CLINICAL PRACTICE

Co-trimoxazole prophylaxis in HIV: The evidence

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Human immunodeficiency virus (HIV) damages the body's immune system, making secondary (or opportunistic) infections more common. Treatment and prevention of such infections is integral to the management of patients with HIV infection. Co-trimoxazole is a prophylactic treatment that has a wide range of action against common bacteria, parasites, fungi and yeasts. As part of a minimum care package, UNAIDS/WHO recommends co-trimoxazole prophylaxis for HIV-infected adults with symptomatic disease (WHO stage II, III or IV), or asymptomatic individuals with CD4 counts ≤500 cells/μl, and for all HIV-positive pregnant women after the first trimester.[1] Co-trimoxazole is also recommended for use in children with proven HIV infection and infants exposed to HIV (from 4 - 6 weeks of age until infection with HIV is ruled out).[2]

The object of this report is to summarise the effects of co-trimoxazole prophylaxis on morbidity and mortality among HIV-infected individuals.

Beneficial effects

In HIV-positive adults not receiving antiretroviral therapy (ARV), a Cochrane Review (including three randomised controlled trials (RCTs)) found that co-trimoxazole prophylaxis reduced the risk of death by almost a third (Table I).[3] The beneficial effect was similar for early (CD4 ≥200 cells/μl) and advanced (CD4 <200 cells/μl) disease. The frequency of admissions to hospital and the incidence of bacterial, parasitic and *Pneumocystis carinii* pneumonia (PCP) infections were also significantly reduced (Table I). A further RCT among HIV-positive adults in Malawi newly diagnosed with tuberculosis[4] found no significant difference in bacterial pneumonia (hazard ratio (HR) 1.07 (95% confidence interval (CI) 0.56 - 2.06)) and the probability of survival (HR 1.11 (95% CI 0.72 - 1.71)) between participants allocated 480 mg v. 960 mg of co-trimoxazole.

Table I. Effects of co-trimoxazole v. placebo (Cochrane Review)[3]

Outcome	No. of trials	No. of participants	RR (95% CI)
Death	3	1 318	0.69 (0.55 - 0.87)
Hospital admissions	3	764	0.66 (0.48 - 0.92)
Serious morbid events	3	1 384	0.76 (0.64 - 0.90)
Bacterial infections	3	1 405	0.48 (0.37 - 0.62)
Parasitic infections	3	1 405	0.37 (0.24 - 0.58)
Pneumocystis carinii pneumonia (PCP)	1	60	0.31 (0.13 - 0.74)
Adverse events	3	1 405	1.28 (0.47 - 3.51)

RR = relative risk

In children, support for co-trimoxazole prophylaxis came from a randomised placebo-controlled trial (*N*=541) conducted in an area in Zambia with high levels (60 - 80%) of *in vitro* resistance to this antibiotic.[5,6] Children ≤5 years were given a daily dose of 240 mg co-trimoxazole while those >5 years received a daily dose of 480 mg. Co-trimoxazole significantly reduced mortality by 33% (RR 0.67; 95% CI 0.53 - 0.85) and hospital admission rates by 23% (RR 0.77; 95% CI 0.62 - 0.95). Follow-up was reported to be excellent and few patients stopped their medication. The beneficial effect was seen across all ages and CD4 counts, and effectiveness of the drug did not diminish during periods of use up to 18 months' administration.

Harmful effects

The Cochrane Review found a higher risk of adverse effects in adults on co-trimoxazole compared with placebo, but this difference was not statistically significant (Table I). The RCT in Zambian children found no difference between treatment and control groups in the incidence of one or more grade 3 or 4 adverse drug reactions (HR 0.76; 95% CI 0.39 - 1.5). No allergic reactions to co-trimoxazole occurred in this study. In HIV-infected patients with a previous history of mild or moderate hypersensitivity to co-trimoxazole who required prophylaxis, desensitisation (stopping treatment and recommencing treatment with dose escalation over a period of days) compared with co-trimoxazole rechallenge (stopping treatment and starting at the full dose) resulted in fewer treatment

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discontinuations before 6 months (RR 0.64; 95% CI 0.45 - 0.91) and overall adverse reactions (RR 0.51; 95% CI 0.36 - 0.73).[7]

Comments

No randomised studies provide information on the optimal time for initiating prophylaxis in adults, or on when to stop prophylaxis. None of the trials included in the review focused on patients receiving treatment with antiretrovirals. Current studies neither report on the effects of prolonged co-trimoxazole use on bacterial resistance nor evaluate whether co-trimoxazole affects resistance of malaria parasites to sulfadoxine pyrimethamine (with which co-trimoxazole shares a component).

Conclusions

Co-trimoxazole is highly effective in reducing mortality and morbidity in HIV-infected adults and children not receiving antiretroviral treatment. Similar benefits are seen in early and advanced HIV disease. Co-trimoxazole is well tolerated, with minimal side-effects. Further research is required on the optimal time for commencement of co-trimoxazole prophylaxis and to evaluate its use in patients on antiretrovirals.

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