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Effects of dopaminergic drugs on the cardiovascular system and on insulin release in normotensive, hypertensive and type II diabetic subjects

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Diabetes mellitus is one of the most common diseases in the world, being a public health problem due to its acute and chronic complications. Hypertension is also another medical problem and in some cases it is combined with diabetes with certain incidence. Dopamine is a neurotransmitter derived from the catecholamines that acts primarily through two receptors: receptor DA1 and receptor DA2. Dopamine also acts on the adrenergic receptors alpha and beta. The receptor DA1 is located at the postsynaptic level in the smooth muscle of the renal, mesenteric, hepatic, and cerebral and coronary arteries. Its activation produces vasodilation and diminution of the peripheral resistance. The receptor DA2 is localized in the terminations of the sympathetic causing diminution of the release of norepinefrine and inducing a diminution of the systolic pressure. In the present study we examined 30 normal subjects, hypertensives and diabetics type 2, divided into three groups of 10 subjects. The subjects were submitted to a design experimental in which we administered a saline solution during a period of 30 minutes, after which we administered by IV metoclopramide at a dose of 7.5 micrograms/kg/min during a period of 30 minutes, at the final time we administered by IV dopamine IV at a dose of 1 microgram/kg/min during a period final of 30 minutes. The following parameters were measured at the end of the saline solution, at the end of metoclopramide and at the end of dopamine: arterial blood pressure, heart rate, lipid profile and levels of insulin. Additionally we measured the sympathetic reactivity with the presoria by cold. In normal subjects there was a pressure increase of 11.20 mmHg and an increase of heart rate of 5.30 beats/min during the metoclopramide plus dopamine period. Metoclopramide did not alter significantly the cardiovascular parameters. In diabetic patients there was an increase of heart rate of 4.90 beats/min but no changes in the arterial blood pressure during the metoclopramide period. In hypertensive patients the metoclopramide produced a decrease of systolic pressure of 9.27 mmHg and a decrease of diastolic pressure of 7.27 mmHg. During metoclopramide plus dopamine there was an increase of heart rate of 8.45 beats/min but no significant changes in blood pressure. During the cold pressoria in both diabetic and hypertensive patients there was an increase of arterial blood pressure and heart rate. In relation to insulin levels in normal and hypertensive patients the tend to increase in normal subjects and diabetics while the hypertensive patients were atenados in subjects diabetic.

Palabras Claves: diabetes type 2, hypertension, dopamine, receptors of dopamine, release of insulin.
Diabetes mellitus is one of the most frequent diseases all over the world and is a public health problem due to its acute and chronic complications. Hypertension is also another medical problem and in some cases a combined hypertension and diabetes occur with high frequency. Dopamine is a neurotransmitter derived from catecholamines which act through mainly two receptors: DA1 receptor and DA2 receptor. Dopamine also acts on the beta and alpha adrenergic receptor. DA1 receptor is located postsynaptically on the smooth muscle of arterioles of kidney, mesentery, hepatic, coronary and cerebral arteries and its activation induces a vasodilatation and decrease of peripheral resistance. DA2 receptor is located at the sympathetic endings and provokes a decrease of nor epinephrine release and thus induces also a decrease of blood pressure.

In the present study we examined 30 normotensive, hypertensive and type 2 diabetic subjects divided in three groups of 10 subjects. We submitted the subjects to an experimental design in which we gave first saline solution during a period of 30 minutes, then we initiated an IV administration of metoclopramide (MTC) at the dose of 7.5 micrograms/Kg/min during a period of 30 minutes, then while the subjects were receiving MTC, we added dopamine (DM) at the dose of 1 microgram/Kg/min during a final period of 30 min. The following parameters were measured at the end of saline infusion period, at the end of MTC and at the end of MTC plus DM: Blood pressure, heart rate, lipid profile and insulin levels. In addition we measured the sympathetic reactivity by the cold pressor test.

In normotensive subjects there was an increase of systolic blood pressure by 11.20 mmHg and an increase of heart rate of 5.30 beats per minute during the metoclopramide plus dopamine period. Metoclopramide did not alter significantly cardiovascular parameters.

In diabetic subjects there was an increase of heart rate of 4.90 beats per minute but no changes in blood pressure were observed on the metoclopramide plus dopamine period. In hypertensive subjects MTC induced a significant decrease of systolic blood pressure by 9.27 mmHg and also a significant decrease of diastolic blood pressure by 7.27 mmHg. During MTC plus DM period there was an increase of heart rate by 8.45 beats per minute but no significant changes on blood pressure. During cold pressor test in both diabetic and hypertensive subjects there was a significant increase of blood pressure and heart rate. Concerning insulin levels we observed a tendency to increase in normotensive and hypertensive subjects but this was attenuated in diabetic subjects.

Key Words: Type II diabetes, hypertension, dopamine, dopamine receptors, insulin release.
lishing that in both cardiovascular and kidney areas dopamine is able to activate both dopaminergic receptors, DA1 and DA2.

The DA1 receptors of the smooth muscle cells induce vasodilation whereas in renal tubules modulate sodium excretion, induce natriuresis, diuresis and improving renal blood flow and glomerular filtration\textsuperscript{11,12,13}. The DA2 receptors are located in the sympathetic endings and its stimulation reduce nor epinephrine release and thus induce vasodilatation, decrease of heart rate and blood pressure. At higher doses dopamine is able to stimulate beta adrenergic receptors, inducing a positive chronotropic and inotropic effect and increasing blood pressure. At greater doses dopamine stimulate alpha adrenergic receptors causing vasoconstriction\textsuperscript{14,15,16}.

Metoclopramide is a DA2 dopaminergic antagonist\textsuperscript{18,19,20,21}. In patients during the postpartum period metoclopramide increases prolactin secretion through a dopamine antagonism on the hypothalamus\textsuperscript{22,23}.

In the present study we report the cardiovascular and insulin release effects under metoclopramide and dopamine infusion by using an acute comparative design with the infusion of both drugs. We have also measured the cold pressor response to evaluate the sympathetic activity of the subjects.

We examined a total of 30 subjects, 10 normotensive, 10 hypertensive and 10 diabetic type 2 subjects, with gender either male or female, with ages varying between 25 and 60 years. Hypertensive and diabetic type 2 subjects had the medical condition for a period longer than five years and were well controlled with antihypertensive therapy and antidiabetic therapy respectively (Table 1). The condition of Diabetes mellitus was defined through the criteria of the American Diabetes Association (1997) and the condition of high blood pressure was followed according to the recommendations of the VII Report of National Committee on Hypertension (2003). The study was approved by the ethical Committee of our institution and we followed the Helsinki declaration rules.

For the selection of subjects we followed the following criteria: 1) oral consent for participation in the study, 2) high blood pressure with diastolic values without antihypertensive therapy, between 90 and 100 mmHg, 3) isolated systolic blood pressure, 4) type II diabetes mellitus. Serum glucose and blood lipids were measured by colorimetric and enzymatic methods. At the entrance to the study we gave to all subjects a complete history and physical exam, in addition a complete laboratory battery tests were done: complete haematology, lipid profile, hepatic profile, serum glucose, serum creatinine, blood urea nitrogen and urinanalysis. In addition we measured glycosilated haemoglobin by the method of exchange resin and complemented with colorimetric method. Insulin levels were measured by RIA method. Then we evaluated the following medical parameters:

Weight, height, body mass index, waist-hip index and hemodynamic variables such as blood pressure, heart rate and a complete electrocardiogram. The antihypertensive drugs in the hypertensive patients were discontinued two weeks prior to the study. The antidiabetic drugs were maintained in the diabetic type II subjects.

The subjects were divided in three groups: 10 normotensive, 10 hypertensive and 10 type 2 diabetic. In all subjects we used an acute placebo comparative experimental design: 1) placebo was saline solution 0.9% during a period of 30 minutes, 2) Metoclopramide (MTC) at an intravenous dose of 7.5 mcg/kg/min during a period of 30 minutes and 3) on the top of MTC infusion we added dopamine as an intravenous infusion of 1 mcg/kg/min during a period of 30 minutes. The cardiovascular variables were measured by a mercury sphygmomanometer and dynamap. The MTC infusion technique was undertaken as previously reported\textsuperscript{22} and the dopamine infusion technique was undertaken as previously reported\textsuperscript{21}. Cold pressure test (CPT) was undertaken by asking the subjects to immerse hand right to the wrist in ice water(4°C) as previously reported (Velasco et al, 1982)\textsuperscript{20} at the middle (time: 15, 45 and 75 minutes) of each infusion period.

Statistical analysis was performed by calculating means and standard deviations. We also used t student test, Wilcoxon test and analysis of variance of two tails. For groups comparison we used Bonferroni test. We consider a significant value if $P$ was less than 0.05.

!! Table 1. Clinical characteristic of experimental subjects. !!

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>NORMOTENSIVES</th>
<th>TYPE 2 DIABETICS</th>
<th>HYPTENSIVE</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE, years</td>
<td>37.3±8.9</td>
<td>49.5±5.2</td>
<td>49.2±6.9</td>
<td>9.527*</td>
</tr>
<tr>
<td>WEIGHT, Kg</td>
<td>75.6±13.2</td>
<td>81.2±13.4</td>
<td>70.2±15.5</td>
<td>1.584</td>
</tr>
<tr>
<td>HEIGHT, m</td>
<td>1.64±0.04</td>
<td>1.66±0.03</td>
<td>1.62±0.04</td>
<td>2.901</td>
</tr>
<tr>
<td>BMI</td>
<td>28.0±4.4</td>
<td>29.3±4.4</td>
<td>26.5±6.0</td>
<td>0.775</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index
* Statistically significant at $p<0.05$
lic blood pressure by 9.27 mmHg and a significant decrease of diastolic blood pressure by 7.27 mmHg only in hypertensive subjects. When dopamine was added in metoclopramide-pre-treated subjects at the dopaminergic dose (1 microgram/kg/min) there was a significant increase of systolic blood pressure by 11.20 mmHg in normotensive subjects. In Tables 6 and 7 we can observe the effects of dopaminergic drugs on the heart rate in normotensive, hypertensive and type 2 diabetic subjects.

We observe that metoclopramide did not alter significantly heart rate; however, when dopamine was added in metoclopramide-pre-treated subjects at the dopaminergic dose of 1 microgram/kg/min, the heart rate increased significantly by 5.30 beats per minute in normotensives, by 4.90 beats per minute in type 2 diabetics and by 8.45 beats per minute in hypertensive subjects. As we observe dopamine caused an increase of blood pressure and heart rate in hypertensive patients but these changes were not observed in diabetic type 2 subjects. 

When we measured serum cholesterol and serum triglycerides we were not able to find significant changes by the effect of dopaminergic drugs. There was a tendency to an increase of insulin levels in normotensive and hypertensive subjects when they were treated with dopamine but this was attenuated in diabetic subjects. Cold pressor test (CPT) caused in all subjects a significant increase of blood pressure during treatment with placebo, metoclopramide and metoclopramide plus dopamine.

| Table 4. Effects of dopaminergic drugs on diastolic blood pressure |
|------------------|---------------|---------------|---------------|---------------|
| GROUPS | PLACEBO | MTC | MTC+DM |
| NORMOTENSIVES N=10 | 75±9 | 72±9 | 72±12 | 75±13 |
| TYPE II DIABETICS N=10 | 79±7 | 79±8 | 74±9 | 75±6 |
| HYPERTENSIVES N=10 | 91±10 | 91±13 | 84±13 | 86±12 |

Values are shown as Mean ± SD. 30 min: 0.9% saline solution; 60 min: metoclopramide; 90 min: metoclopramide plus dopamine

| Table 5. Effects of dopaminergic drugs on systolic blood pressure |
|------------------|---------------|---------------|---------------|
| GROUPS | PLACEBO | MTC | MTC+DM |
| NORMOTENSIVES N=10 | -0.50 | -0.01 | 2.00 |
| TYPE II DIABETICS N=10 | -0.80 | -4.70 | 1.30 |
| HYPERTENSIVES N=10 | 0.09 | -7.27* | 2.55 |

Values are expressed as % of change. DBP, Systolic blood pressure. MTC: metoclopramide; MTC plus DM: metoclopramide plus dopamine

*Statistically significant at level of p < 0.05.

Discussion

In this study we are reporting the effects of dopaminergic drugs, dopamine and metoclopramide, on the cardiovascular system and on the insulin levels. Metoclopramide decreased significantly systolic blood pressure but did not alter heart rate. This finding is in agreement with a previous report from our laboratory. We attributed this hypotensive effect of metoclopramide to an alpha adrenergic blocking effect but not to an antidopaminergic effect. Metoclopramide is a DA2 dopaminergic blocker...
and we use this drug in the postpartum patients to increase lactation by its action on the hypothalamus. Dopamine caused an increase in blood pressure and heart rate especially in hypertensive patients but not in diabetic type II subjects. This attenuated effect of dopamine in these latter subjects has been interpreted as a lack of action of dopamine due to the well known defect on the sympathetic nervous system and endothelial function which make to be hyporeactive to dopamine; this finding has not been reported in the literature. This finding is now been explored further in our laboratory by measuring nitric oxide and endothelin 1 and angiotensin II levels.

The fact that dopamine increased blood pressure and heart rate, is obvious that this finding was due to beta adrenergic and alpha adrenergic receptors stimulation and not to dopaminergic receptor stimulation. In a previous study we demonstrated that dopamine caused a decrease of blood pressure in labetalol-pretreated patients.

As we know labetalol is a combined alpha and beta adrenergic blocker and allowed us to observe the hypotensive effect of dopamine by stimulating the dopaminergic receptors and at the same time we reported an insulin increase by dopamine which was blocked by the use of metoclopramide. In the present study we did not treat the subjects with labetalol due to obvious reasons since our patients had diastolic blood pressure values between 90 and 100 mmHg.

In conclusions, 1) There is a pharmacological interaction between metoclopramide, an antidopaminergic drug, and dopamine, a dopaminergic receptor agonist and beta and alpha adrenergic agonist, 2) The pressor effects of dopamine are due to activation to beta and alpha adrenergic receptors, and 3) The cardiovascular effects of dopamine in type II diabetic subjects are attenuated by a probable defect in sympathetic system and endothelial function.

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References


