International Child Health Review Collaboration

The Usefulness of Azole Prophylaxis against Cryptococcal Meningitis in HIV-positive children.

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *The Usefulness of Azole Prophylaxis against Cryptococcal Meningitis in HIV-positive children.*

The **WHO Pocketbook of Hospital Care for Children** recommends that if a HIV positive child has cryptococcal meningitis then treat with amphotericin for 14 days then fluconazole for a further 8 weeks. Fluconazole prophylaxis is then started after treatment. (Pocketbook page 218)

Introduction:

Cryptococcal meningitis (CM) is a form of meningitis which is found in children and adults infected with the human immunodeficiency virus (HIV)[1-2].

The causative organism in cryptococcal disease is *Cryptococcus neoformans*, an encapsulated yeast and the disease spectrum includes pneumonia, cutaneous lesions and most commonly and morbidly meningitis.

The most recent guidelines by the US Public Health Service and Infectious Disease society of America recommend that "antifungal prophylaxis not be used routinely to prevent cryptococcosis because of the relative infrequency of cryptococcal disease, lack of survival benefits associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost." Life-long secondary prophylaxis however is recommended for patients who have completed initial therapy for cryptococcal infection[i]. No specific guidelines exist for children and all the current recommendations are based on adult data.

The development of highly active antiretroviral therapy (HAART) has reduced the need for prophylactic treatment for several opportunistic infections such as *Pneumocysitis carinii* pneumonia (PCP)[2] and disseminated *Mycobacterium avium*[2]. Low availability of HAART, higher incidences of CM in developing countries however have brought into question whether the current guidelines discouraging the routine use of fluconazole prophylaxis are indeed adequate for countries with low resources[2].

Methodology

The Cochrane library, EMBASE and Medline were searched systematically using the keywords meningitis, cryptococcal, cryptococcus neoformans, crypto$.mp, cryptococcosis, HIV, acquired immunodeficiency syndrome, prophylaxis, fluconazole, itraconazole and azoles.

Results

No studies conducted in children, or with paediatric patients as a subset of the study sample were identified. The adult literature was therefore assessed. Three studies, including a Cochrane review, which assessed 5 randomised controlled trials, on the topic of primary fluconazole prophylaxis in HIV positive adults were identified[11,12,13,14,15,16,17]. Four studies investigating the need for secondary prophylaxis after the treatment for CM in HIV positive adults were also included in this review[18,19,20,21]. .

Research conducted in Adults

Both fluconazole and itraconazole are effective at preventing CM in HIV-positive adults[2-6] but are only associated with a survival benefit in patients with either very low CD4 counts (<100 cells/µl) or living in areas where CM has an increased incidence[3,12]. Due to heterogeneity between the studies no definite conclusions can be drawn concerning which antifungal agent is superior or what dose/timing would be best.

Even though antifungal prophylaxis should not be prescribed routinely for all HIV-positive individuals it has a role in preventing CM in patients with very low CD4 counts, living in endemic areas, who are naïve to HAART or in the early stages of treatment. Once immune reconstitution has taken place to >200 cells/µl it appears safe to discontinue secondary prophylaxis when serum cryptococcal antigen is negative[2-6] but further randomised blinded studies with more participants are needed to confirm this finding. If HAART is not available, fluconazole prophylaxis should be used as an alternative means of preventing opportunistic cryptococcal infections.

Applicability of the Research to Children

In order to assess how applicable this research was to children the literature search was conducted to assess the safety of fluconazole in children. The safety profile of fluconazole has been studied in large paediatric trials and appears to be just as favourable as in adults[2,3]. To reach equivalent levels of fluconazole exposure in children compared to adults the per kilogram dose has to be increased[2] due to differences in volume of distribution. Of note is also the decreased incidence of CM in children, which may reduce the efficacy of a prophylactic intervention. Accurate epidemiological data on the prevalence of CM in children does not exist, but limited data suggests that it is less prevalent than in adults[2]. Its prevalence may however be underestimated as some CM may be misdiagnosed as tuberculous meningitis. Furthermore few hospitals are able to conduct Cryptococcus antigen tests and rely on India ink staining the cerebrospinal fluid for diagnosis of Cryptococcus neoformans, which has a poorer sensitivity than antigen testing[3].

Discussion and Summary

The issues surrounding antifungal prophylaxis against cryptococcal meningitis are complex and not fully elucidated, even in adults. Fundamental to deciding how useful azole prophylaxis against CM would be in HIV positive children is accurate epidemiological data. Once the extent of the problem has been identified the need for prophylaxis can be assessed more accurately. Studies conducted in HIV-positive children aged 6-18 assessing the usefulness of azole prophylaxis against CM are needed to clarify the question. These studies should be conducted in developing countries, as differences in access to health care and antifungal therapies as well as differences in the incidence of HIV and CM will affect the need and argument for prophylaxis. Care must be taken to evaluate the possibility of the development of resistant strains when azole prophylaxis use is being assessed.

International public health efforts to make HIV testing as well as HAART more available for children and adults in countries with low resources will almost certainly be the most effective measure to diminish the morbidity associated with CM. Further data on the epidemiology of CM in HIV positive children is needed in order to assess more accurately the usefulness of azole prophylaxis.

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