CRITICAL ANALYSIS

Fluconazole donation and outcomes assessment in cryptococcal meningitis

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The industry donation of fluconazole to the South African public sector for the management of oesophageal candidiasis and cryptococcal meningitis was one of the earliest positive therapeutic steps in local public-service HIV management. In 2004 it was estimated[1] that training health care professionals in the use of this agent in 12 countries had cost over $2 million, and that the wholesale worth of the donated product was $100 million. Programmatic success has been judged mainly using pharmaceutical logistical criteria such as medication volumes distributed and numbers of patients treated. Information on clinical outcomes is difficult to find.

Among patients receiving prophylaxis after cryptococcal meningitis, the number of repeat scripts filled per patient may serve as a coarse measure of clinical outcome. Because the donation agreement requires patient-level recording of all fluconazole scripts dispensed, this information is available in the registers of all participating public-service pharmacies.

Review process

The fluconazole donation programme has been in operation since 2003 at Frere and Cecilia Makiwane hospitals, now called the East London Hospital Complex (ELHC). The proportion of individuals returning for monthly script repeats from January 2003 to December 2005 was extracted from the pharmacy department fluconazole registers. Trends in amphotericin usage in the ELHC and fluconazole availability at district level were assessed.

Results

During the 3 years, 629 patients (mean age 34.5 years, standard deviation (SD) 8.98, 309 from hospital 1, 320 from hospital 2) were started on suppressive fluconazole therapy (200 mg daily) for cryptococcal meningitis. Only 31.5% of patients (N = 198) returned at 2 months of outpatient therapy, and at 4 months 77% of the patients did not return for repeat scripts. After 1 year, only 6% of patients were returning regularly to the ELHC.

Amphotericin usage

Using failure to return for a further script as a surrogate for outcome, a Cox proportional hazards model was generated to compare outcomes between the two hospitals in the light of differential use of amphotericin B as initial therapy. During 2004, amphotericin was given to 91% of patients with cryptococcal meningitis at hospital 1 and to 56% at hospital 2. There was no difference in return rates between the two institutions (hazard ratio (HR) 1.01, 95% confidence interval (CI): 0.77 - 1.32). The use of fluconazole in the ELHC drainage region doubled during the study period, but even if all fluconazole dispensed at other sites was given entirely to patients initially managed at the ELHC, there would only have been sufficient fluconazole dispensed to treat patients for 7.3 months in 2003, 5.2 months in 2004 and 4.4 months in 2005, assuming unrealistically that all patients were alive and on treatment and that the referring hospitals never initiated treatment.

Only 62 patients were started on antiretroviral (ARV) therapy during this period (3.7% of those receiving fluconazole in 2003, 10.1% in 2004, and 16.6% in 2005).

Discussion

This pharmacy-based retrospective observational survey raises concerns about adequacy of treatment adherence and highlights the scale of the epidemic. An unpublished audit in one of the two hospitals identified only 19 patients with cryptococcal meningitis in the 5 years up to 1996. Ten years later, the same hospital sees over 100 new patients per year.

Patients failing to return for follow-up may do so for at least four reasons: (*i*) they might be healthy in spite of lack of ongoing secondary prophylaxis; (*ii*) they might be obtaining secondary prophylaxis from another site; (*iii*) they might have been started on ARVs and reconstituted immunity such that their caregivers decided it was safe to stop secondary prophylaxis; or (*iv*) they might have died. Studies from elsewhere in Africa[2,3] suggest that survival in the absence of secondary prophylaxis is poor. Patients may have obtained ongoing fluconazole treatment from other sites, but even in the

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very unlikely event that all the patients registered elsewhere in the region had started therapy at the ELHC, this would still not account for the discrepancy. Assuming that patients had no other access to fluconazole and were not on ARVs, and that there is a 50% annual mortality in patients without secondary prophylaxis, it is speculated that many of the patients failing to return for repeat scripts were no longer alive 2 years after their last visit, although pharmacy registry information is clearly inadequate to answer this.

It is difficult to draw robust conclusions about the true clinical benefit to the country of the fluconazole donation based on the information routinely collected as part of the patient registration programme. The assumption that a therapy of proven value in clinical trials[4] will necessarily provide equivalent benefits in real-world situations warrants verification for each individual medication.[5] Vertical programmes driven by a national directorate may not be the best way of handling donations, and consideration should be given to a more integrated approach based on quantifiable clinical outcomes rather than a 'get the pills to the patient' paradigm. A similar pattern appears to be emerging with the ARV programme, where there is greater political and administrative emphasis on measuring roll-out than on quantifying sustained clinical benefit.

The contribution of amphotericin to outcome in patients surviving to discharge may merit further study, and more emphasis on adherence counselling may be worthwhile. Of equal or greater urgency is the need to establish simple unified ways of formally measuring the clinical impact of the ARV programme in different health care environments around the country (and not just at pilot sites run by enthusiasts), rather than being faced later by similar unquantifiable doubts about overall efficacy.

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HPCSA waives penalty restoration fees for erased practitioners

The Health Professions Council of South Africa (HPCSA) is offering amnesty to all medical doctors whose registration has lapsed and who want to re-register without having to pay the penalty restoration fees.

Upon enquiry, the HPCSA informed SAMA that the Council agreed to a once-off waiver of penalties for those practitioners, both local and abroad, who had failed to pay their annual registration fees on time, or who allowed their registration to lapse without informing Council. The amnesty period started on 1 February 2007 and will expire on 30 April 2007. The amnesty applies to those practitioners – living locally and abroad – whose registrations have lapsed and who have not practised for up to 2 years, as well as practitioners who have been resident and practising in other countries.
Certain conditions apply for doctors to qualify for the waiver. These include:

- the duration of the lapse in registration (various categories exist)
- an assessment of professional skills and adherence to continuing professional development
- performing **100 hours of community service** within 6 months at a public sector facility, and proof of compliance with this.

Practitioners whose registration has lapsed and who do not make use of this opportunity will be liable for the full restoration penalty. According to an amended HPCSA regulation in 2005, the restoration fees payable by doctors who apply for the restoration of their names to the register within 6 months after erasure are equivalent to twice the annual fee for the current year, as well as the outstanding fees.
After a period of 6 months, but within 12 months of the erasure date, the amount is equivalent to four times the applicable annual fee plus the outstanding fees. Those who pay after more than 12 months from the erasure date will pay five times the applicable annual fee for the current year, plus the outstanding fees.
Before the 2005 amended regulation, the restoration fees were as high as ten times the annual HPCSA fee.

The **annual fee of R834.68** payable by doctors registered with the HPCSA is due on 1 April 2007.
SAMA calls on members to distribute information about the amnesty to their colleagues who live and work outside South Africa.