Hyperthermic Peritoneal Perfusion System in Canines

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ABSTRACT

The thermal infusion filtration system was designed to manage malignant effusions and treat metastatic cancers of the intracavitary serosa. Hyperthermia, chemotherapy, and cell and debris filtration were administered by a dynamic fluid flow. Preclinical evaluations of surgical procedure, temperature studies, fluid dynamics, and physiology were carried out in 15 dogs (17.2 to 25.4 kg) with peritoneal perfusion at 41 °C and 10 liters/hr flow. Results suggest that the dynamics of flow achieve total intracavitary equilibrium in 7 min. The time essential to elevate animal body mass temperature from ambient to 41 °C varied as a function of mass. The hyperthermia induced expected nonlethal responses in physiology. The system was determined to be safe for clinical procedure.

INTRODUCTION

A major problem encountered in cancer management is the development of intracavitary effusions which occur from metastatic cancers capable of growing on serosal surfaces. These effusions are a significant source of morbidity and contribute to the early demise of the host. Reports in the literature describe various modes of management, the properties of these effusates, the pathophysiology of their production, and their underlying neoplasms (1, 2, 5). The systemic effects of hyperthermia have been evaluated in humans (4). The effects on tumor therapy of hyperthermia (7, 9—11) and of peritoneal chemotherapy (3) have also been described. Drawing from all this experience, a delivery system for the management of intracavitary effusions has been designed and constructed by Dr. Charles E. Dunlap and Dr. Stanley R. Bull at the University of Missouri, Columbia, Mo., in response to performance specifications of Dr. John S. Spratt, and is described by Pahta (6).

The TIFS\(^2\) was designed to recirculate intracavitary effusions aseptically through the combined actions of dynamic fluid flow, free-cell and debris filtration, hyperthermia, and adjunctive chemotherapy. The unit is intended to remove, infuse, or recirculate fluids of manageable viscosity. The system is driven by a Cole-Parmer Model 7555-40 variable-speed pump (Cole-Parmer Instrument Co., Chicago, Ill.), accommodating a 0.952-cm outside diameter (0.635-cm inside diameter) Tygon medical-grade tubing, which passes a perfusate stream through a sequential dual-filter system and a subsequent warming coil and conduit from which it may be recontaminated. This positive-head, variable-speed tubing pump provides a constant speed under varying load conditions. The sequential dual-filter system is composed of a 40-μm Pall SQ40 blood transfusion filter (Pall Corporation, Glen Cove, N. Y.), incorporated to protect the main filter from clogging by large clots, and a 3-μm Gelman 12104 cartridge filter (Gelman Instrument Co., Ann Arbor, Mich.); elements include inlet and outlet tubing for aseptic operation. The filter system has a combined surface area of 1700 sq cm and is suitable for the largest effusion volumes (approximately 5 liters) to be processed in a reasonably short time.

An Abbott Model 4663 disposable blood-warming coil (Abbott Laboratories, North Chicago, Ill.) placed in a circulating water bath (B. Braun Instruments, San Mateo, Calif.) provides the heat exchange surface. Heat is provided by B. Braun Model 1450 immersion heaters and Model 1460 booster heaters. A B. Braun Model 1430 temperature safety monitor overrides the heating system if preset maximum temperatures are exceeded by 0.5° within the range of 30—50°. A schematic of the TIFS is presented in Chart 1.

MATERIALS AND METHODS

The preliminary assessment of the TIFS in simulated cavities using the model described has provided a good approximation of mixing dynamics and steady-state time that might be expected in the animal model. However, the variability of the biological system becomes the final determinant. A preclinical experimental protocol using the dog model was designed to coordinate the clinical use of TIFS.

The evaluation of the TIFS operation has concentrated upon surgical application, temperature studies, fluid dynamics, and physiological changes. Fifteen female mongrel dogs weighing from 17.2 to 25.4 kg were subjected to hyperthermic peritoneal perfusion. Only the circulating effusate was used to induce the hyperthermia.

The first 10 trials, utilizing acute dogs, evaluated surgical technique, reliability of the TIFS temperature control shut-down system, the relationship of animal mass versus the time required to elevate core temperature (measured rectally) to 41° at 10 liters/hr, and flow dilution dynamics at 10 liters/hr with 0.5% Evans blue solution. Nembutal anesthesia (60 mg/kg) was used in each dog. Peritoneal dialysis catheters (McGaw Laboratories, Glendale, Calif.) were placed at both the right and left lateral gutters in the peritoneal cavity of each animal. A small incision was required for each placement. The catheters were held in site by a purse-string suture. The infusing catheter was oriented to infuse toward the diaphragm. The sump catheter, in the opposing lateral gutter, was directed into the pelvic cavity. An artificial effusate (350 to 400 ml dog plasma and 1650 to 1800 ml sterile 0.9% NaCl solution), which provided effusion-like conditions in all dogs, was introduced i.p.

A final 5 studies required chronic dogs, perfused at 41° (peritoneal cavity temperature) for 2 hr under physiological monitoring. These animals remained under observation for 2 weeks with subsequent evaluation of adhesions, peritonitis, and histology. Tissue specimens were then taken from liver,
spleen, kidney, pancreas, stomach, adrenal, bowel, mesentery, and aortic nodes.

Thermistor probes attached to a thermistor thermometer (Yellow Springs Instrument Co., Yellow Springs, Ohio) were placed in the rectum and peritoneal cavity of each animal. An esophageal probe was placed in 2 chronic cases. All probes were calibrated at 45 ± 0.5°C (S.D.) in the constant temperature bath of the unit and were accurate to ±0.2°C.

RESULTS

All 15 dogs survived the hyperthermic perfusion without noticeable distress. The 5 chronic animals were fully recovered at 24 hr and survived the 2-week observation period without noticeable behavioral or physiological changes. Small amounts of chronic i.p. bleeding were noted but apparently resulted from incision bleeding. Some leakage of perfusate at insertion sites occurred in early runs but was corrected with refinement of placement technique and a change of catheters.

Each effusate infusion resulted in a fully distended abdomen. In 8 acute animals, 0.5% Evans dye solution (2 ml) injected into the system, reached peritoneal equilibrium in approximately 7 min at 10 liters/hr flow rate and approximately 9 min at 6.0 liters/hr (Chart 2). Samples were taken at 1-min intervals for the first 10 min and then at 5-min intervals for the remainder of a 2-hr interval. Percentage of transmittance was read at 540 nm on a Beckman DB spectrophotometer (Beckman Instruments, Inc., Fullerton, Calif.).

A relationship between heat exchange and mass was sought. However, the time necessary to heat the mass of each animal to 41°C varied (Table 1). Generally, the greater the weight of the dog, the longer was the necessary hyperthermic exposure. Exceptions occurred, however, in the 2 smallest animals. The reason is not known. Each trial was standardized at a flow rate of 10 liters/hr and a water bath temperature of 45°C (the maximum allowable at desired distance), using a 6-ft line distance from water bath to infusion site. Because of the weight versus time variability, an equation predicting the time to induce hyperthermia by the weight of the subject has not been developed. However, 1.5 to 2.0 hr with 45°C bath temperature and 10 liters/hr circulation rate was sufficient in most cases to bring rectal temperatures (used as a measure of core temperature) to 41°C. Flow rates less than 8 liters/hr failed to reach 41°C in 100% of the attempts for perfusion periods up to 3.5 hr.

Evaluation of chronic dogs at the end of 2 weeks revealed minimal peritoneal adhesions with no gross defects in the peritoneum, omentum, or abdominal organs. Gram-positive wound site infections were prevalent in all chronic dogs but were restricted to cutaneous tissue. No peritoneal, abdominal, or organ infection was noted.

The animal studies did not reveal undesirable effects due to the TIFS perfusion procedure over 1.5 to 2 hr. The accumulated data regarding the effects of hyperthermia at the end of a 2-hr perfusion period (Table 2) generally fell within values of expectation.

DISCUSSION

The temperature-controlled shut-down system worked at 100% reliability when the thermostat was adjusted to heat fluid + 0.5°C past the 41°C end point temperature. The TIFS unit, therefore, was determined to be safe for clinical application. The surgical procedure for placement of the dialysis catheters was unremarkable. Hyperthermia was induced at a steady increase without a significant temperature differential between the heat exchange bath and the body mass (rectal probe) or peritoneal effusate (direct peritoneal temperature probe). Placement of the probe directly into the peritoneal cavity was considered the most conservative approach for monitoring and controlling hyperthermia in routine procedure.

<table>
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Table 1

Weight versus time needed to induce 41°C (rectal) hyperthermia by i.p. perfusion

The time necessary to heat dog body mass (N = 8) to 41°C generally increases with weight. The 2 smallest dogs proved to be exceptions to the statement. Temperature at the rectum was used as the indicator of core or body mass temperature. The mean ambient temperature of the dogs prior to perfusion was 37.5°C.
Temperature at the rectal site lagged behind that of the peritoneal cavity by approximately 0.4° as indicated in Table 2. There was a 2.1° lag at the esophagus in the 2 cases attempted. This lower temperature was due to airway cooling. Such differences are relatively insignificant at these nonlethal temperatures. However, because significance might increase as lethal temperatures are approached in animal tolerance models, further study of the differences among temperature probes in the rectum and the esophagus, as well as in the intercavitary environment, is indicated.

Dilution studies suggest that a dynamic equilibrium is established between the intracavitary compartments within minutes when the cavity is fully distended with a fluid reserve. However, further studies utilizing fluoroscopic controls are indicated to confirm the suggestions. Blood pressures, heart rates, and cardiac indices were expected to be elevated under conditions of hyperthermia. These expectations were confirmed, but the results were not as remarkable as expected.

In the animal experiments, the TIFS unit met design expectations for controlled intracavitary hyperthermia. The increased dynamics of flow is important in achieving the optimal distribution of perfusate and in any adjunctive chemotherapeutic treatments. Furthermore, hyperthermic conditioning prior to chemotherapy is obtainable for the preferential destruction of neoplastic cells. These 2 characteristics, along with the potential of mechanical filtration of malignant cells, distinguish TIFS as a unique integrated unit.

Results to date have permitted the planning of specific physiologic and pharmacokinetic evaluations, and the continued exploration into cell removal rates, percentage of cell recovery expectations, and fluid distribution relative to intracavitary surface exposure. Continued developmental research regarding thermal infusion filtration therapy as it pertains to the conditions defined by the TIFS unit appears to be highly warranted to refine TIFS for clinical application.

The expansion of basic studies should be directed toward evaluations of tolerance following surgical resections of various intracavitary tissue and organs, such as the omentum, bowel, spleen, and lung, and toward subsequent evaluations of late adhesions in short- and long-term perfusion programs. Studies of chemotherapeutic drugs in relation to adsorption and visceral toxicity, with and without concomitant resections, should be undertaken under controlled hyperthermia. These evaluations would require investigation of effects on the cardiovascular system, liver, and intestines with respect to injury, rate of recovery from injury, hemolysis, physiological tolerance, infections, hemopoietic suppression and recovery, and other parameters dictated by the experimental investigations. Chronic or repetitive perfusions should follow the recommendations of Tenkchoff (8) with appropriate considerations given to the dynamics of this system.

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REFERENCES

8. Tenkchoff, H. Chronic Peritoneal Dialysis. A Manual for Patients, Dialysis Personnel, and Physicians. Seattle, Wash.: Division of Kidney Diseases, Department of Medicine, University of Washington School of Medicine, 1974.
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