New drugs, old drugs – dear drugs, cheap drugs

Bernard Hirschel, Jorge Garbino

Division des Maladies infectieuses, Hôpital cantonal universitaire, Genève, Switzerland

The current issue of SMW contains two articles dealing with anti-fungal drugs. K. Furrer et al. present data from a particularly difficult group of patients, i.e. those with bone marrow transplants needing cyclosporine at the same time as amphotericin B. Both of these drugs are nephrotoxic and impaired renal function was indeed observed: Mean serum creatinine concentration at discharge was 132 µmols/L in the group with both drugs, as compared to 96 µmols/L in the group receiving cyclosporine A only. However, that there was a difference is perhaps less remarkable than the fact that this difference was quite small, with no cases of end-stage renal failure and no case requiring dialysis in the combined-therapy group. The authors believe that this relatively favourable outcome was due to their method of administering amphotericin B deoxycholate by continuous 24 hour infusion (continuous ampho B).

Lipid formulations of amphotericin B are among the new antifungal drugs discussed by Groll et al. Echinocandin (Cancidas® – MSD) and voriconazole (Vfend® – Pfizer) are two others which have recently become available in the United States and parts of Western Europe. They are efficacious, have excellent pharmacokinetics and few side effects.

Their costs, however, are a problem. We currently have a patient with chronic granulomatous disease with a voriconazole-resistant aspergillus infection of the chest wall, being treated with liposomal amphotericin B (Ambisome® – Fresenius Kabi) and echinocandin (Cancidas®). These drugs cost approximately 20,000 Swiss francs per week. This is admittedly an extreme example – but most patients with systemic fungal infections are somewhat extreme.

Prices are easiest to compare between old and new preparations of amphotericin. 1 mg of amphotericin B (Fungizone® – BMS) deoxycholate costs 0.9 Swiss francs, or about 60 c. 1 mg of Ambisome® costs 10 times more, i.e. 9 Swiss francs per mg. Unfortunately, this is not all there is to the cost increase. Because of doubts about the bio-equivalence of traditional and liposomal amphotericin B, and because of the life-threatening nature of fungal infections in neutropenic patients, there is a tendency to give higher doses of Ambisome® (up to 5 mg/kg/d, compared to 0.5 to 1 mg/kg/d for amphotericin B deoxycholate). In addition, treatment of suspected infection is often empirical. Most patients with prolonged neutropenia have fever at some time and receive antibiotics. Why not antifungals in addition? The one thing which held back prescribers was the toxicity of amphotericin B deoxycholate. Ambisome® is less toxic [1], so that the tendency will be towards earlier administration in cases where fungal infection is possible, albeit neither likely nor proven. Higher price per mg times higher doses times more patients means that expenses for lipid formulations of amphotericin can easily multiply expenses for amphotericin B deoxycholate by a factor of 50.

"Why not", I hear you say, "use Furrer's method for continuous administration of amphotericin B deoxycholate, if it is cheaper, and just as effective at similar toxicity as liposomal amphotericin?" Why not indeed? Let's look at the quality of the evidence.

Furrer et al. suspected that the low toxicity Ambisome® was due to the gradual release of free amphotericin B from liposomes, and that 24 hour continuous administration would mimic such gradual release. They compared discontinuous and continuous administration of ampho B deoxycholate in a small randomised study and showed that patients with continuous administration had less renal toxicity and less fever [2]. However, advocates of Ambisome® would argue that the new standard for toxicity is liposomal, not conventional amphotericin [1, 2]. Before continuous can be substituted for liposomal amphotericin, a study must show that continuous and liposomal amphotericin have similar toxicity and efficacy.

I hear you say: "Why didn't Furrer et al. do such a study?" *The answer is money.*

Equivalence studies are notoriously difficult to do because for statistical reasons the number of patients enrolled has to be very high [3]. Costs for clinical studies vary, but a reasonable estimate for an equivalence study enrolling 500 to 1000 patients would be 5 to 10 million US$.

Who provides the money for clinical research? In the vast majority of cases, it is the drug companies. They invest in studies which establish the value of new drugs and recoup their investment

through sales during the lifetime of the patent. But who would invest in a study comparing liposomal with continuous amphotericin? Certainly not the manufacturers of Ambisome® or Abelcet®; they have all to lose and nothing to gain. And certainly not the manufacturers of amphotericin B, a cheap substance without patent protection; the costs of the study could never be recovered.

"But", you object, "how about the public interest? The sickness funds and the Federal Social Insurance Office have most to gain from cheaper treatment; don't they invest in cost-effective medicine?" *The answer is No.*

Let's look at the sickness funds first. They have no tradition of furthering any research. By law, they must use the funds they receive for paying medical bills and for nothing else. They could spend money on research from what they receive for complementary (private, semiprivate) insurance. However if they wanted to do that, they would face another problem: Their investment in research is not patentable. Sickness fund A, if it paid for Furrer's hypothetical equivalence study, might save some money, but so would sickness fund B who paid nothing. Here is a quote from a letter signed by E. David, the president of Helsana and a member of the Swiss parliament[1]: "This (financing research) is not the task of a medical insurance company, which has to compete in the market with other insurers."

The Federal Social Insurance Office claims that they have no legal mandate nor any money for research into cost-saving measures, and recommends the Swiss Foundation for Health Promotion and the parent organisation of the sickness funds, Santé Suisse. However, the Foundation's mission does not include financial health, and specifically excludes medical research, whereas Santé suisse claims they can only do something if the Federal Office provides the legal mandate – at which time even the most persistent researcher will be slightly discouraged. The more so because his sense of urgency is not shared by the officials he has approached; on the contrary, they consider his request a bother to be disposed of, not a mission to be accomplished. Why should he persist? Much easier to accept the offer to study some promising new antifungal drug, complete with invitations to symposia in nice places, and consultancy contracts of 2000 US$ per day.

Mind you, I am not criticising the drug companies here. They are doing their job: developing new drugs and selling them at a profit. What I am criticising are those people in health politics and health insurance who do not recognise their enlightened self-interest, do not realise that research into cost effectiveness will not occur without investment and continue the refrain: "that's not my business".

There are faint stirrings of what the French call a "prise de conscience". The Swiss Council of Science and Technology has recently published a position paper on the state of clinical research in Switzerland, calling for action to increase education and career possibilities at university medical schools. The Swiss National Research Fund, so far almost exclusively involved in basic biomedical research, is planning to add a division of clinical research for its next budget period starting in 2004. It will be interesting to see how this proposal fares when resources are allocated. Don't bet on it.

Correspondence:
Professor Bernard Hirschel, M.D.
Division des Maladies infectieuses
Hôpital cantonal universitaire
CH-1211 Genève 14
E-Mail: bernard.hirschel@hcuge.ch.

[1] Answering an inquiry into financing a study of cost-saving ways to treat HIV infection.

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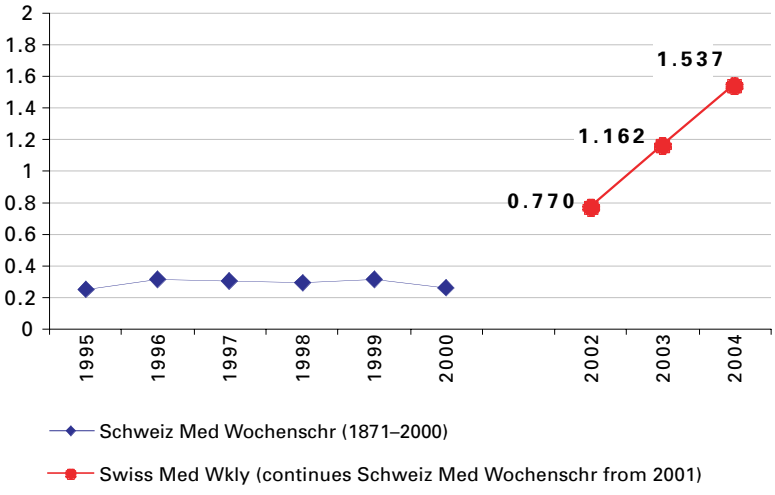

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