Pyelonephritis Therapy in Rats: Random Association with Excreted Urinary Antibacterial Activity

S. E. BURROWS, R. FREEDMAN, R. E. CHAMBERLAIN, AND R. P. BASSON

Eaton Laboratories, The Norwich Pharmacal Company, Norwich, New York 13815

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In vitro activities or excreted urinary activities of 56 generic and experimental drugs against two organisms commonly associated with human pyelonephritis, Escherichia coli and Proteus mirabilis, are not correlated with the in vivo activities of these compounds as measured by reduction of viable organisms in kidneys in experimental pyelonephritis.

It has been widely assumed, mostly tacitly (2-4) and in the absence of convincingly reproducible models in which to test the validity of the assumption, that a compound evincing high in vitro activity, especially in urine, would be a better candidate for kidney infections than a compound with relatively low urinary activity. In the course of developing a rat pyelonephritis model in our laboratories (1), considerable data were also generated on the urinary antibacterial activities and minimal inhibitory concentrations (MIC) of a number of compounds, including many which have been tested clinically. The number of clinically effective compounds which could be compared on an equal basis in our system against the same strains of two of the most common organisms implicated in pyelonephritis, Escherichia coli and Proteus mirabilis, afforded an excellent opportunity to test this general assumption simply by plotting sufficient data for an objective mathematical approach to the question.

MATERIALS AND METHODS

Pyelonephritis was induced in five 160- to 180-g CFN (Wistar) rats of either sex by the procedure described previously (1); all compounds were given in an oral regimen, twice daily for 14 days, starting 3 days after infection. Titration of viable bacteria per kidney, also previously described (1), was either by direct plate count or by dilution end point in Brain Heart Infusion Broth (BHIB) of appropriate saline dilutions of whole kidney homogenate 18 or 19 days after infection. The log₁₀ of the geometric mean of the individual viable titer of the five infected kidneys was used to provide a single numerical value with which to compare objectively the effects of various compounds; the number of standard deviations of reduction below the control value was then deemed a satisfactory measure of efficacy for our purposes. The same strains of E. coli and of P. mirabilis were used in all experiments. Each organism was isolated from an individual with clinical pyelonephritis. Conventional methods were used to determine MIC values and urinary antibacterial activities by twofold dilution end point assay in BHIB inoculated with about 10⁵ viable organisms from an overnight broth culture. Urinary antibacterial activities were measured on urines collected during two 4-hr intervals after administration of a single oral dose of the test compound to groups of five 200-g rats which had been fasted overnight.

RESULTS AND DISCUSSION

Figure 1 is a summary of the urinary antibacterial activities (expressed as the RID, or reciprocal of the highest inhibitory dilution) of various compounds as a function of the number of standard deviations of reduction of the log₁₀ of the geometric mean of the viable kidney titer elicited by the same dosage levels of the compounds in question. The only criterion for inclusion in Fig. 1 was activity in at least one parameter. The list of compounds represented includes mandelamine, ampicillin, demethylchlordetracycline, sulfisoxazole, sulfamethoxazole, gentamicin, furazolidone, cephalxin, nitrofurantoïn, kanamycin, cephaloglycin, nifuradene, nalidixic acid, kasugamycin, and other nongeneric putative potential therapeutic antimicrobials. A modified Spearman's coefficient of rank correlation was determined to be (+) 0.033 for these data; thus, there is no evidence of correlation between the two parameters. It is true that the vast majority of compounds tested in a blind screen fall in the zero-zero category; i.e., they exhibit no activity by either parameter. This treatment of the data ignores urine volume, recycling and concentration in the kidney, possible metabolites, and per cent recovery of the parent compound simply because it is easier to do so when hundreds of compounds are examined in a relatively short period of time. However, the classical manipulations (e.g., multiplying urine volume by its RID and then calculating "per cent recovery" of total ingested MIC values) were performed on most of
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the compounds whose activities are given in Fig. 1. A plot of these data merely gives larger numbers (although the relative positions of many individual compounds are shifted) and a similarly random distribution of values.

The data for the MIC values of the compounds in Fig. 1 were also plotted against their RID figures; a lack of correlation was also found for these data [modified Spearman's coefficient = (+) 0.022].

These data, with those published earlier (1), emphasize the great value of reproducible animal model infections and the limited value of in vitro antibacterial activities when seeking better chemotherapeutic agents for pyelonephritis.

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Fig. 1. Rat urinary antibacterial activities of 56 generic and experimental drugs, plotted as a function of the efficacy of the same compounds in lowering the viable titers of the bacteria associated with experimental pyelonephritis in the rat.