Correlation Between the Pharmacokinetics and Pharmacodynamics of Dopamine in Healthy Subjects

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Summary. The pharmacokinetics and the pharmacodynamic action of dopamine were investigated in 5 healthy subjects. Dopamine was given in different doses (200, 400 and 800 μg/min) by constant intravenous infusion over 90 min. In order to control the influence of the procedure on the measured parameters the subjects also received a similar infusion of saline. Dopamine, noradrenaline and adrenaline levels in plasma were followed for up to 6 h after the infusion, and arterial pressure and heart rate were monitored. Dopamine reached a steady state level within 15 to 30 min after commencement of the infusion; the steady state levels averaged 36.5 μg/l at 200 μg/min, 73.8 μg/l at 400 μg/min and 207 μg/l at 800 μg/min. The corresponding total clearances were 5.81/min, 5.51/min and 3.91/min suggesting non-linear kinetics. The kinetics could not be described by compartmental model. Noradrenaline and adrenaline levels were found to be elevated during infusion of dopamine. Noradrenaline had returned to its pretreatment level within 15 to 30 min after cessation of the infusion, whereas the adrenaline level did not return to the pretreatment value within the observation period. Heart rate was increased by the dose of 400 μg/min, and the systolic and mean arterial pressures were elevated, whereas diastolic blood pressure remained unchanged. Elevated systolic blood pressure was better correlated with plasma dopamine than with noradrenaline concentration. This finding, in conjunction with the unchanged diastolic blood pressure, indicates that elevation of the systolic blood pressure is a direct rather than an indirect effect of dopamine. The increased heart rate was not correlated with the dopamine level.

Key words: dopamine; pharmacokinetics, pharmacodynamics, adrenaline plasma level, noradrenaline plasma level, blood pressure

Dopamine, which elicits its effects by reacting with several distinct catecholamine receptors in the cardiovascular system, has been recommended for a number of years as an inotropic agent with urine flow enhancing properties (Goldberg 1972; Zarolinski 1977). Despite its wide use in patients with congestive heart failure (Rosenblum et al. 1972; Beregovich et al. 1974) and cardiogenic shock (Loeb et al. 1971; Holzer et al. 1973; Reid et al. 1975; Thompson 1977; Francis et al. 1982) few date are available for the plasma level of dopamine with which to correlate its pharmacodynamic action and its pharmacokinetics. In patients with thyroid or upper abdominal surgery Järnberg et al. (1981) reported plasma levels of dopamine, noradrenaline and adrenaline 1 h after termination of anaesthesia when doses of 2 μg/min/kg and 5 μg/min/kg respectively had been administered.

The inotropic effect of dopamine has been considered to be mediated, at least in part, by release of stored myocardial catecholamines (Nash et al. 1968; Tuttle and Mills 1975) and Kho et al. (1980) reported elevated noradrenaline levels during dopamine therapy. Thus, it would be of interest to measure plasma noradrenaline and adrenaline as well as dopamine during administration of dopamine, in order to be able to separate the direct and indirect effects of dopamine. The aim of the present study was to measure the levels of dopamine, noradrenaline and adrenaline plasma levels.

Table 1. Details of the subjects and treatment schedule

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age [years]</th>
<th>Height [cm]</th>
<th>Weight [kg]</th>
<th>Sex</th>
<th>Dopamine [μg/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>26</td>
<td>171</td>
<td>64</td>
<td>f</td>
<td>saline 400 200</td>
</tr>
<tr>
<td>B</td>
<td>29</td>
<td>168</td>
<td>74</td>
<td>m</td>
<td>saline 400 200</td>
</tr>
<tr>
<td>C</td>
<td>27</td>
<td>177</td>
<td>67</td>
<td>m</td>
<td>400 800 saline</td>
</tr>
<tr>
<td>D</td>
<td>34</td>
<td>170</td>
<td>62</td>
<td>m</td>
<td>400 saline 800</td>
</tr>
<tr>
<td>E</td>
<td>25</td>
<td>182</td>
<td>87</td>
<td>m</td>
<td>saline 400 800</td>
</tr>
</tbody>
</table>
adrenaline during administration of dopamine and to correlate some of its effects, namely on heart rate and arterial blood pressure, with the measured plasma levels of catecholamines. The study was done in healthy subjects in order to exclude any influence of disease on catecholamine levels, and to permit administration of more than one dose to each subject and the inclusion of placebo treatment.

**Materials and Methods**

**Subjects**

Five healthy subjects volunteered for the study after their written informed consent had been obtained. Further information is given in Tab. 1. Each subject was normal on physical examination, including ECG and laboratory investigations. No medication was allowed during the study.

**Study Procedure**

After an overnight fast the subjects received a light breakfast. Coffee and tea were not allowed. The subjects received 3 different treatments at intervals of 4 weeks. On two occasions dopamine was given at different infusion rates by constant infusion, and on the third occasion the control treatment with infusion of saline was given to determine the influence of the procedure on endogenous catecholamine levels and pharmacodynamic parameters.

On the first day the subjects were randomly allocated either to saline or dopamine infusion at 400 µg/min. If systolic blood pressure rose more than 20 mmHg at this infusion rate the second dose of dopamine was 200 µg/min. If it did not the second dose of dopamine was raised to 800 µg/min. If saline was the first treatment, the second treatment was dopamine 400 µg/min. If 400 µg/min dopamine was the first treatment, for the second treatment the subjects were randomly allocated either to saline or dopamine 200 or 800 µg/min (Table 1).

Dopamine was infused via an indwelling needle (butterfly No 1), by constant intravenous infusion over 90 min, using an infusion pump (Perfusor, Braun, Melsungen, FRG). 10 ml blood samples were withdrawn from an indwelling cannula inserted in a contralateral arm vein 30 min before commencing the infusion (Braunuelle No.1, Braun, Melsungen, FRG). Blood samples were transferred to plastic tubes containing EDTA (1 ml, 0.2 M) and ascorbic acid (0.2 ml, 0.6 M) and were centrifuged immediately at 4 °C. Plasma was stored at -20 °C until analysed.

Blood was collected 15 min and immediately before the infusion and 1, 3, 5, 8, 10, 12, 14, 16, 30, 45, 60, 75 and 90 min after its start. The infusion was then stopped and blood was withdrawn after 1, 2, 3, 5, 7, 10, 20, 30, 40, 60, 90, 100, 120, 240 and 360 min. At the same times blood pressure was measured by the Riva Rocci method and the pulse rate was continuously recorded.

**Catecholamine**

Plasma concentrations of dopamine, adrenaline and noradrenaline were determined using the double isotope derivative method of Engelman and Portnoy (1970). With this procedure, a high dopamine concentration did lead to incorrect measurement of noradrenaline and adrenaline in the same sample. Therefore, plasma noradrenaline and adrenaline levels estimated in plasma samples after commencement of the dopamine infusion had to be corrected for the dopamine concentration in the same sample. In order to establish the correlation between dopamine and noradrenaline and adrenaline concentrations, different amounts of dopamine were added to human plasma and the 3 catecholamines were estimated in quadruplicate. Linear correlations were found between dopamine estimated in the sample and the corresponding noradrenaline and adrenaline concentrations, so linear regression was used to correct the measured noradrenaline and adrenaline levels.

The coefficient of variation of the dopamine assay was up to 6% in the concentration range 1 to 150 ng/ml. The coefficient of variation for noradrenaline was up to 10% in the concentration range 0.2 and 2.0 ng/ml. Adrenaline showed the greatest coefficient of variation – 22% in the range 0.1 to 1.0 ng/ml. The coefficient of variation for noradrenaline and adrenaline were determined in presence of dopamine (100 ng/ml). For technical reasons plasma concentrations in the samples from Subject E could not be determined.

**Data Analysis**

Pharmacokinetic analysis of the plasma concentration versus time data for dopamine was done with the FUNFIT program on a Wang 2000 desk computer (Heinzle et al. 1977). The open two-and three-compartment model was applied to describe the experimental data. Total clearance was calculated in a model – independent way by dividing the dose by the steady-state level (Cltot = D/min/css).

Catecholamine concentrations versus effect were also plotted on the classical semilogarithmic graphs.