Effect of TCV-309, a Novel Platelet Activating Factor Antagonist, on Hemodynamics in Dogs with Endotoxin-Induced Shock

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ABSTRACT. The therapeutic effects of TCV-309, a novel platelet activating factor antagonist, on hemodynamics in endotoxin-induced shock were evaluated. Ten Beagle dogs were used under general anesthesia and artificial ventilation. After intravenous injection of endotoxin (3 mg/kg), TCV-309 (1 mg/kg) was administered intravenously to the dogs. The results showed that the depression of mean aortic pressure, cardiac output, left ventricular stroke work index and urine volume which occurred in endotoxin shock was significantly improved by administration of TCV-309. These results suggested that TCV-309 was a useful therapeutic for the circulatory disturbance in endotoxin shock. - KEY WORDS: endotoxin shock, hemodynamics, TCV-309 (PAF-antagonist).


Pathological characteristics of endotoxin-induced shock, circulatory disturbance, disseminated intravascular coagulation and pulmonary disorder have been given much attention in relation to platelet activating factor (PAF) [1, 2, 8, 11]. The depression of blood pressure and a lethal effect seen in endotoxin-induced shock can be reproduced in animals by administration of PAF [1] and can be controlled with a PAF-antagonist [3-5, 16, 18].

TCV-309 used in this experiment is a newly developed PAF-antagonist, and its anti-PAF titer has been estimated to amount to several hundred times that of CV-3988 which is well known as a PAF-antagonist [17]. In the present study, the hemodynamic action of TCV-309 was investigated in dogs with experimentally induced endotoxin shock in order to evaluate its therapeutic effect.

The experiment was performed basically by the method previously reported [12]. Ten clinically healthy Beagle dogs (aged 1-5 years, weight 7-14 kg) without fialarial infection were used. The experiment was carried out under general anesthesia with sodium pentobarbital and artificial ventilation.

Pre-experimental data were collected after confirming the stabilization of hemodynamic parameters. Endotoxin (Escherichia coli 055:B5 Difco, Detroit, U.S.A., 3 mg/kg) was intravenously injected over 5 min in all dogs. In the TCV-309 group (n=5), TCV-309 (Takeda Chemical Industries Ltd., Osaka, Japan, 1 mg/kg) was intravenously injected over 10 min immediately on completion of endotoxin treatment, and physiological saline in the control group (n=5). Changes in hemodynamics were observed for 360 min after administration of endotoxin.

The data were expressed as mean ± standard deviation. Statistical analysis was performed using Student’s t test or Mann-Whitney test. P value <0.05 was considered to be statistically significant.

Table 1 shows the effects of TCV-309 on hemodynamics. The mean aortic pressure decreased by endotoxin administration was increased significantly at 30 min in the TCV-309 group. This anti-hypotensive effect was promin-

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Table 1. Effect of TCV-309 on hemodynamics of dogs with experimentally-induced endotoxic shock

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>Pre</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
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<tbody>
<tr>
<td></td>
<td>TCV-309</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR(m)</td>
<td>control</td>
<td>145.0±7.8</td>
<td>175.4±37.6</td>
<td>159.2±43.6</td>
<td>174.4±33.4</td>
<td>162.6±36.2</td>
<td>154.0±21.5</td>
<td>146.0±27.8</td>
<td>158.6±30.1</td>
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<tr>
<td>MAP(m)</td>
<td>control</td>
<td>130.2±33.7</td>
<td>158.2±24.3</td>
<td>159.6±34.6</td>
<td>171.4±38.4</td>
<td>175.8±35.3</td>
<td>166.4±29.7</td>
<td>171.0±30.9</td>
<td>161.5±31.1</td>
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<tr>
<td>MPAP(m)</td>
<td>control</td>
<td>124.5±24.7</td>
<td>108.6±30.3</td>
<td>79.3±29.6</td>
<td>77.9±31.4</td>
<td>100.5±30.3</td>
<td>113.7±28.6</td>
<td>116.1±23.4</td>
<td>130.2±24.9</td>
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<tr>
<td>CI(m)</td>
<td>control</td>
<td>8.7±2.8</td>
<td>8.8±1.2</td>
<td>9.0±1.3</td>
<td>9.9±1.8</td>
<td>10.3±3.3</td>
<td>11.6±5.5</td>
<td>13.2±5.0</td>
<td>14.4±6.8</td>
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<tr>
<td>SVI(l/min/m²)</td>
<td>control</td>
<td>11.3±2.3</td>
<td>10.5±3.1</td>
<td>8.4±1.4</td>
<td>9.5±2.1</td>
<td>10.8±0.6</td>
<td>11.6±0.7</td>
<td>13.1±2.5</td>
<td>15.0±5.2</td>
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<td>SVR(mEq/l/min/m²)</td>
<td>control</td>
<td>3.2±0.7</td>
<td>2.3±0.3</td>
<td>2.3±0.5</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
<td>0.9±0.3</td>
<td>0.8±0.3</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>PVR(mEq/l/min/m²)</td>
<td>control</td>
<td>2.3±0.8</td>
<td>2.3±0.3</td>
<td>2.3±0.5</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
<td>0.9±0.3</td>
<td>0.8±0.3</td>
<td>0.8±0.2</td>
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<tr>
<td>LVSWR(mEq/l/min/m²)</td>
<td>control</td>
<td>5.9±0.1</td>
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<td>5.9±0.1</td>
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<tr>
<td>RPP(mEq/l/min/m²)</td>
<td>control</td>
<td>397±117</td>
<td>496±130</td>
<td>599±128</td>
<td>598±188</td>
<td>592±68</td>
<td>572±81</td>
<td>700±203</td>
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<td>UVR(mEq/l/min/m²)</td>
<td>control</td>
<td>34±8.4</td>
<td>37.2±11.9</td>
<td>18.7±7.1</td>
<td>15.9±10.8</td>
<td>19.4±16.0</td>
<td>25.2±19.5</td>
<td>27.5±8.4</td>
<td>28.2±9.4</td>
</tr>
</tbody>
</table>

Data represent mean±standard deviation.

- a) heart rate (beat/min), b) mean aortic pressure (mmHg), c) mean pulmonary arterial pressure (mmHg), d) cardiac index (l/min/m²), e) stroke volume index (ml/min/m²), f) systemic vascular resistance (dyne-sec-cm⁻²), g) pulmonary vascular resistance (dyne-sec-cm⁻²), h) left ventricular stroke work index (g-m/beat/m²), i) rate pressure product (mmHg/min), j) urinary volume (ml/kg/hr), k) not determined, l) p<0.05 versus control, m) p<0.01 versus control.

so no difference might be produced in peripheral vascular resistance between the two groups. Thromboxane A₂, another chemical mediator of endotoxic shock, elevates pulmonary vascular resistance [19], and TCV-309 inhibits the increase in circulatory thromboxane A₂ [20]. As indicated Table 1, there were tends to decrease the pulmonary peripheral vascular resistance in the endotoxin shock by administration of TCV-309. The diuretic effect of TCV-309 seemed to reflect its anti-hypotensive effect or TCV-309 seemed to have a direct diuretic effect on kidney [7].

Therapeutic effects of PAF-antagonists on endotoxic shock have been often documented. Differences in experimental condition and method preclude simple comparison of these effects, but Terasita et al. [17] described that TCV-309 had five times as much effect to improve endotoxin-induced hypotension as WEB2086 and 208 times as much as CV-3988. Furthermore, TCV-309 is free from side-effects found in CV-3988 such as hemolytic action and injurious action on blood vessels [15, 17].

TCV-309 significantly improved the depression of blood pressure, cardiac output and urine volume caused in experimentally induced endotoxin shock under anesthesia. These results suggested the usefulness of TCV-309 for the improvement of circulatory disorders in endotoxin shock.

Fig. 1. Effect of TCV-309 on mean aortic pressure of dogs with experimentally-induced endotoxin shock. Data represent mean±standard deviation. ●: TCV-309, ○: control, •: p<0.05 versus control, ★: p<0.01 versus control.
REFERENCES


