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Letter to the Editor

Is empirical use of the antibiotic combination of cefuroxime and clavulanic acid rational?

Sir,

The fixed-dose combination (FDC) of cefuroxime and clavulanic acid (4:1 and 2:1) has been approved and introduced in some countries [1], although it is not approved by the US Food and Drug Administration (FDA). It is being marketed by at least 45 and 36 different pharmaceutical companies in India and Bangladesh, respectively (as per the online drug indices 'CIMS India' and 'medex.com.bd') and is being aggressively promoted for various indications such as respiratory tract infections, urinary tract infections and even surgical prophylaxis.

We performed a literature search on this combination to determine whether there is adequate data to support its use and to find out the supported indications. The English language literature published until 31 July 2018 was searched in PubMed and the Cochrane Library using the search term '(cefuroxime) AND (clavulanic OR clavulanate)'. In addition, a general search was also performed using the Google search engine. The search term produced 779 abstracts in PubMed and 75 results in the Cochrane Library, of which, surprisingly, only 1 article was found on the combination of cefuroxime and clavulanic acid [2]. Two more studies were found by general internet search [3,4].

In the first study, from Pakistan, the authors compared the activity of this combination versus cefuroxime alone against *Staphylococcus aureus*, and increased susceptibility was shown with the combination [2]. A zone of inhibition of >14 mm in diameter was considered susceptible, although the source of this breakpoint was not mentioned.

In the second study, the antimicrobial activities of five FDC antibiotics commercially available in India, including cefuroxime plus clavulanic acid (500:125 mg), were compared using the broth dilution method [3]. Of the two authors, the second author was from a pharmaceutical company. In contradiction to the first study, the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the cefuroxime/clavulanate combination were reported to be higher than the MIC and MBC for cefuroxime alone for all of the organisms tested (*S. aureus*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Escherichia coli* and *Streptococcus pneumoniae*).

The third study, also from India, compared the activity of cefuroxime with cefuroxime/clavulanate (2:1 ratio) using the disk diffusion method against 100 different isolates of biofilm- and/or β-lactamase-producing bacteria obtained from clinical specimens [4]. Among the isolates that produced only biofilm (β-lactamase negative), susceptibility to the combination (42.9%) was significantly higher than susceptibility to cefuroxime alone. On the other hand, amongst the isolates that were 'only β-lactamase producers', susceptibility to the combination was just 19.1% and, contrary to expectations, it was not significantly better than susceptibility to cefuroxime alone. The susceptibility of Gram-negative bacilli to the combination (25%) was also not statistically better than the susceptibility to cefuroxime alone.

Thus, the overall results of even these three in vitro studies are not quite supportive of the combination. No clinical studies could be found addressing the safety profile, interactions and indications for this FDC.

Unlike amoxicillin, cefuroxime itself is resistant to the β-lactamase produced by methicillin-susceptible *S. aureus*, and theoretically, addition of clavulanic acid will provide no additional advantage. Similarly, cefuroxime alone is as effective as amoxicillin/clavulanate against *E. coli* and β-lactamase-positive *H. influenzae*. Clavulanate has no role in infections by extended-spectrum β-lactamase-producing organisms or methicillin-resistant *S. aureus* (MRSA). In general, the FDCs of cephalosporins and clavulanate are considered irrational.

One of the three studies mentioned above showed higher MICs for the combination compared with cefuroxime alone [3]. This may be because of the very good enzyme-inducing property of clavulanic acid for chromosomal AmpC β-lactamases [5]. These enzymes, besides being resistant to clavulanic acid, are also resistant to other β-lactamase inhibitors, including tazobactam and sulbactam. Thus, it may be not just irrational but actually dangerous to combine clavulanate with cefuroxime because of this enzyme-inducing property. Concerns regarding the detrimental effects of clavulanate-based antimicrobials have also been raised by other authors [5].

The synergistic effect of clavulanate results from inhibition of the class A β-lactamase produced by the *blaZ* gene of *S. aureus*. Apart from its usual β-lactamase inhibitor action, clavulanic acid has been shown to bind to penicillin-binding proteins. This might explain the enhancing effect of clavulanate on β-lactams against β-lactamase-negative bacteria, as reported in the third study by De et al. [4]. Such findings further underline the point that the choice of empirical antibiotic cannot be made solely on the basis of theoretical reasoning, but should depend on direct evidence from microbiological and clinical studies. As evident from our literature search, sufficient high-quality studies do not exist to support the use of this FDC. Some 'irrational' FDCs were recently banned by the Indian government, but this FDC was not included in that list [6]. The statutory bodies of countries where this FDC has been approved need to take cognisance and ensure that this as well as similar other FDC antibiotics undergo adequate in vitro as well as clinical testing before being marketed. Otherwise, it not only adds to treatment costs and toxicity but, more importantly, leads to increasing antimicrobial resistance.

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Competing interests

None declared.

Ethical approval

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