

Tigecycline in-vitro susceptibility and antibiotics' fitness for gram-negative pathogens

Subhash C. Arya, MBBS, PhD, Nirmala Agarwal, MBBS, FRCOG.

ABSTRACT

الأهداف: من أجل تحديد مدى تعرض عنصرتايجيسايكلين داخل الجسم وملائمة المضادات الحيوية للممرضات سالبة الجرام من الالتهابات الخطيرة بدلهي، الهند.

الطريقة: أجريت الفحوصات الطبية لتحديد مدى تعرض عنصرتايجيسايكلين داخل الجسم لدى 50 من الممرضات سالبة الجرام من الالتهابات الخطيرة بمستشفى سانت بارماناند - دلهي - الهند، خلال الفترة مابين يوليو 2007م وحتى أكتوبر 2007م. تم تحديد تركيزات تثبيط عنصرتايجيسايكلين عند الحد الأدنى بتوظيف طريقة اختبار AB Biodisk - E.

النتائج: تبين وجود 24% من المعزولات مقاومة لعنصرتايجيسايكلين أو بشكل جزئي. مدى مقاومة المعزولات كان أقل من ميروبينيم، ولكن مشابه لعقار بيبيريستيلين-تازوبكتام، اموكسيسيلين-حمض كلافلولانيك وواميكاسين.

خاتمة: كانت مقاومة عقارتايجيسايكلين شائعة لدى المعزولات سالبة الجرام من الالتهابات الخطيرة قبل التسويق في الهند. يجب عدم اختبار أي مضادات حيوية مسوقة للمعالجة ضد الالتهابات سالبة الجرام بشكل ذاتي (اوتوماتيكلي). ينبغي تقييمها بشكل متوازي مع المضادات الحيوية مع ملفات مدى التعرض المحلية الممتازة في الفترة الأولى لتسويقها.

Objectives: To determine the tigecycline in-vitro susceptibility of naïve gram-negative pathogens from serious infections in Delhi, India.

Methods: During July to October 2007 investigations were carried out to determine the tigecycline in vitro susceptibility of 50 consecutive gram-negative pathogens from serious infections at the Sant Parmanand Hospital, Delhi, India. Minimum tigecycline inhibitory concentrations were determined employing the E test method (AB Biodisk).

Results: Twenty-four percent of isolates were found to be tigecycline resistant or partly susceptible. Susceptibility of the isolates was lower than meropenem but similar to piperacillin-tazobactam, amoxicillin-clavulanic acid, and amikacin.

Conclusion: Tigecycline resistance was prevalent in the gram-negative isolates from serious infections prior to its marketing in India. The choice of any recently marketed antibiotic for a pilot treatment against serious gram-negative infections should not be automatic. In the initial phase of its marketing, it should be evaluated in parallel with the antibiotics with excellent local susceptibility profiles.

Saudi Med J 2008; Vol. 29 (11): 1558-1560

From the Departments of Microbiology and Infection Control (Arya) and Obstetrics and Gynecology (Agarwal), Sant Parmanand Hospital, Delhi, India.

Received 26th May 2008. Accepted 14th October 2008.

Address correspondence and reprint request to: Dr. Subhash C. Arya, Sant Parmanand Hospital, 18 Alipore Road, Delhi 110054, India. Tel. +91 (11) 9810642269. Fax. +91 (11) 23974706. E-mail: subhashji@hotmail.com

Tigecycline, a glycylycylone is a structural analogue of minocycline designed to avoid tetracycline resistance mediated by ribosomal protection and drug efflux. It is indicated for the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infections and is available for intravenous administration only.¹ Tigecycline, with a broad spectrum of activity against multidrug-resistant gram-positive and gram-negative pathogens is expected to be useful in the treatment of conditions caused by these pathogens.² The intravenous formulation exhibits linear pharmacokinetics with a rapid distribution along with a large volume of distribution and extensive tissue penetration. The long terminal elimination half-life of around 40 hours allows a twice-daily administration. Tigecycline undergoes very limited metabolism and the unchanged drug is eliminated through the feces, with glucuronidation and renal routes.³ Recently, tigecycline was reported as a promising recipe for gram-negative infections.⁴ In Philadelphia, the clinical, and microbiological response to tigecycline therapy in 18 patients with serious multidrug-resistant gram-negative

organisms was far from ideal.⁵ During 2007, tigecycline marketing was initiated in India.⁶ We investigated the susceptibility or otherwise of local gram-negative isolates during the pre-introduction phase. In-vitro susceptibility assays were carried out at the Sant Parmanand Hospital, Delhi, India, a 140-bedded, multi-specialty, tertiary care, hospital in Delhi. Susceptibility profiles to gram negative pathogens associated with serious infections were not that optimistic.

Methods. During July and October 2007, 50 successive gram-negative isolates from patients with intense infection, including those in the intensive care units, medical, surgical, neonatal, were evaluated. Prior approval from the Ethics Committee was not required. Isolates were drawn from urine (25 isolates), blood and purulent material (10 isolates each), and pulmonary tissues (5 isolates). Tigecycline susceptibility was measured as the isolates' minimum inhibitory concentration (MIC) values. Isolate susceptibility was simultaneously evaluated against the locally favored antibiotics in such cases.⁶ Identification was based on gram staining, biochemical reactions with sugars, including indole, urea, citrate, lysine iron agar, triple sugar iron, and phytyl pyruvic acid reactivity. Isolates included *Escherichia coli* (*E. coli*) (17 isolates), *Klebsiella species* (30 isolates), *Proteus species* (1 isolate), and *Pseudomonas species* (2 isolates). They were drawn from urine (28 isolates) purulent material (12 isolates), blood (4 isolates) and pulmonary tissues (6 isolates). Tigecycline susceptibility was determined using the E test method (AB Biodisk, Solna, Sweden). For other antibiotics, disk diffusion method, employing disks (Difco or Oxoid), was employed. The interpretations, depending on diameter of the zone of inhibition, were according to the clinical Laboratory Standards Institute (CLSI) criteria. Tigecycline isolates with MIC values of ≤ 2 $\mu\text{g/ml}$ were regarded as susceptible, 2 - ≤ 8 $\mu\text{g/ml}$ partially resistant, and ≥ 8 $\mu\text{g/ml}$ resistant. Isolates were labeled to be susceptible or resistant to others, in

accordance with the guidelines of the CLSI.

Eight isolates including *E. coli* (3 isolates) and *Klebsiella* (5 isolates) were tested for extended-spectrum beta-lactamase (ESBL) production. Extended-spectrum beta-lactamase production was determined according to CLSI guidelines employing a disk combination of ceftazidime, ceftazidime-clavulanic acid, cefotaxime, and cefotaxime-clavulanic acid (Becton Dickinson, Sparks, Maryland).

Results. Tigecycline MIC was ≤ 2 $\mu\text{g/ml}$ in *E. coli* (11 isolates), *Klebsiella* (20 isolates) and there was only one *Proteus* (isolate). An MIC of 2 - ≤ 8 $\mu\text{g/ml}$ was observed in *E. coli*, 2, *Klebsiella*, 4 and *Pseudomonas*, 1. An MIC ≥ 8 $\mu\text{g/ml}$ was recorded in *E. coli* (2 isolates), *Klebsiella* (4 isolates), and *Pseudomonas* (1 isolate), shown in Table 1. Of the 4 tigecycline resistant/partly susceptible *E. coli*, all were susceptible to meropenem, 3 to piperacillin-tazobactam, 2 to amoxicillin-clavulanic acid and amikacin. Of the 6 tigecycline resistant/partly susceptible *Klebsiella*, 5 were susceptible to meropenem, and piperacillin-tazobactam each, and 3 to amoxicillin-clavulanic acid and amikacin each. Concurrently, in the 2 *Klebsiella* or *E. coli* resistant either to meropenem, piperacillin-tazobactam, and amoxicillin-clavulanic acid or amikacin, only one was tigecycline susceptible. The 5 ESBL-producer *E. coli* and *Klebsiella* were susceptible to tigecycline. Extended-Spectrum beta-Lactamase negatives included one tigecycline susceptible *E. coli* and *Klebsiella*, while one *Klebsiella* was partially susceptible/partially resistant. All the *Klebsiella* isolates, which were resistant to piperacillin-tazobactam, amoxicillin-clavulanic acid, and amikacin, shown in Table 1 were resistant to tigecycline as well.

Discussion. Marketing of new antibiotics in developing countries is accompanied by extensive dissemination of information regarding its superiority over the antibiotics in common usage locally. Investigations on tigecycline naïve pathogens in the

Table 1 - In-vitro susceptibility to tigecycline and other popular antibiotics at Sant Parmanand Hospital, Delhi.

Isolate	Tigecycline MIC			Meropenem		Piperacillin-tazobactam		Amoxicillin-clavulanic acid		Amikacin	
	<2 $\mu\text{g/ml}$	2- ≤ 8 $\mu\text{g/ml}$	≥ 8 $\mu\text{g/ml}$	S	R	S	R	S	R	S	R
<i>Escherichia coli</i>	11	2	2	14	0	13	2	13	2	13	2
<i>Klebsiella</i>	20	4	2	24	2	23	3	24	2	23	3
<i>Proteus</i>	1	0	0	1	0	1	0	1	0	1	0
<i>Pseudomonas</i>	0	1	1	1	0	2	0	1	0	2	0
Total	32	7	5	40	2	39	5	39	4	39	5

S = number susceptible, R = number resistant

Indian capital metropolis of New Delhi were carried out before its local marketing.⁶ A comparison was aimed with the therapeutic options in serious infections by gram negatives, including ESBL-producers, in the hospital. The current choice has been of meropenem, piperacillin-tazobactam, amoxicillin-clavulanic acid, and amikacin.⁷ Tigecycline resistant or partially susceptible isolates among the above 50 consecutive gram-negatives were 24%: 95% confidence interval 10.6-42.6%. The total isolates susceptibility to tigecycline was lower than meropenem (Fisher's $p=0.0079$), however, resembled piperacillin-tazobactam, amoxicillin-clavulanic acid, and amikacin. Furthermore, there was not a single isolate that was exclusively susceptible to tigecycline.

The above investigations have been confined to a solitary hospital but the isolates had been tigecycline naïve. One would have to be very guarded to attempt any extrapolations. Nevertheless, even with not very many isolates, one could infer that tigecycline would be very unlikely to be the exclusive recipe in the future. That would be important for any empirical therapy before report on in-vitro antibiotic susceptibility was known. The above in-vitro data on tigecycline efficacy supports the University of Philadelphia Hospital clinical and microbiologic data.⁵ In all probability, chances of tigecycline emerging as the first favorite for clinicians' in severe gram negative infections would be remote.

To conclude, those responsible for treatment of serious infections would be obliged to offer the most efficient recipe. They should also bear in mind risks for emergence of antimicrobial resistance during clinical use of antibiotics. Their hard work to manage patients with use of the most potent agents around could affect the prevalence of antimicrobial resistance.⁸ The antibiotic prescription practices would vary dramatically in different countries. In several countries, a prior in-vitro susceptibility result on patient's isolates would be necessary before prescribing any newer antimicrobial. On the contrary, in counties with over-the-counter availability of antimicrobials and no antibiotics policy around, clinicians would be tempted to prescribe recently

marketed antibiotics. To prescribe newer antibiotics expecting a swift and optimistic response might not be rational all the times. A better strategy towards patient cure would be the retrospective antibiotic susceptibility profiles, shown in Table 1 in the above study, to select the ideal empirical therapy in serious gram negative infections.

Acknowledgment. *The technical assistance of Ms. Dolly Wadhwa and Ms. Rehana Jamil, and the secretarial assistance of Ms. Sarita Kumar are acknowledged. The help with the susceptibility testing of Tigecycline from Dr. John Wain, Tropical Bacteriology, Wellcome Trust Sanger Institute, Cambridge is gratefully acknowledged.*

References

1. Wikipedia, the free encyclopedia. Tigecycline. [updated 2008; (cited 2008 September 7). Available from <http://en.wikipedia.org/wiki/>
2. Doan TL, Fung HB, Mehta D, Riska PF. Tigecycline: a glycolcylcline antimicrobial agent. *Clin Ther* 2006; 28: 1079-1106.
3. Meagher AK, Ambrose PG, Grasela TH, Ellis-Grosse EJ. Pharmacokinetic/pharmacodynamic profile for tigecycline-a new glycolcylcline antimicrobial agent. *Diagn Microbiol Infect Dis* 2005; 52: 165-171.
4. Hawkaey P, Finch R. Tigecycline: in-vitro performance as a predictor of clinical efficacy. *Clin Microbiol Infect* 2007; 13: 354-362.
5. Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. *Clin Infect Dis* 2008; 46: 567-570.
6. Reuters. Wyeth launches antibiotic Tygacil for Indian market. [updated 2007 June 22; Cited 2008 February 10]. Available from: <http://www.reuters.com/article/health-SP/idUSBOM16513520070622>
7. Arya SC, Agarwal N, Solanki BS, Agarwal S. Use of cefepime for the treatment of infections caused by extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. *Singapore Medical Journal* 2007; 48: 600-601.
8. Rice LB. The Maxwell Finland Lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. *Clin Infect Dis* 2008; 46: 491-496.