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Cover Story

Intraperitoneal delivery of paclitaxel with injectable hydrogel: “Seeing” is not always “believing”

Intraperitoneal chemotherapy is an appealing option for locoregional therapy of ovarian cancer, which is primarily confined to the peritoneal cavity. The premise of intraperitoneal therapy is that the administered drug remains locally and avoids extensive systemic absorption, leading to toxic side effect. Several clinical trials demonstrated significant survival benefit following intraperitoneal chemotherapy [1,2], as confirmed by the National Cancer Institute [3]. Clinical application of the therapy, however, has been hampered by problems associated with the use of an indwelling catheter, which is necessary for long-term drug delivery but frequently associated with pain and infection. In this issue, two articles deal with injectable, sustained release drug delivery systems for intraperitoneal chemotherapy [4,5].

Professor Allen's team employed an injectable hydrogel based on chitosan derivative as a carrier of docetaxel [5]. They found that single administration of their drug delivery system achieved high drug distribution for a prolonged period not only in intraperitoneal organs and tumors but also in tumors remote from the peritoneal cavity. This result highlights the ability of intraperitoneal drug delivery system to supply a drug for local and systemic absorption for a prolonged period of time. Professor Yeo's group used another injectable carrier system based on hyaluronic acid derivatives, which crosslink in situ to form a flexible hydrogel, for paclitaxel delivery [6]. The hyaluronic acid hydrogel formulation also maintained high intraperitoneal level of paclitaxel as compared with other formulations that did not have a means to retain paclitaxel for extended periods of time. Interestingly, despite clear differences in the intraperitoneal paclitaxel level, the extent of tumor reduction was not much different across the drug-treated animal groups. The authors explained that the lack of difference was related to precipitation of paclitaxel within the hydrogels [6]. Paclitaxel, a poorly water-soluble drug, started to precipitate as soon as it was exposed to hydrogel, providing an aqueous environment. While this helped paclitaxel remain in the hydrogel, and thus in the peritoneal cavity, the level of dissolved paclitaxel was quite low. Consequently, the extent of tumor reduction was not any different from other formulations that rapidly disappeared from the peritoneal cavity. This limitation may be overcome, according to

the authors, by incorporating a strategy to prevent paclitaxel precipitation and/or to improve the solubility of the drug in the hydrogel.

This study provides a classic example that the drug must dissolve in aqueous solution to be effective, i.e., it is not the total drug amount but the amount dissolved in aqueous solution that is important. Much attention has been paid to examine the amount of a drug delivered to the target site, but not enough attention has been directed toward examining the drug concentration responsible for pharmacological effect. The successful application of localized drug delivery requires a strategy to dissolve poorly soluble drugs. For poorly soluble drugs, seeing is not necessarily believing. Formulation of poorly soluble drugs has been a serious challenge in pharmaceuticals for decades, and its importance has not faded away.

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Kinam Park
Purdue University
Department of Biomedical Engineering and Pharmaceuticals
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu