EFFECT OF PENTOXIFYLLINE ON BIOCHEMICAL PARAMETERS IN ENDOTOXAEMIC NEW ZEALAND WHITE RABBITS

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Abstract
Effect of pentoxifylline on biochemical values in endotoxaemic rabbits was investigated. Forty rabbits were divided into four equal groups. Group 1, served as a control group, group 2: lipopolysaccharide was injected intravenously, group 3: pentoxifylline was injected intraperitoneally, group 4: lipopolysaccharide and pentoxifylline were injected simultaneously. Serum samples were collected 6 h after the treatments. Serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, creatinine, urea, glucose, total protein, albumin, triglyceride, cholesterol, sodium, potassium, chloride, phosphorus and magnesium levels were measured. Pentoxifylline induced protective effect on the liver and kidney in endotoxaemia, but did not show any protective effect on lipid metabolism.

Key words: rabbits, endotoxaemia, pentoxifylline, biochemical values.

Severe Gram negative bacterial infection lead to the development of endotoxic shock, which is characterized by fever, acute haematological, cardiovascular and respiratory disorders, multiple organ failure, and even death. Lipopolysaccharide (LPS), outer membrane of Gram negative bacteria, is released during bacterial lysis and causes endotoxic shock. LPS stimulates the production of arachidonic acid metabolites, complement factors, cytokines and coagulation cascades. Endotoxic shock causes high mortality in intensive care patients (3, 5, 8).

Pentoxifylline (PEN) is a phosphodiesterase inhibitor that inhibits tumour necrosis factor-alpha (TNFα) release and neutrophil activation. PEN has been used to the treatment of sepsis/endotoxaemic shock in last years (12, 16, 19). TNFα is the key mediator in endotoxaemia, and PEN reduces LPS-induced TNFα level and changes in some interleukin levels (1, 7, 13).

Changes in biochemical values are observed in the specific organ failure or damage. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and total bilirubin (Tbilirubin) levels are measured as indicators of hepatotoxicity (4, 18), while creatinine and urea are measured as indicators of nephrotoxicity (18). Triglyceride and cholesterol are measured for monitoring the lipid metabolism, and sodium (Na), potassium (K), chloride (Cl), phosphorus (P) and magnesium (Mg) levels are measured for monitoring the fluid-electrolyte balance.

Many studies were conducted on the effect of PEN on cytokines in endotoxaemia, but those on the effect of PEN on biochemical values are rare. In this study, the possible protective effect of PEN on biochemical parameters that are accepted as indicators of hepatotoxicity, nephrotoxicity, lipid metabolism and fluid-electrolyte balance in endotoxaemia has been investigated. Glucose, total protein (Tprotein) and albumin were measured as well.

Material and Methods
Forty New Zealand white rabbits (male, 8-10 months, 2-2.5 kg, Kombassan Research Center, S U Konya) were randomly divided to four equal groups. Group 1 served as a control group. Group 2: LPS (Escherichia coli 0111:B4, Sigma) was injected intravenously (400 µg/kg, auricular vein). Group 3: PEN (Trental® amp, Hoechst Marion Roussel, Istanbul, Turkey) was injected intraperitoneally (50 mg/kg). Group 4: PEN (50 mg/kg, intraperitoneally) and LPS (300 µg/kg, intravenously) were injected simultaneously. Blood samples were taken from auricular vein 6 h after the treatments. Serum samples were collected for the determining of the biochemical parameters.
ALT, AST, GGT, Tbilirubin, creatinine, urea, glucose, Tprotein, albumin, cholesterol, triglyceride, P and Mg levels were measured with an auto-analyser (TMS 1024, Tokyo Boeki Medical System). Na, K, and Cl levels were measured with Starlyte™ III analyser (Schiapparelli Biosystems Inc, Eni Diagnostic Division).

All the values are expressed as mean± SE. The results were analysed by Tukey multiple range test (SPSS for windows, release 10.0). In all cases, probability of error of less than 0.05 was selected as the criterion for statistical significance.

Results

Effect of PEN on biochemical parameters is presented in Table 1. LPS caused statistically significant increases in AST, ALT, GGT, creatinine, urea, triglyceride, cholesterol, and Mg levels. Although statistically significant changes of parameters such as glucose, Tprotein, albumin, P, and Cl were obtained, these values were within the reference range. PEN decreased AST and ALT levels in endotoxaemia.

Table 1

Effect of pentoxifylline on biochemical parameters in endotoxaemic New Zealand white rabbits (mean±SE)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=10)</th>
<th>LPS (n=10)</th>
<th>PEN (n=10)</th>
<th>LPS+PEN (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST U/L</td>
<td>62.3±6.05 ab</td>
<td>153±30.3 c</td>
<td>40.4±4.01 a</td>
<td>125±17.2 b</td>
</tr>
<tr>
<td>ALT U/L</td>
<td>72.3±5.15 a</td>
<td>183±21.5 b</td>
<td>65.8±6.56 a</td>
<td>109±16.9 a</td>
</tr>
<tr>
<td>GGT U/L</td>
<td>6.80±1.55 a</td>
<td>51.7±8.77 b</td>
<td>8.30±0.84 a</td>
<td>27.3±17.3 c</td>
</tr>
<tr>
<td>Tbilirubin mg/dL</td>
<td>0.03±0.01 a</td>
<td>0.03±0.01 a</td>
<td>0.02±0.01 a</td>
<td>0.04±0.01 a</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>2.10±0.07 a</td>
<td>3.33±0.11 b</td>
<td>1.94±0.09 a</td>
<td>3.25±0.19 b</td>
</tr>
<tr>
<td>Urea mg/dL</td>
<td>42.18±2.27 a</td>
<td>98.4±3.63 b</td>
<td>49.1±2.93 a</td>
<td>67.8±4.95 b</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>133±5.24 a</td>
<td>139±11.7 a</td>
<td>99.1±6.49 b</td>
<td>144±8.63 a</td>
</tr>
<tr>
<td>Tprotein g/dL</td>
<td>6.76±0.08 a</td>
<td>6.17±0.24 ab</td>
<td>5.81±0.14 a</td>
<td>6.08±0.14 b</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>3.94±0.03 a</td>
<td>3.60±0.13 b</td>
<td>3.54±0.09 a</td>
<td>3.66±0.06 ab</td>
</tr>
<tr>
<td>Triglyceride mg/dL</td>
<td>101±8.29 a</td>
<td>481±68.2 b</td>
<td>183±76.3 a</td>
<td>557±79.5 b</td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td>25.9±1.61 a</td>
<td>59.7±11.8 b</td>
<td>43.3±8.94 a</td>
<td>60.1±6.56 b</td>
</tr>
<tr>
<td>Na mmol/L</td>
<td>147±0.79 a</td>
<td>144±2.91 a</td>
<td>127±1.93 b</td>
<td>145±1.56 a</td>
</tr>
<tr>
<td>K mmol/L</td>
<td>4.51±0.29 a</td>
<td>4.03±0.17 a</td>
<td>3.92±0.20 a</td>
<td>4.17±0.28 a</td>
</tr>
<tr>
<td>Cl mmol/L</td>
<td>105±0.68 a</td>
<td>105±0.99 a</td>
<td>101±1.42 b</td>
<td>109±1.29 a</td>
</tr>
<tr>
<td>P mg/dL</td>
<td>4.46±0.17 a</td>
<td>6.39±0.44 b</td>
<td>4.32±0.40 a</td>
<td>6.16±0.38 b</td>
</tr>
<tr>
<td>Mg mg/dL</td>
<td>2.77±0.08 a</td>
<td>3.97±0.33 b</td>
<td>2.60±0.12 a</td>
<td>3.64±0.27 b</td>
</tr>
</tbody>
</table>

a,b,c; different letter in the same row indicates that the value is statistically different from others (P<0.05). PEN; pentoxifylline, LPS; lipopolysaccharide.

Discussion

Changes of biochemical values are generally observed in organ failure or damage. Increases in serum AST, ALT and GGT activities are suggestive of hepatic damage (4, 18), and changes in creatinine and urea levels are suggestive of renal damage (18). In the present study, LPS caused increases in AST, ALT, GGT, creatinine, urea, triglyceride, cholesterol and Mg levels. It may be stated that LPS causes renal and hepatic damage, and disorders in lipid metabolism. These increases were suppressed by the administration of PEN except for triglyceride, cholesterol and Mg. On the other hand, PEN decreased sodium level in healthy rabbits. Many authors reported that LPS caused increases in ALT, GGT, triglyceride, cholesterol, VLDL, Mg and K levels (2, 6, 9-11, 14, 15, 17). These reported results are in agreement with our results. Yang et al. (20) reported that increased ALT activity in sepsis was reduced by PEN, and this result is similar to our finding, as well. PEN suppressed the biomarkers of hepatic and renal damage. It was stated that hyperlipidaemia might occur in sepsis (18). In our study, LPS increased triglyceride and cholesterol levels, but PEN did not suppress these increases.

As results, LPS increased hepatic and renal damage markers and changed some lipid values. It may be stated that PEN has protective effect on the liver and kidney in endotoxaemia, although it does not have any protective effect on lipid metabolism of endotoxaemic rabbits.

References


