BASIC AND CLINICAL STUDIES ON BAY A 1040* WITH SPECIAL REFERENCE TO ITS INFLUENCE ON THE CORONARY, SYSTEMIC RESISTANCE AND CAPACITANCE BLOOD VESSELS

SHOJI HAYASE, SENRI HIRAKAWA, SADAMASA HOSOKAWA,
NORIYASU MORI, HIROYASU ITO, YASUSHI KONDO,
KUNHIKO HIEI, AND SHOHACHI BANNO

A NEW anti-anginal agent, Bay a 1040 has been recently introduced to clinical medicine. As many others, the present authors have also found Bay a 1040 as given orally in a daily dose of 60 mg to be highly effective in preventing the occurrence of anginal attacks in patients with angina at rest who had stenotic sites demonstrable on selective coronary angiography and who were resistant to most other anti-anginal drugs other than nitroglycerine. No study was made, however, to see if this agent gives an immediate symptomatic relief to anginal attacks. This agent seems to represent a new addition to the list of the useful anti-anginal drugs.

The mechanism by which anti-anginal agents give relief to anginal pain is not clearly defined. More than a few factors may be involved; e.g., (a) decrease in left ventricular external work, internal work and wall tension through decreased systemic arterial blood pressure, (b) decrease in the left ventricular internal work and decreased rate of the development of the myocardial tension through decreased size of the left ventricle, (c) dilatation of the main coronary artery and collateral channels around the sites of the obstruction without affecting the resistance vessels which normally control flow.

In the beating heart of hypervolemic dogs,

Key Words: Anti-anginal Drug
Bay a 1040
Coronary Circulation
Hemodynamics
Mean Circulatory Pressure

Rolett et al. (1965) found an indirect evidence that the myocardial oxygen consumption was directly related to the ventricular size, independently of the intraventricular pressure. In variably after-loaded, isotonicly contracting papillary muscle of cat in which the process of energy production has been blocked, energy utilization ($\sim P$) correlated linearly with both internal work (contractile element work) and external work; in terms of energy utilization, internal work was more than twice as costly as external work (*Pool et al.*, 1968). Thus the time-course of the active tension development is an important determinant of energy utilization ($\sim P$) at least in such a preparation.

This is a preliminary report describing (a) the effect of Bay a 1040 on the resistance to flow of an coronary artery under perfusion with a constant pressure head in closed-chest dogs, with the intracoronary or systemic administration of the agent, (b) the influence of Bay a 1040 on the systemic resistance and capacitance vessels of open-chest dogs, the latter being inferred from changes in the mean circulatory pressure (MCP), (c) the short-term (20 minutes) effect of the orally administered Bay a 1040 on the hemodynamics of the patients with or without ischemic heart disease, and (d) clinical efficacy of Bay a 1040 (60 mg given orally) in preventing the occurrence of anginal attacks in the patients with angina at rest, a series of therapeutic trials, using active and placebo tablets administered for a period of one week each, in cross-over fashion.

(Received for publication, May 26, 1971)

The 2nd Department of Medicine, Gifu University School of Medicine, Gifu

* An antianginal drug produced by Farbenfabriken Bayer AG., with chemical structure:
4-(2'-Nitrophenyl)-2,6-Dimethyl-1,4-Dihydropyridin-3,5-Dicarbonsäuremethylester

Fig.1. Experimental arrangements for the perfusion of a large branch of the left coronary artery with constant pressure head in closed-chest dogs.

- A: Cournand's catheter (No.8)
- B: Inlet for injection
- C: Ringer's solution
- D: Transducers
- E: Blood reservoirs
- F: Thermostat
- G: Cannula in the femoral artery for measurement of the arterial blood pressure
- H: Polyethylene tube in the femoral vein for controlled bleeding.

METHODS

The influence on the coronary resistance to flow in closed-chest dogs

Three mongrel dogs, weighing between 7.6 and 11.6 kg (9.4 kg on the average), were used for experiments with the intracoronary injection of Bay a 1040 and another dog was used for an experiment where it was injected systemically. These experiments aimed at disclosing the influence of the intracoronary and systemic Bay a 1040 on the mean coronary resistance to blood flow, i.e., perfusion pressure divided by mean rate of volume flow. The dogs were anesthetized with 25–30 mg/kg of intravenous pentobarbital and maintained on natural respiration.

The catheterization of a large branch of the coronary artery was performed under fluoroscopic control by Hayase's method (Hayase 1957, Ito 1969). Fig.1 shows the experimental arrangements diagrammatically. A Cournand catheter was advanced, under fluoroscopic guiding, in the left coronary artery and wedged in either anterior descending artery or left circumflex artery. The area of the heart distal to the occluding tip of the catheter was perfused with oxygenated blood that was supplied, through the catheter from a

reservoir of blood, under a constant pressure head, approximating the mean blood pressure. The coronary blood flow was recorded with an electro-magnetic flowmeter (MF-2, Nihon Kohden Kogyo Co., Ltd., abbreviated hereafter as NKK) as the mean rate of volume flow. Arterial blood pressure was recorded from a femoral artery with an electromanometer (MP-24 T, NKK). Electrocardiogram was also recorded. These parameters were recorded by a multi-purpose polygraph (RM-150, NKK). With the same experimental arrangement it was shown by Ito (1969) of this laboratory that, in non-reserpinized and reserpinized dogs, d-, dl-, and l-isomers of propranolol produced an early and transient increase in the coronary flow (i.e., coronary dilatation) in dose-dependent fashion as the result of their pharmacological, not beta-receptor-blocking, action; after the completion of each experiment the perfused coronary vascular bed was proved to be capable of constriction with 0.5–1 U of vasopressin (Parke Davis, water soluble).

For the intracoronary injection of Bay a 1040, a liquid preparation supplied through the courtesy of Bayer Pharmaceutical Co. Ltd., containing 0.2 mg in 2 ml ampoule was diluted with physiological saline solution up to the doses of 0.1, 1.0 and 10.0 ug, all in a volume of 0.1 ml. The 3 doses of Bay a 1040 were injected, one after another, at intervals of 5 minutes, into the perfusion system at the proximal end of the coronary catheter (point B in Fig.1) instantaneously. It has been ascertained that an agent, injected in this manner, reached the coronary vascular bed in 15–20 seconds.

For the systemic injection, 5 µg/kg was injected intravenously in a dog with the same experimental arrangements as shown in Fig.1, so that the circulating Bay a 1040 acted on the whole body except the part of the heart where the coronary resistance to flow was being studied.

The influence on the systemic resistance and capacitance vessels in open-chest dogs

The influence of the intravenous Bay a 1040 on the systemic resistance vessels was estimated from the changes in the total peripheral resistance (TPR), calculated as $(MBP - RAP) / CO$ where MBP is the mean blood pressure, RAP is the right atrial pressure and CO is cardiac output. The influence on the capacitance vessels was estimated from the change in the mean circulatory pressure (MCP), a concept and a quantity thoroughly

Fig.2. Experimental arrangements for the measurements of circulatory parameters, including the mean circulatory pressure (MCP), in open-chest dogs.

EMFM: Electro-magnetic flowmeter recording the aortic blood flow

R.A.: Right atrium, pressure of which is recorded with a saline-filled cardiac catheter.

A: Femoral artery, the site of the entry of an arterial catheter advanced until the tip reached the descending thoracic aorta.

V: Femoral vein.

studied by Guyton (1955, 1959, 1963a, 1963b). The MCP is a measure of the ratio of the blood volume to the capacity of the circulatory system and it represents the degree of filling of the circulatory system with blood (Guyton *et al.*, 1956). Since these experiments were performed without addition or loss of the blood, changes in the MCP represent the changes in the capacitance ($\Delta V/\Delta P$) of the circulatory system. The method used to measure MCP in open-chest dogs was the same as reported earlier from this laboratory (Hirakawa 1969), a method essentially the same as that described by Smith *et al.* (1967) except that experiments were performed on open-chest dogs.

A total of 5 dogs were used. One dog was examined for the hemodynamic responses other than that of MCP and 4 other dogs were studied for hemodynamic responses, including the MCP. Mongoreal dogs weighing between 11 and 15 kg were used. The dogs were anesthetized with

25–30 mg/kg sodium pentobarbital and heparinized with 300–400 U/kg of sodium heparin. The chest was opened at the 4th intercostal space. The experimental arrangements are shown in Fig.2. An electromagnetic flowprobe, model MF-5 (NKK) was placed around the root of the aorta to measure the cardiac output (excluding the coronary flow). The artificial respiration was continued throughout the course of the experiment. The blood pressure was recorded from the left carotid artery via a T-tube with an electromanometer, and also from the right atrium through a saline-filled cardiac catheter. A system of the arterio-venous shunt was installed between the descending aorta and bilateral femoral veins, and a cum-pump was placed mid-way in the shunting circuit, so that, when the shunt system was opened and cum-pump was activated, blood could be translocated at a rate of 40 ml/sec from the arterial into venous circuit. The zero-reference point for pressure measurement was set

TABLE I A LIST OF PATIENTS WHO WERE EXAMINED FOR THE HEMODYNAMIC RESPONSES TO A SINGLE ORAL DOSE OF 20 MG.

Case of No.	Name	Sex	Age	Diagnosis
1	A.N.	M	59	Angina at rest
2	D.M.	M	45	Old myocardial infarction
3	K.W.	M	59	Angina at rest Essential hypertension
4.	H.S.	M	53	Angina of effort Essential hypertension
5	Y.M.	M	50	Angina of effort Diabetes mellitus
6	M.T.	M	70	Angina at rest
7	T.K.	M	18	Pituitary dwarfism
8	M.S.	F	35	Chronic nephritis
9	S.S.	M	23	Diabetes mellitus

visually at the level of the right atrium.

It was with all these arrangements but without going further for measuring MCP that one dog was studied for the hemodynamic responses to the intravenous injection of 5 μ g/kg delivered over 1 minute. In other 4 dogs the MCP was measured as follows: the heart was fibrillated with a shock of 15 volts AC applied to the pericardium-covered portion of the heart; immediately after inducing ventricular fibrillation, the shunt tubes were opened and pump was activated, and the blood was translocated rapidly from the arterial into venous circuit; systemic arterial blood pressure fell and the right atrial pressure rose; the point at which the two pressures equal was termed the mean circulatory pressure (MCP). Once the pressure reached equilibrium, the heart was defibrillated with a shock of 30 watt sec DC. The time required from the start of the ventricular fibrillation to the equilibration of the two pressure was 3.0 ± 0.6 (SD) seconds. The parameters of the cardiovascular function that were measured were: (1) heart rate (HR), (2) arterial blood pressure, and the electrical mean arterial

blood pressure (MBP), (3) right atrial pressure (RAP), (4) cardiac output (CO), (5) peak velocity of the left ventricular ejection (PVLVE), measurable from the aortic flow curves within the inertia-limited errors intrinsic to the pen-writing recording system, (6) total peripheral resistance (TPR), calculated as $(MBP - RAP)/CO$, (7) approximate left ventricular external work (LVEW) calculated as $MBP \times CO$, and (8) the mean circulatory pressure (MCP). From 33 pairs of the two successive measurements of MCP 10 minutes apart during the control period, the MCP was found reproducible with errors of 0.15 ± 0.45 (SD) mmHg, recently in this laboratory (Ito et al. 1971).

Bed-side hemodynamic studies

A total of 9 patients, consisting of 6 patients with ischemic heart disease and anginal attacks and 3 non-cardiac patients were examined at bed-side for the acute hemodynamic effect of Bay a 1040 given in a single oral dose of 20 mg. A list of the patients studied is given in Table I. The number of the patients was small and age-distribution was far from nearly equal. The average age of the patients with ischemic heart disease was higher, 56 ± 8.8 (SD) years, than that of non-cardiac patients, 25 ± 5.5 (SD) years. The two groups also differed in that the total peripheral resistance was lower, 10.4 ± 2.2 (SD) mmHg·min·L⁻¹, in non-cardiac patients than in the patients with ischemic heart disease, 17.0 ± 5.1 (SD) mmHg·min·L⁻¹.

Before and at the end of 20 minutes after the oral administration of the compound, they were studied for blood pressure recorded sphygmomanometrically at the upper arm and the cardiac output in supine position. Cardiac output was measured with a radiocardiograph (Metro Electronics, Japan), an apparatus for recording the dilution curve of the injected radioactive indicator, ¹³¹I-labelled radio-iodinated human serum albumin (RISA), with a scintillation counter collimated against the "heart" on the left parasternal line at the level of the 4th intercostal space. Principles and technics of this method were described by MacIntyre et al. (1958) and Pritchard et al. (1958). The method used in this study was essentially the same as that described by Kinoshita (1968) with a minor change in that the blood volume was measured by Volumetron (Ames). For the measurement of cardiac output RISA was injected as a bolus of 1 ml into the right or left antecubital vein in dose

of 30–40 microcuries followed immediately by a 10 ml saline flush. It was ascertained in a separate series of study in this laboratory that the cardiac output measured simultaneously by this method and by dye-dilution technic using indocyanine green agreed within errors of $\pm 15\%$ (SD), and that the measurement of cardiac output by this method was reproducible with errors of $\pm 6\%$ (SD).

From systolic (S) and diastolic (D) blood pressure, mean (M) blood pressure was calculated, in approximation, as $M = D + (S - D)/3$. Approximate systolic mean pressure (Psm), i.e., the mean pressure during the systolic interval, was calculated as $Psm = (S + M)/2$. Validity of this approximation is supported, in parts, by the following observation in dogs: systolic mean pressure that was obtained planimetrically from the carotid arterial pressure pulse curves (Psm.pl.) was virtually equal to the approximate systolic mean pressure calculated as $Psm = (S + M)/2$, where S is the systolic and M is the electrical mean blood pressure recordable with an electro-manometer. Thus a relation, $Psm.pl. - Psm = 0.6 \pm 4.1$ (SD) mmHg was found in 16 pairs of spot measurements. The difference, 0.6 ± 4.1 mmHg, was small and not significant statistically. A product of Psm., Q-T interval of electrocardiogram and heart rate was termed the pressure-time-product (PTP) in this paper; thus $PTP = Psm \times (Q-T) \times HR$. It was thought, but not proved, that directional changes in the pressure-time-product would parallel the directional changes in tension-time-index (TTI) of *Sarnoff et al.* (1958) and pressure-time per minute (PTM) where $PTM = (\text{left ventricular pressure during systole}) \times (\text{systolic ejection period}) \times (\text{heart rate})$, a parameter that was found to be a fair index of the myocardial oxygen consumption in the beating heart (*Rolett et al.* 1965). Approximate left ventricular external work index (LVEWI) was calculated as $LVEWI = CI \times MBP$ where CI is cardiac index. Total peripheral resistance (TPR) was calculated as $TPR = MBP/CO$.

Clinical trial

Bay a 1040 was put to a clinical trial in a total of 5 patients with angina pectoris admitted to the 2nd Department of Medicine, Gifu University Hospital. Four patients had angina at rest (more correctly, angina of effort plus angina at rest) and 1 patient had angina of effort. Sites of stenosis could be demonstrated in most cases on selective coronary arteriography. A summary of

the clinical status of these cases is given in Table III, together with the result of the clinical trial, which will be described later.

The design of the trial was as follows: the patients were placed, during the first period, about one week, on placebo tablets in oral "dose" of 6 tablets given in 3 divided portions after meals. During the next period, one week or two, they received active tablets in dose of 60 mg in the same way as above, followed by another period of placebo trial, and the last period of active treatment. The design of the cross-over trial was, in most cases, P-A-P-A where P is the

Fig. 3. Time-course changes in the coronary blood flow (C.F.) and arterial pressures, systolic (S) and diastolic (D), after the intra-coronary injection of physiological saline solution (top panel) and graded doses of M Bay a 1040 (lower 3 panels). Changes are given in percent of the control value (C). Maximum changes in coronary flow occurred early, at about the end of 30 seconds, and this is shown as M. Each point and bar indicates the mean and standard error of the mean. Experiments in 3 dogs.

Fig.4. Time-course changes in coronary flow (C.F.) and systolic (S.B.P.) and diastolic (D.B.P.) blood pressures after the intravenous injection of Bay a 1040 in dose of 5 µg/kg. (See text for explanation).

placebo and A is the active treatment with Bay a 1040. This clinical trial thus used a single-blind and cross-over design, because the yet prevailing uncertainty as to the dosage and mode of the administration, e.g., uncertainty as to if the drug is fast-acting or slow-acting, made it difficult for us to employ a rigid program of a clinical trial. Patients were allowed to take tablets of isosorbide dinitrate (Nitrol) as they like whenever an anginal attack occurred. The reported number of attacks per day gave a semi-quantitative index of the frequency of anginal attacks.

RESULTS

Mean coronary resistance to flow and the intracoronary injection of Bay a 1040

Fig.3 shows the effect of 3 graded doses of Bay a 1040 injected intracoronarily as a bolus of 0.1 ml, upon the mean coronary blood flow for constant pressure head, as an average of 3 experiments (3 dogs). With 0.1 µg injected intracoronarily, there was a transient increase in the coronary flow that was not different, in magnitude and duration, from the case of physiological saline. With 1.0 µg injected intracoronarily, there was a transient increase in that the duration of the augmented flow was slightly longer than in control. With 10.0 µg, the period of the augmented blood flow was still longer (3 minutes), but, again, the magnitude of the increase was not impressive. It must be noted that, with 10.0 µg

Fig.5. Time-course changes in circulatory parameters other than MCP that occurred in an open-chest dog after the intravenous injection of Bay a 1040 in dose of 5 µg/kg.

HR: Heart rate MBP: Mean blood pressure
RAP: Right atrial pressure CO: Cardiac output
PVLVE: Peak velocity of left ventricular ejection
TPR: Total peripheral resistance LVEW: Left ventricular external work.

of Bay a 1040, both systolic and diastolic blood pressure fell appreciably at the point of time when the coronary flow reached peak. To explain the early phase of the last-mentioned depressor reaction, one may invoke (1) depressor effect of a portion of the injected agent that has traversed coronary bed and appeared in the systemic or pulmonary circuit, (2) direct depressant action on the contractile force of the heart and/or (3) activation of coronary chemoreflex(es) of Bezold-Jarisch type. The late phase of the augmented coronary blood flow, with 10.0 µg, is most probably due to the systemic effect of Bay a 1040 that has "spilled" from the heart into the general circulatory system.

Mean coronary resistance to flow and the systemic injection of Bay a 1040

This point was studied only in one dog. As

Fig.6. Circulatory parameters, including MCP, before (C) and at the end of 3 and 30 minutes after the intravenous injection of Bay a 1040 in dose of 5 μ g/kg. Each point represents mean and standard error of the mean. Experiments in 4 open-chest dogs.

MCP: Mean circulatory pressure MBP: Mean blood pressure TPR: Total peripheral resistance CO: Cardiac output RAP: Right atrial pressure HR: Heart rate LVEW: Left ventricular external work PVLVE: Peak velocity of left ventricular ejection.

shown in Fig.4, 5 μ g/kg of Bay a 1040 injected intravenously produced a fall in both systolic and diastolic blood pressure down to a low plateau level in one minute. In spite of the fact that, in all probabilities, the area of the heart that was being perfused with blood via a coronary-artery-catheter has been "sequestered" from the action of the circulating Bay a 1040, the coronary flow increased and remained elevated during the first 7 minutes. From this fact it follows that, probably, circulating Bay a 1040 produces a "passive" coronary dilatation. Alternative interpretations will be discussed later.

Influence on the systemic resistance and capacitance vessels in open-chest dogs

Fig.5 illustrates the time-course change in the circulatory parameters other than MCP that occurred in an open-chest dog. With 5 μ g/kg delivered over 1 minute intravenously, there was a transient change in heart rate, mean blood pressure, cardiac output and total peripheral resistance. Decrease in left ventricular external work

(LVEW) was very transient. Peak velocity of left ventricular ejection (PVLVE) increased also transiently. These changes are indicative of a transient dilatation of systemic resistance vessels and a somewhat longer but slight "bradycardia".

Fig.6 summarizes the results of similar studies including the measurement of MCP in another series of 4 dogs. Since MCP was measured at three points of time, i.e., control period (twice) and at the end of 3 and 30 minutes after the intravenous injection in dose of 5 μ g/kg delivered over 1 minute, all other circulatory parameters are given also for these 3 points of time. In view of Fig.5, 3 minutes after the injection corresponds to the peak of the circulatory reactions to the intravenous Bay a 1040.

After the circulatory parameters except MCP were measured first, the heart was fibrillated and the MCP was measured and the heart was immediately defibrillated. This sequence was repeated at the 3 points of time.

Inspection of Fig.6 shows that, soon after the intravenous injection, at least at the end of 3

TABLE II CHANGES IN HEMODYNAMIC PARAMETERS WITH A SINGLE ORAL DOSE OF 20 MG.

	Ischemic Heart Disease			Non-cardiac Disease		
	Control (C)	1040 (D)	D/C × 100	Control (C)	1040 (D)	D/C × 100
Number of Cases	6			3		
Age	56 ± 8.8			25 ± 5.5		
Blood Pressure	127.7	108.5 ^{†††}	84.0 ^{††}	116.7	110.7	95.4
Systolic (S) (mmHg)	27.9	30.9	9.5	23.1	18.0	4.1
Diastolic (D)	79.5	64.8	80.9	79.5	64.8	80.9
	14.7	21.5	19.3	14.7	21.5	19.3
Mean (M) [*]	95.6	79.4 ^{†††}	81.5 ^{††}	78.8	72.8	92.4
	16.1	23.3	12.8	17.2	16.7	5.4
Approx. Syst. ^{**}	111.6	94.0 ^{†††}	83.0 ^{†††}	95.2	87.9	92.1
Mean (Psm)	21.1	26.6	9.8	10.3	16.6	9.8
Heart Rate	62.0	64.3	104.3	60.3	63.7 [†]	105.5 [†]
(beats/min)	7.5	6.0	11.0	13.1	13.9	1.6
Cardiac Index	3.7	3.8	103.7	5.2	5.6	109.9
(L.min ⁻¹ .M ⁻²)	0.8	0.8	12.8	0.7	2.0	38.3
TPR	17.0	13.9	79.3	10.4	9.0	89.6
(mmHg.min.L ⁻¹)	5.1	6.4	22.0	2.2	1.7	24.8
LV External Work	358.1	302.4 ^{†††}	83.5 ^{†††}	409.8	431.5	101.5
Index (mmHg.L.min ⁻¹ .M ⁻²)	96.6	100.2	7.2	113.1	256.1	36.4
Pressure-Time ^{***}	2876	2375 ^{†††}	82.4 ^{†††}	2163	2190	100.4
Product (mmHg.sec/beat)	551	517	5.8	393	562	7.4

The values are expressed as the means ± SD

*: $M = D + (S - D)/3$

** : Approximate systolic mean, $Psm = (S + M)/2$

***: $Psm \times (Q - T) \times HR$

TPR: Total peripheral resistance

Value are given for control period (C) and at the end of 20 minutes after the administration of Bay a 1040 (D). Values in percent of the control value, D/C × 100, are given in the 3rd column of each group.

†††: 0.005 > P

††: 0.01 > P > 0.005

†: 0.025 > P > 0.01

†: 0.05 > P > 0.025

minutes, there was a conspicuous decrease in the mean blood pressure (MBP), increase in cardiac output (CO) associated with increased peak velocity of the left ventricular ejection (PVLVE), and decreased total peripheral resistance (TPR). Left ventricular external work (LVEW) was unchanged, as expected from the briefness of the change in this parameter as seen in Fig.5. Right

atrial pressure (RAP) rose a little transiently and heart rate (HR) was unchanged. Interestingly enough, MCP was unchanged at the studied points of time, indicating the absence of any effect on the capacitance of the circulatory system, at least under this experimental condition. In short, with 5 µg/kg injected intravenously, there occurred circulatory changes indicative

TABLE III CLINICAL STATUS AND THE EFFICACY OF THE ORAL BAY A 1040 IN DAILY DOSE OF 60 MG IN 5 PATIENTS WITH ISCHEMIC HEART DISEASE

Case No.	Name	Sex	Age	Diagnosis	Number of anginal attacks per day (mean $\pm$ SD)				Effect
					P	A	P	A	
1	A.N.	M	59	Angina at rest	3.6 $\pm$ 1.1	1.5 $\pm$ 0.7	3.4 $\pm$ 1.5	—	improved
2	H.S.	M	53	Angina of effort Essential hypertension	1.7 $\pm$ 1.0	0	0.6 $\pm$ 0.5	—	much improved
3	S.Y.	M	48	Angina at rest	9.8 $\pm$ 3.9	0	2.2 $\pm$ 2.4	0	much improved
4	T.W.	M	58	Angina at rest	1.3 $\pm$ 0.4	0.7 $\pm$ 2.8	3.1 $\pm$ 2.3	0	much improved
5	H.S.	M	52	Angina at rest	3.0 $\pm$ 0.7	1.3 $\pm$ 0.7	2.7 $\pm$ 1.6	1.2 $\pm$ 0.7	improved

Frequency of anginal attacks is shown as an average number of attacks per day. Variance is expressed in standard deviation of the mean. Zero or minimal incidence per day of attacks during the treatment with active tablets (A) forms a sharp contrast with frequent incidence of attacks when the patients were placed on placebo tablets (P).

of a transient dilatation of systemic resistance vessels without any change in the capacitance vessels. This is in a sharp contrast with the recent finding obtained in this laboratory (Ito *et al.* 1971) that nitroglycerine in intravenous dose of 70 μ g/kg produces a transient, precipitous fall in TPR and MCP in open-chest dogs.

Bed-side hemodynamic studies

With Bay a 1040 administered orally in dose of 20 mg and measurements repeated at the end of about 20 minutes, depressor effect was observed in the patients with ischemic heart disease, while no appreciable depressor effect was observed in the group of non-cardiac patients, younger in age and having a lower TPR, to begin with, than the patients with ischemic heart disease. Table II summarizes the results of this study. The ischemic heart disease group showed a fall in systolic and mean blood pressure, an insignificant percentage decrease in TPR, while cardiac index remained unchanged, a circulatory change indicative of the "dilatation" of systemic resistance vessels. Left ventricular external work index and pressure-time-product were also diminished, suggesting, but not demonstrating, decreased myocardial oxygen consumption after the oral administration of Bay a 1040. Absence of any depressor effect in the non-cardiac group may be due, at least in parts, to the low TPR that prevailed at the outset, but a definite statement cannot be made at the present moment in view of the severely limited number of observation.

Clinical trial

The results of the clinical trial are summarized in Table III. While there were 3 to 13 attacks of angina pectoris per day before the start of this treatment, all patients except case No.5 became attack-free during the period of the administration of active tablets of Bay a 1040. Furthermore, attacks of anginal pain that occurred in case No.5 during the period of the active treatment were that of vague sensation, milder in degree as compared with the chest pain that used to occur. Thus it can be stated that the treatment with Bay a 1040 was strikingly effective in all cases. During the course of the treatment with active tablets there was not a single patient who took tablets of isosorbide dinitrate. Moreover, there were no signs of side-effects during the course of the treatment.

A typical case (case No.3) will be described in some details in the following paragraphs.

Case No.3, S.Y., male, age 48, a restaurant manager was admitted to this hospital with the chief complaint of attacks of oppression and pain in the left precordium. Family history was not contributory. Past history was that of the pulmonary "infiltration" at age of 20. The present illness was as follows: in July 1969 he noticed, during physical exertion, palpitation and cold sweat which disappeared upon taking rest. During the subsequent months he had attacks of left precordial oppression and pain once or twice a month. The frequency of the attack increased gradually and he was hospitalized elsewhere and

Fig.7. Selective arteriogram of the left coronary artery in case No.3, in right anterior oblique position. A short segment of narrowing is seen near the origin of the left anterior descending artery.

treated for anginal attacks with isosorbide dinitrate. He was discharged in an improved condition but, by July 1970, he became a victim of frequent attacks of precordial discomfort and pain that occurred about 15 times a day; the duration of an attack was about 1 minute and it subsided soon after he took a pill of isosorbide dinitrate. His appetite and sleep was good and he had a stool daily.

Physical examination at the time of admission revealed a medium-sized man, well-nourished and weighing 62 kg. Pulse rate 76 and regular. Chest and abdomen normal. Tendon reflexes normal. Pathologic reflexes absent. Blood pressure 112/76.

Laboratory examination at the time of admission were as follows: RBC 400×10^4 , WBC 9400, hematocrit 43%, hemoglobin contents 14.4 g/dl, serum protein 6.6 g/dl, A/G ratio 1.91, ZTT 4.7, TTT 1.4, total cholesterol 147 mg/dl, alkaline phosphatase 10.4 (Bodansky), SGOT 20, SGPT 49, LDH 340, RAT negative,

CRP three plus, ASLO 12, Na 143 mEq/L and K 3.6 mEq/L for serum. Blood serological examination negative. Cubital venous pressure 12 mmH₂O. Mild supine leg exercise caused it to rise by 18 mmH₂O. Measured with a radio-cardiograph, cardiac output was 6.0 lit/min, cardiac index 3.4 lit/min/M², stroke volume 95 ml per beat with heart rate 63. Blood volume measured with R¹³¹ISA was 64 ml/kg. Chest roentgenogram was normal.

Selective coronary angiography revealed no marked abnormality in the right coronary artery. The left coronary artery had a short segment of narrowing near the origin of the anterior descending artery (Fig.7). This narrowing was thought to be due to an organic, localized stenosis arising on the basis of the coronary atherosclerosis.

Fig.8 illustrates the clinical course of this patient, with emphasis placed on the variation in the frequency of anginal attacks with therapeutic regimens. For a few days after admission he had 3 to 10 attacks per day of angina pectoris. During the course of placebo regimen, initiated on the 7th hospital day with daily "dose" of 6 tablets, he persistently had 2 to 13 attacks of anginal pain per day and each time he took pills of isosorbide dinitrate. The treatment with active tablets of 1040 was initiated on the 15th hospital day and he became free from attacks from the very first day and onwards. He remained attack-free for a short while after a regimen with placebo tablets was re-instituted, but, in 5 days, he started again suffering from anginal attacks 2 to 6 times a day. Switched again to a regimen with active tablets, he promptly became attack-free. During the course of this clinical trial, there were no significant changes in blood pressure or heart rate.

DISCUSSION

Some of the proposed mechanisms by which anti-anginal agents give relief to anginal pain have been enumerated at the outset of this paper. Apart from the mechanism by which anti-anginal agents give relief to, or prevent the occurrence of, anginal pain, the present study was primarily concerned with the characterization of the vascular action of Bay a 1040.

There were at least 3 points of particular interest in this study.

First, under the experimental conditions used, e.g., intracoronary injection of Bay a 1040 instantaneously as a bolus of 0.1 ml, Bay a 1040

Fig.8. Clinical course of case No.3. Systolic and diastolic blood pressures, heart rate and the frequency of anginal attacks per day are shown. During the initial period of placebo regimen (8 days) anginal attacks occurred from 2–13 times (9.8 ± 3.9 times as mean $\pm$ S.D.) per day. With active tablets of Bay a 1040 he became attack-free. Switched to placebo regimen, he remained attack-free for 6 days but attacks started appearing again 1–6 times a day. For the 2nd period of placebo regimen (15 days) frequency of the attack was 2.2 ± 2.4 as mean $\pm$ S.D. per day. With re-institution of active Bay a 1040 regimen, he became attack-free again. Daily dose was 60 mg given in 3 divided portions after meals.

appeared to produce minimal “active” coronary dilatation at the dose level of $1.0 \mu\text{g}$ (Fig.3), while it produced “passive” coronary dilatation (Fig.4). The “coronary effect” of the systemically administered Bay a 1040, such as shown in Fig.4 might be explained by other mechanisms; for instance, one may surmise that the areas of the heart adjacent to the catheter-perfused segment “drained” blood, during systemic hypotension, from the extracorporeal blood reservoir, because of a lower perfusion pressure head in such areas than in the pressure-head-fixed, catheter-perfused area. This is another way of saying that there are low-resistance, inter-coronary anastomotic channels between the catheter-perfused artery and the adjacent coronary artery, i.e., a very unlikely situation in view of the well-known scarcity of low-resistance, inter-coronary anastomotic channels in normal heart. However, there is a need of repeating the same experiments on a greater number of animals in order to draw a definite conclusion

about the ability of the systemically administered Bay a 1040 to produce strong “passive” coronary dilatation.

Second, with $5 \mu\text{g/kg}$ injected intravenously, there was a marked fall in TPR but no effect was seen in the MCP. In this point Bay a 1040 is quite different from nitroglycerine. Nitroglycerine was found to dilate both systemic resistance and capacitance vessels (Ito *et al.* 1971). Isosorbide dinitrate (0.5 mg/kg , i.v.) and trimethazidine (2 mg/kg , i.v.) also failed to affect MCP at the dose level where TPR decreased (Ito *et al.* 1971). In potency, however, Bay a 1040 seems to be at least 100–400 times as potent as these antianginal agents as a systemic resistance vessel dilator.

Third, this agent, as given orally in daily dose of 60 mg, exerted an obvious “preventive” effect on the occurrence of anginal attacks in the patients with angina of effort plus angina at rest.

These points are interesting not only because they provide much, if not rich, materials for

speculation but also because they give clues to the future investigation.

SUMMARY

A series of basic and clinical studies on a new anti-anginal agent, Bay a 1040, revealed the following facts.

1. With the artificial perfusion of a large branch of the coronary artery under a constant pressure head in closed-chest dogs, and with intracoronary injection as a bolus of 0.1 ml, 1.0 μ g of Bay a 1040 produced a transient and minimal decrease in the mean coronary resistance to flow without any change in blood pressures. With 5 μ g/kg injected intravenously, the mean resistance to flow decreased in the coronary area that was not exposed to the circulating Bay a 1040. From these observations it is probable that Bay a 1040 produces a mild "active" coronary dilatation, as well as "passive" coronary dilatation.
2. With 5 μ g/kg injected intravenously in open-chest dogs, the evoked circulatory change was that of transient dilatation of the systemic resistance vessels without any change in the capacitance of the circulatory system.
3. Middle-aged patients with ischemic heart disease responded to the oral administration of 20 mg with "dilatation" of the systemic resistance vessels. Left ventricular external work and pressure-time-product were also diminished.
4. A clinical trial with cross-over design revealed an outstanding, "preventive" efficacy of this agent, as given in daily dose of 60 mg in 3 divided portions, on the occurrence of anginal attacks in the patients with ischemic heart disease.

REFERENCES

1. GUYTON, A. C.: Determination of cardiac output by equating venous return curves with cardiac output curves. *Physiol. Rev.* 35: 123, 1955.
2. GUYTON, A. C. & GREGANTI, F. P.: A physiologic reference point for measuring mean circulatory pressure in the dog—particularly venous pressure. *Am. J. Physiol.* 185: 137–141, 1956.
3. GUYTON, A. C.: Cardiac output and venous return in heart failure, In: *Cardiology*, vol. 4, McGraw-Hill, New York, 1959. p.18.
4. GUYTON, A. C.: Venous return, In: *Handbook of Physiology*, section 2, volume II, American Physiological Society, Washington, D.C., 1963 a, p.1099.
5. GUYTON, A. C.: *Circulatory Physiology: Cardiac output and its regulation*, Saunders, Philadelphia, 1963 b.
6. HAYASE, S.: Coronary circulation, its physiological aspect, *Jap. Circulation J.* 21: 1–25, 1957.
7. HIRAKAWA, S.: Cardiac function and mean circulatory pressure in acute impediment to venous return, *Jap. Circulation J.* 33: 1547–1556, 1969.
8. ITO, H.: Mechanisms of the action of propranolol and phenoxybenzamine on the coronary artery tone, an experimental study, *Jap. Circulation J.* 33: 1099–1120, 1969.
9. ITO, H., HIRAKAWA, S., HAYASE, S., KONDO, Y., HIEI, K., & BANNO, S.: The influence of some anti-anginal agents on the resistance and capacitance vessels with special reference to the mean circulatory pressure, *Proceeding of 48th Annual Meet. Jap. Physiol. Soc.* 4a26, April 4, 1971, Tokyo.
10. KINOSHITA, M.: Studies on cardiac output to blood volume, and renal circulation in chronic congestive heart failure, *Jap. Circulation J.* 32: 249–270, 1968.
11. MACINTYRE, W. J., PRITCHARD, W. H., & MOIR, T. W.: The determination of cardiac output by the dilution method without arterial sampling. I. Analytical concepts. *Circulation* 18: 1139–1146, 1958.
12. POOL, P. E., CHANDLER, B. M., SEAGREN, S. C., & SONNENBLICK, E. H.: Mechanochemistry of cardiac muscle II. The isotonic contraction, *Circ. Res.* 22: 465–472, 1968.
13. PRITCHARD, W. H., MACINTYRE, W. J., & MOIR, T. W.: The determination of cardiac output by dilution method without arterial sampling, II. Validation of the precordial recording. *Circulation* 18: 1147–1154, 1958.
14. ROLETT, E. L., YURCHAK, P. M., HOOD, W. B. Jr., & GORLIN, R.: Pressure-volume correlates of left ventricular oxygen consumption in the hypervolemic dog, *Circ. Res.* 17: 499, 1965.
15. SARNOFF, S. J., BRAUNWALD, E., WELCH, G. H., CASE, R. B., STAINSBY, W. N., & MACRUZ, R.: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time-index, *Am. J. Physiol.* 192: 148, 1958.
16. SMITH, E. E. & CROWELL, J. W.: Influence of hypoxia on mean circulatory pressure and cardiac output, *Am. J. Physiol.* 212: 1067–1069, 1967.