TABLE IV—Mean (±SD) sucking rate, peak sucking pressure, and milk consumption in naloxone- and placebo-treated infants up to 48 hours after birth.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Placebo</th>
<th>Naloxone</th>
<th>P</th>
<th>Placebo</th>
<th>Naloxone</th>
<th>P</th>
<th>Placebo</th>
<th>Naloxone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>23.9±21.7</td>
<td>42.8±10.4</td>
<td>0.009</td>
<td>4.57±3.4</td>
<td>6.91±1.54</td>
<td>0.004</td>
<td>0.31±0.2</td>
<td>0.61±0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>8</td>
<td>29.6±19.3</td>
<td>44.1±11.3</td>
<td>0.02</td>
<td>4.98±2.93</td>
<td>6.57±1.62</td>
<td>0.009</td>
<td>0.32±0.2</td>
<td>0.6±0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>12</td>
<td>17.4±17.0</td>
<td>44.6±6.2</td>
<td>0.0001</td>
<td>4.00±3.84</td>
<td>6.90±1.62</td>
<td>0.02</td>
<td>0.27±0.3</td>
<td>0.55±0.1</td>
<td>0.007</td>
</tr>
<tr>
<td>24</td>
<td>26.3±23.0</td>
<td>41.3±15.3</td>
<td>0.05</td>
<td>4.40±3.40</td>
<td>6.66±2.52</td>
<td>0.05</td>
<td>0.34±0.34</td>
<td>0.63±0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>48</td>
<td>27.2±20.3</td>
<td>48.9±10.2</td>
<td>0.001</td>
<td>5.59±2.89</td>
<td>7.94±2.04</td>
<td>0.02</td>
<td>0.46±2.4</td>
<td>0.72±0.3</td>
<td>0.05</td>
</tr>
</tbody>
</table>

TABLE V—Mean (±SD) sucking rate, peak sucking pressure, and milk consumption at 24 and 48 hours after birth in infants from unmedicated mothers4 and naloxone-treated infants whose mothers had pethidine during labour.

<table>
<thead>
<tr>
<th>Time after birth (hours)</th>
<th>Unmedicated group</th>
<th>Naloxone group</th>
<th>P</th>
<th>Unmedicated group</th>
<th>Naloxone group</th>
<th>P</th>
<th>Unmedicated group</th>
<th>Naloxone group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>41.7±21.2</td>
<td>41.3±15.3</td>
<td>0.09</td>
<td>9.11±3.61</td>
<td>6.66±2.52</td>
<td>0.06</td>
<td>0.49±0.25</td>
<td>0.63±0.32</td>
<td>0.2</td>
</tr>
<tr>
<td>48</td>
<td>49.6±21.2</td>
<td>48.9±10.2</td>
<td>0.09</td>
<td>10.7±3.19</td>
<td>7.94±2.04</td>
<td>0.01</td>
<td>0.58±0.25</td>
<td>0.72±0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Copies of the unpublished tables and figure may be obtained from
Dr M Rosen, Department of Anaesthetics, University Hospital of
Wales, Heath Park, Cardiff CF4 4XW.

References

(Accepted 20 April 1977)

SHORT REPORTS

Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen

Some asthmatic patients get attacks after taking aspirin and certain other analgesics. The chemical structures of these drugs differ, but all strongly inhibit prostaglandin (PG) production. We have studied the effect of diclofenac and naproxen, two new non-steroidal anti-inflammatory drugs, on lung function in aspirin-sensitive patients and compared it with the ability of these drugs to inhibit PG cyclooxygenase.

Patients, methods, and results

Eleven aspirin-sensitive asthmatic patients (six women and five men, with a mean age of 39 years) consented to participate in the study. Three were being maintained on corticosteroids but none was being treated with disodium cromoglycate. All the patients were challenged with aspirin, diclofenac, and naproxen by mouth. These tests2 consisted in clinical observations and measurements of peak expiratory flow (PEF) over a four-hour period after ingestion of each drug, beginning with the smallest dose and increasing the dose on subsequent days until the patient reacted. The dose sequence for aspirin and naproxen was 30, 40, 60, and 80 mg and for diclofenac 5, 10, 20, and 25 mg. The drugs were tested for inhibition of PG synthetase in bovine seminal vesicle microsomes as well as for binding to bovine serum albumin.2

All the patients reacted to the challenge. The reactions began 20 to 240 minutes after ingestion of the drug and consisted of rhinorhoea, tightness in the chest, wheezing, and dyspnoea. The fall in PEF ranged from 21% to 64%. The lowest doses of aspirin and naproxen that caused a reaction were 30 or 40 mg in eight patients, 60 mg in two, and 80 mg in one. The corresponding doses of diclofenac were 10 mg in five patients, 20 mg in three, and 25 mg in three. Patients in whom very low doses of aspirin precipitated dyspnoea also reacted to very low doses of diclofenac and naproxen. The intensity of bronchoconstriction and the incidence of other adverse symptoms were similar with all three drugs. The adverse reactions could all be reversed within minutes or in up to one hour by isoprenaline or aminophylline or both. Three patients received additionally 75 mg hydrocortisone.

In five patients aspirin challenge was repeated after pretreatment with sodium cromoglycate inhaled in a daily dose of 240 mg on two consecutive days. This completely protected two sensitive patients and diminished the reaction in three others.

The results of in-vitro tests are shown in the table.

Inhibition of prostaglandin synthetase in bovine seminal vesicle microsomes and binding to bovine serum albumin by aspirin, naproxen, and diclofenac

<table>
<thead>
<tr>
<th>Drugs</th>
<th>PG-synthetase inhibition (Km)</th>
<th>Albumin binding (µmol/l)</th>
<th>Calculated relative activity in vivo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>164</td>
<td>5600</td>
<td>2 2</td>
</tr>
<tr>
<td>Naproxen</td>
<td>134</td>
<td>1000</td>
<td>2 2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.42</td>
<td>1500</td>
<td>105</td>
</tr>
</tbody>
</table>

*Calculated by the method of Gryglewski.3 The predicted index of potency to inhibit PG synthetase in vivo by each drug is the ratio of albumin binding to PG-synthetase inhibition. Figures represent relative calculated activities of the drugs in vivo.

Comment

Neither diclofenac nor naproxen should be given to aspirin-sensitive patients. Both drugs inhibit PG biosynthesis in vitro, diclofenac more so than naproxen or aspirin. Only analgesics which inhibit PG biosynthesis produce bronchospasm in aspirin-sensitive patients. The respiratory system generates both bronchodilator PGEs and bronchoconstrictor PGFs, but in experimental animals mostly PGEs are released during histamine-induced bronchoconstriction.4 We believe that PGFs and not PGEs play an essential part in maintaining the bronchial tone in aspirin-sensitive asthma.

Removal of PGFs by PG synthetase inhibitors leaves the effects of endogenous bronchoconstrictors unopposed. Furthermore, lack of PGFs promotes the release of histamine in vitro.4 This mechanism might be clinically important since aspirin challenge leads to a significant rise in plasma histamine in aspirin-sensitive asthmatics.5 On the other hand, disodium cromoglycate, which inhibits the release of histamine from mastocytes, protected our patients against broncho-

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constriction induced by aspirin. Thus histamine seems to be one of the mediators of bronchial spasm precipitated by inhibitors of prostaglandin biosynthesis in aspirin-sensitive patients with asthma.


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Is infusion phlebitis preventable?

Sterile disposable plastic cannulae have been used to give fluids intravenously for over 30 years. Superficial phlebitis is a complication which causes the patient discomfort, and there is a risk of potentially fatal septic complications. The duration of the cannulation has been known to be important in determining the incidence of phlebitis for 25 years. This study reports the current incidence of infusion-associated phlebitis in a general surgical unit.

Methods and results

All patients admitted to the unit during a four-week period and receiving fluids through an intravenous cannula for over four hours were included in the study. Patients received 0.9%, saline or 5% dextrose, supplemented in some cases by blood or dextran as clinically indicated. Two different cannulae were used: one (Medicut) made of polypropylene, and one (Bard-A-Cath) of fluoropropylene (FEP). The patients receiving each cannula were comparable for age, sex, diagnosis, and surgical management and received similar fluid regimens. A record was kept of any antibiotics administered while a cannula was in place. Veins were inspected once a day while cannulated and until the patient left hospital.

Fifty-three of the 93 veins observed developed clinically apparent phlebitis, which was defined as erythema and tenderness along the line of the vein. The incidence increased rapidly from 4-3% after 24 hours of infusion to 100% after five days. The mean time before a cannula-induced phlebitis was 2-47 days. The mean time for the group of patients coincidentally receiving antibiotics was 2-40 days (number of patients receiving antibiotics – 36). The mean times for the polypropylene and FEP cannulae were 1-97 and 3-0 days, respectively (t = 3-02, Student’s t test; P < 0.01).

Discussion

Three explanations have been proposed for infusion-associated thrombophlebitis: local infection, a chemical phlebitis induced by alkaline or acid infusion fluids, and a chemical or mechanical phlebitis induced by the cannula itself. Our results show that coincidental therapeutic exposure to systemic antibiotics does not significantly delay the onset of phlebitis. The importance of local bacterial infection is not clear. In one series half of the cannulae showed bacterial colonisation after withdrawal, but there was little association between positive culture and clinical phlebitis. Cases of fatal septic phlebitis starting at the site of an intravenous cannula often show no clinically apparent local phlebitis.

The appearance of phlebitis was slightly delayed by the use of a fluoropropylene cannula, and was only 13% at two days, though by five days there was no difference in the incidence of phlebitis. The FEP cannulae cost almost twice as much as the propylene variety. Collin et al found almost no difference in the time of onset of phlebitis induced by a polypropylene and a teflon cannula. This study confirms this but found a much reduced incidence during the first hours of infusion with a FEP teflon cannula.

We conclude that the incidence of phlebitis after infusions is directly related to its duration. Its incidence following an infusion for 24 hours is less than 7%. We suggest that to reduce the incidence drips should be taken down at night and replaced in the morning or, if continuous intravenous infusions are required, the cannula should be replaced every 24 hours whenever feasible.

We thank Mr D A D Macleod, Mr A A Gunn, and Mr N A Gray for permission to report patients under their care.

1 British Medical Journal, 1971, 1, 66.
3 Thomas, E T, Evers, W, and Racz, G B, Anaesthesia and Analgesia, 1970, 9, 150.

(Accepted 25 March 1977)

Bioavailability of talampicillin

Talampicillin (BRL 8988), the phthalidyl ester of ampicillin, is well absorbed from the gastrointestinal tract. During absorption it is hydrolysed by non-specific esterases to release ampicillin resulting in a greater biological availability of ampicillin than can be achieved by the administration of an equivalent dose of ampicillin itself. This report describes a large-population, four-part cross-over study conducted to compare the bioavailability of ampicillin after administration of commercially available formulations of ampicillin and talampicillin to fasting and non-fasting subjects.

Population, methods, and results

Healthy volunteers aged 19 to 59 years within a weight range of 53-98 kg were studied. Those with a personal or family history of penicillin allergy and those who had taken drugs within the past month were excluded. The study was conducted in 32 subjects according to a randomised cross-over design in four parts, with an interval of four days between each part. Each subject received 250 mg ampicillin or 250 mg Talpen. Volunteers fasted from 10 pm the day before each part of the study and were dosed from 9 am on the study day. Non-fasting subjects were dosed half an hour after a standard breakfast. A similar breakfast was given to fasting subjects after the two-hour blood sample had been taken. Fluid intake was carefully controlled throughout the study. Blood samples were taken immediately before dosing and at 20, 40, 60, and 90 minutes and 2, 4, and 6 hours after...