B. Thoerner Andersen, M. Joergensen, J. Lorenzen

Pivmecillinam in the Treatment of Therapy Resistant Urinary Tract Infections
A Comparison with Pivmecillinam, Pivampicillin and Their Combination

Summary: Pivmecillinam is a new penicillin-like compound belonging to the so-called amidinopenicillins and characterized by a high antibacterial activity against *Enterobacteriaceae* and by demonstrated synergism when combined with other β-lactam antibiotics. In this prospective trial geriatric patients with a stationary indwelling catheter and significant bacteruria caused by *Enterobacteriaceae* were treated for four weeks with pivmecillinam, pivampicillin or various combinations of the two compounds. Urine specimens were obtained weekly, and in eight patients receiving pivmecillinam 75% of the urine samples were free from *Enterobacteriaceae* during the period of treatment. The figure was 91% in 24 patients receiving combination therapy. In seven patients treated with an equimolar dose of pivampicillin alone 43% and 23% of the urine specimens, controlled during the first and the second halves of the treatment period respectively, *Enterobacteriaceae* was eradicated. In this group there was a marked and increasing tendency towards infections caused by more resistant strains of *Enterobacteriaceae* as the treatment progressed. The latter is in keeping with the observation that pivmecillinam, as opposed to ampicillin, apparently does not cause any selection of resistant *Enterobacteriaceae*.


Introduction

Preliminary studies on pivmecillinam, the orally active prodrug of mecillinam, a new and potent antibiotic, indicate that it is a valuable agent in treatment of urinary tract infections (1–9).

Pivmecillinam is the pivaloyloxymethyl ester of mecillinam and, in contrast to the latter, is readily absorbed from the gastrointestinal tract. After absorption pivmecillinam undergoes simultaneous enzymatic hydrolysis with liberation of mecillinam (10). In this respect pivmecillinam resembles pivampicillin which is a prodrug of ampicillin.

Mecillinam is the first member of a new class of penicillanic acid derivatives, the so-called amidinopenicillins (11) which chemically can be considered as substituted formamidines (Figure 1). The drug shows a remarkably high activity against *Enterobacteriaceae* (Escherichia coli, Klebsiella spp., Proteus spp., Salmonella spp., Shigella spp., Serratia spp., Yersinia spp.) whereas its activity against other gram-negative organisms and also gram-positive bacteria is relatively low. *Pseudomonas spp.* and *Streptococcus faecalis* are resistant to mecillinam (12, 13).

It has been shown that mecillinam interferes with the biosynthesis of the bacterial cell wall, and although its specific mode of action has not yet been fully elucidated, bacteriological and enzymatic studies have shown that its mode of action differs essentially from that of the penicillins (14). It has been shown that mecillinam, unique

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Dr. B. Thoerner Andersen, Syrenvænget 25, DK-3520 Farum, Denmark;
Dr. M. Joergensen, Broderskabsejvej 21, DK-2000 Copenhagen F, Denmark;
Dr. J. Lorenzen, Ouroegade 40, DK-2100 Copenhagen Ø, Denmark
among the β-lactam antibiotics, exerts a high specificity against one of the six known penicillin-binding proteins (PBP II) in the gram-negative bacterial cell wall. Binding to PBP II probably involves inhibition of the enzymatic step in the cell-wall synthesis resulting in morphological changes of the normal rod-shaped bacteria into large ovoid cells, which are then lysed.

Synergy has been observed when mecillinam is combined with another β-lactam antibiotic such as penicillin, carbenicillin, ampicillin, or a cephalosporin (15, 16). Synergy is not always present when testing in vitro or in mice protection studies. However, against many strains of Enterobacteriaceae marked synergistic action is found, also in cases where the organism is resistant to one or the other component.

In the present study the antibacterial effects of pivmecillinam and pivampicillin were compared in the treatment of bacteriuria in geriatric patients who, because of underlying diseases, had a stationary indwelling catheter. Due to the synergistic possibilities of the two compounds, various combinations of the two drugs were evaluated in comparison with single drug therapy for both the antibiotics.

Materials and Methods

Patients: Forty-five geriatric patients with a urinary tract infection caused by E. coli, Klebsiella spp. or Proteus spp., demonstrated in at least one pre-treatment specimen of urine (≥ 10⁴ Enterobacteriaceae/ml), were included in the investigation. All patients had a stationary indwelling catheter because of incontinence. Excluded were patients with a presumed allergy to penicillin, stones or malformations in the urinary tract, impaired renal function (serum creatinine >2 mg%), or patients who had