Brief Communication

Relative Potency of Different Generic Brands of Meropenem, Colistin and Fosfomycin: Implications for Antimicrobial Therapy and Antimicrobial Formulary

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Abstract

There is a need of a relatively simple and inexpensive method for the determination of relative potency of various generic brands of antibiotics in comparison to original products. The current study describes an agar diffusion method which can be performed in any microbiology laboratory, is cheap (costs $2 per test) and its results can be available after overnight incubation. The results show that neither all generics are reliable nor are all generic antibiotics of poor quality.

Keywords: Agar diffusion, colistin, fosfomycin, generic brands, meropenem, relative potency

Introduction

A general perception exists among practitioners in infectious diseases that generic antimicrobial agents are inferior to innovator products. This perception has arisen from empirical evidence and anecdotal reports. Generic medicines when tested under controlled laboratory conditions or used in clinical practice were sometimes reported to have inadequate pharmacological quality or clinical response. Generic drugs are considered to be equivalent to the innovator formulation if they have the same active pharmaceutical ingredient (API), pharmaceutical form and bioequivalence compared to reference medicinal product. The main concerns regarding the effect of poor-quality generic drugs have been the possible increased duration of disease because of suboptimal quality of products used during treatment and possible therapeutic failure. Supraoptimal concentration of generic drug can also be detrimental by exposing patients to an increased risk of dose-dependent side effects.[1] However, the technical challenges in testing quality of generic antimicrobial agents against innovator products are significant, and this has resulted in a situation where very few clinical users are having adequate understanding about the actual quality of generic antibiotics. High-performance liquid chromatography (LC) along with mass spectrometry (MS) are the standard methods for quality checks, and these techniques are generally not used in routine laboratory practice because of high equipment cost, expertise needed in standardisation and quality control and cost of tests. Therefore, there is a need of a low-cost and relatively simple technique which can enable resource-constrained laboratories in testing generic antibiotics locally.

Procedure

The current study was done in the microbiology department of Tata Medical Center, Kolkata, India. Test methodology for relative potency testing was based on the agar diffusion technique. Antibiotic samples from generic or innovator brands were reconstituted (with the diluents provided or analytical grade sterile Milli-Q water), and the initial stock solution started with concentration based on the median Cmax of meropenem, colistin or fosfomycin reported in previous pharmacokinetic studies. Standard strains used to test relative

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potency were selected as per the Clinical Laboratory Standard Institute recommendations. Each test was carried out in triplicate, and median zone diameter was used for calculation of product lot relative potency.[2] The zone diameters were read after overnight incubation, and the turnaround time of the test was 1 day. Cost of consumables (except the cost of the antibiotics) for doing the agar diffusion test was ~$2 per 5 antibiotic brands tested.[3]

Our results showed a difference of +1.7% to −48% in relative potency of meropenem brands, 0% to 0.98% for colistin brands and −10% to −57% for fosfomycin brands when compared against the original research brand [Tables 1a-c].

During the relative potency testing of all the three drugs (meropenem, colistin and fosfomycin brands), it was observed that the price was not necessarily an indicator of quality. The second observation was that the potency varied with regard to quality control (QC) strains used, and the third major observation was that the brand name was not necessarily a good way to judge the potency of a specific drug. Sometimes, inexpensive brands performed as well as the original brand. For example, Merolan and Meronem with respect to pseudomonas had similar relative potency, although its cost was much lower than Meropen or Menem. Second, the performance of the brand or a company also seemed to vary with its molecule, for example, colistin from United Biotech was equally good as other colistin products used in this study whereas it was significantly inferior when it comes to its meropenem product. It was reassuring to note that most colistin brand available in the market had little variation in potency; however, the same was not true about fosfomycin brands where larger variations were noted in the indigenous brand compared to the international brand.

Testing for pharmaceutical equivalence, bioequivalence, therapeutic equivalence by *in vitro* and *in vivo* models are technically demanding, time-consuming and resource intensive. These techniques are beyond the scope of most prescribers and generally can only be done by focussed research centres or regulatory organisations. For example, in one study, generic brands were compared using microbiological susceptibility testing, LC/MS and *in vivo* (neutropenic guinea pig soleus infection model and neutropenic mouse thigh–brain–lung infection models).[4]

Apparently insignificant chemical deviations among bioequivalent generic antibiotics can lead to therapeutic

Table 1a: Zone diameters of different generic brands of meropenem against the innovator brand as determined by the agar diffusion method

Median zone diameters (mm) of different brands of meropenem by agar diffusion method against various bacterial isolates										
Manufacturer	**Product name**	**Vial strength (g)**	**Lot number**	**Price in US dollar**	***Klebsiella pneumoniae* ATCC 700603 (MIC ≤1 mg/L)**	**Variation (%)**	***Escherichia coli* ATCC 25922 (MIC ≤1 mg/L)**	**Variation (%)**	***Pseudomonas aeruginosa* (MIC ≤2 mg/L)**	**Variation (%)**
Mylan Pharmaceutical	Merolan	1	MI0116019A	6.22	39	+1.7	39	−19	39	Same
United Biotech (P) Ltd	Menem	1	MNDJ5B8	28.10	37	Same	37	−45	34	−26
Zuventus Healthcare Ltd	Merotec	1	Z1D16005	8.70	35	−34	37	−45	35	−11
Fusion Healthcare	MeroReach	1	1716002	11.20	34	−48	37	−45	34	−26
Lupin Ltd	Merotrol	1	ZLM6107	12.30	36	−20	37	−45	37	−10
AstraZeneca Pharma India Ltd	**Meronem**	**1**	**MJ984**	**34.06**	**37**	**NA**	**40**	**NA**	**39**	**NA**

The comparator brand is at the end row of each table in bold. NA: Not available, MIC: Minimum inhibitory concentration, ATCC: American type culture collection

Table 1b: Zone diameters of different generic brands of colistin against the original brand as determined by the agar diffusion method

Median zone diameters (mm) of different brands of colistin by agar diffusion method against various bacterial isolates										
Manufacturer	**Product name**	**Vial strength (g)**	**Lot number**	**Price in US dollar**	***Klebsiella pneumoniae* ATCC 700603 (MIC ≤1 mg/L)**	**Variation (%)**	***Escherichia coli* ATCC 25922 (MIC ≤1 mg/L)**	**Variation (%)**	***Pseudomonas aeruginosa* (MIC ≤2 mg/L)**	**Variation (%)**
Cipla	Xylistin forte	2 MIU	A060630	25.53	31	+0.98	29	None	31	None
Gufic Bioscience Ltd	Sudostar	2 MIU	AP08513	16.39	30	None	29	None	31	None
Glenmark Pharmaceutical Ltd	Promistin-DS	2 MIU	44160016	19.05	30	None	28	−0.97	31	None
United Biotech	Colicraft Forte	2 MIU	CQDF6B4	17.38	30	None	28	−0.97	31	None
Glenmark Pharmaceutical Ltd	**Coly Monas**	**2 MIU**	**44170003**	**21.66**	**30**	**NA**	**29**	**NA**	**31**	**NA**

The comparator brand is at the end row of each table in bold. NA: Not available, MIC: Minimum inhibitory concentration, ATCC: American type culture collection

Table 1c: Zone diameters of different generic brands of fosfomycin against the innovator brand as determined by the agar diffusion method

Manufacturer	Product name	Vial strength (g)	Lot number	Price in US dollar	*Klebsiella pneumoniae* ATCC 700603 (MIC ≤64 mg/L)	Variation (%)	*Escherichia coli* ATCC 25922 (MIC ≤64 mg/L)	Variation (%)
Cipla	Crifos	4	CFSAQO316	54.07	41	−57	14	−30
Glenmark	Fonyl	4	DFSAQO216	55.23	45	−28	17	−17
Intas	Fosfotas	4	AFSAQO116	42.31	47	−24	18	−10
Northeast Pharmaceutical Group Co., Ltd.	**Fosfomycin sodium**	**2**	**NA**	**122.84**	**49**	**NA**	**22**	**NA**

Zone diameters marked in bold represent the highest diameter in each experiment. NA: Not available, MIC: Minimum inhibitory concentration, ATCC: American type culture collection

non-equivalence. In a Columbian study, it was found that trisodium adducts in a bioequivalent generic of meropenem made a meropenem brand more susceptible to dehydropeptidase hydrolysis and less stable at room temperature, resulting in therapeutic non-equivalence. These failing generics are compliant with the United States Pharmacopeia requirements and would remain undetectable under many current regulations.[5]

Another Columbian study showed that for therapeutic equivalence of drugs like metronidazole, pharmaceutical, pharmacokinetic and pharmacodynamic identities are required. The generic and the innovator products can be identical in terms of the concentration and potency of the API, chromatographic and spectrographic profiles, minimum inhibitory concentration and minimal bactericidal concentrations and mouse pharmacokinetic model and yet differ in therapeutic equivalence.[4]

A post-marketing clinical study on healthy volunteers in Italy reported lack of pharmacokinetic bioequivalence between generic and branded amoxicillin formulations. The mean pharmacokinetic profiles showed that the area under the curve value of branded amoxicillin was 8.5% and 5.4% greater than that estimated for generic A and B, respectively.[6] The results of relative potency testing using similar methods in our previous study showed a difference of −11%–−36% of the potency of the generic brands of piperacillin–tazobactam when compared against the original research brands.[3]

Despite all the negative publicity, there are good financial and clinical reasons why generic drug market sustains and flourishes. Generic medicines are widely used in developing countries because of low costs and easy accessibility. The side effect profile and patient acceptances were sometimes comparable to innovator products. An observational study among patients with chronic diseases attending a public hospital in Kolkata, India, reported that 93% of generic and 87% branded drug users believed that their drugs were effective in controlling their ailments. No significant difference (9% generic and 10% branded drug users) was observed in reported adverse effects between generic and branded drug users. Moreover, 82% and 77% of patients were adherent to generic and branded drugs, respectively.[7] This study is important because, since 2012, the local government in India had initiated exclusive generic drug outlets called 'fair price medicine shop' inside the government hospital premises in a 'public–private partnership' model.[7] Clinical studies on generic antibiotics in Thailand had previously demonstrated non-inferiority (overall clinical outcome, mortality and adverse effects) of some generic products of piperacillin–tazobactam.[8] Another study from Thailand reported therapeutic equivalence of generic imipenem–cilastatin with innovator brands in terms of mortality and adverse effect.[9]

Conclusion

Agar diffusion method represents a relatively inexpensive, simple test which could be performed in basic microbiology laboratories for determination of relative potency of antibiotic formulations. The information available from such studies may be useful to provide feedback to pharmaceutical companies, drug manufacturers and drug controllers and help in deciding hospital antibiotic formularies. It is important that more accurate techniques on multiple batches using LC-MS be used to verify API concentration. Our results also show that in terms of API, not all generics are inferior.

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Conflicts of interest

There are no conflicts of interest.

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