Intraperitoneal Drug Therapy: Physical and Biological Principles

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Background

Although improvements in the management of gastrointestinal cancer and ovarian adenocarcinoma have been made in recent years, there still are significant problems managing the spread of these cancers throughout the peritoneal cavity, a process called peritoneal carcinomatosis (PC) [1]. Researchers now recognize that peritoneal spread can also occur with endometrial carcinoma [2] and esophageal cancer [3]. Traditional treatments of these diseases include a combination of surgery, radiation therapy, and systemic chemotherapy. Until recently, the prognosis for patients with PC has been dismal. Sugarbaker [4] has reported some success with careful peritonectomy and the use of perioperative intraperitoneal (IP) chemotherapy. There are, however, a number of problems with this technique, including trauma to the peritoneum during surgical removal of tumours that may result in further metastases [5]. Innovative techniques such as perioperative, hyperthermic chemotherapy to treat these residual microscopic lesions after peritonectomy have resulted in five-year survival of 80% [6].

The major challenges for IP therapy consist of: (a) sufficient residence time or duration of actual contact time with treatment solution to effect a cure, (b) coverage of the targeted area by the IP treatment solution (peritoneal contact area), and (c) the penetration or distance that the agent transports into the targeted tumour tissue in sufficient concentration to treat the tumour. The residence time becomes important because the solution can move from place to place in the cavity, and even relatively large volumes in the cavity only cover 30-40% of the anatomic peritoneum [7-9]. Studies in normal mice and rats [9,10] demonstrate that a solution placed in the peritoneal cavity for 24 hours covers all of the surfaces of the peritoneum. This might work well if the drug has absolute killing power on the instant that it reaches the surface of the tumour. However, most medications depend on some duration of exposure to transfer enough drug to effect a change in the tissue. In humans [8], the actual area covered by a large volume such as 2 to 3 liters in a human being is approximately 25 to 30 percent of the anatomic peritoneum.
Depending on adhesions and other abnormalities in the peritoneal cavity, the flow of the treatment fluid may be quite irregular and the residence time of the drug adjacent to the tumour nodule may be quite short or quite long. Once the drug is adjacent to the surface of the tumour, it must penetrate the tumour in order to reach the tumour cells. Since nodules of 0.5 to 1 centimeter in diameter may be missed by the oncologic surgeon in the initial peritonectomy [11-13], it may be anticipated that drugs will have to treat and cure this sized nodule. This chapter will deal with these delivery issues such as residence time, peritoneal contact area, and the penetration of antineoplastic agents administered intraperitoneally.

**IP Versus Systemic (IV) Chemotherapy**

Because the IP route of therapy is less convenient than IV and fraught with hazard for the inexperienced clinician, the case needs to be made for the advantage of IP therapy. Is there a pharmacokinetic advantage of administering the drug IP vs IV? One major advantage would be the attainment of very high concentrations in the peritoneal cavity relative to concentrations in the systemic circulation. This would minimize side effects and toxicity from systemic administration while increasing the therapeutic advantage in the peritoneal cavity [14].

**Pharmacokinetic Advantage**

The pharmacokinetic rationale for IP administration of drugs in the treatment of microscopic residual ovarian carcinoma was established in 1978 by Dedrick and colleagues [14]. The quantitative formula for pharmacokinetic advantage ($R_d$) in its simplest form is [14,15]:

$$R_d = \left( \frac{C_P}{C_B} \right)_{IP} \left( \frac{C_P}{C_B} \right)_{IV}$$

(1)

where $C_P =$ the concentration in the peritoneal cavity and $C_B =$ concentration in the systemic circulation and the subscripts indicate the route of administration.

Pharmacokinetic studies have established the advantage of the IP vs IV route for treatment of intraabdominal cancer. Goel and colleagues [16] studied the IP administration of cisplatin in combination with etoposide and attempted to protect the kidney against platinum toxicity through the intravenous administration of sodium thiosulfate. The regional pharmacokinetic advantage was 26 compared to patients receiving IV therapy without simultaneous thiosulfate infusion. This is similar to the value of 16 found by Piccart and colleagues [17]. 5-fluorouracil values of $R_d$ have been determined to be as high as 124 as noted by Speyer and colleagues [18] and 298 by Sugarbaker and colleagues [19]. Other drugs have shown similar pharmacokinetic advantages. Antibiotics are often administered IP in