Clinical Science and Molecular Medicine (1976) 51, 575s-578s.

Vasodilating drugs: contrasting haemodynamic effects

R. C. TARAZI, H. P. DUSTAN, E. L. BRAVO AND A. P. NIARCHOS
Research Division, The Cleveland Clinic Foundation, and
The Cleveland Clinic Educational Foundation, Cleveland, Ohio, U.S.A.

Summary

1. We investigated the haemodynamic effects of intravenously administered hydrallazine, diazoxide and nitroprusside and orally administered minoxidil to determine whether vasodilators (such as nitroprusside) which do not increase cardiac output might be better treatment for hypertensive complications associated with, or caused by, myocardial failure than those that do.

2. Hydrallazine and diazoxide caused increases in heart rate, cardiac output, cardiopulmonary blood volume, the ratio of cardiac output to cardiopulmonary volume, and pulmonary artery pressure. Nitroprusside, although decreasing pressure and vascular resistance, caused no significant change in the other functions except for reducing pulmonary artery pressure. Minoxidil, when given orally, had the potential for causing pulmonary hypertension. This seemed explained by increased flow (hyperdynamic type) in some but by congestive cardiac failure in others; the latter condition was probably intensified by the marked fluid retention that the drug can cause.

3. On the basis of these results a classification of vasodilators was constructed which depends on the presence or absence of a venodilating effect. Vasodilators which produce no (or little) venodilatation, increase heart rate, cardiac output, cardiopulmonary blood volume and pulmonary artery pressure. In this class are diazoxide, hydrallazine and minoxidil. Those that cause venodilatation do not stimulate the heart nor do they cause pulmonary hypertension. Nitroprusside and nitroglycerine are drugs of this type.

4. These results suggest that drugs producing both venodilatation and arteriolar dilatation may be more specific therapy for hypertensive complications associated with cardiac failure than those that cause only arteriolar dilatation.

Key words: anti-hypertensive drugs, pulmonary hypertension, vasodilators.

Introduction

Development of vasodilating drugs that are orally active has long been considered a therapeutic goal in the continued search for specific treatment of hypertension. Such drugs have been shown also to be useful in normotensive cardiac failure (Franciosa, Guiha, Limas, Rodriguera & Cohn, 1972; Cohn, Mathew, Franciosa & Snow, 1974). However, those that have been reported on have little effect on cardiac output and heart rate (Chatterjee, Parmley, Ganz, Forrester, Walinsky, Crexells & Swan, 1973; Kovick, Tillisch, Berens, Bramowitz & Shine, 1976), in contrast to the vasodilators that are traditionally used for treatment of hypertension (Freis, Rose, Higgins, Finnerty, Kelley & Partenope, 1953; Wilson & Okun, 1963). These differences may result from differences in cardiac function or may represent variations in pharmacological action. In the latter case, these variations might determine the usefulness of a particular vasodilator in the therapy of hypertension, depending on the degree of cardiac impairment present.

We have therefore investigated the haemodynamic effects of hydrallazine, diazoxide and nitroprusside given intravenously and minoxidil given orally in a group of patients with hypertension of various degrees of severity but without cardiac decompensa-
tion. The results suggest that vasodilators that produce venodilatation in addition to arteriolar dilatation are better suited for treatment of hypertension with significant hypertensive heart disease, than are those that primarily cause arteriolar dilatation.

Methods

Studies were carried out in forty-five hypertensive patients; thirteen were given diazoxide, and seven hydralazine, by single intravenous injection; twelve were given an infusion of nitroprusside sufficient to reduce arterial blood pressure by at least 20 mmHg. Thirteen patients were treated with minoxidil, either alone or in addition to other oral anti-hypertensive agents. Most of the patients investigated were either untreated or had discontinued all forms of treatment at least a month before the investigation. None of the patients receiving nitroprusside had other medication whereas five of the thirteen patients given diazoxide as well as two of the seven given hydralazine were on propranolol therapy. The results during propranolol treatment, however, did not differ from those obtained in untreated patients so are included here. The collaboration of each patient was obtained by carefully explaining the nature of the study and its importance both individually and generally.

Haemodynamic measurements were performed in the morning in the fasting state without premedication. After local anaesthesia, an arterial catheter was introduced percutaneously and advanced to the ascending aorta, and a Swan-Ganz venous catheter was advanced into the pulmonary artery. Cardiac output (CO) and cardiopulmonary volume (CPV) were calculated from dye-dilution curves (Indocyanine Green) from classical formulae based on the Stewart Hamilton technique. The ratio of cardiac output to cardiopulmonary blood volume (CO/CPV) was taken as an index of cardiac performance. The methods used to determine flow, pressure and heart rate and to calculate derived indices have been described in detail (Tarazi, Ibrahim, Dustan & Ferrario, 1974).

In studies with intravenously administered drugs, control measurements were obtained in triplicate, after which seven patients were given 20 mg of hydralazine and thirteen were given 300 mg of diazoxide as single injections. Seven patients received an infusion of sodium nitroprusside sufficient to reduce mean arterial pressure from an average of 136 to 114 mmHg. In each instance haemodynamic measurements were repeated after the reduction of arterial pressure. For the thirteen patients treated with minoxidil, control measurements were made before the drug was given and then repeated days or weeks after treatment had been started. A total of thirty-three studies was obtained, one per patient in six and a median of four per patient in the other seven. Four patients received minoxidil alone as initial therapy; in the remaining nine, minoxidil was added to diuretics or sympathetic-blocking agents. The doses of minoxidil ranged from 10 to 40 mg/day.

Results

The haemodynamic effects of the three intravenously administered vasodilators are summarized in Table 1. Each reduced systemic arterial pressure and total

<table>
<thead>
<tr>
<th></th>
<th>Hydralazine (n = 7)</th>
<th>Nitroprusside (n = 12)</th>
<th>Diazoxide (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>P</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>70</td>
<td>90</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>120</td>
<td>100</td>
<td>&lt;0·005</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4·48</td>
<td>6·34</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>TPR (u/m²)</td>
<td>47</td>
<td>28</td>
<td>&lt;0·005</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>14·9</td>
<td>18·8</td>
<td>&lt;0·02</td>
</tr>
<tr>
<td>CPV (ml)</td>
<td>818</td>
<td>913</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>CO/CPV</td>
<td>5·5</td>
<td>6·9</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>
Peripheral resistance and increased heart rate significantly. With sodium nitroprusside these changes were not accompanied by consistent modification in CO, CPV or the CO/CPV ratio; pulmonary arterial pressure fell significantly in all thirteen patients. In contrast, with both hydralazine and diazoxide, CO, CPV, CO/CPV and pulmonary artery pressure rose significantly.

Minoxidil had effects similar to those of diazoxide and hydralazine but, as treatment continued, these were modified by fluid retention as well as by changes in cardiac function (Dustan, Tarazi & Bravo, 1975). Pulmonary hypertension was encountered frequently but did not occur invariably; thus pulmonary arterial pressure > 30/15 mmHg was found in eight of thirteen patients (it occurred in three of six who had only one haemodynamic investigation, and in five of seven with repeated haemodynamic investigations). The haemodynamic pattern associated with the rise in pulmonary arterial pressure differed among the seven patients; in four, pulmonary hypertension was associated with marked increases in CO and responded to the addition of propranolol therapy. In three patients, however, the rise of pulmonary arterial pressure was accompanied by a decline in CO from the value obtained before pulmonary hypertension occurred. These patients also showed more blood volume expansion and greater rises in pulmonary wedge pressure than did the four with sustained increases in CO.

Discussion

The haemodynamic pattern produced by hydralazine and diazoxide may be best explained by predominant arteriolar dilatation with little or no venodilatation; under these conditions arteriolar dilatation leads to a more rapid transfer of blood to the venous side, increased venous return, central location of blood and increased cardiac output. In this regard our results are in agreement with previous studies showing that neither diazoxide (Thirlwell & Zsoter, 1972) nor hydralazine (Nickerson, 1970) has an important effect on veins. The pulmonary hypertension we observed is mostly hyperkinetic in nature, reflecting increased output from the right ventricle and implying little or no pulmonary dilatation. Further, the rise in pulmonary arterial pressure is expected to be more accentuated in case of diminished left ventricular compliance, such as occurs in hypertension, or in the presence of a fixed obstruction (mitral stenosis) to pulmonary venous return (Aitchison, Cranston & Priest, 1955). No consistent changes were found in pulmonary vascular resistance, but then none of the patients had a markedly elevated resistance. A reduction in pulmonary vascular resistance has been reported only in few patients with initially high resistance (Just & Stein, 1969), and it is conceivable that a mild pulmonary vasodilating effect may be amplified under those conditions.

As indicated earlier, effects of hydralazine and diazoxide were not modified by pretreatment with propranolol. Reasons for this are not apparent but since α-adrenoreceptors are left unopposed by such treatment, any reflex sympathetic stimulation that results from fall in arterial pressure produced by vasodilatation may cause further decrease in venous capacitance, a somewhat greater distribution of blood centrally and tachycardia similar to that observed with volume expansion (Vatner, Boettcher, Heyndrick & McRitchie, 1975).

Pulmonary hypertension occurred frequently during minoxidil therapy. Two haemodynamic patterns were associated with the rise in pulmonary arterial pressure and neither suggested a paradoxical vasoconstrictor effect of minoxidil on the pulmonary circulation. The first, termed 'congestive pulmonary hypertension', seemed to reflect diminished cardiac efficiency, probably because of marked fluid retention and increased preload. It was associated with marked increase in pulmonary wedge pressure and expansion of total blood volume. Sequential studies showed that cardiac output decreased as pulmonary arterial pressure increased; although output was higher at that time than before minoxidil treatment, it was lower than the value obtained when pulmonary artery pressure was normal. In contrast, the 'hyperkinetic pulmonary hypertension' was less pronounced and was associated with lesser rise in pulmonary wedge pressure and smaller expansion in total blood volume. It was characterized by marked increase in cardiac output and was usually responsive to propranolol therapy. A typical example is given by a patient in whom pulmonary arterial pressure rose from 28/15 to 40/20 mmHg as cardiac index was doubled (2.8 to 5.6 1 min⁻¹ m⁻²) and mean arterial pressure fell only from 192 to 159 mmHg. The addition of propranolol reduced cardiac index (4

Abbreviations: CO, cardiac output; CPV, cardiopulmonary volume.
controlled mean arterial pressure (116 mmHg) and returned pulmonary arterial pressure to normal (23/13 mmHg). Thus exact haemodynamic characterization of the pulmonary hypertension allowed a rational decision in the adjustment of the therapy.

These results indicate that vasodilator agents have different haemodynamic patterns that may be important in the choice of therapy in different hypertensive conditions. Our results do not suggest that the increase in CPV is the basic mechanism responsible for the rise in pulmonary arterial resistance; the latter probably reflects the increased pulmonary flow. However, changes in CPV are a marker of the degree of central distribution of blood and of the systemic effects of venodilatation. A reduction in pulmonary arterial pressure with nitroprusside irrespective of changes in cardiac output suggests an additional direct pulmonary vasodilator effect; it is interesting that the vasodilators that cause venodilatation seem also to affect the pulmonary circulation similarly.

Acknowledgments

This study was supported in part by grants from the National Heart, Lung and Blood Institute (HL 6835) and the U. A. Whitaker Fund.

References


