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SESSION IV

# The Treatment of Urinary-Tract Infections with an Oral Carbenicillin

**Marvin Turck**

*From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington*

An orally absorbed indanyl ester of carbenicillin was investigated in 26 patients with bacteriuria. The 26 patients, who were treated with 2.0 or 4.0 g of drug per day for 14 days, included 15 with *Escherichia coli,* five with *Proteus,* five with *Pseudomonas,* and one with *Klebsiella* bacteriuria. No serious adverse reactions to the drug were encountered although most patients noted a bitter taste. Bacteriuria was eradicated during therapy in 19 patients, including three infected with *Pseudomonas.* Concentrations of drug were determined in serum and urine of five subjects after administration of 500 or 1,000 mg of antibiotic. Although peak concentrations in the serum were low (less than 10 μg/ml), concentrations in the urine generally exceeded the minimal inhibitory concentrations for many Enterobacteriaceae and *Pseudomonas.*

Carbenicillin (disodium carboxybenzyl penicillin) is a penicillin that has a wide spectrum in vitro against most urinary pathogens [1–3]. However, poor oral absorption or acid lability, or both, have heretofore restricted use of the drug to administration in hospitals.

Recently, the indanyl ester of carbenicillin has been shown to be a form of the antibiotic that is acid-stable and is absorbed orally; thus, it is a potentially useful agent in ambulatory patients [4, 5]. Once absorbed, the ester is rapidly hydrolyzed to carbenicillin. The present communication summarizes the use of the ester in the treatment of 26 patients with infections of the urinary tract.

## Materials and Methods

*Clinical studies.* The efficacy, toleration, and toxicity of the carbenicillin ester were assessed in 26 ambulatory patients with well-documented infections of the urinary tract. All patients were treated for 14 days; those with bacteriuria due to *Pseudomonas* were given 4 g of drug per day, and the others received 2 g daily. Concentrations of carbenicillin in the serum and urine of five normal subjects were determined after the ingestion of 500 and 1,000 mg of the carbenicillin ester. Assays of the antibacterial activity of serum were performed at 0, 0.5, 1, 2, 4, and 6 hr. The urinary excretion of the drug during the first 6 hr after administration of an oral dose was also determined. The Ellsworth strain of *Pseudomonas aeruginosa,* for which the MIC is 2.5 μg/ml, was used as the test organism in a cylinder-cup-plate assay. Chromatographic studies have shown that the indanyl ester is excreted as carbenicillin in the urine; therefore, activity of the ester in serum and urine is expressed as activity of carbenicillin.

Please address requests for reprints to Dr. M. Turck, 325 Ninth Avenue, Seattle, Wash. 98104.

## Results

The effect of the indanyl ester of carbenicillin in the treatment of 26 ambulatory patients with infections of the urinary tract is summarized in table 1. The initial pathogen was eradicated from the urine during therapy in 19 patients, including 13 with *Escherichia coli,* three with *Pseudomonas* and three with *Proteus mirabilis.* Of the seven patients in whom bacteriuria persisted during therapy, three had infections that were highly resistant to carbenicillin before treatment with the carbenicillin ester. In two patients, one with *Pseudomonas* and one with *Proteus vulgaris,* the initial isolates acquired increasing resistance to carbenicillin during treatment. The persistence of bacteriuria during therapy by the remaining two patients is unexplained.

**Table 1.** Effect of carbenicillin ester on bacteriuria.

| Organism | No. patients | No. sterile | |
|---|---|---|---|
| | | During treatment | At 6 weeks |
| *Escherichia coli* | 15 | 13 | 8 |
| *Pseudomonas aeruginosa* | 5 | 3 | 3 |
| *Proteus mirabilis* | 4 | 3 | 2 |
| *Proteus vulgaris* | 1 | 0 | 0 |
| *Klebsiella* | 1 | 0 | 0 |
| Total | 26 | 19 | 13 |

Six weeks after cessation of therapy, 13 of the 19 patients who achieved sterile urine during treatment (or 50% of the total group of patients) remained free from infection with the initial infecting organism. Among the four patients who relapsed with the same strain after cessation of treatment were two with proven renal sites of infection.

*Toleration and toxicity.* Although not severe, adverse reactions and side effects of the drug were frequent (table 2). Those most often noted by patients were a bitter taste, unpleasant aftertaste, and nausea. It was necessary to discontinue the antibiotic before completing the prescribed course of treatment in three patients. No alteration in any laboratory test assessing effect on bone marrow or on renal or hepatic function could be attributed to the antibiotic.

*Antibacterial activity in serum and urine.* Peak concentrations of carbenicillin in the serum were less than 10 μg/ml, even when a 1,000-mg dose of the ester was ingested. However, the drug was excreted in the urine in high concentration (table 3), with approximately one-third of the orally administered dose appearing in the urine during the first 6 hr. Doubling the oral dose resulted in the excretion of twice as much drug. Random urinary concentrations ranged between 274 and 2,160 μg/ml, exceeding the MIC for most strains of urinary pathogens.

**Table 2.** Adverse effects of carbenicillin ester.

| Side Effect | No. of patients |
|---|---|
| Bitter taste | 11 |
| Nausea | 9 |
| Diarrhea | 7 |
| Flatulence | 4 |
| Abdominal cramps | 2 |
| Vomiting | 1 |
| Dizziness | 1 |
| Dry mouth | 1 |
| Itching eyes | 1 |
| Pruritus | 1 |

**Table 3.** Urinary excretion of carbenicillin assayed by a cylinder-plate method following oral administration of the carbenicillin ester.

| Subject | Dose administered | |
|---|---|---|
| | 500 mg | 1,000 mg |
| 1 | 168 (33.5%)* | 346 (34.6%) |
| 2 | 189 (37.8%) | 325 (32.5%) |
| 3 | 167 (33.4%) | 317 (31.7%) |
| 4 | 147 (29.3%) | 308 (30.8%) |
| 5 | 161 (32.3%) | 314 (31.4%) |

* Amount (mg) and percent of administered dose excreted during first 6 hr following ingestion.

## Discussion

Of the many antimicrobial agents currently available for the treatment of ambulatory patients with infections of the urinary tract, few have a spectrum encompassing the majority of likely pathogens. In addition, many have other drawbacks; drug intolerance or toxicity and the propensity to evoke rapid emergence of resistance often accompany limitations of antibacterial spectrum. In contrast, carbenicillin is relatively nontoxic, as are most penicillins, and it also has a wide spectrum in vitro against most urinary pathogens, including many for which only parenteral therapy has previously been available. Therefore, an oral form of this drug might have potential usefulness in the treatment of urinary-tract infections.

However, whether the orally administered carbenicillin ester described in the present communication will achieve this purpose is not entirely clear. In the search for a carbenicillin that can be administered orally, considerable antibacterial effectiveness may be sacrificed because the concentrations achieved in the serum are suboptimal. Although this may not affect the outcome of treatment of acute or chronic infections limited to the urinary tract, the drug probably should not be given to patients in whom there exists the possibility of bacteremia or infection outside the urinary tract. The relatively large number of failures in patients with bacteriuria in this study following cessation of the carbenicillin ester is not surprising. Many of these patients had previously received antimicrobial therapy with various agents, but in-

fection had persisted or recurred. Although the majority did not have structural abnormalities, three had renal calculi and two others had upper-tract infection substantiated by ureteral catheterization. Previous studies reported from our laboratory have demonstrated that renal bacteriuria is more refractory to drug therapy than is infection confined to the bladder [6]. An effective antimicrobial agent must do no less than render the urine sterile during therapy, and persistence of the initial pathogen, even in low numbers, is invariably associated with recrudescence of significant bacteriuria after cessation of treatment. Although most patients with infections of the urinary tract probably can be treated successfully with the indanyl ester of carbenicillin, for practical purposes it performs no better than a host of drugs already available for treatment of most urinary-tract infections due to common infecting organisms [7]. In addition, its widespread use may limit the usefulness of the parenteral form of carbenicillin by causing selection of resistant strains of *Pseudomonas* in hospitalized patients.

The chief advantage of this drug may be that it will provide an effective, nontoxic agent for use in urologic patients who often have persistent or recurrent urinary infections due to pathogens such as *Pseudomonas, Enterobacter,* and indole-positive *Proteus* species. These organisms heretofore have been difficult to treat with drugs that can be administered orally even when bacteriuria is believed to be confined to the bladder. Whether prolongation of treatment with the indanyl ester of carbenicillin beyond 14 days in patients with renal bacteriuria will also result in more permanent eradication of infection is not known.

**References**

1. Silverblatt, F., Turck, M. Laboratory and clinical evaluation of carbenicillin (carboxybenzyl penicillin). Antimicrob. Agents Chemother. 1968:279–285, 1969.
2. Bodey, G. P., Terrell, L. M. In-vitro activity of carbenicillin against gram-negative bacilli. J. Bacteriol. 95:1587–1590, 1968.
3. Brumfitt, W. A., Percival, A., Leigh, D. A. Clinical and laboratory studies with carbenicillin: a new penicillin active against *Pseudomonas pyocyanea.* Lancet 1:1289–1293, 1967.
4. Butler, K. Metabolism and laboratory studies with indanyl carbenicillin. Del. Med. J. 43:366–375, 1971.
5. Taylor, W. A., Holloway, W. J. Clinical experience with oral carbenicillin. Del. Med. J. 43:381–383, 1971.
6. Turck, M., Ronald, A. R., Petersdorf, R. G. Relapse and reinfection in chronic bacteriuria. II. The correlation between site of infection and pattern of recurrence in chronic bacteriuria. N. Engl. J. Med. 278:422–427, 1968.
7. Turck, M. Broad spectrum penicillins and other antibiotics in the treatment of urinary tract infections. Ann. N.Y. Acad. Sci. 145:344–353, 1967.