Oral Faropenem Sodium – Implications for Antimicrobial Resistance and Treatment Effectiveness

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Rising antimicrobial resistance (AMR) is causing therapeutic failures with antibiotics. Inappropriate use is a contributing factor. One such antibiotic on the radar is faropenem, a broad spectrum antibiotic approved in 2005 in India. Recently, faropenem sodium suspension was approved for use in children. There is a potential danger of overuse due to the convenience of oral administration. Other carbapenems such as meropenem are used parenterally. Overuse of faropenem may promote cross-resistance with other carbapenems making them ineffective.

Keywords: *AMR risk, Carbapenems, Rational use*.

The burden of antimicrobial resistance (AMR) is rising rapidly in the world and also among children and neonates [1]. Irrational antibiotic use is a major driving force towards rising resistance, and therefore, responsible use is paramount [2]. Respiratory infections are one group of infections where antibiotics are misused. Evidence-based National and International guidelines recommend use of amoxicillin as the first line antibiotic for community acquired respiratory infections due to its effectiveness against leading res-piratory pathogens such as *Streptococcus pneu-moniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* [3,4]. Severe cases of pneumonia need to be treated with injectable co-amoxiclav or ceftriaxone. Carbapenems, which have the broadest spectrum of activity among all the beta-lactam antibiotics, is usually reserved for use for multidrug resistant infections, especially caused by aerobic gram negative bacilli [3].

Faropenem is an oral beta-lactam antibiotic belonging to the same class as carbapenems. Faropenem is available in many countries including India and is increasingly being used. Unfortunately, there are also reports of faropenem resistance causing cross resistance to other carbapenems [5]. This raises serious concerns since the other carbapenems such as meropenem, imipenem and erta-penem are usually reserved as life-saving antibiotics, especially in situations where the patients are critically ill due to multi-drug resistance organisms. Widespread use of faropenem, which is oral and relatively cheaper, therefore may have dangerous implications towards rising AMR and treatment ineffectiveness. We will address some of these aspects with the aim to sensitize stakeholders regarding the need to curb the use of faropenem in the interest of the society.

THE MOLECULE AND ITS APPROVAL

Faropenem is structurally similar to the other carbapenems except for a sulfur atom at position one [6]. The Clinical and Laboratory Standards Institute (CLSI) classifies faropenem and carbapenems under the penem class of antibiotics. The World Health Organization classifies faropenem as a 'reserve' antibiotic and therefore not to be used routinely without laboratory evidence [7]. It is produced as an oral formulation of the prodrug faropenem medoxomil (also known as faropenem daloxate) and faropenem sodium. Similar to other beta lactam antibiotics, it exerts its bactericidal action by inhibiting the cell wall synthesis of bacteria. It has a broad spectrum of activity including non-penicillin-susceptible *S. pneumoniae* and β-lactamase *H. influenzae* and *M. catarrhalis*, Gram-negative bacteria, including extended spectrum beta-lactamase (ESBL)-producing Enterobacteriales and anerobic bacteria [8]. There are no clinical breakpoints defined by the CLSI or European Committee on Antimicrobial Susceptibility Testing (EUCAST) for routine antimicrobial susceptibility testing by laboratories [9]. The adverse effects reported are mainly mild in nature and include diarrhea, nausea and abdominal pain.

Faropenem was approved for use in Japan in 1997. However, the United States Food and Drug Administration in 2006 stated that the drug was "non-approvable" for the applied indications of acute bacterial sinusitis, community-acquired pneumonia, acute exacerbations of chronic bron-chitis, uncomplicated skin and skin structure infections and urinary tract infections [10]. Faropenem is also not in the public data base of the European Medicines Agency (EMA) containing all medicines authorized in Europe [11]. In 2010, the Central Drugs Standard Control Organisation (CDSCO) approved its use for the above conditions in India as tablet faropenem sodium in 2005, and recently in 2021, as its oral suspension [12].

IMPLICATIONS FOR AMR

India and China are leading consumers of faropenem [13]. The faropenem consumption as a proportion of total penems was estimated at 58.4% on average for India and 6.8% in China between 2005 and 2014 [13]. Between 2010 and 2014, faropenem consumption in India sky rocketed by 154% [14]. Both the above reports highlight the fact that the consumption of faropenem had exceeded the total consumption of other carbapenems in India.

The global faropenem sodium market size is projected to grow at a compound annual growth rate (CAGR) of 9.03% reaching USD 281.99 million by 2026 [15]. This rising trend could be due to the ease of use as an oral formulation, its relative low cost and aggressive marketing as an 'effective antibiotic.' In contrast, the other carbapenems such as meropenem, imipenem and ertapenem have to be used parenterally, often in intensive care situations, and are comparatively expensive. The increasing use of faropenem is of critical relevance due to the evidence that induced resistance by faropenem can lead to development of cross-resistance to carbapenems among *E. coli* isolates con-taining *CTX-M-15-type* ESBL enzymes [5]. Additio-nally, another factor which may contribute to resistance is that the faropenem sodium formulation available in India has poor oral absorption (20-30%) in comparison to its prodrug, faropenem medoxomil, which has much higher bio-availability (70-80%) [13]. Therefore there is an imminent risk of prolonged exposure of gut bacteria to this drug and increase in gut colonization of resistant gram negative bacteria amongst its consumers [16]. The wide usage of faropenem therefore can endanger the effectiveness of other carbapenems, which are used in life saving situations and when first and second line antibiotics are not effective due to rising AMR.

STRATEGIES FOR OPTIMAL USE

Antibiotic stewardship encourages compliance towards updated evidence based guidelines and the use of existing antibiotics over newer antibiotics unless there is a critical need. The Indian Council of Medical Research (ICMR) guidelines on treatment of infections do not mention the need for faropenem [3]. Faropenem is also not listed in the Essential medicines list of our country or the WHO list [17]. There is no pressing need for encouraging a broad spectrum new antibiotic for treatment of community acquired respiratory infections when other effective and narrower spectrum antibiotics are still available. The convenience of oral administration can facilitate easier widespread misuse of the antibiotic among children in the community, thereby fuelling AMR, and difficulty in treatment of critical infections with carbapenems unless strict stewardship measures are undertaken.

Urgent measures are therefore needed to limit the use of oral faropenem sodium among children and the wider community. Currently, faropenem is listed under Schedule H1 in the Drugs and Cosmetics Act, 1940 [18]. This means that faropenem is to be sold by registered retail pharmacies only with a prescription from a registered medical practitioner. Also, all sales of this drug and relevant details need to be maintained in a separate register by retail pharmacies. It would be interesting to ascertain whether this is being followed strictly in each state, and also whether compliance is being monitored on a regular basis. Over the counter use of faropenem will have a devastating impli-cation for rising AMR. It is also imperative that the Drug Controller General of India (DCGI) and ICMR have wider discussions with stakeholders on the risks and benefits of continuing with faropenem in the market. It is our hope that an urgent and balanced decision must be made taking into account the critical nature of rising AMR. Last, but not least, it is important that all stakeholders, including physicians, other healthcare professionals, policymakers, the media and the public, understand the implications of over-usage of faropenem. Imbibing a risk versus benefit approach, not just individually, but for the society, will hopefully change behavior and improve appropriate use.

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