Assessment of the Cardiohemodynamic Effects of Ibopamine, an Orally-Active Dopamine Analogue, in the Anesthetized Open-Chest Guinea Pig and the Isolated Guinea Pig Atria

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Abstract—In the anesthetized open-chest guinea pig, ibopamine (10–300 μg/kg, i.v.), epinine (10–100 μg/kg, i.v.) and dopamine (10–300 μg/kg, i.v.) produced dose-related increases in heart rate (prevented by 20 μg/kg pindolol, i.v.), left ventricular dP/dt max and aortic flow. Ibopamine produced pressor effects (prevented by 0.5 mg/kg phentolamine, i.v.), while dopamine produced a slight depressor effect. A biphasic response (the pressor phase followed by a depressor) was observed after epinine, although the depressor phase was not significant. Calculated total peripheral resistance (TPR) tended to be increased after ibopamine and epinine (initial phase), while it was decreased after dopamine. Pindolol potentiated the increase in TPR produced by ibopamine and epinine, while the increase in TPR was converted to the decrease after phentolamine. Decreases in TPR produced by epinine and the highest dose of dopamine were inhibited by pindolol. In the isolated guinea pig atria, ibopamine (10^{-6}–10^{-4} M) increased the atrial rate and the developed tension in a concentration-related manner. The positive chronotropic and inotropic effects of ibopamine were of the same order as those of epinine.

Traditionally, chronic heart failure has been treated with either one of the following three types of drugs or two or three of them in combination: 1) positive inotropic agents that increase the contractility of depressed cardiac muscle, 2) diuretics for reduction of the volume overload, and 3) peripheral vasodilators for reduction of the preload and/or afterload (1). Although digitalis glycosides have been the most commonly used positive inotropic agents, they have a drawback in that the substances have relatively low therapeutic ratio because of cardiac toxicity (1, 2). Recently, catecholamines such as dopamine have been used as substitutes. It is claimed that dopamine has another advantage in that it can improve the renal performance (3, 4). However, the duration of action of this substance is short and the availability by oral administration is negligible. Thus, orally effective dopamine-like agents are badly needed. Several animal studies (5–7) have demonstrated that ibopamine (the di-isobutyric ester of N-methyl dopamine) is an orally active cardiotonic dopamine analogue, which can increase renal blood flow and produce diuresis. There are also clinical reports suggesting that ibopamine can increase cardiac performance, renal clearance of creatinine, excretion of electrolytes and produce diuresis (8–13). Although it is presumed that ibopamine is a prodrug of epinine (N-methyl dopamine), precise analyses of cardiohemodynamic actions of these two drugs have not been conducted yet.

In the present study, an attempt was made to precisely compare the cardiohemodynamic and cardiac effects of ibopamine in the anesthetized open-chest guinea pig and the isolated guinea pig atria in comparison with those of epinine to settle the issue of whether ibopamine exerted effects as such or after
being converted to epinine or some other compounds. To assess the clinical usefulness of this drug, the effects of ibopamine were also compared with those of dopamine.

Materials and Methods

**Hemodynamic studies in the anesthetized open-chest guinea pig**: Male Hartley guinea pigs (300–700 g) were anesthetized with thiobutabarbital sodium (90 mg/kg, i.p.). Animals were placed on their backs on a heating pad, and their legs secured with tape. The body temperature was maintained within normal range (36–37°C). The trachea was cannulated, and the animals were respirated artificially with a small-animal respirator (Takashima Shoten TB-101). The respiration rate was set at 54/min and the tidal volume, at 0.8–1.0 ml/100 g. The right carotid artery was cannulated with PE-50 tubing previously filled with heparin (1000 units/ml) and attached to a pressure transducer (Statham P-50). The right jugular vein was cannulated with a hand-made cannula for intravenous drug administration. After opening the thorax by midsternal incision, the ascending aorta was dissected free from surrounding tissues to place an electromagnetic flowmeter probe with an i.d. of 2.5–3.0 mm (Statham SP2201). Intraventricular pressure was recorded by inserting a 22G needle previously filled with heparin (1000 units/ml) and attached to a P-50 Statham pressure transducer by a 3-way stopcock into the left ventricular cavity approximately at a 20° angle. The ventricular pressure signal was electronically differentiated to obtain left ventricular dP/dt. The heart rate was continuously monitored with a cardiotachometer triggered by the R wave of the ECG (Standard Lead 2). The blood pressure, aortic flow, left ventricular pressure, left ventricular dP/dt; and heart rate were displayed on a linearly recording thermosylus oscillograph (Graph-tec Mark 7). The total peripheral resistance is calculated as: mean blood pressure/aortic flow. After an adequate stabilization period of at least 20–30 min after completion of surgery, drugs were injected in a volume of 0.03 to 0.2 ml over a period of 10 sec via the cannulated right jugular vein. In some experiments, the duodenum was dissected and cannulated with PE-50 tubing for intraduodenal drug administration.

**Isolated guinea pig atria**: Male Hartley guinea pigs weighing about 450 g were sacrificed by cervical dislocation. The right and left atria were quickly excised. The right atrial preparations, which retained a spontaneous rhythm, were used to assess the chronotropic effect; and the left atrial preparations, stimulated at a constant rate by a square-wave electronic stimulator (Nihon Kohden MSE-3) at the frequency of 1 Hz with voltages of approx. 30% above the threshold (duration=1 msec), were used for the study of the inotropic effect. The right and left atrial preparations were mounted in 20 ml organ baths. The incubation medium. Krebs-Henseleit solution (118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 24.9 mM NaHCO3, 1.2 mM MgSO4, 1.2 mM KH2PO4 and 11 mM glucose), was kept at 32.5±0.1°C and bubbled with 95% O2+5% CO2. The initial resting tension of the preparation was set at about 0.5 g, and the contractile tension was recorded on a linearly recording thermostylus oscillograph (Watanabe Sokki Mark 5) with the aid of a force-displacement transducer (Toyo Baldwin, T7–30–240). The spontaneous rate of right atrial preparations was recorded on a linearly recording thermosylus oscillograph by means of a cardiotachograph (Nihon Kohden RT-5). The increase in contractile force and spontaneous beating rate induced by 10⁻⁷ M of isoproterenol after a 30 min equilibration period was taken to be 100%, and the subsequent response to test compounds were expressed as %.

**Drugs and analysis**: Ibopamine hydrochloride was provided by Yoshitomi Pharmaceutical Industries Co., Ltd. Other drugs used were: thiobutabarbital sodium (Iactin, Promonta Werke Hamburg), dopamine hydrochloride (Sigma), epinine hydrochloride (Sigma), phentolamine mesylate (Regitin, Ciba-Geigy), dl-pindolol (Carvisken, San-kyo), I-isoproterenol hydrochloride (Proternol-L, Nikken), I-phenylephrine hydrochloride (Neo-Synesin, Kowa). Ibopamine, dopamine and epinine were dissolved in saline solution.

All results are expressed as the mean±
S.E.M. The significance between mean values was analyzed with Student's t-test for paired or non-paired data, and they were judged to be significant when P values were less than 0.05.

**Results**

**Control values for measured parameters in the anesthetized guinea pig:** The control values for systolic and diastolic blood pressure, aortic flow, left ventricular dP/dt max, heart rate and total peripheral resistance (TPR) were 67.1±3.7 mmHg, 35.2±1.8 mmHg, 62.7±4.7 ml/min, 1823±127 mmHg/sec, 235±26 beats/min and 0.74±0.05 mmHg/ml/min (n=10), respectively. The values for mean blood pressure, dP/dt and heart rate are approximately in agreement with other published data for the anesthetized guinea pig (14-16). The value of mean blood pressure was approximately 20 mmHg lower than that of the conscious guinea pig (17). Electromagnetic blood flow measurement has been applied to the rat as a reliable procedure for measurement of the aortic flow, but not yet used in the guinea pig. The value of aortic flow obtained in the present experiment resembled that of the anesthetized rat (18). The calculated value of TPR per 100 g was about half the value obtained in the anesthetized dog (4). Insertion of a 22G needle into the left ventricular cavity and attachment of the flow probe to the aorta did not produce any change in the blood pressure response, and all cardiohemodynamic parameters were reasonably steady over the period required for testing drugs (within -7 to 4% of the initial values) (Fig. 1).

**Fig. 1.** Stability of the mean blood pressure (BP), aortic flow (AF), left ventricular dP/dt max (dP/dt max) and total peripheral resistance (TPR) over a 90 min period. Each point represents the mean±S.E.M. of 4 guinea pigs.
guinea pig: Time courses of changes in blood pressure, heart rate, dP/dt and aortic flow evoked by intravenous administration of ibopamine, dopamine and epinine are shown in Fig. 2.

Figures 3–6 depict the maximum changes in blood pressure, heart rate, dP/dt and TPR (the first phase of a biphasic response) produced by these compounds. Ibopamine and epinine produced a dose-related rise of blood pressure, while dopamine produced a decrease at lower doses and an increase at higher doses. Epinine-induced rise of the blood pressure was followed by a slight depressor phase. There was a dose-related increase in heart rate and dP/dt with all the three compounds. As shown in Fig. 6, the TPR calculated as blood pressure/aortic flow tended to increase with ibopamine and epinine, although a significant rise in TPR was observed only with an intermediate dose of ibopamine. Dopamine produced a dose-related decrease in this parameter (Fig. 6).

The effects of α- or β-adrenergic receptor blockade on the cardiohemodynamic effects of ibopamine, epinine and dopamine in the anesthetized guinea pigs were assessed in separate groups of animals. As shown in Fig. 3, the pressor effects of ibopamine and epinine and those of the higher doses of dopamine were reduced or reverted to the depressor ones after a dose of phentolamine (0.5 mg/kg, i.v.) which reduced the pressor response to a 10 μg/kg, i.v. dose of phenyle-
phrine by about 90%, indicating the involvement of the α-adrenoceptor in the observed rise of the blood pressure. The positive chronotropic and inotropic effects of these substances were inhibited by pindolol (20 μg/kg, i.v.) (Figs. 4 and 5) which nearly abolished the positive chronotropic response (ΔHR=34±3 beats/min) elicited by 0.1 μg/kg isoproterenol, i.v. However the increase in dP/dt induced by ibopamine was not significantly inhibited by pindolol. As shown in Fig. 6, the increases in TPR induced by ibopamine and epinine were much potentiated after pindolol, while they were reverted to decreases after phentolamine. Pindolol produced a significant inhibition of the decrease
Fig. 5. Effects of pindolol (20 μg/kg, i.v.) on the peak changes in left ventricular dP/dt induced by ibopamine, epinine and dopamine. Each column represents the mean±S.E.M. of % changes from predrug values. Numbers in parentheses are the numbers of experiments. *Significantly different from the value before administration (\( tP<0.05 \), \( tttP<0.01 \), \( ttttP<0.001 \)). *Significantly different from the control responses (*\( P<0.05 \), **\( P<0.01 \), ***\( P<0.001 \)).

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Fig. 6. Effects of pindolol (20 μg/kg, i.v.) and phentolamine (0.5 mg/kg, i.v.) on the peak changes in total peripheral resistance (the first phase of biphasic response) induced by ibopamine, epinine and dopamine. Each column represents the mean±S.E.M. of % changes from predrug values. Numbers in parentheses are the numbers of experiments. *Significantly different from the value before administration (\( tP<0.05 \), \( tttP<0.001 \)). *Significantly different from the control responses (*\( P<0.05 \), **\( P<0.01 \), ***\( P<0.001 \)).

in TPR produced by the highest dose of dopamine. The decreases in TPR produced by the low doses of ibopamine were potentiated after phentolamine.

Figure 7 depicts the dose-response relation of the changes in heart rate, dP/dt and TPR induced by ibopamine, epinine and dopamine after phentolamine treatment. The rank order of \( \beta \)-adrenergic potency as assessed by increases in heart rate and increases in dP/dt was epinine>dopamine>ibopamine, while the rank order of the potency as a vaso-
dilatory agent was dopamine > ibopamine = epinine. At a dose inducing an increase in heart rate of 10%, the change in TPR induced by ibopamine, epinine and dopamine were -21.0, -12.0 and -28.4%, respectively. Likewise, at a dose inducing an increase in dP/dt of 60%, changes in TPR of -23.0, -14.5 and -28.0%, respectively, were observed. Thus, dopamine was the most selective vasodilator among the three compounds, while epinine was the least selective agent.

As shown in Fig. 8, intraduodenal administration of ibopamine (3, 10 and 30 mg/kg) resulted in dose-related increases in mean blood pressure, aortic flow and dP/dt which were qualitatively similar to those produced by intravenous administration. The increase in heart rate was observed only at the highest dose used, i.e., 30 mg/kg; the increase in aortic flow and dP/dt observed in low doses was not accompanied by any increase in heart rate. Figure 9 depicts the second phase of the biphasic changes in TPR induced by intravenous and intraduodenal administration of ibopamine and intravenous injection of epinine. While the decrease in TPR induced by intravenous administration of ibopamine was not significant, a significant decrease in TPR was observed with ibopamine given via the intraduodenal route, just as it was with intravenous administration of epinine. The doses necessary to induce the effects of a similar magnitude via the intraduodenal route were a hundred times higher than those necessary via the intravenous route.

Effects on isolated guinea pig atria: Exposure of isolated guinea pig right atria to ibopamine and epinine resulted in a concentration-dependent increase in heart rate (Fig. 10). The threshold concentration was approximately 10^-3 M for both. Maximum positive chronotrophic effects induced by these two amines at a concentration of 10^-4 M were 92.7±2.1 and 93.9±3.4%, respectively. Doses of ibopamine and epinine producing 50% increase in heart rate were approximately 6.8×10^-6 M and 9.1×10^-8 M. Ibopamine and epinine increased the developed tension of the guinea pig left atria in a concentration-related manner (Fig. 10), and the maximum responses were 113.7±14.8 and 130.7±
Fig. 8. Effects of intraduodenal administration of ibopamine (3–30 mg/kg) on cardiohemodynamic parameters of the anesthetized guinea pig. Each point represents the mean±S.E.M. of % change from predrug values (n=5). Abbreviations are the same as in Fig. 2.

18.1%, respectively. The threshold concentrations for this effect were around 10^{-6} M for both compounds. The concentrations necessary for producing half the maximum response were 8.5×10^{-6} M and 1.5×10^{-5} M. The onset of the positive chronotropic and inotropic actions of ibopamine was slower, and it took a longer time to achieve the maximum response as compared with epinine. When compared at concentrations that increased the heart rate and developed tension by 50%, ibopamine and epinine were nearly equipotent.

Discussion

Ibopamine and epinine produced a dose-related increase in blood pressure. Epinine-induced pressor response was followed by a slight depressor phase, in agreement with the previous findings in anesthetized cats (6). However, a definite dose-related increase in TPR was noted with ibopamine and epinine only after pindolol, indicating that these two compounds were strong activators of the \( \beta \)-adrenoceptors in peripheral blood vessels. The high potencies of these compounds as stimulants of the vascular \( \beta \)-adrenoceptors were evident from the findings that a definite dose-related decrease in TPR was observed with these two compounds after phentolamine. Thus, these two compounds activated both the \( \alpha \)- and \( \beta \)-adrenoceptors of the peripheral blood vessels. In accord with previous reports (4, 19), dopamine produced a decrease in blood pressure at lower doses and an increase at higher doses.

All the three compounds produced an increase in heart rate and dP/dt, which was inhibited by pindolol. Thus, it is clear that all the three amines have the capability of activating the cardiac \( \beta \)-adrenoceptors. The rank order of \( \beta \)-adrenergic agonist potency as
assessed by increases in heart rate was epinephrine > dopamine > ibopamine.

The decreases in TPR induced by the lower doses of dopamine were not affected by pindolol, indicating the capability of this substance to activate a receptor or receptors other than α-receptors in the peripheral blood vessels. Although the effects of dopamine antagonist on the decrease in TPR were not tested, the dopaminergic receptor may be the most likely candidate. There was a quantitative difference as regards to the magnitude of the vasodilation that can be induced with equipotent doses as α-agonists of ibopamine, epinephrine as well as dopamine (at doses inducing 10% increase in heart rate and 60% increase in dP/dt, the rank order of vasodilatory potency was dopamine > ibopamine > epinephrine). This finding is compatible with this interpretation, although the possibility that this may merely be a reflection of the difference of the α-receptor in the heart and in the peripheral blood vessels cannot be ruled out. The activation of the dopaminergic receptor have also been implicated as a mechanism of vasodilatation induced by ibopamine in the renal and peripheral vessels (13).

The effects of intravenous ibopamine on the peripheral vasculature differed from those of epinephrine not only quantitatively, but also qualitatively. While ibopamine produced only a rise of TPR, epinephrine produced a biphasic change in this parameter: an initial rise followed by a fall. However, when ibopamine was given via the intraduodenal route, the effects of this substance on TPR became very much like those of epinephrine, supporting the idea of conversion of this substance to epinephrine. As demonstrated in this study,

Fig. 9. Effects of intravenous and intraduodenal administration of ibopamine and intravenous administration of epinephrine on the total peripheral resistance (the second phase of a biphasic response). Each column represents the mean±S.E.M. of % changes from the predrug values. Numbers in parentheses are the numbers of experiments. *Significantly different from the control responses (*P<0.05, ***P <0.001).

Fig. 10. Positive chronotropic (upper graph) and inotropic (lower graph) effects of ibopamine and epinephrine (10^-7-10^-4 M) in the isolated right and left atrial preparations of the guinea pig. Each point represents the mean±S.E.M. of the maximal response (%) to isoproterenol (10^-7 M). Numbers in parentheses are the numbers of experiments.
ibopamine (10⁻⁶–10⁻⁴ M) produced positive inotropic and chronotropic effects in a concentration-dependent manner in the isolated guinea pig atria. When compared at the concentration inducing the 50% increase in the atrial rate and contractile tension, ibopamine and epinine were nearly equipotent. However, the onset of actions of ibopamine was slower, and it took a longer time to achieve the maximum response as compared with epinine. These findings are compatible with the idea of prior conversion of ibopamine to some other substances. Epinine could be a candidate for such a metabolite.

In the present study, the increase in dP/dt produced by ibopamine was not significantly inhibited by pindolol. Furthermore, the increase in aortic flow and dP/dt observed in the present experiments after intraduodenal administration of low doses ibopamine was not accompanied by any increase in heart rate, and it was reduced by phenolamine (data not shown), suggesting the possibility that the part of the increase in aortic flow and dP/dt that was inhibited by phenolamine was due to an increase in venous return as a consequence of venous constriction produced by this compound. Participation of the α-adrenoceptor in the myocardium is not conceivable, since it has been reported that α-adrenoceptors were not involved in the restoration of mechanical and/or electrical responses in the depolarized isolated guinea pig ventricular muscle (20, 21).

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