Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Supristol†.

Co-trimazine *(BAN)*

Trimetoprima y sulfadiazina.
CAS — 39474-58-3.
ATC — J01EE02.

Profile

Co-trimazine, a mixture of 5 parts of sulfadiazine and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations are available in some countries which contain trimethoprim and sulfadiazine in proportions different to co-trimazine.

Co-trimoxazole *(BAN)*

Cotrimoxazol; Ko-trimoksazol.
CAS — 8064-90-2.
ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Stability. Diluted infusion solutions of co-trimoxazole have a limited stability and eventually form a precipitate: this happens more rapidly at higher concentrations. The manufacturers recommend a dilution of 480 mg in 130 mL, which is usually stable for up to 6 hours, but more concentrated solutions should be used within shorter periods of time, and a dilution of 480 mg in 80 mL should be used within 1 hour. The usual diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, have been stated to be compatible for adequate periods.

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components (see Sulfamethoxazole, p.340, and Trimethoprim, p.355). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, below).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] predominantly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the prescribing of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, below), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and remained predominantly in elderly patients.

1. Committee on Safety of Medicines. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al.* Co-trimoxazole toxicity. *BMJ* 1985; **291:** 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; **291**: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; **ii**: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; **ii**: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; **345:** 1118–19.
8. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Precautions

As for Sulfamethoxazole, p.340 and Trimethoprim, p.355.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of skin rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al.* Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; **25:** 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; **1:** 687–91.

G6PD deficiency. It has been suggested that co-trimoxazole should be avoided by people with G6PD deficiency.[1]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67**: 601–11.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in **patients with AIDS** being treated for *Pneumocystis carinii* pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

The occurrence of high serum concentrations of trimethoprim and sulfamethoxazole in patients has been proposed as a contributing factor to the high incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the **dose** of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] demonstrated no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine **metabolites** of sulfamethoxazole which produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p.340.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92–106.
2. Gordin FM, *et al.* Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
3. Jaffe HS, *et al.* Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; **ii**: 1109–11.
4. Mitsuyasu R, *et al.* Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535.
5. Colebunders R, *et al.* Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **107**: 599–600.
6. Sattler FR, *et al.* Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **109**: 280–7.
7. Stevens RC, *et al.* Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35**: 1884–90.
8. Para MF, *et al.* Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; **24:** 337–43.
9. McLean I, *et al.* Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; **ii**: 857–8.
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16. Absar N, *et al.* Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93:** 1001–5.
17. Cortese LM, *et al.* Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; **30:** 184–6.
18. Caumes E, *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133:** 465–9.
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