Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

NEW ANTI-INFECTIVE AGENTS IN 2003 : SPECTRUM AND INDICATIONS

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Ertapenem

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Development of carbapenems

- Thienamycin (1970) (*Streptomyces cattleya)*

- Imipenem (N-formimidoyl) (1977) → 1988
- Meropenem (1984) → 1997
- Ertapenem (1989) → 2002 (EU) (2003 Belgium ?)

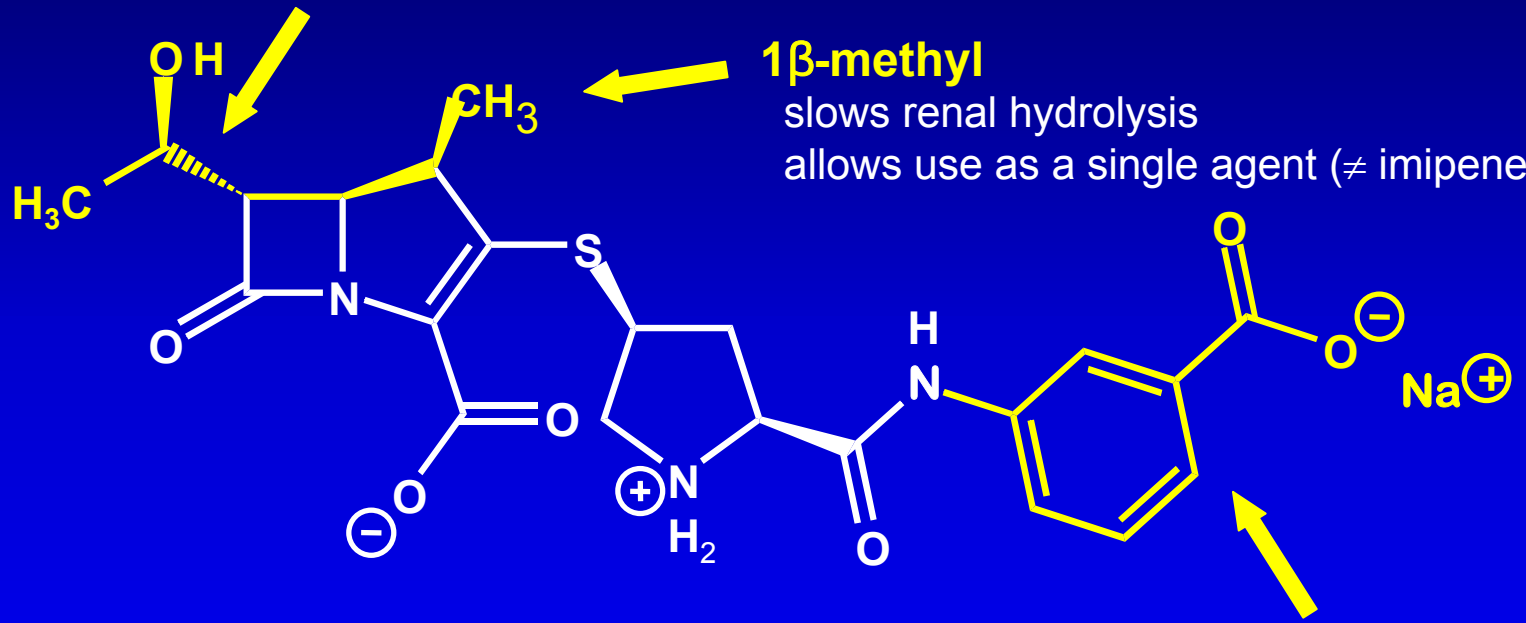
Microbiologic properties of carbapenems

- Broadest spectrum of activity (G+, G-, anaerobes)
- Rapid penetration through outer membrane of G- bacteria
- High stability to hydrolysis by plasmidic or chromosomal ß-lactamases (ESBL, AmpC enzymes)
- Binding to essential PBPs (mainly PBP-2)
- Rapid bactericidal activity against G- bacilli and G+ cocci (MBC ≈ 2x MIC)
- Post-antibiotic effect (against G +) : 1.5-2.0 h

Ertapenem: structure-activity relationship

unique to carbapenems
contributes to β-lactamase stability

***Trans* hydroxyethyl**



1β-methyl
slows renal hydrolysis
allows use as a single agent (≠ imipenem)

Benzoate moiety

changes overall molecular charge, making it highly protein bound (>90%), and thereby, increases $t_{1/2}$ (≈4 h) , allowing once-a-day dosing

Ertapenem: spectrum of activity

- Broad spectrum (G+, G-, anaerobes):
  - Stable to most plasmidic and chromosomal β-lactamases including ESBL and AmpC (Cephalosporinases)

  - Gram -: ERTA ≈ MERO > (2-8x) IMIP (*Enterobacteriaceae*) ($MIC_{90} \leq 1$ µg/ml)
  - Gram +: IMIP (x2-4) > ERTA ≈ MERO
  - Anaerobes: MERO ≥ IMI ≥ ERTA

- Poor activity against: *P. aeruginosa*, *Acinetobacter* spp., *S. maltophilia,* Enterococci, MRSA, PRSP

In vitro activity of ertapenem against *Enterobacteriaceae* isolates in Belgian ICUs

Organisms	n° of isolates	Range	MIC_{50}	MIC_{90}	% not susceptible*
E. coli	367	0.06-0.25	0.06	0.06	0.0
K. pneumoniae	112	0.06-1	0.06	0.12	0.0
K. oxytoca	91	0.06-16	0.06	0.06	1.3
P. mirabilis	86	0.06-1	0.06	0.06	0.0
P. vulgaris	23	0.06-0.12	0.06	0.12	0.0
E. aerogenes	180	0.06-32	0.25	1	5.5
E. cloacae	146	0.06-32	0.06	1	3.4
S. marcescens	71	0.06-4	0.06	0.25	0.0
M. morganii	56	0.06-16	0.06	0.12	1.7
P. stuartii	11	0.06-0.25	0.06	0.12	0.0

* according to NCCLS susceptibility breakpoint criteria

Belgian NPRS 6 Multicentric Survey (2000-1), unpublished data

Comparative activity of ertapenem and other carbapenems against *E. aerogenes*

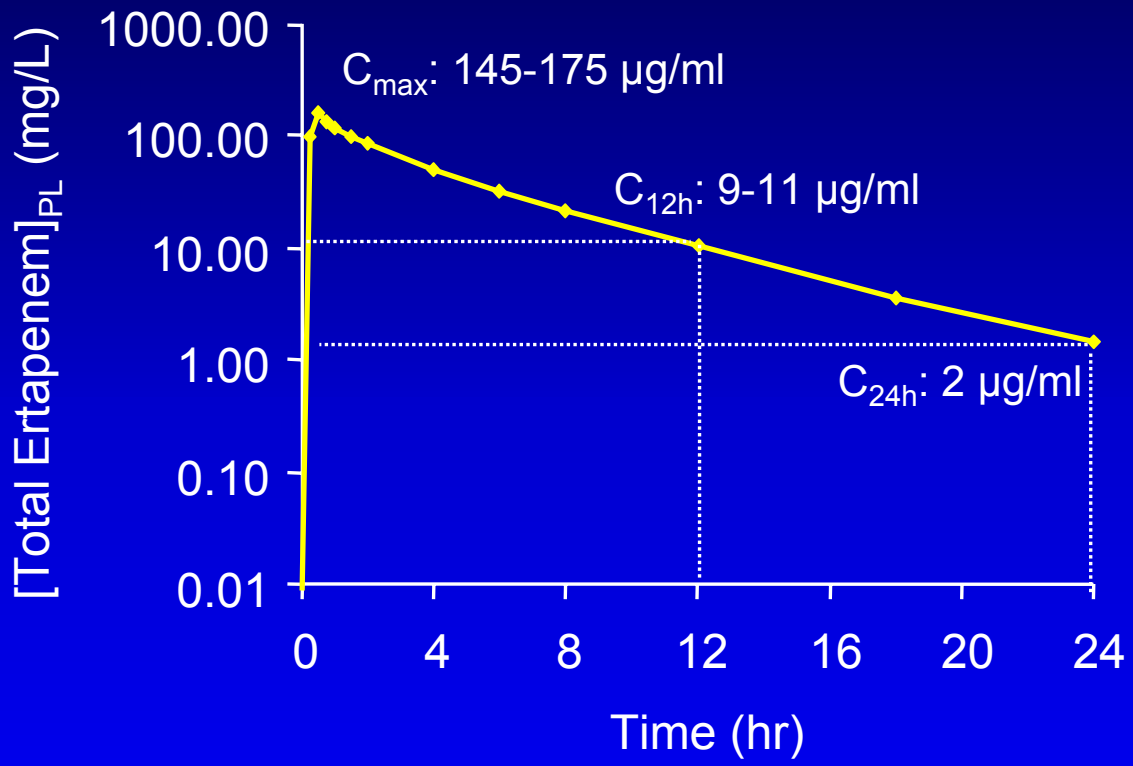
Antibiotics	Range	MIC_{50}	MIC_{90}	% not susceptible*
ESBL +ve (181)				
Ertapenem	0.03->32	0.5	1	2.5
Imipenem	0.03-8	0.25	1	2.2
Meropenem	0.03-8	0.03	0.25	1
ESBL -ve (104)				
Ertapenem	0.03-1	0.25	0.5	0.0
Imipenem	0.03-2	0.12	1	0.0
Meropenem	0.03-0.25	<0.03	0.12	0.0

Glupczynski et al., Abstract 13th ECCMID, Glasgow, May 2003

Ertapenem: pharmacokinetics

Properties	Imipenem	Meropenem	Ertapenem
Half-life (h)	1	1	3.8-4.4
Nr adm./d	3-4	3-4	1
Peak serum [ ] (µg/ml)			
0.5 g IV	40	25-35	70-85
1.0 g IV	70	55	145-175
% protein binding	15-25	<20	85-94
Elimination route	Renal (20% active)	Renal (65-75% active)	Renal (80%, 40-45% active)
[CSF] (% [serum])	10-40	6-42	?

Ertapenem Total Plasma Concentrations versus MIC_{90} of Common Pathogens



MIC_{90} (mg/L)	Organism
16	*P. aeruginosa,* other nonfermenters, *Enterococcus,* MRSA
1.0	Anaerobes (all), *B. fragilis* group, PRSP
0.25	*MSSA, S. pneumoniae* (all), *Enterobacter*
0.125	*H. influenzae, S. agalactiae*
0.03	*Klebsiella, S. pyogenes*
0.016	*E. coli, M. catarrhalis*

NCCLS Interpretive Susceptibility Criteria for Ertapenem

Organism	Breakpoints					
	Dilution MIC*			Disk Diffusion*		
	S	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2	4	≥8	≥19	16-18	≤15
Staphylococcus spp	≤2	4	≥8	≥19	16-18	≤15
Haemophilus spp.	≤0.5			≥19		
S. pneumoniae (non-meningitis)	≤1	2	≥4	-	-	-
Streptococcus spp. (ß-hemolytic)	≤1			-	-	-
Anaerobes	≤4	8	≥16	-	-	-

* MIC in mg/L; disk diffusion zone size in mm

Ertapenem
Pharmacokinetic-Pharmacodynamic Correlations

- Key PK/PD parameter is “time above MIC”
  - mean time above MIC to achieve static effect as proportion of dosing interval in anephric neutropenic mice

Organism	Total Drug	Free Drug
Gram-negative bacilli	34.5%	16.5%
S. aureus	43.0%	24.7%
S. pneumoniae	24.2%	6.2%

Ertapenem: Resistance

- *Enterobacteriaceae*
  - Resistance rarely observed ($MIC_{90} \leq 0.25$ µg/ml) even in ESBL or AmpC β-lactamase producing organisms
  - Little inoculum effect (identical MIC at 10^7 cfu and 10^5 cfu)
  - Second mechanism (reduced uptake, efflux) required for resistance
  - *Enterobacteriaceae* pre-Rx isolates from clinical studies
    - ERTA susceptible 97.4%
    - IMIP susceptible 99.3%
  - ESBL-positive organisms (*E. coli*, *Klebsiella* spp., *Enterobacter* spp.)
    - ERTA susceptible 96.5%
    - IMIP susceptible 98.8%

Ertapenem: Resistance

- *Enterobacteriaceae*
  - Less persisting strains in patients treated with ERTA than with comparators (PIP/TAZO)
  - Less bowel colonization by resistant *Enterobacteriaceae* isolates following Rx with ERTA than with PIP/TAZO (≤1% vs 14%)

Ertapenem: Resistance

- *P. aeruginosa*
  - ERTA not active against most (60-70%) *P. aeruginosa* isolates susceptible to other carbapenems
  - In vitro surveillance data: cross-resistance to carbapenems

IMIP-susceptible:	1.8% MERO-resistant
MERO-susceptible	4.6% IMIP-resistant
ERTA-resistant	68.3% IMIP/MERO-susceptible
IMIP-resistant	100% ERTA-resistant

MSD data on file
Friedland et al. 13th ECCMID, Glasgow, May 2003

Ertapenem: Cross-resistance to carbapenems in *P. aeruginosa*

In vitro selection of various efflux/impermeability resistance mechanisms following exposure to ERTA

Mechanism of resistance	Ertapenem	Meropenem	Imipenem
↓ OprD2 mutants	R	I/S	R
OprM efflux	R	R	S
MK-X efflux	R	R	S

Type of mutation selected variable and dependent on strain background

Friedland et al. 41thICAAC meeting, Chicago 2001

Ertapenem: Concern about resistance in *P. aeruginosa*

- No selective pressure for resistance mechanisms in naturally resistant organisms
- No selective pressure if antibiotic does not meet the micro-organism
  - Target population rarely colonized with *P. aeruginosa* (non-ICU patients, community-acquired mixed infections)
  - Short duration of treatment anticipated (7-14 days)
- Origin of resistance in *P. aeruginosa* more frequently due to spontaneous mutations occurring in vivo than to clonal spread (cf. ESBL-producing *Enterobacteriaceae*)
- Selection of carbapenem-resistant isolates rarely found in development clinical trials so far (will the risk ↑ once marketed ?)

Ertapenem: Indications

	FDA	EMEA
Intra-abdominal infection	+	+
Acute gynaecological infection	+	+
Community-acquired pneumonia	+	+
Complicated SSTI	+	-
Complicated UTI	+	-

Ertapenem: Clinical trials

8 international multicenter DB RCT (>20 countries; >5000 pts treated)

ERTA (1g/od) **vs Pipe/ Tazo** (3.375 g/q6h)

- Intra-abdominal infection
- Acute gynaecological infection
- Complicated SSTI

ERTA (1g/od) **vs Ceftriaxone** (1 g/od)

- Community-acquired pneumonia (2 studies)
- Complicated UTI (2 studies)
- Intra-abdominal infection (CTX + metronidazole)

Ertapenem:Clinical trials

- **Intra-abdominal infection**
  - Solomkin JS, et al. Ann Surg 2003; 237: 235-45
  - Yellin AE et al, et al. Int J Antimicrob Agents 2002; 20:165-73
- **Community-acquired pneumonia**
  - Ortiz-Ruiz G, et al. Clin Infect Dis 2002; 34: 1076-83
  - Vetter N, et al. Clin Ther 2002; 24: 1770-85
- **Complicated SSTI**
  - Graham D, et al. Clin Infect Dis 2002; 34: 1460-8
- **Complicated UTI**
  - Tomera KM, et al., Antimicrob agents 2002; 14: 483-91
  - Jimenez-Cruz F et al., Urology 2002; 60: 16-22
- **Acute gynaecological infection**
  - Not yet published

Ertapenem: Clinical trials

- **Clinical cure rates equivalent to comparator**
  - Intra-abdominal infection (ERTA 1g/d vs PIP/TAZO 3.375g q6h)

m ITT	79.3%	versus	76.2%
PP	86.7%	versus	81.2%

  - Community-acquired pneumonia (ERTA 1 g/d vs CTX 1 g/d)

m ITT	85.2%	versus	84.8%
PP	92.3%	versus	91.0%

- **Failures not related to resistance**

Ertapenem: Clinical trials

Intra-abdominal infections		**ERTA**	**P/T**
• Primary site:	appendix	47%	47%
	colon	17%	21%
	cholecystitis	8%	4%
• Infectious process:	generalized peritonitis	30%	29%
	localized peritonitis	35%	34%
	single abscess	29%	34%
	multiple abscesses	5%	3%
	post-operative	12%	13%
• APACHE II score:	0 - 9	70%	75%
	10 -14	21%	18%
	≥ 15	9%	7%

Solomkin, Ann Surg 2003; 237: 235-45

Ertapenem:
Treatment of generalized peritonitis

- Complicated intra-abdominal infection
  DB RCT (N=185 of 623 pts. (30%) with generalized peritonitis

- ERTA (N=60) versus Pip/Tazo (N=53)

  - 113 pts (61%) clinically and microbiologically evaluable
  - Median duration: 7 d - 8 d
  - Polymicrobial infection at entry: 92% - 83%
  - post-operative infection: 7% - 16%

- APACHE II score $\geq$ 15: 14% - 10%
- Cure rates at end of Rx: 90% - 81%
- Cure rates at TOC (4-6 w): 83% - 74%
- Microbiological response: 74% - 70%

Teppler et al., 13thECCMID, May 2003

Ertapenem: Clinical trials

CAP

- Median duration of IV treatment 4 days; then amoxi/clav PO for 8 days (median)

	ERTA	CTX
• Age ≤ 65 years	50%	52%
> 65 years	33%	31%
> 75 years	17%	17%

- Pneumonia severity index (Fine. NEJM 1997; 336: 243-50)

PSI ≤ 3	76%	72%
PSI > 3	24%	28%

- Microbiological documentation: 41.6%

S. pneumoniae	51%	(22% Peni non-susc SP)
H. influenzae	21%	

Ortiz-Ruiz, Clin Infect Dis 2002; 34: 1076-83

Ertapenem: Clinical trials

CAP

- Ertapenem group: N= 121 (with COPD); N=246 (without COPD)
- Post-hoc analysis of patients with CAP in 2 DB RCT (62 centers worldwide)
- Outcome in patients with COPD (n=264) / without COPD (n=593)

Males:	68% vs 54%
Age >65 years:	66% vs 30%
PSI > 3:	44% vs 19%
H. influenzae	13% vs 6% (no difference for SP and Enterobact.)

- Clinical cure (TOC at 7-14d): 90% vs 93%
  - Age > 65 years: 94%
  - PSI > 3: 88%

Woods et al., abstract 13thECCMID, May 2003

Ertapenem:
Health-care associated pneumonia acquired outside the ICU (024/025 study group)

- Nursing home + hospital ward (non ICU)
- ERTA (N=150) versus Cefepime(+/- metronidazole) (N=153)
  - 195 pts (64%) clinically & microbiologically evaluable
  - Median duration: 10 days (in both Rx groups)
  - Switch to oral Rx (≥ 3 days): 59% - 53%
- APACHE II score ≥ 15: 24% - 21%
- Clinical outcome (TOC at 7-14 d): 87% - 86%
- Bacterial eradication:
  - Gram – bacilli 82% - 79%
  - *S. Pneumoniae* 93% - 87%

Friedland et al., abstract 13thECCMID, May 2003

Clinical Adverse Experiences

Ertapenem Drug-Related Adverse Experiences

During Parenteral Phase Across Phase II-III

Adverse events	ERTA (1, 1.5, 2 g) N=1960	PIP/TAZO (3.375 g q6h) N=775	CTX (1, 2 g) N=912
Diarrhea	4.3%	6.6%	3.7%
Nausea	2.8%	3.2%	2.6%
Vomiting	1.0%	1.5%	0.9%
Headache	2.1%	1.0%	2.2%
Infused vein complication	3.8%	5.5%	4.3%
Phlebitis/thrombophlebitis	1.2%	1.3%	1.4%
Seizures	0.2%	0.3%	0%

Laboratory Adverse Experiences
Ertapenem Drug-Related Adverse Experiences

During Parenteral Phase Across Phase II-III

	ERTA (1, 1.5, 2 g) N=1960	PIP/TAZO (3.375 g q6h) N=775	CTX (1, 2 g) N=912
↑ ALT	5.5%	4.4%	3.7%
↑ AST	4.9%	4.5%	4.2%
↑ Alkaline phosphatase	3.0%	3.9%	1.4%
↑ Platelets	1.9%	3.9%	0.4%

Ertapenem positioning and reimbursement: Belgian situation

- **Ongoing discussion at the CRM-CTG about appriopriate use and reimbursement**
  - **CAP 3 & 4**
    - Guidelines (IDAB + other guidelines)
    - Comparators with narrower spectrum more suitable for CAP3
    - No/few data for CAP4
    - Price versus comparators
  - **Intra-abdominal / gynaecological (post-op) infection**
    - Convenience (once daily) / efficacy and safety
    - Moderate/severe–community-acquired or early hospital-acquired infections
    - Severity ≠ resistant pathogens
    - Comparators (narrower spectrum) for this indication
    - Price versus comparators

Price comparisons in Belgium
(per day of treatment)

Intra-abdominal infection / Acute pelvic infection

- Ertapenem
  - 1g x 1 = 45.00 €
- Amoxy-clav + amikacin
  - 3 x 2 g (17.18 €) 1 x 1g (20.11€) = 37.29 €
- Cefuroxime + metronidazole
  - 3 x 1.5 g (19.91 €) 3 x 500 mg (11.58 €) = 31.49 €
- Piperacillin-tazobactam + amikacin
  - 3 x 4 g (67.95 €) 1 x 1g (20.11€) = 88.06 €
- Ciprofloxacine + metronidazole
  - 2 x 400 mg (69.58 €) 3 x 500 mg (11.58 €) = 81.16 €

Ertapenem: possible future options

- **CAP: need to focus on specific patient groups**
  - Nursing home-acquired pneumonia
  - Aspiration pneumonia
  - Early hospital-acquired pneumonia (non-ICU setting)
- **ESBL producing pathogens**
  - Changing evolution of epidemiology in hospitals / community (MR Enterobacter aerogenes ?)
- **Switch therapy after administration of carbapenems/cefepime for infections with difficult-to-treat organisms**
  - IV line problems, out-patient therapy