5-Fluorocytosine and Amphotericin B in Bronchial Secretions

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Received for publication 6 June 1974

The penetration into and clearance from bronchial secretions of 5-fluorocytosine and amphotericin B were studied in a dog model. After a single intravenous dose of 35 mg/kg, 5-fluorocytosine intrabronchial concentrations were greater than the minimal inhibitory concentration for 80 to 90% of Candida species. These inhibitory concentrations persisted up to 3 h. In contrast, amphotericin B in intravenous doses of 0.6 and 1.2 mg/kg penetrated the blood-bronchus barrier poorly.

Colonization of the tracheobronchial tree with Candida species (usually C. albicans) is not uncommon in debilitated and immunosuppressed patients. Endotracheal intubation or tracheostomy (9), and the use of broad-spectrum antibiotics (18), render patients especially prone to candida colonization. The incidence of candidemia or invasive pulmonary infection which results from this colonization is unknown. However, an increasing problem with disseminated candidiasis and candida pneumonia in these patients has been reported (7, 8).

Antibiotics, administered to respiratory mucosal surfaces via aerosol spray, have been effective in reducing the incidence of gram-negative bacterial colonization of the respiratory tract in certain groups of patients (6, 9). Attempts at eradicating oropharyngeal candida using local nystatin therapy have been less successful, particularly in leukopenic patients (8). Effective control of mucosal candida colonization and infection may depend upon using systemic therapy in such patients (8).

Although low-dose amphotericin B therapy has been advocated for certain superficial candida infections (14), use of this potentially toxic drug in a debilitated patient is usually reserved for life-threatening fungal infection. Five-fluorocytosine (5-FC) has proven to be clinically useful in treating candida infections and is relatively nontoxic (1). To assess the potential value of 5-FC in controlling respiratory tract colonization with candida, a study of 5-FC penetration into bronchial secretions was done, using a dog model. For comparison, amphotericin B concentrations in bronchial secretions were also evaluated.

MATERIALS AND METHODS

Animal studies. A dog model (15) for the study of antibiotic diffusion into and clearance from normal bronchial secretions was used in this study. American foxhounds (approximately 20 kg) were anesthetized with 2.5% sodium thiopental and intubated with a rubber endotracheal tube. Subcutaneous pilocarpine HCl was given (0.5 mg/kg every 45 min) to stimulate an adequate flow of bronchial secretions (about 1 ml/h) for specimen collection. Volumes were small so that significant dilution did not occur. Previous work has demonstrated little change in the constituents of bronchial secretions after pilocarpine administration (15). Bronchial secretion specimens were aspirated via the endotracheal tube using a small-bore (1.25 mm) plastic catheter inserted to maximal depth within a mainstem bronchus. A syringe attached to the catheter provided adequate suction. Bronchial secretion specimens were each approximately 0.5 ml in volume with a pH generally between 7 and 8.

Sera and bronchial secretions were assayed for antibiotic concentrations within 24 h of each experiment. Assays of specimens for 5-FC and amphotericin B concentrations were done by the radial diffusion bio-assay systems described by Block and Bennett (3). The assay was adapted to the measurement of bronchial secretion concentrations by using pooled dog bronchial secretions as diluent in constructing the standard curves that were used to determine the unknown bronchial secretion concentrations. 5-FC (Hoffman-LaRoche, Inc., Nutley, N.J.) and amphotericin B (Fungizone, E. R. Squibb and Sons, Princeton, N.J.) were evaluated in the dog model. Four dogs were used for the study of 5-FC. The drug was dissolved in 5% dextrose and water to a final concentration of 25 mg/ml. After baseline blood and bronchial secretion specimens were collected, an intravenous injection of 5-FC was given in a dose of 35 mm/kg (average dose per 20-kg dog was 700 mg). The maximal recommended dose of 5-FC for humans is 35 to 40 mg/kg per dose (given every 6 h). Therefore, the dose used in this study was near the maximal single-dose recommendation. Blood and concomitant bronchial secretion specimens were collected at 5, 15, 30, 60, 120, and 180 min after 5-FC injection.

Amphotericin B was supplied as sterile lyophilized powder and was reconstituted with sterile water. The final dilution was made in 150 ml of 5% dextrose in

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water. After baseline bloods and bronchial secretions were collected, the amphotericin was given intravenously to two dogs over a period of 30 min. In one dog the dose was 0.6 mg/kg and in the other a dose of 1.2 mg/kg was used. Both dogs had normal blood urea nitrogen concentrations before and 1 week after infusion. Concomitant blood and bronchial secretion specimens were obtained at the end of the infusion and then 1, 2, and 3 h later.

RESULTS

5-FC appeared in bronchial secretions promptly and remained near 20 \( \mu g/ml \) for at least 180 min (Fig. 1). In contrast to serum, 5-FC concentrations in bronchial secretions had no distinct peak. Three hours after injection, the mean intrabronchial concentration of 5-FC was 76% of the mean serum concentration.

Amphotericin B penetrated into bronchial secretions much less efficiently. In the dog receiving 0.6 mg/kg, both serum and bronchial amphotericin concentrations were \(<0.1 \mu g/ml\) (0.1 \( \mu g/ml \) is the lower limit of sensitivity of the assay system) immediately after infusion and in all subsequent specimens. In the dog that received 1.2 mg/kg, the amphotericin concentration in serum was 1.36 \( \mu g/ml \) and in bronchial secretions was 0.16 \( \mu g/ml \) immediately postinfusion. All subsequent bronchial specimens were \(<0.1 \mu g/ml\).

DISCUSSION

Effective intrabronchial antimicrobial drug therapy depends upon achieving adequate inhibitory concentrations of drug in bronchial secretions (11, 12). The minimal inhibitory concentration of 5-FC for Candida species is below 10 to 20 \( \mu g/ml \) for 80 to 90% of organisms (1). This level was achieved for periods up to 3 h after a single dose of 5-FC in this study. The serum concentrations of 5-FC achieved in dogs were roughly equivalent to those expected in humans given similar milligram-per-kilogram doses (3). Therefore, the excellent penetration of 5-FC into bronchial secretions indicates potential clinical efficacy for 5-FC in intrabronchial candida therapy.

5-FC has been shown to penetrate other tissue barriers well, including meninges (3) and aqueous humor (16). The low molecular weight and minimal protein binding of 5-FC (4) may account for its ability to pass easily across membranes, including the blood-bronchus barrier. The persistence of 5-FC in bronchial secretions up to 3 h may reflect accumulation of the drug in respiratory secretions because of slow reabsorption and clearance. Some investigators have postulated an active concentrating mechanism at the blood-bronchus barrier for certain antibi-otics (13, 17), and this also might be involved for 5-FC.

Amphotericin B penetrated into bronchial secretions poorly. This drug is 95% protein bound (4) and has been found to diffuse poorly into other fluids as well, including saliva (2), urine (10), cerebrospinal fluid (10), and aqueous humor (5).

Since Candida species are normal inhabitants of the human oropharynx (19), the significance of candida-positive sputum cultures is often uncertain. However, candida overgrowth of the tracheobronchial tree occurs frequently in debilitated patients and in some cases may lead to invasive and disseminated candidiasis. If systemic therapy of tracheobronchial candida is clinically indicated, 5-FC appears to be an effective agent in achieving intrabronchial concentrations above the usual minimal inhibitory concentration for this organism.

ACKNOWLEDGMENTS

We appreciate the assistance of Margaret A. Huber with the antibiotic assay and the help of David A. Battle with animal management. We also thank John E. Bennett for his critical appraisal of the manuscript.

LITERATURE CITED