Pharmacokinetics of antibiotics in burns patients

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Sir,

There are a paucity of data relating to the pharmacokinetics of many antibiotics in burns patients, so it was interesting to read the article by Sampol *et al.*[1] They should be congratulated for undertaking such research. From their study of six patients they conclude that their results 'demonstrate that it is not necessary to change the standard dosage of cefepime in burns patients'. I would like to suggest that whilst they might be correct, it is yet to be proven.

Burn patients share in common the presence of a burn and the accompanying physiological changes. However, the net effect on drug handling produces a highly heterogeneous population with patients spread over an extremely wide base. Thus, a common theme in many publications is the great variability in individual patient pharmacokinetic parameters.

When studying burns patients this heterogeneity must be taken into account. For example, although it is generally accepted that the dosage requirements for aminoglycosides in this patient group are substantially altered, there have been reports suggesting no difference.[2,3] Presumably this relates to the population being sampled. Some burns patients do not require increased aminoglycoside dosage. The key is to encompass a wide range of patients in any study. Thus, in relation to the paper by Sampol *et al.*[1] their sample population is neither sufficient in number or breadth to justify the dosage recommendation. Some burns patients have extremely high creatinine clearance values (in excess of 200 mL/min) but have not been represented in their study.

Small studies like this are nonetheless extremely worthwhile. Other centres need to be encouraged to undertake similar work, so data may then be pooled in an attempt to include large numbers of patients, in order to represent the extremes of drug handling. For this to succeed there needs to be agreement in advance over the various parameters to be measured, patient eligibility and target antibiotic levels. Many previous studies have been flawed for a variety of reasons. This includes measuring antibiotic levels within the first 48 h of injury, a time not only when sepsis is unlikely to occur but also, more importantly, when renal performance is impaired.[4]

How can a change in the way such studies are conducted be implemented? Ideally a working party should be set up to produce guidance on conducting future pharmacokinetic studies. To be successful their recommendations will need the support of both pharmaceutical companies and relevant medical journals.

It is 25 years since the alteration in aminoglycoside pharmacokinetics was first described. Despite this, there is little to support the current dosage recommendations for many other classes of antibiotic. To ensure the optimum therapy for every burns patient, standardization of pharmacokinetic studies needs to be introduced.

References

1. Sampol, E., Jacquet, A., Viggiano, M., Bernini, V., Manelli, J. C., Lacarelle, B. *et al.* (2000). Plasma, urine and skin pharmacokinetics of cefepime in burns patients. *Journal of Antimicrobial Chemotherapy* **46**, 315–7.

2. Zaske, D. E., Sawchuk, R. J., Gerding, D. N. & Strate, R. G. (1976). Increased dosage requirements of gentamicin in burns patients. *Journal of Trauma* **6**, 824–8.

3. Polk, R. E., Mayhall, G. C., Smith, J., Hall, G., Kline, B. J., Swensson, E. *et al.* (1983). Gentamicin and tobramycin penetration into burn eschar: pharmacokinetics and microbiological effect. *Archives of Surgery* **118**, 295–302.

4. Weinbren, M. J. (1999). Pharmacokinetics of antibiotics in burns patients. *Journal of Antimicrobial Chemotherapy* **44**, 319–27.

Termination of development of D0870

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Sir,

We refer to the recent papers concerning D0870 and Chagas' disease by Molina and colleagues[1,2] in the July 2000 and January 2001 issue of your journal. Your readers should be aware that Zeneca (now AstraZeneca) terminated the development of this azole antifungal in 1995 due to an adverse event in an HIV-positive patient receiving the drug for fluconazole-resistant oropharyngeal and oesophageal candidosis (OPC). She was enrolled in a dose-ascending trial of D0870 for patients with low CD4 counts and OPC unresponsive to azoles.

We had already shown that D0870 was well tolerated and effective at doses as low as 10 mg for fluconazole sensitive infections[3] and also at intermediate doses for some patients with fluconazole-resistant OPC.[4]

Early toxicity work had shown a propensity to QT prolongation in beagle dogs so that plasma concentrations of D0870 above 3000 ng/mL increased QT, with changes proportional to serum concentrations. However, it was only at above 30 000 ng/mL and up to 70 000 ng/mL that three dogs died of sudden cardiac events.

Pharmacokinetic modelling was performed and doses were selected with the aim of ensuring that no patients achieved levels in excess of 3000 ng/mL, and that this level was approached gradually. Only patients with a normal ECG and QTc less than 450 ms were recruited. Concurrent agents known to interact with azoles or prolong the QT interval were excluded.

An ascending-dose study in a population of patients with few or no other therapeutic avenues (late-stage AIDS patients with azole-refractory oral and/or oesophageal candidosis) was initiated. Careful QT monitoring and contemporaneous serum D0870 concentrations were an integral part of the study. Two patients had QTc prolongation to >500 ms (though one was withdrawn because of hypokalaemia) before the 47th of the 48 planned potential enrollees. QTc interval rose from 406 to 535 ms and the drug was stopped. She received haloperidol, bromazepam, pentamidine and prednisolone, and 3 days later suffered dizziness associated with bradycardia, gross T wave changes and a short run of ventricular tachycardia, followed by a cardiac arrest from which she was resuscitated. It was determined retrospectively that her plasma D0870 concentration was 3241 ng/mL at the time of the event.

Subsequent to this more was learned about the pharmacokinetics of D0870 in man. Human liver microsomal work showed that D0870 is a potential inhibitor of CYP 2C9 and 2C10 (greater than licensed azoles). There was some inhibitor activity of CYP 3A4 but less than licensed oral azoles.

These *in vitro* results, together with the large data set of patient pharmacokinetic samples, indicated that the kinetics of D0870 were unpredictable. Given the QT prolongation at modest serum concentrations and the single cardiac adverse event, Zeneca stopped development of the drug, despite its impressive clinical activity.

References

1. Molina, J., Brener, Z., Romanha, A. J. & Urbina, J. A. (2000). *In vivo* activity of the bis-triazole D0870 against drug-susceptible and drug-resistant strains of the protozoan parasite *Trypanosoma cruzi*. *Journal of Antimicrobial Chemotherapy* **46**, 137–40.

2. Molina, J., Urbina, J., Gref, R., Brener, Z. & Rodriguez, J. (2001). Cure of experimental Chagas' disease by the bis-triazole D0870 incorporated into 'stealth' polyethyleneglycol–polylactide nanospheres. *Journal of Antimicrobial Chemotherapy* **47**, 101–4.

3. de Wit, S., Dupont, B., Cartledge, J. D., Hawkins, D. A., Gazzard, B. G., Clumeck, N. *et al.* (1997). A dose comparison study of a new triazole antifungal (D0870) in HIV positive patients with oral candidiasis. *AIDS* **11**, 759–64.

4. Cartledge, J. D., Denning, D. W., Dupont, B., Clumeck, N., de Wit, S., Midgley, J. *et al.* (1998). Treatment of HIV related fluconazole-resistant oropharyngeal candidiasis with D0870, a new triazole antifungal. *AIDS* **12**, 411–6.

In vitro inactivation of *Chlamydia trachomatis* and of a panel of DNA (HSV-2, CMV, adenovirus, BK virus) and RNA (RSV, enterovirus) viruses by the spermicide benzalkonium chloride

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Sir,

We read with interest the article by Bélec *et al.*[1] on the inactivation of *Chlamydia trachomatis* and various DNA and RNA viruses by benzalkonium chloride (BZK). The authors undertook the tests by adding each of the infectious agents to dilutions of BZK, incubating the mixtures at 37°C for various time periods, centrifuging the mixtures at high speed, washing the deposits and then introducing the resuspended deposits into appropriate sensitive cell cultures. Under these conditions it was shown unequivocally that after incubation for 5 min, BZK was very effective in inactivating enveloped viruses, including HSV-2 and CMV, but less so for non-enveloped viruses. Furthermore, it killed *C. trachomatis* after incubation for 1 min at low concentration. We appreciate that used as a vaginal microbicide, BZK is likely to be active against extracellular *C. trachomatis* and other infectious agents introduced in semen, although the effect that the semen per se might have on the inactivation process was not assessed. We should emphasize, however, that women in both industrialized and developing countries who may be at increased risk of infection from their partners are often already infected with *C. trachomatis* and other intracellular agents such as *Neisseria gonorrhoeae* and viruses. While BZK may be active against extracellular infectious agents in semen, its ability to kill intracellular organisms is far less likely. This would be reminiscent of povidone-iodine, which kills *C. trachomatis* organisms rapidly *in vitro*,[2] but is of no value as a means of treating established chlamydial infections,