Is cephalosporin safe for clinical use? A Bayesian viewpoint

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Cefepime hydrochloride is approved for pneumonia, empirical therapy for febrile neutropenia, uncomplicated and complicated urinary tract infections, uncomplicated skin and skin structure infections and complicated intra-abdominal infections. A recent meta-analysis by Yahav et al. (Lancet Infect Dis 2007; 7: 338–48) concluded that cefepime was associated with a statistically significant increase in mortality (risk ratio 1.26, 95% confidence interval 1.08–1.49) when compared with other antibiotics. The US FDA decided to re-evaluate the meta-analysis data in collaboration with the drug sponsor. Two years later the FDA Alert summarized that ‘data do not indicate a higher rate of death in cefepime-treated patients. Cefepime remains an appropriate therapy for its approved indications.’ However, a thorough evaluation of the 52-page FDA report still shows that safety remains an unresolved issue. A Bayesian re-appraisal of the findings by the FDA and by Yahav et al. indicates that there is a 90.9% (by FDA trial-level meta-analysis), 80.8% (by FDA patient-level meta-analysis) and 99.2% (by Yahav et al. meta-analysis) probability that cefepime raises mortality in neutropenic fever patients, which translates into the following numbers needed to harm (NNH), i.e. to cause one extra death with the use of cefepime: FDA trial-level meta-analysis, NNH = 109; FDA patient-level meta-analysis, NNH = 76; Yahav et al. meta-analysis, NNH = 54. A similar harmful probability was observed with skin structure infections but not with pneumonias, intra-abdominal infections and urinary tract infections. In conclusion, cefepime should be avoided in patients with neutropenic fever or with skin structure infections.

Keywords: cephalosporin, statistics, adverse events

Introduction

Cefepime hydrochloride, which was approved for clinical use on 16 May 1997, is a broad-spectrum cephalosporin antibiotic widely used by clinicians and surgeons. The label indications are: pneumonia; empirical therapy for febrile neutropenia; uncomplicated and complicated urinary tract infections; uncomplicated skin and skin structure infections; and complicated intra-abdominal infections.1

What is the problem?

A recent systematic review and meta-analysis by Yahav et al.2 published in 2007 concluded that cefepime was associated with a 26% (statistically significant) increase in the mortality of all included patients [risk ratio (RR) 1.26, 95% confidence interval (CI) 1.08–1.49] and a 42% increase in the mortality of patients with neutropenic fever (RR 1.42, 95% CI 1.09–1.84), independently of the type of antibiotic used in comparator arms. This meta-analysis included only randomized clinical trials and followed strict methodological guidelines.

In the same year as the Yahav et al. publication, the US FDA issued the following statement: ‘FDA is working with the manufacturer of cefepime, Bristol-Meyers Squibb, to further evaluate the finding of increased mortality in patients who received cefepime. It will take about 4 months to complete this evaluation at

which time FDA will communicate the conclusions and any resulting recommendations to the public. Until the evaluation is completed, healthcare providers who are considering the use of cefepime should be aware of the risks and benefits described in the prescribing information and the new information from this meta-analysis.’3

Nineteen months later (June 2009), the FDA issued its final verdict: ‘FDA reviewed this study data and conducted additional analyses based on additional data, including data submitted by Bristol-Meyers Squibb. FDA has determined that the data do not indicate a higher rate of death in cefepime-treated patients. Cefepime remains an appropriate therapy for its approved indications.’4

How should the new FDA analysis be interpreted in the context of previous studies?

Because cefepime has been part of my clinical armamentarium and many of my patients require broad-spectrum antibiotics, I decided to read the full 52-page statistical review and evaluation report just published by the FDA;5 this analysis has also been published in a more concise format.6 Unfortunately, the FDA Alert for healthcare professionals did not do justice to their own full report.

First, the FDA results show a potential mortality increase with cephalosporin by both trial-level and patient-level meta-analysis: risk
included trials. This sensitivity analysis showed a significantly higher (52%) risk of death with cefepime in trials that met the criteria for adequate allocation-sequence generation (RR 1.52, 95% CI 1.20–1.92). More recently, Leibovici et al. described several problems with the FDA analysis, including the remarkable finding that the mortality risk based on peer-reviewed and published studies was significantly increased with cefepime (1.23, 95% CI 1.07–1.42), while the mortality risk based on unpublished studies provided by Bristol-Myers Squibb to the FDA was significantly decreased with cefepime (0.80, 95% CI 0.66–0.97).

What is the solution?

It is beyond the scope of this letter to speculate about all the possible biological reasons why the mortality rate is increased with cefepime. Even though a cause–effect relationship cannot be established with certainty, the current best evidence is consistent with respect to the increased mortality risk for patients with neutropenic fever or skin structure infections. These two clinical indications are known to be associated with a low mortality rate (0–6%). So why continue administering cefepime? Why use a drug that has a high probability of being associated with increased mortality (80%–99% for neutropenic fever and 87% for skin infections) and a clinically meaningful number needed to harm (NNH=54–109 for neutropenic fever and NNH=56 for skin infections), while there are several other available drugs (e.g. piperacillin, ticarcillin, ceftazidime, aztreonam, imipenem and meropenem), as well as a number of combinations of β-lactams with aminoglycosides or quinolones?

What needs to happen next?

It is important to note that a new Phase III trial to address this safety issue with cefepime will not be feasible for the following reasons: (i) the expected number of events in the control arm would be small and thousands of patients would be required for this trial; (ii) the statistical power of this trial would have to be based not on efficacy but on safety, which would require a further increase in sample size; and (iii) financial support for this mega-trial would be unlikely since the drug is already off patent. The only possible solution for this conundrum will be through a carefully orchestrated FDA and European Agency for Evaluation of Medicinal Products Phase IV safety registry database. A useful approach to addressing the real-life safety concerns with cefepime would be through a pharmacoepidemiology design, which could be achieved with a cross-linked computerized population-based database. In the meantime, current evidence indicates that cefepime should be avoided in patients with neutropenic fever or with skin structure infections, but continued for the treatment of pneumonias, intra-abdominal infections and urinary tract infections.

Conclusion

In summary, the FDA’s new meta-analysis gives further support to the results from the meta-analysis of Yahav et al. Both studies showed that the mortality increase associated with cefepime administration continues to be a concern in clinical practice, especially for patients with neutropenic fever or skin structure infections.

difference (RD) 5.38 per 1000 (95% CI −1.53 to 12.28) and 4.83 per 1000 (95% CI −4.72 to 14.38), respectively (please note that FDA measured risk differences and Yahav et al. measured risk ratios). These results were not statistically significant, but the majority of the 95% CI clearly resided in the harm side (i.e. increased mortality with cefepime). In fact, based on these new FDA findings, there is a 71% probability that the risk of death is increased with cefepime compared with other antibiotics when all trials and all patients are analysed by the use of a uniform prior (Bayesian approach). This probability was 99% by the original Yahav et al. meta-analysis.

Second, both meta-analyses indicate that the mortality is increased with cefepime for neutropenic fever patients: Yahav et al., RR 1.42 (95% CI 1.09–1.84); FDA trial level, RD 9.67 (95% CI −2.87 to 22.21); and FDA patient level, RD 18.10 (95% CI −9.22 to 45.42). These results show that there is a 90.9% (by FDA trial-level meta-analysis), 80.8% (by FDA patient-level meta-analysis) and 99.2% (by Yahav et al. meta-analysis) probability that cefepime raises mortality in neutropenic fever patients. If we translate these risks to another common outcome measure such as the number needed to harm (NNH), i.e. the number needed to treat with cefepime to cause one extra death in patients with neutropenic fever, we obtain the following results: Yahav et al. meta-analysis, NNH=54; FDA trial-level meta-analysis, NNH=109; FDA patient-level meta-analysis, NNH=76. Similarly, the FDA meta-analyses indicate a statistically significant mortality increase with cefepime for skin structure infections for both trial-level and patient-level analyses: RD 17.97 (95% CI 3.73–32.21) for both analyses. Yahav et al. did not analyse the skin infection population. The FDA results for skin structure infection are associated with 87.5% probability of harm with cefepime, and the NNH for these patients is 56. The outcome results for the pneumonia indication were less consistent between trial- and patient-level meta-analyses, and the ones for the urinary tract infection and intra-abdominal indications showed 95% CIs mostly on the side of benefit with cefepime.

Third, similar cefepime mortality trends are observed when we look into the analyses by drug comparator—the point estimates sit in the harm side when cefepime is compared with cefotaxime, piperacillin and imipenem. Also, independently of age (18 to >65 years), gender or if any pathogen was recovered (or not) at baseline, most mortality risk point estimates do not favour cefepime.

Fourth, consistent trends for mortality increase in these subgroups of clinical importance were observed in both trial-level and patient-level FDA meta-analyses, as well as in both intent-to-treat (ITT) and microbiological ITT populations.

Lastly, it is concerning that the new FDA analysis found 50 ‘new’ trials (not analysed in the Yahav et al. study), including many ‘unpublished trials’ provided by Bristol-Myers Squibb, without describing each of these studies in more detail, as well as the reasons why these trials were never published in peer-reviewed journals (e.g. were they ever sent for publication or were they rejected by peer review?). The FDA report did not provide a sensitivity analysis based on the quality of the trials (e.g. were their methods rigorous and was the randomization process appropriate?) that they included in their evaluation, while the Yahav et al. study performed a specific analysis based on the different methodological quality among all included trials. This sensitivity analysis showed a significantly
Acknowledgements
I thank Ms Ashley Calhoon for outstanding administrative support.

Transparency declarations
None to declare.

References