0	1.5	-0.5	0	450	540	570	+90	+120
7	1.25	1.0	0	-0.25	-1.25	420	120	0	-300	-420
8	1.25	3.5	2.5	+2.25	+1.25	570	600	600	+30	+30
9	4.0	3.5	2.5	-0.5	-1.5	780	750	870	-30	+90
10	0.5	0.5	0	0	-0.5	180	420	0	+240	-180
11	3.0	2.0	2.5	-1.0	-0.5	555	600	750	+45	+195
12	0.75	1.5	1.5	+0.75	+0.75	240	600	720	+360	+680
Mean	1.67	1.62	1.42	+0.04	-0.025	437.9	475.0	527.5	+37.1	+106.1
Standard error	0.33	0.36	0.29	0.22	0.22	54.3	52.3	92.9	50.0	90.0

TABLE 4

DURATION OF ANGINA AFTER EXERCISE—TOLERANCE TESTS

Case no.	Duration of angina (seconds)			Change in duration of angina (seconds)	
	Control period	Benziodarone	Placebo	Benziodarone	Placebo
1	184	120	197	- 64	+ 13
2	139	193	117	+ 54	- 22
3	144	197	151	+ 53	+ 7
4	96	80	62	- 16	- 34
5	389	270	352	-119	- 37
6	83	76	99	- 7	+ 16
7	276	185	168	-91	-108
8	99	93	118	- 6	+ 19
9	120	180	201	+ 60	+ 81
10	183	200	108	+ 17	- 75
11	187	369	224	+182	+ 37
12	61	68	68	+ 7	+ 7
Mean	163.4	169.2	155.4	+ 5.8	- 8.0
Standard error	26.7	25.9	23.4	23.0	14.7

trocadiographic control, which relies as little as possible on the patient's interpretation of his response to treatment.

Gillott (1959) reported considerable improvement with benziodarone in 77% of 180 anginal patients but since assessment was mainly subjective and entirely uncontrolled the value of these observations is dubious. Similar criticism applies to studies carried out by Verduyssen and Geysens (1962) and Dailheu-Geoffroy and Nataf (1961). The present study showed that benziodarone was no better than a placebo in reducing the frequency of anginal attacks and in addition no

objective improvement either in exercise tolerance or myocardial ischaemia resulted from its use.

Summary

A controlled double-blind and objective evaluation of benziodarone (Cardivix), a new coronary vasodilator, in the prophylactic treatment of angina pectoris has been carried out in 12 patients.

The drug failed significantly to influence either the frequency of anginal attacks or exercise tolerance and the resulting electro-cardiographic changes of myocardial ischaemia.

The importance of a controlled double-blind study and objective criteria of improvement in the assessment of an anti-anginal drug is emphasized.

We are indebted to Mr. M. K. Cameron for technical assistance with the exercise tolerance tests, and to Dr. G. F. Davey of Genatosan Ltd., who kindly supplied the tablets of benziodarone and placebo.

REFERENCES

- CHARLIER, R. (1959): Un nouveau dilateur coronarien de synthese. Etude pharmacologique, *Acta Cardiol. (Brux.)*, Supp. 7.
- DAILHEU-GEOFFROY, P., and NATAF, J. (1961): Premiers essais cliniques avec un nouveau vasodilatateur coronarien, La Benziodarone, *Presse med.*, **69**, 971.
- EVANS, W., and HOYLE, C. (1933): The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, *Quart. J. Med.*, **2**, 311.
- GILLOTT, P. (1959): Valeur therapeutique du L.2329 dans l' angine de poitrine, *Acta Cardiol. (Brux.)*, **14**, 494.
- GREINER, T., GOLD, H., CATTELL, M., GRAVELL, J., BAKST, H., RINZLER, S. H., BENJAMIN, Z. H., WARSHAW, L. J., BOBB, A. L., KWIT, N. T., MODEL, W., ROTHENDLER, H. H., MESSELOFF, C. R., and KRAMER, M. L. (1950): A Method for the Evaluation of the Effects of Drugs on Cardiac Pain in Patients with Angina of Effort. A Study of Khellin (Visammin), *Amer. J. Med.*, **9**, 143.
- KATZ, L. N. (1956): The Design of Proper Experiments to Investigate Clinical Angina Pectoris and the Importance of Knowing the Determinants of Coronary Flow in Considering Therapy of Angina Pectoris, *Ann. N.Y. Acad. Sci.*, **64**, 507.
- LLOYD-THOMAS, H. G. (1961): The Exercise Electrocardiogram in Patients with Cardiac Pain, *Brit. Heart J.*, **23**, 561.
- MASTER, A. M., and ROSENFELD, I. (1961): Criteria for the Clinical Application of the Two-step Exercise Test. Obviation of False Negative and False Positive Responses, *J. Amer. med. Ass.*, **178**, 283.
- RUSSEK, H. I., ZOHMAN, B. L., and DORSET, V. J. (1955): Objective Evaluation of Coronary Vasodilator Drugs, *Amer. J. med. Sci.*, **229**, 46.
- SANDLER, G. (1961): Clinical Evaluation of Pheniprazine in Angina Pectoris, *Brit. med. J.*, **i**, 792.
- (1963): Glyceryl Trinitrate in Angina Pectoris, *Lancet*, **i**, 1130.
- VERCRUYSEN, J., and GEYSSENS, W. (1962): Experimentation clinique d'un vasodilatateur coronarien recent, *Revue Med. Louvain*, **1**, 11.