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Panipenem/Betamipron

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Contents

Abstract

▲ Panipenem is a parenteral carbapenem antibacterial agent with a broad spectrum of *in vitro* activity covering a wide range of Gram-negative and Gram-positive aerobic and anaerobic bacteria, including *Streptococcus pneumoniae* and species producing β-lactamases.

▲ Panipenem is coadministered with betamipron to inhibit panipenem uptake into the renal tubule and prevent nephrotoxicity.

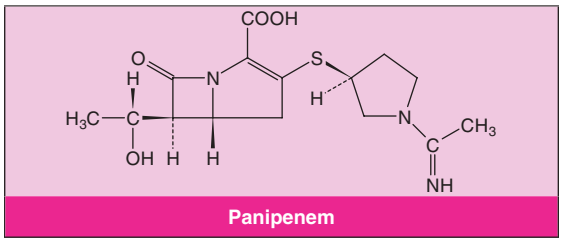
▲ In large, randomised clinical trials, panipenem/betamipron demonstrated good clinical and bacteriological efficacy (similar to that of imipenem/cilastatin) in adults with respiratory tract or urinary tract infections.

▲ Panipenem/betamipron was also effective in adults with surgical or gynaecological infections, and in paediatric patients with respiratory tract and urinary tract infections in noncomparative trials.

▲ In small trials in elderly patients reported as abstracts, panipenem/betamipron demonstrated clinical efficacy similar to intravenous piperacillin and greater than oral ofloxacin in urinary tract infections. Elderly patients with respiratory tract infections also responded to therapy.

▲ Panipenem/betamipron is well tolerated with few adverse events reported in clinical trials, most commonly elevated serum levels of hepatic transaminases and eosinophils, rash and diarrhoea.

Features and properties of panipenem/betamipron (Carbenin®)	
Indication	
Treatment of bacterial infections (lower respiratory tract, urinary tract, obstetrical/gynaecological and surgical infections)	Launched in Japan, China and Korea
Antibacterial class	
Carbapenem	
Mechanism of action	
Panipenem	Inhibits bacterial cell wall synthesis
Betamipron	Inhibits panipenem uptake into the renal tubule
Dosage and administration	
Recommended usual dosage	
Adults	0.5/0.5g twice daily
Children	30–60/30–60 mg/kg/day in 3 divided doses
Route of administration	Intravenous infusion over 30–60min
Pharmacokinetic profile (0.5/0.5g single intravenous infusion in healthy adult volunteers)	
Peak plasma concentration	27.5/15.6 mg/L
Terminal elimination half-life	70/40 minutes
Renal clearance	0.09/0.73 L/h/kg
Adverse events	
Most frequent	Skin rash, diarrhoea, eosinophilia, ↑ serum hepatic transaminases



Of all the β-lactams, the carbapenems have the broadest spectra of antibacterial activity. Their coverage extends to many Gram-negative and Gram-positive aerobic bacteria and also includes anaerobic bacteria. Carbapanems are bactericidal and inhibit bacterial wall synthesis, bind strongly to essential penicillin-binding proteins, penetrate well into Gram-negative bacteria and are stable to hydrolysis by a variety of β-lactamases, all of which reduce the likelihood of resistance.[1,2]

Panipenem is an intravenously administered 1H-carbapenem developed in Japan. Panipenem, like imipenem,[3] but unlike biapenem[4] and meropenem,[5] is not stable to hydrolysis by human renal dehydropeptidase-I (DHP-I),[6] but it is nonetheless indicated for a wide variety of infections including respiratory tract and severe urinary tract infections.[7] Panipenem is coadministered with betamipron, an organic anion tubular transport inhibitor with very low toxicity that inhibits the active transport of panipenem in the renal cortex, thereby reducing the nephrotoxic potential of the antimicrobial agent.[8-10]

This drug profile reviews the antibacterial activity, clinical efficacy and tolerability of panipenem/betamipron (Carbenin®[1]) in the treatment of lower respiratory tract, urinary tract, obstetric/gynaecological and surgical infections in adults as well as respiratory and urinary tract infections in children and the elderly.

1. Antibacterial Activity

In Vitro Activity

The *in vitro* activity of panipenem has been investigated in numerous studies in Japan (n = >150 isolates/study). Betamipron has no antimicrobial activity[11] and was not included in these studies. *In vitro* activity refers to the minimum inhibitory concentrations (MIC) for an agent as determined by broth or agar dilution techniques and a bacterial inoculum size of 10^4 to 10^5 colony forming units (cfu). Results are expressed as the minimum concentrations inhibiting 50% and 90% of bacterial strains (MIC_{50} and MIC_{90}).

As stated by the Japanese Society of Chemotherapy, the breakpoints for panipenem and other carbapenems (imipenem, meropenem and biapenem) are 2 mg/L for pneumonia and 1 mg/L for respiratory tract infections in general.[12]

Like other carbapenems, panipenem displays a broad spectrum of activity covering numerous Gram-negative and Gram-positive aerobic (see figure 1) and anaerobic bacteria. Importantly, it is active against organisms producing β-lactamases.[13]

Gram-Negative Aerobic Bacteria

- Panipenem displays good activity *in vitro* against many Gram-negative organisms. Figure 1 illustrates the *in vitro* activity of panipenem against various clinically isolated strains of Gram-negative organisms in a large, representative Japanese study.[13]
- Many Enterobacteriaceae are highly susceptible to panipenem, including *Escherichia coli* (MIC_{90} range 0.1–0.39 mg/L),[13-17] *Klebsiella pneumoniae* (MIC_{90} range 0.1–0.78 mg/L),[13-17] *Morganella morganii* (MIC_{90} 1.56–6.25 mg/L),[13,15,17,18] *Proteus mirabilis* (MIC_{90} 1.56–3.13 mg/L)[13-17] and *Citrobacter freundii* (MIC_{90} 0.05–1.56 mg/L).[13-18]
- Panipenem shows variable activity against *Serratia marcescens* (MIC_{90} 0.78–25 mg/L),[13-18] and *Providencia rettgeri* (MIC_{90} 0.2–12.5 mg/L).[13,15,17] It is inactive against *Stenotrophomonas maltophilia* (MIC_{90} >100 mg/L).[13,17,18]

1 Use of trade name is for identification purposes only and does not imply product endorsement.

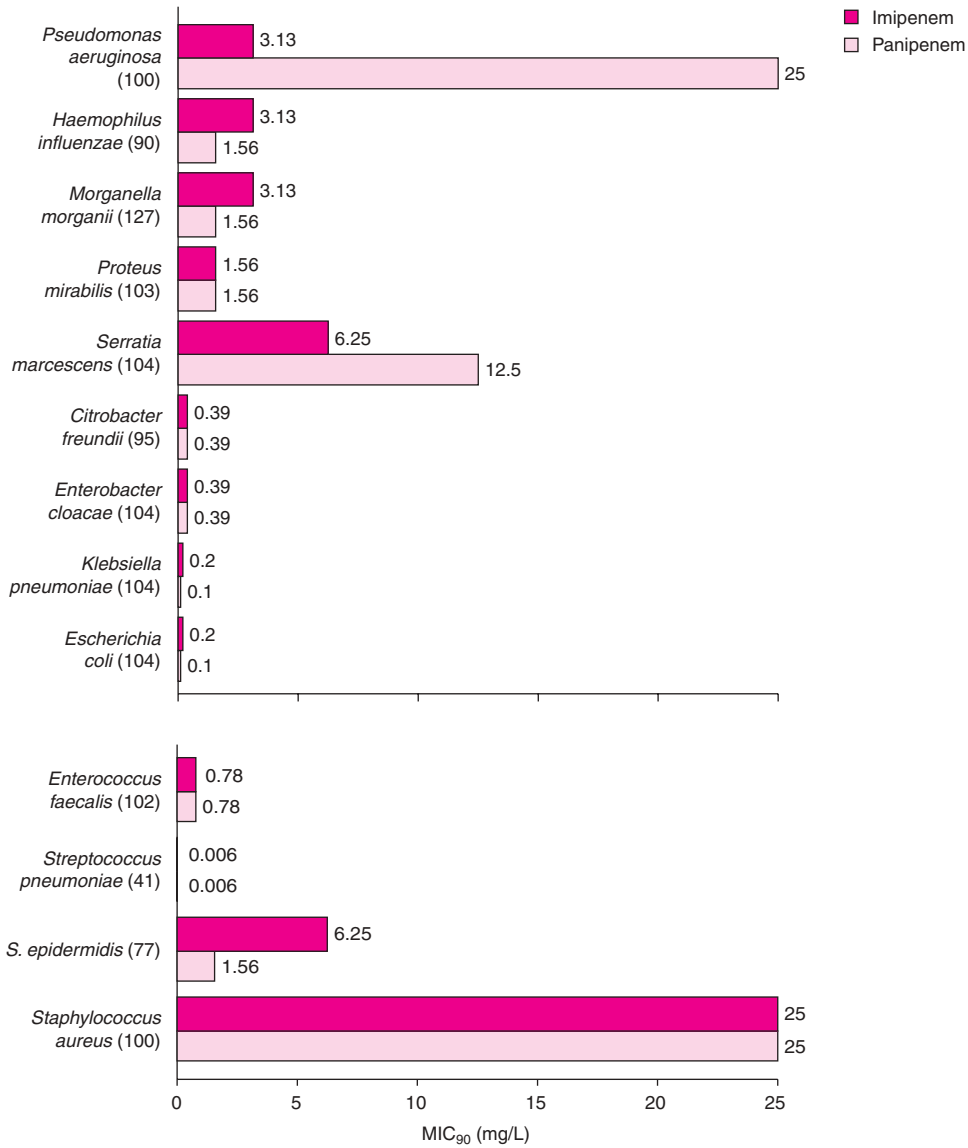


Fig. 1. *In vitro* activity of panipenem and imipenem against Gram-negative (top) and Gram-positive (bottom) pathogens in a large Japanese study. Numbers in parentheses indicate the number of strains tested.[13]

- With regard to common respiratory tract pathogens, panipenem is highly active against *Moraxella catarrhalis* (MIC_{90} 0.025–0.5 mg/L)[13-15,18] and generally shows good activity against *Haemophilus influenzae* (MIC_{90} 0.39–3.13 mg/L).[13-15] Indeed, the percentages of 575 *H. influenzae* isolates (91.8% obtained from the respiratory tract) susceptible to panipenem, imipenem and meropenem at MIC 0.5 mg/L were 86.8%, 77.6% and 100%. Corresponding values at MIC 2 mg/L were 98.1%, 93.4% and 100%.[19]

- In *H. influenzae* isolates obtained from hospitalised paediatric patients (202 isolates in total; 176 from the respiratory tract), panipenem had similar

activity to imipenem (MIC_{90} for both = 1.56 mg/L) and biapenem (3.13 mg/L), while meropenem had the highest activity (0.2 mg/L).[20]

- Panipenem demonstrated good activity against ampicillin-susceptible (MIC_{90} = 0.5 mg/L; n = 31) and β-lactamase-positive (MIC_{90} = 2 mg/L; n = 34) isolates of *H. influenzae*.[21] MIC_{90} values were higher for β-lactamase-negative ampicillin-resistant isolates (8 mg/L; n = 38). Activity against all three subgroups of *H. influenzae* was generally similar for panipenem, imipenem and biapenem, although the MIC_{90} for biapenem against β-lactamase-producing strains was the highest of the carbapenems tested (8 mg/L). Meropenem demonstrated the highest activity (0.125–0.5 mg/L).
- As evidenced by recent *in vitro* studies,[22] the antibacterial activity of panipenem has remained essentially unchanged against many major respiratory pathogens over the last decade, except that MICs increased for *H. influenzae* (MIC_{90} from 1 to 4 mg/L).
- In these studies,[22] the activity of panipenem against *Pseudomonas aeruginosa* increased over the period from 1993–2000 (MIC_{90} decreased from 16 to 8 mg/L). However, *P. aeruginosa* appeared resistant to panipenem (MIC_{90} values ranged from 12.5–25 mg/L) in numerous other investigations, including earlier[13,14,16,18] and more recent[17] studies. MIC_{90}s for panipenem against strains of *P. aeruginosa* resistant to ceftazidime, gentamicin, cefoperazone or piperacillin (n = 15–17 isolates) were also in this range (12–25 mg/L).[18]
- Panipenem had *in vitro* activity against *P. aeruginosa* similar to[14,16,17] or less than[13,15,18] that of imipenem but less than that of meropenem. MIC_{90} values for panipenem, imipenem, biapenem and meropenem were 32, 16, 16 and 8 mg/L, respectively, against 288 clinical isolates of *P. aeruginosa* from hospitalised patients and were 16, 8, 8, and 8 mg/L, respectively, against ceftazidime-resistant strains (n = 75; MIC_{90} ≥16 mg/L for ceftazidime).[23] MIC_{90}s were 32 mg/L for both panipenem and imipenem and 16 mg/L for meropenem against imipenem-resistant isolates (MIC_{90} ≥16 mg/L; n = 39) in another study.[24]
- Panipenem shows stronger activity against *P. aeruginosa* in low amino-acid media, such as a minimal medium, and in biological fluids such as human serum, than in rich test media such as Mueller-Hinton agar.[25,26] The mechanism is considered to be the lessened competition between panipenem and basic amino acids for penetration through the OprD (D2) channel of the *P. aeruginosa* outer membrane in conditions of low amino-acid concentrations.[25,26] Additionally, the bactericidal activity of panipenem against clinical isolates of *P. aeruginosa* was similar to that of imipenem and higher than that of meropenem in an *in vitro* pharmacodynamic model using a minimal medium to simulate plasma carbapenem concentrations in humans.[27]

Gram-Positive Aerobic Bacteria

- Panipenem exhibited excellent activity against many Gram-positive organisms (n = >100 clinical isolates per study)[13-18] (see figure 1). The activity of panipenem was generally similar to that of imipenem in these studies.
- *Streptococcus pneumoniae* is highly susceptible to panipenem; MIC_{90}s for panipenem against this organism ranged from 0.006–0.1 mg/L and were similar to values for imipenem.[14,18] Penicillin susceptibility was not reported in these trials.
- In a recent study panipenem demonstrated excellent activity against penicillin-susceptible (n = 116), -intermediate (n = 81) and -resistant (n = 21) strains of *S. pneumoniae* isolated from children with mainly upper respiratory tract diseases.[28] MIC_{90}s for panipenem were 0.008 mg/L, 0.125 mg/L and 0.25 mg/L, respectively. These values were lower than those for imipenem (0.015, 0.125 and 0.5 mg/L) and meropenem (0.015, 0.5 and 0.5 mg/L), except that the values for panipenem and imipenem against penicillin-intermediate strains were the same. Other studies confirm the activity of panipenem against *S. pneumoniae* regardless of penicillin susceptibility.[22,29]
- Panipenem is also active against methicillin-susceptible *Staphylococcus aureus* (MIC_{90} 0.025–0.39 mg/L),[14,18,22,30] *S. epidermidis* (MIC_{90} 0.1–1.56 mg/L),[13,18] and the common urinary tract pathogen *Enterococcus faecalis* (MIC_{90} 0.78–3.13 mg/

L).[13-16,18,31] However, a recent study reported MIC_{90}s of 6.25 mg/L for both panipenem and imipenem and 25 mg/L for meropenem against the latter organism.[17]

- Panipenem, like imipenem, has negligible activity against *Enterococcus faecium* (MIC_{90} >100 mg/L)[13,15] and methicillin-resistant *S. aureus* (MIC_{90} 6.25–>100 mg/L).[14,22,30,32,33]

Anaerobic Bacteria

- Panipenem showed excellent activity against the Gram-negative anaerobe *Bacteroides fragilis* (MIC_{90} 0.1–1.56 mg/L) and had moderate activity against the Gram-positive anaerobe *Clostridium difficile* (MIC_{90} 3.13–6.25 mg/L).[13,33,34] MICs for panipenem against these and many other anaerobes closely resembled those for imipenem.[11]

Postantibiotic Effects

- A postantibiotic effect refers to the suppression of bacterial growth after drug concentrations have decreased to below the MIC for a particular pathogen. At 2 and 4 times MIC levels after 2-hour incubation, panipenem demonstrated an *in vitro* postantibiotic effect similar to that of imipenem against *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*.[35]

2. Pharmacokinetic Properties

The pharmacokinetics of panipenem/betamipron in single or multiple doses have been investigated in healthy volunteers,[36,37] children[38] and patients with renal failure.[39] Distribution data are provided in small phase I clinical trials.[36,40-47] All information was obtained from fully published studies in Japanese subjects.

Plasma Drug Concentrations

- Panipenem/betamipron displays linear kinetics over the dose range 0.125/0.125–1/1g after a single intravenous dose.[37] Mean maximal plasma concentrations (C_{max}) ranged from 6.8–51.4 mg/L for panipenem and 4.5–35.1 mg/L for betamipron in 22 healthy volunteers. C_{max} after the 0.5/0.5g dose was 27.5/15.6 mg/L and occurred at the end of the 60-minute infusion. Area under the plasma concentration-time curve (AUC) was between 11.7 and 84.8 mg/L • h for panipenem and 5.3 and 31.3 mg/L • h for betamipron over this dosage range.
- There was no drug accumulation after multiple-dose administration of panipenem/betamipron 0.5/0.5g or 1/1g over 60 minutes every 12 hours for 5 days.[36] C_{max} for the panipenem/betamipron 0.5/0.5g dose was 23.3/14.1 mg/L after the first dose and 26.2/16.2 mg/L after the last (ninth) dose; corresponding values for AUC were 39.4/17.7 mg/L • h and 40.3/19.5 mg/L • h.

Distribution

- After intravenous administration panipenem/betamipron is widely distributed to body tissues and fluids such as sputum,[47] saliva,[36] urinary tract,[48] prostate,[41] female pelvic cavity (including the uterus and adnexus),[42-44] bile,[45,46] pus[46] and bone and joint capsules.[40] Protein binding in humans is low for panipenem (6–7%) but is 10-fold higher for betamipron (73%).[36] The volume of distribution after administration of a single panipenem/betamipron 0.5/0.5g dose is approximately 20/25L.[37]

Elimination

- Panipenem undergoes hydrolysis of the β-lactam ring by human renal tubular brushborder DHP-I.[11] As demonstrated in animal models, betamipron significantly reduces the renal clearance of panipenem[49] by preventing panipenem uptake in the renal tubule, unlike cilastatin which inhibits DHP-I activity.[9]
- The proportion of a single 0.5/0.5g dose excreted in the urine of five healthy volunteers was 28.5% for panipenem and 93.2% for betamipron.[37] Renal clearance was similar to plasma clearance for betamipron (0.73 and 0.68 L/h/kg) but was lower for panipenem (0.09 vs 0.31 L/h/kg).
- Mean plasma elimination half-life ($t_{1/2}$) is approximately 70 minutes for panipenem and 40 minutes for betamipron after single- or multiple-dose administration and regardless of dose.[36,37]

Special Populations

Children

● The pharmacokinetics of panipenem/betamipron in children resemble those in adults. At the end of a 30-minute intravenous infusion, plasma concentrations of panipenem/betamipron were maximal and were dose dependent over the range 10/10 to 30/30 mg/kg in 55 children; C_{max} for the 30/30 mg/kg dose was 91.7/50.1 mg/L.[38] $t_{1/2}$ was approximately 60 minutes for panipenem and 30 minutes for betamipron. About 30% of panipenem and 77% of betamipron doses were excreted in the urine within the first 6 hours after starting the infusion.

Patients with Renal Impairment

● C_{max} after a 60-minute 0.5/0.5g infusion of panipenem/betamipron did not differ substantially among 16 patients with renal dysfunction defined as mild (creatinine clearance [CL_{CR}] ≥3.6 L/h), moderate (CL_{CR} ≤3.6 L/h but ≥1.8 L/h) or severe (CL_{CR} <1.8 L/h). C_{max} was 26.0–30.8 mg/L for panipenem and 18.1–25.8 mg/L for betamipron.[39]

● However, urinary elimination was decreased, AUC increased and $t_{1/2}$ prolonged with decreasing renal function.[39] $t_{1/2}$ values for panipenem/betamipron in the three groups were 1.4/0.7 hours, 1.8/1.3 hours and 3.9/5.8 hours, respectively; the corresponding rates of panipenem recovery over 24 hours post-infusion were 35.5%, 28.0% and 11.9%.

● The elimination profiles of panipenem/betamipron after a 0.5/0.5g infusion in eight patients with end-stage renal disease differed according to whether or not high-flux hemodialysis was administered for 4 hours after the end of the infusion.[50] Total body clearances with and without hemodialysis were 9.53 and 2.92 L/h for panipenem and 4.18 and 0.615 L/h for betamipron. With haemodialysis treatment, the elimination profile of panipenem in these patients closely resembled the profile in healthy adults.[50]

3. Drug Interactions

Coadministration of panipenem/betamipron and valproic acid (sodium valproate) is contraindicated (see section 6), as concomitant therapy dramatically reduces serum valproic acid levels and can predispose patients with epilepsy to seizures.[7]

● Serum valproic acid levels declined by at least 60% to subtherapeutic levels in six patients, mainly children, receiving panipenem/betamipron at various dosages.[51,52] Seizures developed in all but one patient within two to three days of starting antimicrobial treatment. Seizure control was regained after increasing the valproic acid dose and discontinuing panipenem/betamipron or substituting alternative antiepileptics.

● The mechanism of the interaction may be enhancement of the valproic acid glucuronidation rate,[53] suppression of enterohepatic recirculation of the antiepileptic[54] or inhibition of valproic acid absorption in intestinal epithelial cells,[55] as shown in rats *in vitro* and *in vivo*.

● Panipenem is among the β-lactams that exert some convulsant activity in animal models. This appears to to be generally less than with imipenem but greater than with meropenem.[56-58] The carbapenems inhibit GABA-mediated inhibitory transmission, suggested to be the mechanism for this effect,[56,57] although GABA inhibition is not consistently associated with convulsant activity.[57]

4. Therapeutic Trials

The efficacy of panipenem/betamipron has been investigated in numerous trials conducted in Japan in adults, the elderly and children. Many of these, however, are small (n < 25) and noncomparative in design, and are not mentioned further in this review unless no other supporting evidence exists. All studies cited herein are fully published except for a few reported as abstracts.[59-62]

In all trials, 'clinical efficacy rates' refer to percentages of patients with 'good or excellent' clinical response; bacterial eradication rates are percentages of patients with presumed or documented eradication of causative pathogens. Efficacy assessed by a committee and by the physician in charge were similar, and thus the committee results are reported herein.

In Adults

This section focuses on three large, randomised phase III trials comparing panipenem/betamipron (0.5/0.5g twice daily) with imipenem/cilastatin (at the same dosage) in adult patients with bacterial pneumonia,[63] respiratory tract infections[64] and urinary tract infections.[65] The duration of treatment was intended to be 14 days for respiratory tract infections[63,64] and 5 days for urinary tract infections,[65] although physicians could discontinue treatment earlier if ineffective. The differences in the odour and other physical characteristics of the two comparator drugs precluded a double-blind design.

Dose-finding trials in patients with pneumonia (n = 54)[66] using imipenem/cilastatin as an active control determined the optimal dosage of panipenem/betamipron to be 1/1g daily given in two divided doses, and this is the dosage used in the trials.

Smaller, noncomparative phase II trials provide information on the efficacy of panipenem/betamipron in surgical and obstetrical/gynaecological infections in adults. Since the trials produced similar results, the larger and more contributory of these have been selected as representative trials for inclusion in this article.

Lower Respiratory Tract Infections

- Panipenem/betamipron demonstrated similar clinical efficacy (>80%; see figure 2) and bacteriological efficacy to imipenem/cilastatin in evaluable hospitalised patients with suspected bacterial pneumonia (n = 127)[63] or various respiratory infections (n = 146)[64] in the two large, randomised trials. Bacteriological efficacy was 76.7% for panipenem/betamipron and 74.4% for imipenem/cilastatin in one trial[64] and 78.3 versus 100% in the other (difference not significant).[63] Suspected respiratory infections included acute aggravation of chronic bronchitis and infections associated with bronchiectasis, bronchial asthma and pulmonary emphysema or fibrosis.[64]

- Clinical efficacy rates did not differ significantly between the two treatment groups in both trials when assessed according to disease severity (generally mild to moderate) or type and number of causative bacteria.[63,64]

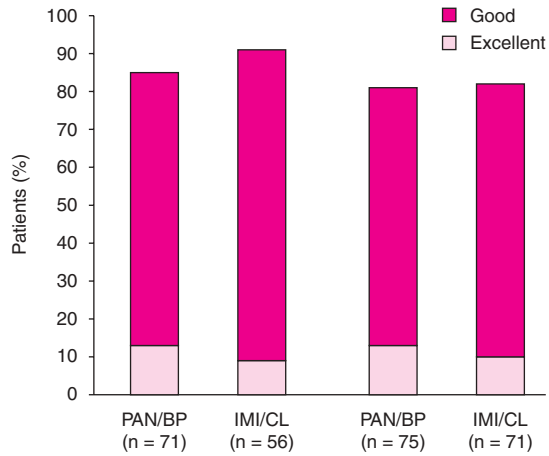


Fig. 2. Clinical efficacy of panipenem/betamipron (PAN/BP) and imipenem/cilastatin (IMI/CL) in respiratory tract infections. Patients with primarily mild to moderate bacterial pneumonia (left columns)[63] or respiratory tract infections (right columns)[64] received PAN/BP or IMI/CL 0.5/0.5g intravenously twice daily for up to 14 days in two randomised trials.

- Bacteriological eradication rates for the most commonly isolated pathogens were high.[63,64] Eradication rates for panipenem/betamipron in both trials were 100% for *S. pneumoniae* (n = 8 and 8 isolates) and *H. influenzae* (n = 4 and 5). Rates for imipenem/cilastatin were 100% for *S. pneumoniae* (n = 7 and 7) and 78% (respiratory tract infections; n = 9 isolates) and 100% (pneumonia; n = 3) for *H. influenzae*. Panipenem/betamipron eradicated *S. aureus* in both patients with respiratory tract infections and in one of three patients with pneumonia, whereas imipenem/cilastatin eradicated this organism in all five patients with either type of infection.

Urinary Tract Infections

- Clinical and bacteriological efficacy rates did not differ significantly in patients with complicated urinary tract infections (n = 201) who received panipenem/betamipron or imipenem/cilastatin in a large randomised trial.[65] Clinical response was excellent or moderate, pyuria was normalised or improved and bacteria eradicated or decreased in num-

ber to a similar extent in both treatment groups (see figure 3).

- Clinical efficacy rates were higher with panipenem/betamipron than with imipenem/cilastatin in patients with monomicrobial infections (94.6% vs 81.5%, p = 0.041), but were similar between the two treatment groups according to types of urinary tract infection.[65]

- Bacteriological eradication rates in both treatment groups were >90% for both Gram-negative organisms, including *E. coli* (n = 17 vs 16 isolates for panipenem/betamipron and imipenem/cilastatin groups) and *K. pneumoniae* (n = 5 vs 8), and Gram-positive organisms (n = 78 vs 64 in total). Rates for *P. aeruginosa* (n = 18 vs 27 strains for panipenem/betamipron and imipenem/cilastatin) and *S. aureus* (n = 14 vs 9) tended to be slightly, but not significantly, lower with panipenem/betamipron.[65] Two noncomparative trials (n = 59[67] and 25[68]) support these results, with clinical efficacy rates of at least 88% achieved in patients given panipenem/betamipron in the same dosage regimen as in the randomised trial.

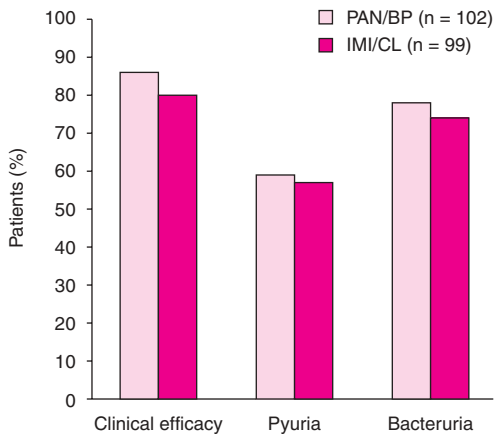


Fig. 3. Efficacy of panipenem/betamipron (PAN/BP) and imipenem/cilastatin (IMI/CL) in patients with urinary tract infections. Patients received PAN/BP or IMI/CL 0.5/0.5g intravenously twice daily for 5 days in a randomised trial. Results are expressed as percentage of patients who had a satisfactory clinical response (excellent or moderate) and improvements in pyuria (normalised or improved) and bacteruria (eradicated or decreased in number).[65]

Obstetrical and Gynaecological Infections

- Panipenem/betamipron is efficacious in women with gynaecological infections. In the largest noncomparative trial (n = 52),[69] panipenem/betamipron 1–2/1–2 g/day for 3–14 days produced clinical and bacteriological efficacy rates of 94.2% and 94.6%. Most patients had intrauterine (n = 29) or pelvic (n = 19) infections. The most common pathogens were *E. coli* and various anaerobes (*Bacteroides* and *Peptostreptococcus* spp.)
- Similar clinical efficacy rates of 91–100% were reported in other small (n = 10–14) noncomparative trials using panipenem/betamipron dosages between 0.5/0.5g and 1/1g twice daily for 3–20 days.[43,44,70-73] Rates were slightly lower in one study of 12 patients with various infections (78.5%)[42] and in another in 17 women with gynaecological cancer and infections (64%).[59]

Surgical Infections

- Panipenem/betamipron (usually 0.5/0.5g or 1/1g twice daily for 3–15 days) yielded clinical efficacy rates of 79–87% in three noncomparative trials (n = 31–48) in patients with surgical infections, primarily intra-abdominal, postoperative and skin and soft tissue infections.[46,74,75] 79% of 19 patients unresponsive to previous treatment had a 'good or better' response to panipenem/betamipron in one trial.[75] Bacteriological efficacy rates ranged from 74–88% in these trials. Isolated strains included a diverse selection of Gram-negative and -positive aerobes and anaerobes; many patients had mixed infection.[46,74,75]

In Elderly Patients

In elderly patients with respiratory tract infections, panipenem/betamipron has been evaluated in noncomparative trials[76,77] and compared with panipenem/betamipron plus clindamycin in a small trial presented as an abstract.[60] In patients with urinary tract infections, panipenem/betamipron has been compared with intravenous piperacillin[62] and oral ofloxacin[61] in studies also reported as abstracts.

Respiratory Tract Infections

- Clinical efficacy rates with panipenem/betamipron (dosage regimen not available) were 74.4% overall, 81.3% in patients with pneumonia, and 57.7% in those with infections secondary to chronic respiratory disease in a multicentre trial in 86 evaluable patients aged ≥65 years.[77]
- Age did not influence efficacy rates, according to analysis of results by 5-year increments.[77] Factors affecting outcome were performance and nutritional status, elevations in body temperature or levels of white blood cell or C-reactive protein, and previous antimicrobial treatment.[78]
- Bacteriological efficacy was high against Gram-positive respiratory pathogens overall (88.9%) and against commonly causative organisms: 100% for *S. pneumoniae*, 91.7% for streptococcal infections and 80% for *S. aureus*. Efficacy was lower against Gram-negative organisms overall (61.1%), and *P. aeruginosa* was not eradicated in any of the five patients with this organism.[77]
- A lower clinical efficacy rate of 56.4% was reported with panipenem/betamipron in a multicentre trial conducted in 43 elderly patients (mean age 76 years) with pneumonia, most with moderate to severe infection.[76] Patients received panipenem/betamipron 0.5/0.5g to 2/2g daily for a mean of 10.2 days. 67.4% of patients had received previous antimicrobial treatment, and 90.7% had concomitant diseases. The bacteriological efficacy rate assessed according to diagnoses was also low (30.8%) but was higher (72.2%) when assessed according to isolated microorganisms.[76]
- Panipenem/betamipron (n = 14) had similar efficacy to panipenem/betamipron plus clindamycin (n = 16) in a randomised trial.[60] Clinical efficacy rates were 71.4% and 75.0%, respectively. No dosage or duration details were given in the abstract.

Urinary Tract Infections

- Panipenem/betamipron 0.5/0.5g twice daily had clinical efficacy similar to piperacillin 2g twice daily intravenously (88% vs 77%)[62] and greater than ofloxacin 200mg orally three times daily (87% vs 63%, $p < 0.05$)[61] in two comparative trials reported as abstracts. All drugs were given for 7 days. The mean age was 79 years in both trials (n = 64[62] and 63[61]).
- Sensitivities (not defined) of isolated strains overall were higher to panipenem/betamipron than to piperacillin (75% vs 61%, $p < 0.05$)[62] or ofloxacin ($p < 0.001$, no numerical values given).[61]

In Children

Two large (n = 188[79] and 374[38]) noncomparative studies evaluated the efficacy of panipenem/betamipron in children aged ≤16 years with primarily respiratory tract but also urinary tract or skin/soft tissue infections. The dosage was 30–60/30–60 mg/kg/day in three divided doses for up to 25 days depending on diagnosis.[38,79] In one trial,[38] clinical efficacy rates were similar whether or not the causative agents were identified; thus, results are given for the group with causative agents identified.

- Clinical efficacy rates overall, and for pneumonia and urinary tract infections, were >91% (see figure 4).[38,79] For skin and soft tissue infections (n = 27),[38] all children but one (with cellulitis) had an 'excellent or good' response (96.3%) in one trial.
- Approximately 93% of pathogenic bacteria were eradicated during panipenem/betamipron ther-

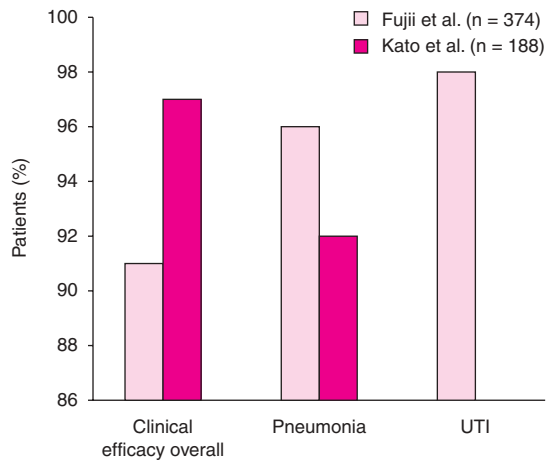


Fig. 4. Clinical efficacy of panipenem/betamipron in children with infections. Patients with various infections, including pneumonia and urinary tract infections (UTI), received intravenous panipenem/betamipron 30–60/30–60 mg/kg/day in 3 divided doses for up to 25 days in two noncomparative trials by Kato et al.[79] and Fujii et al.[38] No results for UTI were available in one trial.[79]

apy.[38,79] The eradication rate was similar (97%) for monobacterial or polybacterial infections in the largest trial, and was high (95.9%) in patients unresponsive to previous treatment (n = 74).[38]

- Panipenem/betamipron therapy eradicated all 23 strains of penicillin-resistant *S. pneumoniae*, which accounted for 57% of all *S. pneumoniae* isolates in this trial.[79]

5. Tolerability

General Tolerability

- Panipenem/betamipron was well tolerated and demonstrated similar tolerability to imipenem/cilastatin in the comparative trials in adults with respiratory or urinary tract infections (see section 4).[63-65] The incidence of adverse effects ranged from 0–3.6% and 1.6–5.7%, respectively, for the two therapies. Mild to moderate rash, diarrhoea and anorexia were the events reported most commonly during panipenem/betamipron treatment.
- A similar profile was observed in children: adverse events occurred in 1.5%[79] and 2.4%[38] of paediatric patients who received panipenem/betamipron in the two large noncomparative trials (see section 4) and resembled those seen in adults.[38,79]
- In the largest trial in elderly patients (n = 95),[77,78] 14.7% experienced adverse effects, with skin disorders (pruritus, rash) accounting for 2.1% and laboratory abnormalities comprising the majority. Adverse events did not increase with increasing age (65–>85 years).
- A postmarketing surveillance study[80] of 17 748 patients conducted over three years found a 9.3% incidence of overall adverse events during panipenem/betamipron therapy. Apart from hepatic function and enzyme disorders, all individual events occurred in <1% of patients.
- Carbapenems have proconvulsant effects (see section 3) and convulsions, including a fatality in an elderly woman,[81] have been experienced by <0.1% of patients receiving panipenem/betamipron according to the manufacturer's prescribing information.[7]

Laboratory Findings

- The most common adverse events documented during panipenem/betamipron therapy are laboratory abnormalities, chiefly elevated serum levels of hepatic transaminases (AST, ALT) and eosinophils. These laboratory abnormalities occurred in similar proportions of patients receiving panipenem/betamipron (7–39.5%) or imipenem/cilastatin (10.1–29%) in comparative studies in adults.[63-65]
- Among 95 elderly patients, mild hepatic dysfunction was observed in 9.5%, serum levels of renal (serum creatinine, blood urea nitrogen) or metabolic markers (lactate dehydrogenase, potassium) were elevated in 2.1% and 4.2%, respectively, and levels of peripheral blood cells (eosinophils, white blood cells) were also altered in 2.1%.[77]
- Approximately 3.9%[79] and 6.6%[38] of children experienced increased serum AST or ALT levels in two large noncomparative trials. White blood count or serum levels of platelets or eosinophils were elevated in 10% of paediatric patients in the largest trial.[38]
- In the large postmarketing study of panipenem/betamipron, hepatic and biliary system disorders were reported in 5.5% of patients, metabolic disorders in 1.7% and white blood cell disorders in 1.2%.[80]

6. Dosage and Administration

The recommended adult dosage of panipenem/betamipron is 1/1g daily administered in two divided doses by intravenous infusion over not less than 30 minutes. In severe or intractable infections, the dosage may be increased to 2g/2g in two divided doses daily infused over not less than 60 minutes. The dosage may be adjusted according to the patient's age and symptoms.[7]

In children, the dosage is 30–60/30–60 mg/kg daily administered in three divided doses over not less than 30 minutes. The dosage can be increased if necessary to a maximum of 100/100 mg/kg daily administered in three or four divided doses, but should not exceed a maximum of 2g daily.[7]

Panipenem/betamipron is contraindicated in patients receiving valproic acid or with a history of shock following exposure to any components of the product.[7]

7. Current Status

Panipenem is an intravenously administered carbapenem antibacterial agent. It is coadminstered with the DHP-I inhibitor betamipron to prevent nephrotoxicity. Panipenem/betamipron is generally well tolerated in paediatric and adult patients including the elderly. The combination has good activity against a broad range of aerobic and anaerobic bacteria and has demonstrated efficacy in adults, the elderly and children with various infections. Panipenem/betamipron is approved in Japan, China and Korea for the treatment of lower respiratory tract, urinary tract, obstetrical/gynaecological and surgical infections.

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