Response to dobutamine and dopamine in the hypotensive very preterm infant

J Christophe Rozé, Catherine Tohier, Catherine Maingueneau, Michèle Lefèvre, Alain Mouzard

Abstract
A randomised double blind study was designed to evaluate haemodynamic response to dobutamine and dopamine in 20 hypotensive preterm infants of less than 32 weeks’ gestation. Neonates initially received dopamine or dobutamine 5 µg/kg/min. If mean arterial pressure (MAP) remained below 31 mm Hg, the infusion rate was increased in increments of 5 µg/kg/min. If 20 µg/kg/min of the initial drug failed to achieve a MAP above 30 mm Hg, it was discontinued and the other drug was administered at the same infusion rate. Left ventricular output (LVO) was measured by pulsed Doppler echocardiography.

Mean (SE) MAP increased significantly from 24.4 (1.0) to 32.0 (1.4) mm Hg at a median dobutamine dosage of 20 µg/kg/min and from 25.6 (1.2) to 37.7 (1.5) mm Hg at a median dopamine dosage of 12.5 µg/kg/min. The percentage LVO increase was +21 (7)% with dobutamine compared with −14 (8)% with dopamine. Dobutamine failed to increase MAP above 30 mm Hg in six infants out of 10, whereas dopamine succeeded in all 10 infants. Six switches from dobutamine to dopamine were thus performed, providing a rise in MAP (29.2 (0.5) to 41.2 (2.0) mm Hg) and drop in LVO (356 (40) to 263 (36) ml/kg/min). These data indicate that dopamine is more effective than dobutamine in raising and maintaining MAP above 30 mm Hg; however dopamine does not increase LVO.

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Cerebral ischaemic lesions are among the major complications of extreme prematurity. Mean arterial pressure (MAP) below 30 mm Hg precedes such lesions1 2 and requires the use of inotropic drugs to increase or maintain MAP above 30 mm Hg.3 The drugs conventionally used are dopamine and dobutamine, each of which has certain advantages and disadvantages. Dopamine is the drug most often used by neonatologists,4 although the predominance of its alpha effect during the neonatal period,5 may induce two risk factors: (i) increase in left ventricular afterload and decrease in heart output6 7 and (ii) increased pulmonary resistance associated with a risk of persistent neonatal pulmonary hypertension.8 9

Theoretically, the beneficial effect of dobutamine is due to its essential β adrenergic action. Its inotropic effect has been demonstrated also in preterm neonates,10 but its ability to increase MAP seems to be more restricted, according to studies in adults11 or young children.12 As few controlled studies on the haemodynamic effects of these two drugs in the very preterm neonate have been reported, we designed a randomised double blind prospective study to analyse haemodynamic response to each drug within a population of hypotensive preterm infants born at less than 32 weeks’ gestation.

Patients and methods

PATIENTS
Institutional approval was obtained for this study. All neonates born before 32 weeks’ gestation and admitted to the neonatal intensive care unit of Nantes University Hospital during two periods, from 1 January to 30 September 1990 and from 15 April to 30 September 1992, were eligible. Several conditions had to be met: (i) infants had to present with a MAP below 30 mm Hg for more than one hour despite vascular fill with 20 ml/kg albumin 4%, (ii) infants had to be able to undergo Doppler echocardiographic examination before and during infusion of a positive inotropic drug, and (iii) informed consent had to be obtained from the parents.

DRUG ADMINISTRATION

Neonates included in the study were randomised to either dobutamine or dopamine and received a continuous infusion of dobutamine or dopamine at an initial dose of 5 µg/kg/min. Whenever MAP could not be maintained above 30 mm Hg, the dose was increased in increments of 5 µg/kg/min up to a maximum dose of 20 µg/kg/min. When that dose failed, a switch was made to the other drug, with infusion at the same 20 µg/kg/min dose. If MAP could not be maintained above 30 mm Hg after the switch, the subject was withdrawn from the protocol. Drugs were prepared and administered by nurses. Each drug was diluted down to 1000 µg/ml. The medical team was unaware of randomisation results and prescribed the dosage by adapting the infusion rate.

DATA ANALYSIS AND MEASUREMENTS

The severity of respiratory distress was determined from the arterial alveolar oxygen tension ratio (a/AlvO2), PAO2 being computed according
to the formula: \( \text{PAO}_2 = 713 \times \text{PAO}_2 - (\text{PACO}_2/R_1) \), where \( R_1 = 1, \text{PAO}_2 \) and \( \text{PACO}_2 \) being expressed as mm Hg. MAP measurements were determined by using either a 3-5 French umbilical artery catheter connected to a pressure transducer (model 60-800, American Edwards Laboratories) via a low compliance tube, or the non-invasive oscillometric method (Dynamap 1846, Critikon Inc). Cuff width on the upper right arm was carefully chosen to minimise errors. Left ventricular output (LVO) was measured by duplex echocardiography (Ultramark 5, Advanced Technology Laboratories). Doppler echocardiographic examination using a 7.5 MHz scanner and a 5 MHz Doppler probe was performed before drug administration, upon delivery of the highest infusion rate delivered, and after the switch if it occurred. The examination included M mode measurement of the end systolic internal diameter of the ascending aorta. Measured at the first examination, this diameter was considered to be constant throughout the study. Variation in aortic diameter between measurements was probably due to methodological error or limitations rather than to true changes with time in aortic diameter. Mean velocity was measured on five consecutive cycles in the ascending aorta, through either the suprasternal or subcostal views. The angle of incidence of the ultrasound beam with the blood flow vector was kept between 0±15 degrees. LVO was determined by multiplying the aortic section area, computed from M mode measured diameter, by mean velocity divided by birth weight in order to express LVO in ml/min/kg. Systemic vascular resistance (SVR), estimated by dividing MAP by LVO and body area, was expressed as dynes×sec/cm\(^5\)/m\(^2\).

**STATISTICAL ANALYSIS**

Results are reported as mean (SE). Fisher’s exact test (two tailed) was used to compare the ability of both drugs to increase MAP above 30 mm Hg. The Wilcoxon paired test and the Kruskal-Wallis test were used to compare variations in haemodynamic parameters respectively within and between groups. A simple linear regression was performed. A p<0.05 threshold was considered as statistically significant.

**Results**

Twenty preterm infants were enrolled in the study: 10 in the dobutamine group and 10 in the dopamine group (see table 1 for clinical data). No patients were withdrawn from the study. Infants in both groups were not statistically different for birth weight (1110 (80) v 1140 (105) g) or gestational age (28-7 (0-5) v 29-0 (0-5) weeks). All 20 neonates were receiving assisted ventilation. The severity of the respiratory distress was not statistically different between both groups. The mean \( a/\text{A}_2 \) ratio upon inclusion was 0.26 (0.04) in the dobutamine group compared with 0.23 (0.03) in the dopamine group; this was not significant.

MAP changes in both groups at different dosages are indicated in fig 1. MAP increased significantly in both groups, from 24-4 (1-0) to 32-0 (1-4) mm Hg (p=0.0006) at a median dosage of 20 \( \mu \)g/kg/min in the dobutamine group and from 25-6 (1-2) to 37-7 (1-5) mm Hg (p=0.0002) at a median dosage of 12-5 \( \mu \)g/kg/min in the dopamine group. MAP increased above 30 mm Hg for all 10 hypotensive neonates receiving dopamine, but remained at or below 30 mm Hg for six of the 10 neonates receiving dobutamine, even at a 20 \( \mu \)g/kg/min dose.

The difference between LVO before drug administration and on the maximum dose was +21 (7)% for the dobutamine group compared with −14 (8)% for the dopamine group (p=0.005). In the dopamine group, we observed a significant positive correlation between \( a/\text{A}_2 \) on entry to the trial and the difference between LVO before dopamine administration and at the highest infusion rate of dopamine (r=0.71, n=10, p=0.02; fig 2). The difference between SVR before drug administration and on the maximum dose was
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Table 2  Comparison of haemodynamic effects of dobutamine and dopamine. Changes in MAP, LVO, and SVR measured before treatment and at the highest infusion rate. Results are mean (SE)

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine (n=10)</th>
<th>Dopamine (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>Highest infusion rate</td>
</tr>
<tr>
<td>Dosage (µg/kg/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>24-4 (1-0)</td>
<td>17-0 (1-7)</td>
</tr>
<tr>
<td>LVO (ml/min/kg)</td>
<td>266 (16)</td>
<td>313 (37)</td>
</tr>
<tr>
<td>SVR (dynes/sec/cm²/m²)</td>
<td>1035 (188)</td>
<td>1171 (237)</td>
</tr>
</tbody>
</table>

*p<0.026 between parameters measured before treatment and at the highest infusion rate, within dobutamine or dopamine groups.

After these six switches from 20 µg/kg/min of dobutamine to the same dose of dopamine, MAP increased from 29-2 (0-5) to 41-2 (2) mm Hg (p=0-05), SVR increased from 837 (86) to 1703 (310) dynes×sec/cm²/m² (p=0-02), and LVO decreased from 356 (40) to 263 (36) ml/min/kg (not significant). The individual variations in MAP, LVO, and SVR during the six switches are indicated in fig 3. In total, 16 hypotensive infants received dopamine infusion (10 at the beginning and six after a switch from dobutamine). MAP rose above 30 mm Hg in 16/16 infants on dopamine compared with 4/10 on dobutamine (p=0.009).

Discussion

Our results show that dopamine was more effective than dobutamine in increasing MAP above 30 mm Hg in hypotensive preterm neonates. The dopamine increase was secondary to an increase in SVR but not in LVO, whereas dobutamine increased cardiac output but had a lesser effect on MAP. The effects of dopamine during the neonatal period, as described in the literature, differ from one study to the other. Though all report an increase in MAP with dopamine, its action on heart output seems to be more variable. Two clinical studies that monitored cardiac output in human neonates reported an increase in cardiac output under dopamine treatment. In the second study, however,
two types of responses were observed after dopamine infusion in six patients: in four cases where LVO was around 100 ml/min/kg before infusion, LVO was increased.\(^22\) Conversely, in the two cases where initial LVO was high, in excess of 300 ml/min/kg, LVO was not or little modified after dopamine infusion. In our study, LVO was high, averaging 245 (23) ml/min/kg in the dopamine group. Conversely, in the study of Walther et al where LVO increased by 76% under dopamine, initial LVO was as low as 114 (26) ml/min/kg.\(^21\) Besides the level of initial LVO, the severity of respiratory distress should also be taken into account. During hypoxia in newborn lambs, it was found that LVO increased only slightly under dopamine, then fell sharply at the highest dopamine doses.\(^7\) In our study, a fall in LVO on dopamine was observed in seven infants; their mean a/Ao2 was 0-18 (0-02) but in the three infants where LVO had increased on dopamine it was 0-32 (0-05) (p=0-03). Moreover, we observed a significant relation between LVO modification on dopamine and a/Ao2. The drop in LVO was secondary to a rise in SVR that increased after the maximum dose. This effect in neonates has been attributed to dopamine stimulation of \(\alpha\) adrenergic receptors.\(^23\) due to early maturation of these receptors.\(^3\) Moreover, hypoxia is known to reduce the density of \(\beta\) adrenergic receptors.\(^24\) This alpha predominant action may also induce pulmonary arterial hypertension\(^9\) which, as in our case 13, can further enhance hypoxia.

Little is known about the effects of dobutamine during the neonatal period.\(^5\) In adults dobutamine improves heart output, reduces SVR, but affects MAP very little, if at all, in terminal heart failure\(^25\) or intensive surgery,\(^12\) except in reducing hypotension during hypovolaemia. Only a few paediatric studies of the haemodynamic effects of dobutamine have been carried out.\(^10\) 11 26 27 Perkins et al reported that the effect of dobutamine on cardiac output was lower in infants under 12 months of age than in older children, whereas MAP was not significantly modified in either group.\(^11\) Conversely, Stopfkuchen et al noted a significant increase in MAP in 12 of 14 cases of preterm infants born at 29 to 36 weeks’ gestation, and demonstrated a significant inotropic effect by measurement of systolic time intervals.\(^10\) In our study MAP increased significantly but insufficiently on dobutamine, lower than with dopamine, remaining below 31 mm Hg in six of 10 cases, despite a 21% increase in cardiac output. The increase in cardiac output can be attributed to the direct inotropic effect of the drug,\(^10\) which is probably limited in the perinatal period.\(^28\)

The initial aim of our study was to increase MAP above 30 mm Hg in order to prevent cerebral ischaemic lesions.\(^1\) The essential question is whether it is better to increase MAP, even if LVO is reduced, or to tolerate lower MAP with higher output. The relation between cerebral flow and MAP, but not between cerebral flow and LVO, has been investigated in autoregulation studies in animal\(^26\) and human\(^30\) neonates. Studies of the relation between systemic haemodynamics and cerebral ischaemic lesions in very preterm neonates\(^1\) have also relied on MAP and not on cardiac output as an indicator of systemic haemodynamics. It is difficult to provide a clear answer to our question as there are few data on the brain flow/LVO relationship. Mean cerebral velocity is apparently more dependent on MAP then on LVO.\(^31\) Thus, there would seem to be a pressure threshold below which there is an increased risk of cerebral ischaemic lesions.

In summary, dopamine would thus seem more suitable than dobutamine as a means of increasing MAP in very preterm neonates. However, dopamine requires special care during hypoxia as there is a significant risk of LVO decrease due to the alpha vasoconstrictor effect. Dobutamine has the advantage of increasing LVO, but has a lesser effect on MAP. Non-invasive LVO monitoring can facilitate the choice of the best inotropic treatment in these hypotensive very preterm neonates.


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