The Antihypertensive Effects of Olanzapine, Magnesium Oxide and Red Grape

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Abstract:

Essential hypertension is one of the widely distributed cardiovascular disorder that shares a problematic pathological causation for several critical body organs including the chronic wear and tear effects on the blood vessels of the retina, coronary, renal and cerebral arteries making hypertension an important etiological factor to be treated. In this current study a trial of provision for the most safe and convenient antihypertensive agents was evaluated for the tranquilizing effect of olanzapine as stress is being one of the significant factors for essential hypertension, in addition to Mg salt and grape as stand for...
agents that prevent dystrophic sequelae of hypertension especially with grape quercitin and anthocyanin that posses a potent antioxidant and kinase inhibiting properties. A model of hypertension was made on local domestic rabbits with 5mg/kg of daily hydrocortisone and NaCL for 7 days followed with daily oral supplement of olanzapine, MgSO4 and red grape for further 7 days that was daily monitored for the mean arterial pressure MAP with mechanical microphone transducer applied on the thigh as compared with prazosin effect. Olanzapine, MgSO4 showed approximately equipotent significant antihypertensive effect to prazosin in that they reduced MAP to 128,130 and 128 mmHg respectively at day 7 as compared with 150 mmHg for the untreated group, However red grape showed the highly significant antihypertensive effect by reducing MAP to 117 mmHg at P<0.05. From the overall results, alternative antihypertensive agents need further emphasis as they could provide more effective and safe support for treating hypertension.

Introduction:

Hypertension shows a prevalence of approximately 25% of all adults and over 60% of persons older than 60 years in the United States and comprises about 15% of the general population.It is one of the major underlying pathology of many chronic neural and somatic degenerative diseases including ischemic cerebrovascular and cardiovascular disturbances in addition to its predisposition to the lipodystrophic disease, atherosclerosis.

With few exceptions many of the classical antihypertensive drugs have depressant effects on the vascular smooth muscle tone through inhibition of Ca channels, ACE, alpha and beta adrenoceptors and induction of diuresis, since essential hypertension is characterized by increased vascular tone either due to hereditary and environmental factors of pathogenesis like obesity, salt intake and stress among the environmental influences whereas autonomous nervous dysfunction, increased contractility of vascular smooth muscle cells and impaired renal handling of sodium are major abnormalities in essential hypertension. However, satisfying these mechanisms is not sufficient to overcome the associating atherogenesis. Drugs that posses an antiplatelet function activity are eventually of therapeutic significance since platelets play a role in mediation of hypertension, thrombosis and atherosclerosis. Many antiplatelets, antioxidants and smooth muscle relaxant agents had been investigated for their antihypertensive and antithrombotic trial like quercetin flavonoid in addition to trials of modulating psychosomatic stress cause of hypertension and atherosclerosis. Anti-calcium strategy is also significant since Ca ion is the major factor for both thrombosis (platelet and coagulation stimulant) and presser for vascular smooth muscles. Magnesium is considered as a natural antagonist to Ca and could be of therapeutic value for these purposes. This trial was directed toward finding well available drug that is used for other purposes and making use of its metabolic and calming effects for further overcoming precipitating causes of hypertension and atherosclerosis.

Animal model trial of induced hypertension is a good method of assessing antihypertensive effects of different drugs.
Materials and Methods:  
Test agents included:  
1. Olanzapine 10 mg tablet (Olan-5. Rabaxy. India).  
3. Prazosin tablet of 5 mg (Kimadia, Jordan).  
4. Red grape (Vitis vinifera) was prepared as a dried powder (500 mg dose).  
   It contains flavonoids e.g. quercetin in addition to anthocyanin as phenolic compounds.

Grouping of the rabbits: First group represents the normal control group, whereas group 2 is a hypertensive induced group and treated by nothing apart from 1 ml distilled water. Group 3 treated with grape juice 500 mg once daily for 7 days. Group 4 treated with Olanzapine 2 mg/kg orally once daily for 7 days. Group 5 treated with MgSO4 powder 200 mg/kg orally once daily for 7 days. Group 6 treated with prazosin 1 mg/kg orally once daily for 7 days.

Animal Model of Hypertension: A model of hypertension was achieved by a 7 days of administration of daily oral hydrocortisone 5 mg/kg with 5% NaCl.

Monitoring and Instrumentation:  
All rabbits were monitored daily for their MAP that was assessed with application of the indirect heart microphone on the left thighs 2 hours after administration of each drug for assessing the mean arterial blood pressure. The transducer was connected to the physiograph with adjustment of sensitivity to 2 cm/mV and 2.5 cm/s of chart speed. This procedure was repeated daily throughout the 7 days. Systolic and diastolic blood pressures were readily measured to calculate the mean arterial blood pressure (MAP). All measurements were estimated at +/- 2 SD and P < (0.05).

Results:  
Table (1): The mean arterial blood pressure values in mmHg of the rabbits induced with hypertension and treated with different test agents throughout 7 days with their paired t test at P<0.05 as compared with the untreated group.

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP in mmHg (+/-2mmHg) of the rabbits groups throughout the days of treatment course</th>
<th>Statistical test of significant T test P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated induced</td>
<td>160 160 156 154 153 150 150</td>
<td>Not significant</td>
</tr>
<tr>
<td>Prazosin</td>
<td>160 152 143 135 130 128 128</td>
<td>Significant decrease</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>162 140 138 137 137 137 130</td>
<td>Significant decrease</td>
</tr>
<tr>
<td>MgSO4</td>
<td>164 153 150 146 142 134 128</td>
<td>Significant decrease</td>
</tr>
<tr>
<td>Grape</td>
<td>158 154 153 150 130 123 117</td>
<td>Highly Significant decrease</td>
</tr>
</tbody>
</table>

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Figure (1): Shows the antihypertensive effects of olanzapine, MgSO4, grape in comparison with the conventional antihypertensive effect of prazosin as estimated with the indirect heart microphone method in hypertension induced rabbits along 7 days of treatment.

Discussion:

Essential hypertension causes a significant problem from the health point of view in that it affects up to 15% of the general population\(^1\) with cumulative arterial destructive consequences, in addition to many rational antihypertensives are although being sufficient in reducing blood pressure, they can no longer overcome the basic causation of hypertension moreover to their economic and to some extent toxic effects that can contribute to their low compliance e.g. captopril, despite its effectiveness, it causes up to 2.4% incidence of cough\(^{12}\), or a condition of postural hypotension, throbbing headache and edema in some vasodilator antihypertensives.

In a trial to find a convenient, safe and potent antihypertensive agents that in addition to its blood pressure lowering activity it may further have antiplatelet, antioxidant, and anti-remodeling cellular stabilizing properties, this work was purposed in this direction.

Rabbits are considered as a good animals for induction of cardiovascular disease model namely hypertension owing to their feasible approach and a relatively accessible peripheral site for blood pressure measuring i.e. rabbit thigh\(^{10}\).

Instrumentation for measuring rabbit blood pressure are now variably available. In this research an indirect mechanical transducer was adjusted to transmit a femoral artery pulsation into the highly sensitive physiographer.

Hydrocortisone cumulatively stimulate pressor effect by sensitizing arteriolar smooth muscle and by its mineralocorticotropic activity especially if combined with Na salts, so that a reliable induced hypertension model could be achieved in this mean.
Olanzapine showed a significant antihypertensive activity in comparison with prazosin in that they had reduced rabbit blood pressure to 130 and 128 mmHg respectively after 7 days of daily treatment. This blood pressure lowering effect of olanzapine was similar to one study on elderly men, could be attributed to its alpha-adrenergic blockade activity in addition to its anti-DR4 tranquilizing effect and neurotransmitters release attenuation. MgSO4 had showed nearly similar effects that was clearly explained with its calcium antagonizing activity in addition, it may have some lipid lowering and free radicals scavenger effects. The most attractive results were noticed with red grape fruit part Vitis vinifera in that it caused highly significant reduction in MAP down to 117 at the 7th day of treatment P<0.05. Red grape effect raise the attention in considering the vasoprotective polyphenolic flavonoid, quercetin which become increasingly evidenced in its antioxidant and kinase suppressing effects in addition to anthocyanin and inositol, levulose, tannin, sugar and malic acid contents in the fruit. Different studies had agreed with our finding verifying that quercetin possesses antioxidant and cytoprotective activities. Moreover alternative mechanism of antihypertension could further support treatment of hypertension.

Recommendations:
1- Further emphasis on the natural antihypertensive agents as adjunct to treatment of hypertension even by including as a dietary item.
2- Attention would be allocated to flavonoids for their purification and pharmacological evaluation.
3- Anxiety in patient with hypertension is to be treated with tranquilizers that posses additive antihypertensive effect.

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