Unfortunately, she developed a severe sepsis with acute renal failure and died a few days after the amputation.

Two pairs of synovial fluid and serum samples (trough levels) were collected before the second dose of 400 mg of voriconazole (i.e. Day 1 of treatment), and before the second dose of 300 mg (i.e. Day 2 of treatment). Samples were immediately frozen at −20°C until analysis. Cortical and medullar bone samples were collected during the amputation (i.e. Day 6 of treatment). The patient medication did not involve drugs that could generate pharmacokinetic interactions with voriconazole. The patient had normal liver function and had a calculated creatinine clearance of 60 mL/min. The serum albumin concentration was low at 11.6 g/L (normal range: 38–46 g/L).

The measurement of voriconazole concentrations was performed using high-performance liquid chromatography coupled with a diode array detector method, as previously described and applied in our pharmacology department. For bone analysis, as there is no published analytical method for voriconazole assay in bone, previously published procedures for extraction in bone tissues were used to develop the assay method. The cortical bone samples were cut into small pieces. After addition of the analytical internal standard, 2 mL of 2 M acetic acid was added to 200 mg of cortical or medullar bone sample. The mixture was vigorously shaken for 10 min, boiled for 10 min and subsequently lyophilized. The stability of voriconazole through these extraction steps was verified. After addition of 500 µL of a saturated NH₄Cl/deionized water mixture (30/70, v/v) adjusted to pH 9.5 with 25% NH₄OH, voriconazole was assayed following the same procedure as for liquid samples. Calibration samples were obtained using voriconazole-free cortical or medullar bone samples and by means of appropriate addition of voriconazole solutions in order to obtain the following spiked bone sample concentrations: 0, 0.25, 1, 5, 10, 20 and 40 µg/g. The calibration curves were linear from 0.25 to 40 µg/g and the inter-assay precision coefficients of variation were lower than 15%.

Voriconazole concentrations in serum and synovial fluid were 2.41 and 0.76 mg/L on Day 1 and 4.09 and 1.07 mg/L on Day 2, respectively. Observed bone concentrations were 20.3, 2.41 and 0.76 mg/L on Day 1 and 4.09 and 1.07 mg/L on Day 2. The correlation coefficient of variation were lower than 15%.

Voriconazole concentrations in serum and synovial fluid were 2.41 and 0.76 mg/L on Day 1 and 4.09 and 1.07 mg/L on Day 2, respectively. Observed bone concentrations were 20.3 µg/g of tissue in the medullar bone and 1.9 µg/g of tissue in the cortical bone. The serum concentrations were higher than those usually observed for this dosing. One explanation could be the low albumin serum level leading to an increase in the free voriconazole concentrations in serum (plasma protein binding of voriconazole is 58%). In the joint fluid, voriconazole concentrations were higher than the MIC for the isolated Aspergillus strain. In the bone, the concentrations were high and similar to those seen with fluoroquinolones or rifampicin, which are known as drugs having a good bone diffusion.

The concentrations of voriconazole in the synovial fluid and bone suggest that voriconazole may have a role in managing infections at these sites. Further studies are needed to confirm these results.

Transparency declarations

None to declare.

References


Improving antimicrobial prescribing through knowledge and skills

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Sir,

In their recent qualitative study of factors influencing antimicrobial prescribing by non-consultant hospital doctors De Souza et al. found that undergraduate education, hospital guidelines and concerns about emerging resistance were minor influences on prescribing practice. Prescribing was more influenced by instruction passed down through a hierarchical system and
Correspondence

subsequently on personal experience. This will lead to poor adherence to local guidelines and inevitably poor prescribing. Poor prescribing by new UK graduates, often due to a lack of an integrated scientific and clinical knowledge base, and the lack of practical prescribing instruction for undergraduates are well-recognized problems. Clinician education has been found to be the most effective workplace intervention on improving antibiotic selection in a recent systematic review. One apparent barrier to appropriate antimicrobial prescribing is the lack of awareness among senior and training grade clinicians of the local and national resources available to support decision making, including local hospital protocols. Prescribing guidelines appear to be ineffective unless accompanied by educational or financial incentives. Whilst in NHS hospitals it is unlikely that we will be able to meaningfully financially reward individuals or even clinical groups it would seem that optimizing prescribing through improving knowledge and clinical skills may be a more pragmatic approach.

At Ninewells Hospital and Medical School in Dundee a concerted and multi-disciplinary effort has been made over recent years to promote and improve prudent antimicrobial prescribing through greater engagement in the undergraduate medical school curriculum and continuing postgraduate educational meetings. Pro-active promotion of local good practice guidance through a variety of educational activities is one such example. Audits of knowledge and behaviour regarding sepsis and antimicrobial therapy among training-grade doctors showed promising improvements between 1999 and 2003 as a result of these initiatives. However, these evaluations and those of others have highlighted the need for clinically focussed and sustainable national learning tools that address the technical and non-technical knowledge and skills of the antimicrobial prescriber.

An outcomes based web-based program (Appropriate Antimicrobial Prescribing for Tomorrows Doctors: APT) for teaching and reflective learning of antimicrobial prescribing has recently been developed by infection specialists and medical educationalists and has been adopted by medical schools throughout the UK. The primary resource for the APT project is an interactive website (http://www.dundee.ac.uk/facmedden/APT/index.htm) with access to clinical worked examples, prescribing exercises, self-assessment tools and a reflective learning logbook. Although the emphasis is on prudent prescribing of antibiotic therapy the principles learned through APT can be applied to all areas of prescribing. In our medical school this forms an integral part of clinical infection teaching in the fourth year that also includes recognition, diagnosis and management of common infections, infection control and health protection aspects of infection. This teaching is delivered by infectious disease physicians, microbiologists, infection control nurses, pharmacists and public health clinicians. Evaluation of this program through student and staff feedback has revealed very positive results and we are presently evaluating student knowledge through a series of short exams at the beginning and end of each attachment, and at the end of the year.

In line with national Scottish Recommendations for improving antimicrobial prescribing practice in Scotland the APT work has been further adapted for providing mandatory online e-based training and assessment for foundation doctors in Scotland through the Doctors Online Training System (DOTS) developed by NHS Education Scotland (NES) (https://www.nhsdots.org/nhsdots/dotsx/login.asp). This site is password protected and linked to the NES Healthcare Acquired Infection portal (http://www.nes.scot.nhs.uk/hai/). At any given time there are more than 1600 foundation doctors in Scotland who will have to undertake this mandatory exercise and show evidence of satisfactory completion of this module. This program, through clinical vignettes, revises, evaluates and then reinforces the principles and practices taught at undergraduate level for foundation doctors. An extension and probable further adaptation of this program is proposed for more senior training and non-training grade doctors and ultimately non-medical prescribers. Any persons outside Scotland interested in this work should please contact dilip.nathwani@nhs.net. Ongoing evaluation of this program will inform its further development and impact.

Transparency declarations

None to declare.

References