A reappraisal of co-trimoxazole

The introduction of co-trimoxazole in 1968 began a new era in antimicrobial therapy. Here was an agent with a broad spectrum of activity against common bacterial pathogens which could be administered by mouth. This property made it extremely attractive as empirical therapy of urinary tract, respiratory tract and skin infections in outpatient and general practice. The efficacy of sulphonamides was already established at this time, and their side-effects were well understood. The combination with trimethoprim appeared particularly inviting as it overcame the resistance to sulphonamides, was synergistic in vitro, and it seemed likely that the combination would retard the further development of resistance. Understandably, this has led to the virtual elimination of "plain" sulphonamide agents from routine clinical prescribing.

However, quite recently, the role of co-trimoxazole has come under close scrutiny internationally, particularly since the introduction of trimethoprim alone. Three factors have received particular attention. First, the emergence of resistance to co-trimoxazole and trimethoprim in common pathogens; secondly, the adverse reaction profile of co-trimoxazole; and thirdly, the comparative efficacies of co-trimoxazole, trimethoprim and other agents. This review will focus on the three areas separately, although, in considering the status of co-trimoxazole, all these factors need to be taken into account.

Emergence of resistance

Resistance in some common Gram-negative pathogens has now developed to significant levels in many countries in the world.1-11 The most-recently published resistance levels in Escherichia coli and Enterobacteriaceae from several countries are shown in Table 1.

Resistance has developed at the same rate to both co-trimoxazole and trimethoprim in countries such as Great Britain and Finland, where both drugs have been in general use for more than a decade. In many countries, the majority of strains that demonstrate trimethoprim resistance also have a high-level resistance to sulphonamides.4-12 The rate and pattern of the development of resistance to trimethoprim has led one group of investigators to conclude "that the sulphonamide moiety was not protecting trimethoprim".13

This concept of the prevention of the development of resistance with a second antimicrobial agent has proved reliable in many clinical situations and can be demonstrated readily in vitro for trimethoprim with sulphamethoxazole.14 Nevertheless, resistance has been shown to develop in colonic Enterobacteriaceae at the same rate with both co-trimoxazole and trimethoprim alone when used in the treatment of urinary tract infections.17

The mechanisms of resistance to trimethoprim have been elucidated in some detail recently.1,4-16 Chromosomal resistance is due to modifications of the target enzyme dihydrofolate reductase (DHFR) and leads to low-level resistance (minimum inhibitory concentration [MIC], 4-512 mg/L), while high-level resistance (MIC, greater than 1000 mg/L) is due to the presence of plasmid- or transposon-encoded additional DHFR that is insensitive to trimethoprim.

High-level resistance in Esch. coli now accounts for 39%–95% of all trimethoprim resistance in many countries, and a significant proportion of such resistance is transferable both among strains of Esch. coli and among Gram-negative organisms of different genera.1,3,8-12 For example, 19% of resistant strains in Finland in 1980–1981,6 60% of strains from South India in 198413 and 50% of strains from Paris in 1984 had transferable resistance.14 Moreover, strains that are resistant to trimethoprim frequently are resistant to other commonly-prescribed antimicrobial agents and, in many instances, these resistances can be cotransferred.1,3,8-12

The development of DNA probes has permitted discrete analysis for plasmids and transposons that code for high-level trimethoprim resistance. Two prevalent types of transposon have emerged. Transposon Tn7, which codes for DHFR type-I resistance, transposes readily into a variety of plasmids. Its prevalence has increased steadily over the years: in Finland, from 42% in high-level resistant strains of Esch. coli in 1980–1981 to 64% of such strains in 1983, and from 47% to 56% among strains of other Gram-negative bacilli.15 It is also the most common reason for trimethoprim resistance in Sweden.16 Transposon Tn402 codes for DHFR type-II resistance and accounts for a smaller proportion of high-level resistance. Less is known about its transmissibility. However, a highly-infectious plasmid that codes for type-II DHFR resistance has accounted for the steady increase in trimethoprim resistance among some Enterobacteriaceae in one US hospital.17 Recently, Amyes has summarized the properties of all known plasmid- and transposon-coded DHFRs.18

The alarming rise in resistance to trimethoprim and co-trimoxazole has now been blamed on the over-the-counter availability of co-trimoxazole in developing countries.9 The figures in Table 1 tend to support this hypothesis; resistances of greater than 30% virtually are confined to developing countries, many of which provide access to antimicrobial agents without a prescription.

There are fewer available data about the level of resistance in the United States and Australia. Figures for co-trimoxazole resistance are shown in Table 2.

**TABLE 1**: Co-trimoxazole and trimethoprim resistance among strains of Esch. coli and Enterobacteriaceae in various countries

<table>
<thead>
<tr>
<th>City and country</th>
<th>Drug tested</th>
<th>Year</th>
<th>Prevalence of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esch. coli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston, USA</td>
<td>Co-trimoxazole</td>
<td>1982</td>
<td>5%</td>
</tr>
<tr>
<td>London, England</td>
<td>Co-trimoxazole</td>
<td>1982</td>
<td>8%</td>
</tr>
<tr>
<td>Various, USA</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>5%</td>
</tr>
<tr>
<td>Santiago, Chile</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>44%</td>
</tr>
<tr>
<td>Bangkok, Thailand</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>40%</td>
</tr>
<tr>
<td>Honolulu</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>38%</td>
</tr>
<tr>
<td>Brazil</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>40%</td>
</tr>
<tr>
<td>Adelaide, Australia</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>5%</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Co-trimoxazole</td>
<td>1983</td>
<td>25%</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Co-trimoxazole</td>
<td>1984</td>
<td>48%</td>
</tr>
<tr>
<td>Turku, Finland</td>
<td>Co-trimoxazole</td>
<td>1984</td>
<td>35%</td>
</tr>
<tr>
<td>Hafia, Israel</td>
<td>Co-trimoxazole</td>
<td>1985</td>
<td>51%</td>
</tr>
<tr>
<td>Kingston, Jamaica</td>
<td>Co-trimoxazole</td>
<td>1986</td>
<td>31%</td>
</tr>
<tr>
<td>Adelaide, Australia</td>
<td>Co-trimoxazole</td>
<td>1986</td>
<td>10%</td>
</tr>
<tr>
<td>Christchurch, New Zealand</td>
<td>Co-trimoxazole</td>
<td>1986</td>
<td>6%</td>
</tr>
<tr>
<td>Glasgow, Scotland</td>
<td>Trimethoprim</td>
<td>1983</td>
<td>10%</td>
</tr>
<tr>
<td>London, England</td>
<td>Trimethoprim</td>
<td>1983</td>
<td>12%</td>
</tr>
<tr>
<td>Paris, France</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>24%</td>
</tr>
<tr>
<td>Helsinki, Finland</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>11%</td>
</tr>
<tr>
<td>Vellore, India</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>64%</td>
</tr>
<tr>
<td>Christchurch, New Zealand</td>
<td>Trimethoprim</td>
<td>1986</td>
<td>7%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>Trimethoprim</td>
<td>1982</td>
<td>19%</td>
</tr>
<tr>
<td>Portsmouth, England</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>12%</td>
</tr>
<tr>
<td>Edinburgh, Scotland</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>36%</td>
</tr>
<tr>
<td>Dar-es-Salaam, Tanzania</td>
<td>Trimethoprim</td>
<td>1984</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Data from routine susceptibility tests at Flinders Medical Centre.*
in five centres in the United States in 1982–1983 showed a prevalence of resistance of between 4% and 6% in *Esch. coli*.

For Flinders Medical Centre, cumulative data are available for a variety of pathogens since 1977. Figures 1 and 2 demonstrate a significant rise in the prevalence of resistance in the two common pathogens in urinary and respiratory tract infections, namely, *Esch. coli* and *Streptococcus pneumoniae*, respectively, the majority of which were community-acquired.

The prevalence of resistance has increased steadily in *Esch. coli* from 1.9% in 1977 to 9.6% in 1986. Since regular testing began in 1980, the prevalence of resistance in *Strept. pneumoniae* has jumped from 5.4% in 1980 to 37.7% in 1986. Clearly, co-trimoxazole or trimethoprim alone can no longer be considered appropriate empirical therapy in respiratory tract infections for patients who are attending Flinders Medical Centre, and the prevalence of resistance in *Esch. coli* is rising to the point where alternative empirical therapies to co-trimoxazole and trimethoprim alone may have to be considered for urinary tract infection in the next few years on the grounds of resistance alone.

The observation of gradually-increasing levels of resistance to co-

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**Figure 1**: Resistance in *Esch. coli* to co-trimoxazole at Flinders Medical Centre, 1977–1986. Numbers in parentheses represent the number of strains that were tested.

**Figure 2**: Resistance in *Strept. pneumoniae* to co-trimoxazole at Flinders Medical Centre, 1979–1986. Numbers in parentheses represent the number of strains that were tested.

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Aboriginal Product Information, Compersion: Soframycin sulphate 5 mg per ml, in a Alcon, Biological and Antibiotic Solution: Sodium chloride, Isopropyl alcohol, Water for Injection.

Central uses: Contraindications: hypersensitivity to Soframycin. Precautions: Cross-sensitization to Soframycin may occur.

Dosage and Administration: Adults: 2 drops every 1 to 2 hours initially, decreasing to 1 to 2 drops three times daily.

Cautions/Warnings: Use caution if there has been use of antibiotics or other treatment during the day. Presentation: Drops 8 ml, Ointment 5 g. Full product information available on request.
trimethoprim certainly is not unique to Flinders Medical Centre. Evolving resistance to co-trimoxazole and/or trimethoprim in Enterobacteriaceae has been documented in many other countries, including the United States, Great Britain, Costa Rica, Finland, Israel, New Zealand and France. It seems likely that the great popularity of the combination has exerted a strong pressure for the selection of resistance internationally. In addition, evolving resistance to trimethoprim to significant levels over eight to nine years has been documented clearly in Salmonella and Shigella species in Great Britain. The problem of resistance to co-trimoxazole in Strept. pneumoniae at the level that is seen currently at Flinders Medical Centre has not been documented previously. Investigations at the Royal Free Hospital in London showed a prevalence of resistance of only 7% in 1981, when the corresponding figure at Flinders Medical Centre reflects antibiotic pressure in the community rather than in the hospital. If this is the case, then we could expect a continued rise in the prevalence of resistance in Esch. coli to the levels that are observed currently in England, Finland and some developing countries.

TABLE 2: Suggested alternative therapies to co-trimoxazole

<table>
<thead>
<tr>
<th>Infection</th>
<th>Common pathogens</th>
<th>Alternative therapies</th>
<th>Cost of five-day course on PBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract infection, otitis media, sinusitis</td>
<td>Enteroxoccili</td>
<td>Amoxycillin</td>
<td>$4.61</td>
</tr>
<tr>
<td></td>
<td>Strept. pneumoniae</td>
<td>Augmentin or erythromycin</td>
<td>$11.01</td>
</tr>
<tr>
<td></td>
<td>Haem. influenzae</td>
<td>doxycycline</td>
<td>$5.10</td>
</tr>
<tr>
<td></td>
<td>Strept. pyogenes</td>
<td>Fluocouloxicillin or cephalxin</td>
<td>$8.57</td>
</tr>
</tbody>
</table>

Adverse reaction profile

Another aspect of the use of co-trimoxazole which recently has been

Haemaccel is a colloidal infusion solution for plasma substitution. It is sterile, pyrogen free, and contains no preservatives. Precautions: Since Haemaccel contains no preservative, the solution may become contaminated by bacteria once the bottle has been opened; bottles containing unused solution should be discarded. Haemaccel should not be administered cold. It has no antigenic effect. However, it may occasionally cause transient skin reactions, rises in temperature, and/or slight chills. Citrated blood should not be mixed with Haemaccel, since the latter's calcium content will cause calcification. However, such blood can be transfused immediately before or after infusion of Haemaccel. Haemaccel and heparinised blood can be mixed freely. If cardiac glycosides are also being given, attention must be paid to the synergistic effect of the calcium. If the suspected blood loss is more than 25% of the normal volume, Haemaccel therapy must be complemented by administration of blood or concentrated erythrocytes. Adverse Reactions: During or after the infusion of any volume expanding solution there may be side effects of varying intensity. Most of the side effects observed with Haemaccel are slight, consisting of urticaria, rises in temperatures and/or chills. However, some very rare cases of anaphylactoid reactions have been reported with bronchospasm, tachycardia and severe hypotension. Quincke's oedema has also been reported in such instances. These side effects are not to be expected when Haemaccel has been rapidly infused because of severe blood loss or marked shock. They seem more likely to occur when Haemaccel is infused rapidly into patients with normovolaemia. These reactions are due to histamine release and not true anaphylactic reactions on an immunological basis. A decrease in blood pressure caused by histamine release due to other drugs (anaesthetics, muscle relaxants, anaesthetics, ganglion blockers and anticholinergics) is not an indication for rapid infusion of Haemaccel.

**Haemaccel**

**Prescribing information**

**Composition:** Each 1,000 mL of sterile aqueous solution (pH 7.2-7.3) contains 5 g (equivalent to 6.3 g nitrogen) degraded gelatin polypeptides cross-linked via urea bridges (polyglucose) (mean MW ca 35,000), sodium 140 mmol, potassium 1 mmol, calcium 6.25 mmol, chloride 145 mmol, and traces of phosphate and sulphate.

**Actions:** Haemaccel is a colloidal infusion solution for plasma substitution. It is sterile, pyrogen free, and contains no preservatives. No disturbances in organ function have been observed, even after high doses. The extent and duration of the effects of Haemaccel depend upon the infusion rate and the patient's volume deficit. Haemaccel is eliminated unchanged via the kidneys and intestines; 50% of the dose is eliminated within two to five hours. Elimination is complete 48 hours after the infusion is stopped. Haemaccel does not impair coagulation and does not interfere with blood typing. If sterility is maintained, Haemaccel can be mixed with other customary infusion solutions (saline, glucose, Ringer's solution, etc.), with solutions used in circulation therapy, and also with corticosteroids, muscle relaxants, barbiturates, vitamins, and antibiotics of the penicillin and tetracycline groups, provided that they are water soluble.

**Indications:** Hypovolaemic shock resulting from loss of blood, loss of plasma, loss of water and electrolytes; in the operation of a heart lung machine or artificial kidney.

**Contraindications:** None relative contraindications are known. If there are relative contraindications, such as manifest cardiac insufficiency, fixed hypertension, or cardiogenic shock, infusion should be made only with proper control.

**Use in pregnancy and lactation:** Haemaccel is not contraindicated in pregnancy in its usual indications. It is not known whether Haemaccel is excreted in breast milk. No harmful effects on the newborn have been reported when it has been employed during and following labour.

**Precautions:** Since Haemaccel contains no preservative, the solution may become contaminated by bacteria once the bottle has been opened; bottles containing unused solution should be discarded. Haemaccel should not be administered cold. It has no antigenic effect. However, it may occasionally cause transient skin reactions, rises in temperature, and/or slight chills. Citrated blood should not be mixed with Haemaccel, since the latter's calcium content will cause calcification. However, such blood can be transfused immediately before or after infusion of Haemaccel. Haemaccel and heparinised blood can be mixed freely. If cardiac glycosides are also being given, attention must be paid to the synergistic effect of the calcium. If the suspected blood loss is more than 25% of the normal volume, Haemaccel therapy must be complemented by administration of blood or concentrated erythrocytes. Adverse Reactions: During or after the infusion of any volume expanding solution there may be side effects of varying intensity. Most of the side effects observed with Haemaccel are slight, consisting of urticaria, rises in temperatures and/or chills. However, some very rare cases of anaphylactoid reactions have been reported with bronchospasm, tachycardia and severe hypotension. Quincke's oedema has also been reported in such instances. These side effects are not to be expected when Haemaccel has been rapidly infused because of severe blood loss or marked shock. They seem more likely to occur when Haemaccel is infused rapidly into patients with normovolaemia. These reactions are due to histamine release and not true anaphylactic reactions on an immunological basis. A decrease in blood pressure caused by histamine release due to other drugs (anaesthetics, muscle relaxants, anaesthetics, ganglion blockers and anticholinergics) is not an indication for rapid infusion of Haemaccel.

**Dosage and Administration:** Haemaccel is administered intravenously. The extent and duration of infusion are determined on the basis of the patient's condition.

**Infusion rate:** 500 mL generally in not less than 60 minutes. The total volume required depends upon the patient's volume deficit and following labour.

**Presentation:** Solution: 500 mL.

**Storage:** Shelf life is 3 years if stored at temperatures up to 30°C.

**Poison schedules:** Nil.
the focus of international attention is the incidence of serious adverse reactions. Two important reports in the last two years have opened considerable debate about this aspect of co-trimoxazole.

In December 1984, the Swedish Board of Health released figures of adverse drug reactions that were reported to the Adverse Drug Reaction Committee between 1972 and 1984. There were 1234 patient reports of 1721 adverse drug reactions that were received. Twenty-three reactions were fatal and about 20% of reactions were considered to be serious, for example, Stevens-Johnson syndrome, haematological and hepatic disorders and anaphylactic reactions. Serious bone-marrow damage, pseudomembranous colitis and fatalities occurred almost exclusively in patients of over 70 years of age.

Co-trimoxazole had been one of the most widely-used medicines in Sweden at the time, approaching one defined daily dose per 1000 inhabitants. Subsequently, the Swedish Board of Health reviewed the approved indications for co-trimoxazole and asked the manufacturers to change their labelling to the effect that such products should not be used for uncomplicated urinary tract infections. Both Swedish producers complied, but the outcome of negotiations with the two major international producers that market co-trimoxazole in that country, Roche and Wellcome, are not known.

In the United Kingdom, the Committee on Safety of Medicines published data in 1985 about deaths that were associated with co-trimoxazole, ampicillin and trimethoprim. There were 50 deaths due to blood dyscrasias and 14 deaths due to skin reactions, which were attributable to co-trimoxazole therapy. Over all, co-trimoxazole was associated with a seven-fold greater incidence of deaths (1.42 per million prescriptions) compared with ampicillin (0.18 per million prescriptions), with a 15-fold greater incidence in patients of over 65 years of age.

The British report triggered a number of editorials and letters on the role of co-trimoxazole, which discussed the concept of restricted use and pointed out that, in most areas of common usage, trimethoprim was of equivalent efficacy to the combination.

However, one editorial concluded that although in some studies trimethoprim usually showed a lower incidence of side-effects than did co-trimoxazole, and that trimethoprim alone is much less likely to affect haemopoiesis, “no studies to date have compared sufficient patients either to encounter serious haematological or cutaneous reactions or to show a significant difference in their incidence” and that therefore “there remains no objective proof that the substitution of trimethoprim alone would significantly reduce adverse reactions”.

One way to overcome this problem is to examine data from countries such as Finland where both trimethoprim alone and co-trimoxazole have been available for many years. For instance, in reviewing reported skin reactions to drugs in hospitalized patients in Helsinki, Finland, between 1971 and 1980, investigators documented 122 (28%) of 430 reactions as caused by sulphonamides and trimethoprim, compared with 34 reactions for ampicillin/amoxicillin/pivampicillin. A breakdown of these figures revealed that 41 (33%) reactions were caused by co-trimoxazole, 66 (54%) reactions were caused by sulphonamides and only 15 (12%) reactions were caused by trimethoprim alone. Severe bullous eruptions occurred in 32 of the 430 reactions, of which 11 eruptions were caused by sulphonamides and none by trimethoprim. Overall, sulphonamides were the most frequent cause of skin eruptions to drugs.

Data from another study show that 43%–45% of the trimethoprim that was prescribed in the Helsinki area of Finland in 1981-1983 was in the form of trimethoprim alone, which suggests that trimethoprim alone is a much less frequent cause of severe and mild cutaneous adverse drug reactions. In addition to this experience in Finland, English clinicians recently have documented a severe and distinctive exanthematous pustular dermatosis that is associated with co-trimoxazole.

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**Brufen 400 acts fast against painful osteoarthritis – and its safety is well established.**

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New Zealand's Committee on Adverse Drug Reactions has been assiduous in the gathering of adverse drug-reaction data over more than a decade, and it reports regularly in the *New Zealand Medical Journal*. In the last three reports, five deaths that were associated with the use of co-trimoxazole have been reported, three of which were due to severe bone-marrow reactions.\(^{30-32}\) In the latest report, the following comments were made:\(^{32}\)

There were considerable numbers of reactions to the sulphamethoxazole/trimethoprim combination, cotrimoxazole. A small number of anaphylactic reactions, one fatal, were attributed to this medicine. Twelve reports of disorders of haemopoiesis were received. Trimethoprim used on its own was not implicated in this way, except possibly in one case where azathioprine \(\text{sic}\) was also being taken.

The Australian experience is similar to that of others. Reports to the Adverse Drug Reaction Advisory Committee (ADRAC) of adverse drug reactions to co-trimoxazole from November 1, 1972 to October 31, 1986 number 2167. This compares with 1267 reports for amoxycillin, a similarly highly-used antibiotic agent, and 19 reports for trimethoprim alone. It is interesting to note that for the year ending June 30, 1985, amoxycillin and co-trimoxazole were the two most-frequently prescribed drugs on the Pharmaceutical Benefits Scheme in Australia, and that amoxycillin was prescribed approximately 50\% more frequently than was co-trimoxazole (6.1 million compared with 4.1 million prescriptions).\(^{33}\) A summary of the specific serious adverse drug reactions to co-trimoxazole, amoxycillin and trimethoprim in Australia since November 1, 1972 is provided in Table 3.

In all serious reactions except colitis, adverse drug reactions to co-trimoxazole were reported significantly more frequently than were adverse drug reactions to amoxycillin. As the majority of reactions that are listed in Table 3 are likely to precipitate or to prolong hospitalization, the economic impact of adverse drug reactions to co-trimoxazole compared with adverse drug reactions to amoxycillin would be considerable. The low market penetration of trimethoprim in Australia accounts for the very low incidence of adverse reactions for this drug at present.

There are obvious limitations on the interpretation of this Australian data. Because of the use of a voluntary reporting scheme, the data that are gathered by ADRAC represent an overview of the adverse drug-reaction profile rather than an accurate reflection of the incidence of adverse drug reactions in the community. Moreover, it is likely that there is an inherent tendency to report the more serious reactions (often those which are seen in teaching hospitals with enthusiastic pharmacy services), rather than the minor reactions of greater frequency which are likely to be seen in general practice. Nevertheless, it is the frequency of serious adverse reactions which often require hospitalization, a prolonged hospital stay or which cause death that has been highlighted in Table 3 and in the Swedish and English reports and that is of concern.

One way to confirm that adverse drug reactions are approximately twice as frequent with co-trimoxazole as with amoxycillin (as

### Table 3: Significant adverse reactions to co-trimoxazole in Australia, 1972–1986 (ADRAC)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Co-trimoxazole</th>
<th>Amoxycillin</th>
<th>Trimethoprim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone-marrow suppression</td>
<td>181</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Accelerated sensitivity</td>
<td>557</td>
<td>234</td>
<td>6</td>
</tr>
<tr>
<td>Major skin eruptions</td>
<td>460</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Colitis</td>
<td>13</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Renal disturbance</td>
<td>46</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic disturbance</td>
<td>69</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>54</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total significant adverse drug reactions</td>
<td>1116 (51.5%)</td>
<td>370 (29.2%)</td>
<td>8</td>
</tr>
</tbody>
</table>

*More than one reaction can occur in one report.*
BRUFEN 400

IBUPROFEN B.P.

ABBREVIATED PRESCRIBING INFORMATION

Composition:
Analgesic anti-inflammatory agent for the treatment of primary inflammatory component. BRUFEN is also recommended on treatment with ibuprofen a maximum daily dosage of 400 mg in three to four divided doses.

Dosage:

Primary dysmenorrhoea initial dosage of 400-800 mg at 4-6 hcurly, with a maximum total daily dose of 1600 mg and bleeding, various skin rashes and (rarely), with the patient recovering after cessation of treatment.

Indications:
Analgesic anti-inflammatory agent for the treatment of primary inflammatory component. BRUFEN is also recommended on treatment with ibuprofen a maximum daily dosage of 400 mg in three to four divided doses.

Contraindications, Warnings, etc.:
As with other nonsteroidal anti-inflammatory agents, BRUFEN should not be given to patients with severe or bleeding, various skin rashes and (rarely), with the patient recovering after cessation of treatment.

Presentations:
BRUFEN tablets 200 mg (magenta, round, biconvex tablets, marked “BRUFEN” in black on one side)
BRUFEN tablets 400 mg (magenta, round, biconvex tablets, marked “BRUFEN 400” in black on one side)

Availability:
N.H.S. General Benefit, 50 tablets, 3 repeats
NOTE: Full Prescribing Information is available on request from The Boots Company, or please consult MIMS Annual.

No deaths occurred, but four of the 10 patients were less than 65 years of age. The enhanced warfarin-effect reactions were particularly worrying as one patient experienced a significant episode of bleeding and this drug interaction should be well known. The almost reflex prescribing of co-trimoxazole in preference to other antimicrobial agents for urinary tract infection (seven of the 11 patients were being treated for urinary tract infections) has led to the problem of an enhanced warfarin effect, which probably occurs much more frequently than is reported. As the effect is due to the sulphonamide component, it does not occur with trimethoprim alone.

Experiences at Flinders Medical Centre in the last two years have highlighted this problem. Eleven serious adverse drug reactions have been reported to the pharmacy service.

No deaths occurred, but four of the 10 patients were less than 65 years of age. The enhanced warfarin-effect reactions were particularly worrying as one patient experienced a significant episode of bleeding and this drug interaction should be well known. The almost reflex prescribing of co-trimoxazole in preference to other antimicrobial agents for urinary tract infection (seven of the 11 patients were being treated for urinary tract infections) has led to the problem of an enhanced warfarin effect, which probably occurs much more frequently than is reported. As the effect is due to the sulphonamide component, it does not occur with trimethoprim alone.

While the severe skin reactions may seem to be of lesser importance, they resulted in prolonged hospitalizations (five to 10 days) and therefore had a significant therapeutic and economic impact.

For all this, the incidence of serious adverse reactions to co-trimoxazole is small. In reviewing 1121 courses of co-trimoxazole in hospitalized patients who were studied in the Boston Collaborative Drug Surveillance Program between 1966 and 1980, 91 (8%) patients experienced an adverse reaction, none of which was severe. More recently, this group has published data on the drug-induced cutaneous reactions that were observed among 15 438 patients who were receiving drugs between 1975 and 1982, which showed a reaction rate of 3.4% to co-trimoxazole. This was second only to amoxycillin as the most common cause of a skin reaction to any drug. No comments were made about the severity of the skin reactions that were observed.

In the three years after the introduction of co-trimoxazole into Japan (in 1976), during which about 70 000 treatment courses were
administered, there were only seven cases of severe bullous skin eruptions or Stevens-Johnson syndrome (one per 10,000 courses), although there were 90 instances of blood dyscrasias (one case per 780 courses). Rates of adverse drug reactions increased with age and increasing drug dose. The Japanese report and the previous report by the British Committee on Safety of Medicines highlight the currently-held belief that co-trimoxazole is much safer in children. This has been supported by further research from the Boston Collaborative Drug Surveillance Program which monitored adverse effects in children in detail and was unable to show any serious adverse reactions to co-trimoxazole that required admission to hospital.

Comparative efficacy of co-trimoxazole

Co-trimoxazole has established efficacy in the treatment and prevention of urinary tract infections, the treatment of upper and lower respiratory tract infections and selected bacterial gastrointestinal infections. It has also gained acceptance in the treatment of infective dermatoses, such as impetigo and infected eczema, although efficacy studies are lacking. The above conditions are the main areas of prescribing in our community. As a number of alternative agents are available today (Table 2), it is useful to compare the efficacy of co-trimoxazole with that of these alternatives where such data exist.

A large number of investigations has compared the efficacy of co-trimoxazole and trimethoprim alone in the treatment of acute urinary tract infections. Results of all trials have shown equivalent efficacy for regimens that range from single doses to 10-day courses. In addition, the incidence of side-effects which were experienced by the patients was equivalent (three studies) or lower (four studies) with trimethoprim. At least equivalent efficacy has also been demonstrated when co-trimoxazole has been compared with ampicillin, cephalexin, cefaclor, nitrofurantoin and nalidixic acid.

The equivalent efficacy that is achieved with trimethoprim alone has led researchers to speculate about the significance in vivo of the synergistic effect of sulphonamides in combination with trimethoprim in vitro. It is now generally believed that synergy is not important in the therapy of urinary tract infections for two reasons. First, the ratio of sulphamethoxazole to trimethoprim in urine is one to one, whereas optimal synergy in vitro occurs at a ratio of 20 to 1 and falls off quickly at lower ratios. Secondly, synergy is only demonstrable in vitro when there are subinhibitory concentrations of one or both agents; as trimethoprim almost always exceeds inhibitory concentrations in urine throughout the dosing interval, maximal antimicrobial activity already is present.

Thus, for practical purposes, the sulphonamide component is not required for the treatment of urinary tract infections. This has also been supported by the findings of several investigators that there is no superiority of co-trimoxazole over plain trimethoprim in the prevention of recurrent urinary tract infections.

An area of efficacy that remains controversial is the efficacy of folate antagonist agents in enterococcal infections. In discussing this problem, Hamilton-Miller and Purves have made several important points: the interpretation of susceptibility tests can be influenced significantly by the presence in the test medium of thymine, thymidine and/or folates; most enterococci are probably trimethoprim susceptible; synergy between sulphonamides and trimethoprim can be demonstrated in vitro even though enterococci are relatively resistant to sulphonamides; resistance to trimethoprim can develop during treatment, although the level of resistance is low and the exact frequency with which it occurs is unknown but appears small in clinical experience; and thus further clinical studies are required to determine the true efficacy of trimethoprim compared with that of co-trimoxazole or those of other drugs in enterococcal infections.

There are few trials to compare the efficacy of co-trimoxazole with that of other agents in respiratory tract infections. Comparative trials in otitis media in children have demonstrated equal efficacy to that of ampicillin, amoxycillin, and cefaclor. The recent upsurge of beta-lactamase-producing Haemophilus influenzae in this condition has suggested a theoretical advantage of co-trimoxazole over ampicillin/amoxycillin, but not over cefaclor. However, the introduction of amoxycillin with clavulanic acid has corrected this deficiency of amoxycillin. In contrast to experience in otitis media, co-trimoxazole is inferior to penicillin, and probably erythromycin, in the treatment of streptococcal pharyngitis.

In acute bronchitis, co-trimoxazole appears to be superior to tetracycline, ampicillin, cephalixin and cefaclor but similar in efficacy to amoxycillin and doxycycline. Two recent trials that compare co-trimoxazole with trimethoprim alone in lower respiratory tract infections have shown equal efficacy. This is not surprising as the penetration of trimethoprim into sputum is excellent, while there are no detectable levels of sulphamethoxazole in sputum after therapeutic doses of co-trimoxazole. Moreover, many strains of Haem. influenzae are resistant to sulphamamide agents. Thus, the only active component in lower respiratory infections is trimethoprim.

The third major area of co-trimoxazole prescribing is for skin and soft-tissue infections. Interestingly, this practice has developed in the relative absence of supporting data, and is probably due to the broad spectrum of the drug against the common skin pathogens. The recent removal of the Pharmaceutical Benefits restrictions on the prescribing of cefuroxime and cephalexin — agents with more suitable spectra against common skin pathogens — should reduce the need to prescribe co-trimoxazole. There are no data on the efficacy of "plain" trimethoprim in skin and soft-tissue infections.

Co-trimoxazole also has established efficacy in the treatment of a number of other infections: gonorrhoea, chlamydial urethritis, typhoid fever, shigellosis, cholera, traveller's diarrhoea, Pneumocystis pneumonia and nocardiosis. However, in only the last two diseases does it appear to be one of the agents of choice. Suitable and usually more standard alternatives exist for all the other indications, and co-trimoxazole need only be administered when other agents cannot be used because of resistance or patient allergy. Recently, trimethoprim alone has been shown to have similar efficacy to that of co-trimoxazole and chloramphenicol in typhoid fever and similar efficacy to that of co-trimoxazole in traveller's diarrhoea. The only established alternative to co-trimoxazole in the treatment of Pneumocystis pneumonia is pentamidine. Recent experience with Pneumocystis pneumonia in the acquired immunodeficiency syndrome has demonstrated that co-trimoxazole and pentamidine have equal efficacy and the same high incidence of adverse effects.

Due to its broad spectrum, co-trimoxazole has also been used for a number of other infections: chancroid, granuloma inguinale, lymphogranuloma venereum, toxoplasmosis, endocarditis, meningitis, brucellosis, plague, melioidosis, Mycobacterium marinum infections and anaerobic infections. In most cases, there is insufficient information to gauge its efficacy compared with that of other agents. In the first three diseases, sulphamamide agents alone are known to be effective, and there does not appear to be a need for the combination. In toxoplasmosis, the drugs of choice for serious infection are pyrimethamine and sulphadiazine, but the toxicity of pyrimethamine in particular has led to the belief that co-trimoxazole, which has the same mechanism of action, may be suitable. However, no controlled efficacy data are available.

The penetration of sulphonamides and trimethoprim through inflamed and uninflamed meninges makes co-trimoxazole a potentially-attractive drug in the treatment of meningitis, particularly that which is caused by beta-lactamase producing Haem. influenzae type b. Certainly, in the small number of patients who have been treated with co-trimoxazole, outcomes have been favourable. However, the recently-introduced, highly-active, third-generation cephalosporin agents largely have solved the therapeutic problem of beta-lactamase producing (and now occasionally chloramphenicol-resistant) Haem. influenzae type b.
The significance of trimethoprim resistance is being realized. Certain bacterial species are now resistant to this drug alone, although often at a higher cost (Table 2). There are still a number of valid indications for the use of the combination (see box). These are mostly serious infections where either the efficacy of trimethoprim alone is unknown or a combination of agents is believed to be superior. At Flinders Medical Centre, co-trimoxazole has been restricted to these indications and the use of the alternative agents is encouraged in order to reduce the "antibiotic pressure" for the development of further resistance and the incidence of adverse drug reactions.

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References
Urinary incontinence secondary to prazosin

Prazosin has been used widely in the treatment of hypertension for over 10 years and usually is effective and well tolerated. Commonly-observed adverse effects include postural hypotension, palpitations, lethargy, headaches andnauses.

Urinary incontinence as an adverse effect to commonly-used drugs is less frequently. Prazosin is first reported as a cause of urinary incontinence in 1978 and since then only a small number of patients have been reported with this adverse effect.

This report documents 56 patients in whom urinary incontinence developed after commencing prazosin therapy. These patients were reported to the Australian Adverse Drug Reactions Advisory Committee between June 1978 and October 1986.

**Patient data**

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) reporting scheme receives voluntary reports from hospital and community doctors and pharmacists throughout Australia. Sixty reports that associated prazosin and urinary incontinence were received between June 1, 1978 and October 31, 1986. Four reports were excluded from further analysis; two of these reports did not document the outcome on the withdrawal of prazosin. In one patient, incontinence ceased on the cessation of another antihypertensive agent (propranolol) and one patient had pre-existing stress incontinence. The remaining 56 patients were all undergoing treatment for hypertension and were reported to have developed urinary incontinence that was related to the use of prazosin. All 56 patients were cured of this symptom on the withdrawal of prazosin or on the reduction of the dosage.

Of these 56 patients, 51 were female (mean age, 65.0 years; range, 34-83 years) and five were male (mean age, 61.8 years; range, 49-74 years). In 38 of the 56 patients the height and weight were recorded and indicated a tendency to mild obesity (mean height, 162.6 cm; mean weight, 68.3 kg).

In 20 patients prazosin was reported to be the only drug that was taken. The daily dose was recorded in 54 of the 56 patients and ranged from 0.5 mg to 15 mg/day (mean, 3.6 mg). In 11 patients, incontinence only occurred when the daily dose was increased. In three other patients, a reduction in dose was accompanied by the disappearance of incontinence.

Typically, it was reported that symptoms of incontinence appeared within a day or two of the commencement of prazosin and persisted until the drug was withdrawn or the dose was reduced. Recognition of prazosin as a causal agent was often delayed. The total duration of symptoms averaged 9.5 months (range, one day to 48 months) in the 50 patients in whom these data were available.

The type of incontinence usually was not specified but reports indicated that both stress and urge incontinence were experienced, sometimes in the same patient.

**Clinical record**

A 78-year-old obese woman (height, 165 cm; weight, 100 kg) was reported to ADRAC on May 30, 1986 to have developed urinary incontinence while taking prazosin. Initially, in 1978, the patient took prazosin for the control of hypertension but refused to continue the drug as she blamed it for a loss of bladder control. The reporting doctor recorded that he blamed the finding of a cystocele for these symptoms but nevertheless withdrew prazosin with a successful return of bladder control. Prazosin was reintroduced in 1984 at a dose of 0.5 mg at night; nocturia occurred. An increase in the dosage to 0.5 mg twice a day was followed within a few days by the development of stress incontinence. The drug was continued until May 22, 1986 when, after publicity in the Australian Adverse Drug Reactions Bulletin concerning the association between prazosin and incontinence, the doctor stated, “I finally believed the patient. She is reactive to a wide variety of tablets and I had attempted to play down her complaints to this otherwise effective drug”.

The withdrawal of prazosin was followed by the disappearance of incontinence. The patient was taking metoprolol tartrate (50 mg twice a day), Moduretic (hydrochlorothiazide and amiloride hydrochloride; one tablet a day), digoxin (0.125 mg a day) and prochlorperazine (5 mg three times a day) concomitantly. These therapies were continued uninterrupted throughout 1984 and 1985 to May 30, 1986. On the basis of the recurrence of the symptoms on re-exposure to prazosin, ADRAc assessed the reaction as being “certainly” due to the drug.

**Discussion**

Prazosin is an effective antihypertensive agent that has few serious adverse effects. This report of 56 patients who developed urinary incontinence that was related temporally to the use of prazosin draws attention to an important but little recognized side-effect of prazosin. The lack of recognition with a consequent delay in adjustment to therapy has led to unnecessary patient suffering, specialist referral and investigation.

This report identifies the group of patients that is most likely to develop urinary incontinence. Women outnumber men by a factor of 10 to 1 and the advanced mean age of the group suggests that the elderly are particularly susceptible. It seems likely that prazosin unmasks a tendency to incontinence (which is probably related to child-bearing, postmenopausal changes in pelvic muscle structure and obesity), which, in the absence of a pharmacological stimulus, would be of little significance. It is perhaps noteworthy that two of the five men who developed incontinence while taking prazosin had a previous history of prostatic hypertrophy with operative correction.

Prazosin produces a hypotensive effect by blocking alpha-adrenergic postsynaptic receptors with consequent peripheral vasodilation. It is now established that the smooth muscle of the bladder neck and urethra in humans is innervated sympathetically and that there is a significant contribution to the maintenance of intraurethral pressure by alpha-adrenergic receptors. Thus, it is not surprising that prazosin may affect voiding and induced incontinence should be regarded as an unwanted effect (or predictable toxicity) rather than as an idiosyncratic side-effect.

The effect of prazosin on urodynamics has been studied. Results confirm an identical pattern to that which is seen with tolterodine, a known alpha-adrenergic receptor blocking agent. Decreases occurred in both the functional length of the urethra and the maximal urethral closure pressure with the administration of prazosin. These effects of prazosin on voiding patterns have led to clinical trials of its use in assisting bladder control and function in patients with uninhibited neurogenic bladders and benign prostatic hypertrophy.