SYNERGISTIC ACTION OF DIMETHOXYPHENYL-PENICILLIN AND CEPHALORIDINE AGAINST GRAM NEGATIVE BACTERIA

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(Received September 14, 1966)

An outline of this investigation was presented at the 14th General Meeting of Japan Society of Chemotherapy on May 26th, 1966.

It has been reported that dimethoxyphenyl-penicillin (DMP-PC) acts as a powerful competitive inhibitor of hydrolysis of 7-Amino-Cephalosporinic acid (7-ACA) by the enzyme from a strain of Pseudomonas aeruginosa, though it itself was not hydrolysed at an appreciable rate. (L.D. SABATH et al., Nature. 204: 1006, 1964) In the combination of these drugs synergistic action can be obtained from this strain in vitro. In view of this idea, a few other investigations using methicillin (DMP-PC) or Methylchloropenilisoxazolyl-PC (MCI-PC) as competitive inhibitor and other penicillin derivatives or 7-ACA together, have been carried out, employing gram negative bacteria. (J.M.T. HAMILTON MILLER et al., Nature. 201: 867, 1964) (R. SUTHERLAND et al., Nature. 201: 868, 1964) We have been working in vitro on similar action of DMP-PC and Cephaloridine (CER) against many clinical organisms isolated from urinary tract infections which were highly resistant to CER. Among 120 strains of gram negative bacilli isolated from urinary tract infections at Keio University Hospital, resistant more than 250 mcg/ml of CER on plates, 16 strains were selected. The strains tested were 2 E. coli, 6 Klebsiella, 2 Providencia, 6 Citrobacter. Pseudomonas strains were eliminated because they produce heavy threads-like masses while shaking, making optical measurement of growth difficult. Penassay broth 'Difco' was used in both of precultures and shaking cultures. Overnight cultures in penassay broth were the inoculates. They were diluted into the media in 'L' tubes which were shaken at 37°C in the incubator. Bacterial growth was followed by optical density at 530 μm with an electrophotometer.

Drug free growth, growth in the tubes containing DMP-PC or CER alone were the controls. Concentrations of CER used were the highest ones which allow uninhibited growth in the preliminary experiments. 500 mg/ml of DMP-PC were employed as potent enzyme inhibitor throughout this experiment. Bacteriolysis as a result of synergistic action was found in 8 strains among 16 isolates. (Table 1) Typical lysis curve is shown in Fig. 1. The in vivo experiments followed by clinical application are now being progressed.

Table 1 The synergistic action of CER and DMP-PC against selected isolates.

<table>
<thead>
<tr>
<th>MIC of CER (tube dilution method)</th>
<th>synergistic action</th>
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<tbody>
<tr>
<td>observed</td>
<td>No. of strains</td>
</tr>
<tr>
<td>500 ≤ mcg/ml</td>
<td>Klebsiella 313</td>
</tr>
<tr>
<td>250 ≤ mcg/ml</td>
<td>Citrobacter 205, 209</td>
</tr>
<tr>
<td>100 ≤ mcg/ml</td>
<td>Citrobacter 208</td>
</tr>
<tr>
<td>50 ≤ mcg/ml</td>
<td>Klebsiella 307</td>
</tr>
<tr>
<td>25 ≤ mcg/ml</td>
<td>Citrobacter 207</td>
</tr>
<tr>
<td>10 ≤ mcg/ml</td>
<td>Citrobacter 206</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
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