Synergy and mecillinam

Mecillinam is a β-amidino derivative of 6-aminopenicillanic acid which differs markedly from conventional β-lactam antibiotics. Many Gram-negative organisms are sensitive to very low concentrations of mecillinam, but *Haemophilus* spp. and *Neisseria* spp. are important exceptions. The sensitivities of the *Klebsiella-Enterobacter-Serratia* group and *Proteus* spp. are less certain because the action of mecillinam on these organisms depends on the osmolality and conductivity of the medium (Neu, 1976a; Tybring & Melchior, 1975). Gram-positive organisms are generally resistant (Lund & Tybring, 1972; Neu, 1976a).

Greenwood & O'Grady (1973) showed that bacterial rods exposed to mecillinam converted to spherical forms which differed from classical penicillin-mediated transformation. Mecillinam blocks an event early in cell construction essential for its normal elongation (James, Haga & Pardee, 1975). Spratt (1975) then showed that mecillinam binds preferentially to the second penicillin binding protein which controls the shape of the bacillus, rather than to the proteins that affect cell elongation or septum formation. These findings suggested that mecillinam might act synergistically with other β-lactam antibiotics which affect the proteins responsible for cell elongation and septum formation.

Using ampicillin and mecillinam, Tybring & Melchior (1975) demonstrated synergy against a few selected strains of *Enterobacteriaceae*. Neu (1976b) examined the effects of various antibiotic combinations with mecillinam against both Gram-positive and Gram-negative bacteria. Organisms highly susceptible to mecillinam did not show synergy if MIC values were considered. Mecillinam was most active in media of low osmolality and conductivity, but even in such media there was often a wide difference between the mecillinam MIC and MBC. Synergy was sometimes demonstrated when MBC values were studied. In media of low osmolality and conductivity most *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Shigella* and *Salmonella* were so susceptible to mecillinam that synergy could not be demonstrated. When conditions were altered, such as by raising the conductivity, so that the organism could resist the lytic action of mecillinam, then synergy with a second β-lactam antibiotic resulted. Organisms completely resistant to both antibiotics, such as *Proteus morganii*, could not be inhibited synergistically. Organisms with intermediate sensitivities to mecillinam often showed synergy whether or not they were resistant to the second antibiotic. However, this synergy was not invariable for all strains in a group, and not all β-lactam antibiotics showed the same effects against a particular organism. For example, mecillinam showed synergy with amoxycillin against a strain of *Klebsiella*, but not with cephalothin or cefoxitin against the same organism. Baltimore, Klein, Wilcox & Finland (1976) also found that the synergy varied from isolate to isolate and from antibiotic to antibiotic.

Neu (1976b) demonstrated that the marked difference between MIC and MBC values for mecillinam was partly due to its destruction by β-lactamase. The addition of cloxacillin to mecillinam blocked the action of β-lactamase and both the MIC and MBC of mecillinam were reduced. It is possible that a combination of cloxacillin, mecillinam and ampicillin would inhibit organisms resistant to both mecillinam and ampicillin. In contrast to the results found with Gram-negative organisms, no synergy was found against Gram-positive organisms. Nor was synergy seen when mecillinam was combined with antibiotics which were not β-lactam compounds. Lorian & Atkinson (1977) studied the effect of mecillinam and ampicillin on the shape and viability of *Proteus mirabilis*. When each drug was given simultaneously synergy was shown. When they were given consecutively the effect
was the same as that of each drug acting separately and no synergy was found.

These findings of in vitro synergy help to explain the action of the antibiotic, but do they have any relevance to the treatment of infections? Grunberg, Cleeland, Beskid & DeLorenzo (1976) treated experimental infections in mice with parenteral mecillinam in combination with various antibiotics. Synergy was demonstrated when mecillinam was given with an equal amount of ampicillin or amoxycillin. The effect was mainly against members of the Enterobacteriaceae but also against some strains of Haemophilus influenzae. Also synergy was seen when mecillinam was combined with other β-lactam antibiotics, but as in the in vitro studies, the effect varied with the organism and the antibiotic tested. Mecillinam also synergized the effect of benzylpenicillin against Staphylococcus aureus but not other Gram-positive organisms. Synergy was not seen with non β-lactam antibiotics. As these studies confirmed the in vitro findings, it was suggested that human trials would be justified.

For which infections would its use then be justified? Mecillinam is an effective antibiotic for uncomplicated urinary tract infections (Clarke, Geddes, McGhie & Wall, 1977). However, it is no more effective than other currently available antibiotics. In certain circumstances such as a hospital outbreak it may be reasonable to use mecillinam combined with amoxycillin to eradicate a specific pathogen, but combination therapy is unlikely to become routine practice. For Gram-negative septicemia many clinicians use an aminoglycoside and are unlikely to choose mecillinam on its own or in combination. Typhoid fever has been treated successfully with mecillinam but the results have not been a marked improvement over those obtained with chloramphenicol or co-trimoxazole (Clarke, Geddes, McGhie & Wall, 1976). The variable response of patients with typhoid to antibiotics is probably a feature of the disease or the patient's immunological response and the addition of a second antibiotic will not give a predictable better result.

In patients with chronic bronchitis the sputum levels of antibiotic may not exceed the MIC for Haemophilus influenzae. Pines (1977) suggested that mecillinam could potentiate the action of amoxycillin against H. influenzae and also suppress β-lactamase producing Enterobacteriaceae. He treated 132 patients during exacerbations of severe chronic bronchitis. Three groups were given (1) amoxycillin 500 mg or (2) amoxycillin 250 mg and pivmecillinam 200 mg; or amoxycillin 500 mg and pivmecillinam 400 mg. Each drug was given three times daily for 10 days. Progress was judged by the general condition of the patient and by naked-eye assessment of sputum purulence. Sputum volumes and respiratory peak flow rates were measured, but detailed bacteriology was not performed. The results were not clear cut. In patients with purulent sputum response was correlated with the dose of amoxycillin given, whilst in those with mucopurulent sputum the addition of pivmecillinam was important. However, Pines felt that the results were encouraging and further trials were justified. Only when the results are available may it be possible to assess the place of mecillinam combinations in the management of patients with chronic lung disease.

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References


Prescription of aminoglycosides by nomogram

Since the introduction of gentamicin in the early 1960's as the first highly active aminoglycoside its dosage has been the subject of more debate than any other antibacterial drug, excepting perhaps antituberculosis agents.

Early problems with ototoxicity, although largely in patients with impaired renal function, led to dosage recommendations of typically 1 mg/kg 8-hourly. These doses based on fear of toxicity were too small to give optimal serum concentrations for treating tissue infections. The last 10 years have witnessed increasing awareness of the role of pharmacokinetics in dosage prediction and, with an enormous expansion of the use of parenteral gentamicin in the face of nosocomial infection with penicillin- and cephalosporin-resistant Gram-negative bacilli, prescribing aids for gentamicin have been designed by Jelliffe (1971), Chan, Benner & Hoeprich (1972), and the Manchester-based group of Mawer et al. (1974). These rely upon a one-compartment model in which the drug is assumed to be evenly distributed, and from which it is cleared almost entirely by the kidneys. To predict the concentration of the drug in the compartment at any one time, assumptions must be made as to its size (apparent distribution volume), and the rates of input from the site of injection (rate constant for absorption in the case of intramuscular administration) and of clearance. For example, Mawer et al. (1974) found the best results were obtained by assuming the apparent distribution volume (litres) to be 0.275 × body mass (kg), and the renal gentamicin clearance to be 0.75 × creatinine clearance (ml/min). Since the creatinine clearance is usually not known it is predicted from the age, sex, mass and serum creatinine concentration of the patient. The Manchester nomogram is designed to utilize these four parameters to give a loading and maintenance dose of gentamicin resulting in serum concentrations in the range 3 to 10 mg/l 2 h after a dose, based on the pharmacokinetic assumptions given above.

Using the same nomogram our own investigations showed that the large majority of 1-h post dose serum concentrations fell into the range 5 to 10 mg/l (Reeves, Bint, Burges, Elliot & Stocks, unpublished data). In both Mawer's and our studies doses prescribed by clinicians not using a nomogram gave a much wider scatter of concentrations, and in our experience they were usually lower than the desired therapeutic range. Using doses given by the Manchester nomogram Tobias, Wrigley, Korde & Shaw (1977) compared the serum concentrations of tobramycin measured with those given by a fixed dose. The nomogram-predicted concentrations were significantly higher although often below the range found by ourselves. This discrepancy is probably due to their use of intravenous bolus injection rather than intramuscular injection, since the pharmacokinetics of tobramycin are very similar to those of gentamicin. Certainly Mawer (1976) could see little use for a separate tobramycin nomogram (Benner, Krauhold & Bush, 1974). Thus in patients with normal renal function or a stable impairment of it, nomogram-predicted doses of gentamicin or tobramycin usually gave satisfactory serum concentrations in the range considered suitable for effective therapy (Noone, Parsons, Pattison & Slack, 1974), at least during the early days of treatment. The nomogram does not necessarily predict satisfactorily low pre-dose (trough) concentrations since they will inevitably be high (>3 mg/l) when the plasma half life is prolonged by renal impairment or if adequate post-dose concentrations are maintained at a reasonable frequency.

The value of designing dose to individual patients rather than using a fixed dose was investigated by Anderton, Hanson & Ræburn (1976). In patients with serious Gram-negative infections and poor renal function, gentamicin was prescribed as a fixed dose of 80 mg at a frequency regulated by renal