Intraperitoneal penetration of ticarcillin/clavulanic acid (Timentin)

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Thirty-eight patients undergoing elective abdominal surgery were given 3.0 g ticarcillin plus 0.2 g clavulanic acid as a single intravenous injection at varying times prior to the operation. Sterile assay discs were placed on the peritoneal surface in order to measure peritoneal fluid levels of each agent. Simultaneous serum levels were also measured.

A total of 38 serum and peritoneal samples were analysed. There was rapid penetration of both agents into peritoneal fluid. The mean peritoneal fluid levels of ticarcillin were 70% (S.D. 13) of the serum level and 67% (S.D. 4) for clavulanic acid. The peritoneal levels of both agents declined in parallel to the serum levels (the half-lives being about 1 h) and the ratio of ticarcillin-clavulanic acid in serum and peritoneal fluid did not vary significantly with time.

Introduction

Combination of the β-lactamase inhibitor clavulanic acid with ticarcillin is highly synergistic in vitro where it has been shown to possess considerable activity against staphylococci and Bacteroides fragilis, as well as Enterobacteriaceae (Hunter et al., 1980). In animals, the combination in a ratio of 15 : 1 (ticarcillin: clavulanic acid), is effective in the treatment of intra-abdominal abscesses (Bansal Prabahala & Thadepalli, 1986).

We studied the intraperitoneal penetration of both clavulanic acid and ticarcillin after intravenous administration using a modification of a reproducible method (Wise et al., 1981).

Materials and methods

Thirty-eight patients (mean age 67.2 years, range 53 to 81 years, male : female 20 : 18) undergoing elective surgery (most commonly cholecystectomy, gastric and colonic resections) were studied. The protocol had previously been approved by the Ethical Committee of Dudley Road Hospital. There were no episodes of peritonitis. Renal function was normal (serum urea < 7 mmol/l and creatinine < 133 μmol/l in all but three patients). All patients had normal liver function.

At varying times prior to surgery 3.2 g of Timentin (containing 3.0 g of ticarcillin and 0.2 g of clavulanic acid) was administered as a bolus intravenous injection over 2–5 min and the time noted. After the abdominal cavity was opened pre-weighed sterile filter paper discs (6 mm diameter) were inserted below the transverse mesocolon.
and left in place for 2–5 min (until saturated with peritoneal fluid). A blood sample was taken at the same time. The discs were removed and placed in pre-weighed sterile bottles and transported immediately with the blood to the laboratory. If the peritoneal cavity was not grossly contaminated by blood, a further set of blood and peritoneal samples were taken towards the end of the operation. The peritoneal samples were then compared macroscopically with previously prepared discs contaminated with 5%, 10% and 20% blood. Peritoneal samples contaminated by >10% of blood were discarded. Serum and peritoneal samples were assayed within 1 h of collection. Three peritoneal discs were assayed for each antibiotic. The assay for ticarcillin was carried out by the agar plate diffusion method using Pseudomonas aeruginosa NCTC 10701 as the indicator organism and Penassay No. 1 (Oxoid, Basingstoke, England) as the antibiotic medium. Serum standards were made up in whole human serum and the peritoneal standards in 20% human serum in phosphate buffered saline pH 6.6. The serum samples were tested undiluted and in a 1 in 10 dilution.

The assay for clavulanic acid was performed in a similar manner. Penassay No. 2 (Oxoid) incorporating 35 mg of benzylpenicillin/l used as the antibiotic medium and the indicator organism was Klebsiella pneumoniae NCTC 1003. The plates were used within 1 h of pouring. The standards and samples were prepared as described above.

Results

The 95% confidence limits of the assays were as follows:— ticarcillin serum and peritoneal fluid ± 18.9 mg/l; clavulanic acid serum and peritoneal fluid ± 16.9 mg/l. The lower limit of sensitivity for the ticarcillin assay was 2 and 0.25 mg/l for clavulanic acid. Three patients were excluded from the study because of abnormal renal function.

![Figure 1. Concentrations of ticarcillin in serum (X) and peritoneal (●) after 3000 mg iv injection; 38 sets of serum and peritoneal fluid data from 31 patients.](http://jac.oxfordjournals.org/)

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Intraperitoneal penetration of ticarcillin/clavulanic acid

Figure 2. Concentrations of clavulanic acid in serum (X) and peritoneal fluid (●) after 200 mg iv injection. 32 sets of serum and peritoneal fluid data from 27 patients.

Thirty-five patients yielding 43 samples were included in the study. Of these, five sets of data were discarded as being contaminated with >10% blood. Thirty-eight sets of data were obtained from 31 patients for ticarcillin and 32 sets of data from 27 patients for clavulanic acid. Figures 1 and 2 show the serum and peritoneal concentrations of ticarcillin and clavulanic acid. It can be seen that both ticarcillin and clavulanic acid penetrate the peritoneal fluid rapidly, high concentrations being found within 30 min of intravenous administration. Clavulanic acid concentration in serum exceeded 4 mg/l over 2 h and in peritoneal fluid exceeded 1 mg/l for over 3 h. A regression line analysis of the data was performed and the serum half-life of ticarcillin was 1.0 h and clavulanic acid 1.1 h. The half-lives of the agents in peritoneal fluid are similar, namely 1.1 h for ticarcillin and 1.2 h for clavulanic acid.

The ratio of the two compounds in the dose as administered was 15:1 (ticarcillin: clavulanic acid). The ratio of the two agents in serum was found to be 26.5:1 (s.D. 14.5) and in peritoneal fluid 28.3:1 (s.D. 14.3). The ratio of the two agents in serum or peritoneal fluid did not vary significantly with time.

The mean percentage peritoneal penetration (peritoneal level x 100/serum level) of ticarcillin was 70% (s.D. 13) and that of clavulanic acid 67% (s.D. 4.0).

Discussion

The intraperitoneal penetration of ticarcillin and clavulanic acid is similar to amoxycillin/clavulanic acid (Wise et al., 1983), and cefoxitin (Wise et al., 1981) with rapid penetration being observed and the half-life in peritoneal fluid being similar to that in serum. The extent of peritoneal penetration for amoxycillin was 84%, being similar to that of ticarcillin 70±13%. The percentage penetration of clavulanic acid however was lower at 67%, a figure similar to the peritoneal penetration of clavulanic acid when given with amoxycillin (66%) (Wise et al., 1983). The lower penetration of clavulanic acid cannot be explained by differences in assay precision alone. Although the relative instability of clavulanic acid in biological fluids is a possible explanation...
for the lower levels observed in peritoneal fluid (compared to ticarcillin), it is unlikely as the samples were assayed within 1 h of being taken. Clavulanic acid is less lipid soluble than amoxycillin (and possibly ticarcillin) and this could account for the slightly different distribution of the agents. Otherwise the pharmacokinetics of the two components in serum and peritoneal fluid are fairly similar.

In-vitro studies of ticarcillin-resistant enterobacteria suggest that a clavulanic acid concentration of 5 to 10 mg/l is required for therapeutic synergy (i.e. a reduction in the minimal inhibitory concentration of ticarcillin to ≤16 mg/l) (Paisley & Washington, 1978). In vivo, however, it is possible that only small amounts of clavulanic acid are needed to allow ticarcillin to exert its bactericidal effects. Extrapolating from previous studies (Wise, Andrews & Bedford, 1978) a clavulanic acid concentration of at least 1 mg/l would seem desirable to potentiate the action of ticarcillin. Lesser amounts of clavulanic acid are required to inhibit the β-lactamases produced by B. fragilis. Consequently intravenous clavulanate potentiated ticarcillin may have to be given at approximately 6-hourly intervals as concentrations of clavulanic acid in the peritoneal cavity fall below 5 mg/l within 0-4–0-7 h and below 1 mg/l after 3-2 h. Increasing the concentration of clavulanic acid in ticarcillin/clavulanic acid would be an alternative pharmacokinetic solution to enable an increase in the interval between doses. Results of clinical trials to assess the efficacy and dosing frequency of ticarcillin/clavulanic acid in preventing intra-abdominal sepsis are awaited and may provide such therapeutic guidelines.

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References


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