A Brief Report on Invited Impact Pharmacy Lecture Series 2023 – Lecture 09
(New connections and New learning)

Date: 23.03.2023

Name of the presenter:
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Title of the presentation:
Fixed Dose Combination of antibiotics: rationality to current clinical practice- Clinical Pharmacist vigilance

Program Organized by:
Dept. of Pharmacy Practice & Pharmacy Education Unit
JSS College of Pharmacy, Ooty

New Connections and New Learning: Pharmacy Practice- "Learning in the flow of work"

Making learning is a part of everyday work – and everyone's experience at work differs of course and it multiplies at different places. Internship training for Pharm D students is an opportunity to learn new and provide service to the needy patient population. To enhance their learning experience, the institute has created new connections and learning opportunity at various practice settings. Our students are very excited to be at new practice site(s) to learn and demonstrate/shape their competencies.

Dr Saidulu Ganta is a PharmD graduate from Warangal and hold membership at Society of Infectious Disease Pharmacists, USA. He has over 08 years of experience as Clinical Pharmacy and obtained his training in the area of antimicrobial stewardship- infectious diseases, and interventional strategies to maximize appropriate antibiotic utilization and improvement in patient outcomes, identify opportunities for improvement regarding anti-infective use, culture monitoring and reporting, performing medication use evaluations and conducting prospective audits and developing antibiotic guidelines, clinical pathways, restriction criteria and policy developments etc. He has published various publications in well reputed international journals.

Dr Ganta started his presentation with a note about his training as clinical pharmacy student at public hospital and his role as infectious disease clinical pharmacist at PD Hinduja Hospital at Mumbai.

Global antibiotic consumption has been changing rapidly, increasing by 65% between 2000 and 2015, mainly in low- and middle-income countries (LMICs). Fixed dose combinations (FDCs) including one or more products with antibacterial activity have previously been noted as a concern, but there has been limited data on the scale of their use.

FDCs are defined by the World Health Organization (WHO) as "A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product". These products can have advantages such as improving treatment response compared to monotherapy, due to synergistic mechanisms (such as sulfamethoxazole/trimethoprim), or by increasing adherence to therapy.

FDCs are well-established in conditions such as tuberculosis, malaria and HIV treatment. However, the consumption of potentially clinically inappropriate antibiotic FDCs has been reported in some countries, raising concerns about the lack of proven efficacy, increasing toxicity or their potential effect on selecting for antimicrobial resistance (AMR).

In 2017, the WHO Essential Medicines List (EML) Working Group classified antibiotics in the EML and EML for Children (EMLc) into three groups: Access, Watch, and Reserve (AWaRe classification). The Access group contains generally narrow spectrum antibiotics recommended as first and second choice for most common clinical infection syndromes. The Watch group contains broader spectrum antibiotic classes corresponding to the highest priority agents on the list of critically important antimicrobial drugs for human medicine.

The Reserve group consists of last resort antibiotics for targeted use in multidrug resistant infections. The new AWaRe classification is intended to be easy to apply to monitor antibiotic use and inform antibiotic stewardship. We therefore aimed to quantify the global consumption of antibiotic FDCs and to describe the types of combinations used. We also identified their approval status with the US Food and Drug Administration (FDA) and compatibility with the WHO's 2017 revision of the Essential Medicines List (EML).

Antibiotic fixed dose combinations (FDCs) can have clinical advantages such as improving effectiveness and adherence to therapy. However, high use of potentially inappropriate FDCs has been reported, with implications for antimicrobial resistance (AMR) and toxicity.

The rationality of FDCs should be based on certain aspects such as:

- The drugs in the combination should act by different mechanisms.
- The pharmacokinetics must not be widely different.
- The combination should not have supra-additive toxicity of the ingredients.

Most FDCs have the following demerits:

- Dosage alteration of one drug is not possible without alteration of the other drug.
- Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.
- By simple logic there are increased chances of adverse drug effects and drug interactions compared with both drugs given individually.

Further, he also added the various clinical efficacy data with different combinations of antibiotics used in various clinical situations. He also shared his experience in managing the different infectious disease patients at his practice site.

The session was then concluded by Dr Ganta by taking questions from staff and students. More than 90 students and staff were fruitfully benefited with this invited virtual guest lecture.

Dr S Ponnusankar

Co-ordinator

FDCs of Antibiotic combinations

BL-BLI combination	Clinical dose (mg) of: BL	BLI
Ceftriaxone-tazobactam[b]	1,000	125
	500	62.5
	250	31.25
Ceftazidime-tazobactam[b]	1,000	125
	500	62.5
	250	31.25
Cefoperazone-tazobactam[b]	1,000	125
	500	62.5
Cefepime-tazobactam	1,000	125
	500	62.5
Cefotaxime-sulbactam[b]	1,000	500
	500	250
	250	125
Ceftriaxone-sulbactam[b]	1,000	500
	500	250
	250	125
Ceftriaxone-sulbactam + EDTA at 37 mg (CSE 1034)	1,000	500
Cefepime-sulbactam	1,000	500
Meropenem-sulbactam	1,000	500

[a]BL, β-lactam; BLI, β-lactamase inhibitor; EDTA, ethylenediaminetetraacetic acid. All tazobactam-based combinations are in an 8:1 ratio, like that of piperacillin-tazobactam. All sulbactam-based combinations are in a 2:1 ratio, like that of ampicillin-sulbactam.
[b]Combination available in China.

- The Ratios extrapolated from older BLBLIs.
- For Tazobactam based combinations: 8:1 ratio.
- For Sulbactam based combinations: 2:1 ratio.

Are these Ratios are appropriate for these BLBLI?

DON'T KNOW,NO DATA

Unorthodox piperacillin β-lactam and β-lactamase inhibitor combinations: flooding antimicrobial stewardship and compromising patient care. Antimicrob Agents Chemother 64:e00188-20. https://doi.org/10.1128/AAC.00188-20.

Are these combinations rational??

Absence of Enzyme stability/kinetics Data:

Absence of standard MIC/Clinical breakpoints:

Antibiotic sensitivity, resistance pattern, efficacy depends upon the clinical breakpoints

Absence of PK/PD studies:

To determine synergy/antagonism and therapeutic target

Sparse clinical trail data(Global RCTs):

To define appropriate dosage regimen(safety and efficacy)

Reference: System of preliminary scrutiny by CDSCO at the time of receipt of application for approval of Fixed Dose Combinations

Current RCT status:

S. No	FDC of antibiotics	Trial Identifier	Clinical trail study(RCT)
1	Ceftriaxone-tazobactam	--	--
2	Ceftazidime-tazobactam	--	--
3	Cefoperazone-tazobactam	--	--
4	**Cefepime-tazobactam**	--	--
5	Cefotaxime-Sulbactam	--	--
6	Ceftriaxone-sulbactam	CTRI/20 12/0 4 /00 2558	Observational study
		CTRI/20 10 / 0 91/000 174	Open labelled RCT
7	Ceftriaxone-sulbactam+EDTA	CTRI/20 13/0 6/00 3761	Observational study
		CTRI/20 13/11/00 4133	RCT (comparative)
8	Cefepime-sulbactam	--	--
9	Meropenem-sulbactam	--	--
10	Meropenem-EDTA	--	--

Absence of Enzyme stability/kinetics Data:

Enzyme Inhibitory Concentration(EIC50%): The concentration of the BLI which is required to inhibit 50 % beta lactamase enzyme activity.

Turnover number(Tn): Number of BLI molecules required to inhibit 1 Beta lactamase enzyme

IC 50 %,Tn are used to used to establish appropriate BLBLI ratios.

Eg: 140 molecules of Tazobactam required to inhibit 1 molecule of TEM-1

160 molecules of Clavunate required to inhibit 1 molecule of TEM-1

10,000 molecules of Sulbactam required to inhibit 1 molecule of TEM-1

Enzyme kinetics studies not available for mentioned BLBLI combinations

Reference: Three Decades of -Lactamase Inhibitors Sarah M. Drawz1 and Robert A. Bonomo

How PK PD differ:

Different BLBLI ratio for same BLI

- **8:1** in Piperacillin/Tazobactam (4.5 gm)
- **2:1** in Ceftolozane/Tazobactam(1.5 gm)
- **1:1** in Cefepime/Tazobactam (4 gm)

Fixed ratio not suitable every beta lactam & Should not extrapolate from other BLBLIs

Different PD target for same BL

- Meropenem: **Time dependent**
- Meropenem/Vaborbactam: **Concentration dependent(AUC/MIC)**
- Ceftolozane /Tazobactam: **Concentration dependent(high inoculum infections)**
- Ceftolozane /Tazobactam: **Time dependent(low inoculum infections)**

How Tazobactam activity differ with Beta lactams(Piperacillin/Ceftolazone)

Piperacillin/Tazobactam

- Piperacillin 4 gm/Tazobactam 500 mg(8:1)
- Dose: TZP 4.5 gm q6h
- Piperacillin may unstable against ESBL
- Lower dose of Tazobactam 500 mg & unable to protect parent Beta lactam

Ceftolazone/Tazobactam

- Ceftolozane 2 gm/Tazobactam 1 gm(2:1)
- Dose: C/T 3 gm q8h
- Ceftolozane is a more stable against ESBLs
- Higher dose Tazobactam 1 gm and able to protect parent Beta lactam

Harris PNA, et al. JAMA. 2018;320(10):984-994

Kollef M, et al. Poster presentation: ECCMID 2019. Amsterdam, Netherlands

Cefepime/Tazobactam: 1000/125 mg

- This combination dose does not affectively inhibit ESBL, Amp C**(regular dosing cefepime 2g q8h)**
- Cefepime hydrolyzed by ESBLs**(CTX-M,TEM-12,SHV-5)** and activity of Tazobactam against these ESBLs unproven and at this ratio, **tazobactam not protect cefepime from ESBLs, Amp C and KPC**
- Cefepime good for Amp C and activity depends on MIC but no clinical break points available for this combination.
- Higher doses 4 gm q8h(1:1 ratio) under clinical evaluation(ESBL P. aeruginosa, ESBL Enterobacteriaceae strains and ceftazidime-non susceptible Enterobacter spp)
- Recent studies does not support use of Tazobactam based BLBLIs for ESBL-Enterobacterales
- Suboptimal doses of **ANY antipseudomonal β-lactam exposure associated with 4% increased risk of new resistance for each additional day.**

Reference:

1. Sader HS, Castanheira M, Mendes RE, Flamm RK, Jones RN. Antimicrob Agents Chemother. 2017 Mar 24;61(4):e02409-16.
2. Teshome et al. Pharmacotherapy 2019;39(3):261-268.
3. Monogue ML, Heil EL, Aitken SL, Pogue JM. Pharmacotherapy. 2021 Oct;41(10):864-880.

Ceftriaxone/ Sulbactam+ EDTA: 1000/500/37.5 mg

PK-PD	Ceftriaxone	Sulbactam	EDTA
$t_{1/2}$	8h	1-1.7 h	1h
Elimination	70 % Major heapatic	Major renal	Renal
Vd	5.8-13.5L	19-22L	3-13 l
Protein Binding	85-95%	28-38%	--
AUC	100 6(1 gm IV SD	120 (1 gm IV SD	--

PK-PD	Ampicillin	Sulbactam
$t_{1/2}$	1-2h	1-1.7h
Elimination	Major renal	Major renal
Vd	17L	19-22L
Protein Binding	18-22%	28-38%
AUC	71(3gm IV SD)	120(1 gm IV SD)