Antineoplastic Compatibility Studies for Oncology System

Introduction

Antineoplastic drugs are common agents that are given during Chemotherapy treatment. Such drugs are therefore required to interact with, and be administered using specific IV equipment. Traditional IV equipment including tubing and plastic components can be affected or degraded by the drug itself. There are two known effects of drug interaction which can both damage the plastic parts, and cause the release of unwanted chemicals, known as 'leaching' into the fluid path which is ultimately delivered to the patient.

Organizations such as NIOSH and USP 797 have recommended the use of specialized IV equipment to help protect the healthcare worker from exposure to chemotherapy agents and to protect the integrity of the drug itself.[1,2] The aim of this paper is to describe the known drug interactions with specific preparation and administraiton devices and to also describe the ICU Medical product compatibility validation process and results for the chemotherapy preparation and administration products.

Plastic Integrity Following Drug Interaction

Solid plastic components can be damaged by interaction with solvent agents such as alcohol. The commonly known antineoplastic drugs which contain solvents are in the etoposide and paclitaxol classes.[3,4] Etoposides contain 30% organic solvent in its undiluted form, while paclitaxol contains 48%. What causes the damage is twofold, component design and plastic composition. While some plastics like ABS are known to breakdown with exposure to solvents, the actual breakdown is also dependent on the design of the component and how much stress is designed into that part. The solvent acts as a stress reliever, where cracks can occur by relieving the stress in the component which may result in drug leakage.

Chemical 'Leaching' and Drug 'Sorption'

Certain chemicals can be released or 'leach' from soft plastic components such as tubing when exposed to antineoplastic drugs. It is well documented that Di(2-ethylhexyl) phthalate, known as DEHP, can be released from flexible PVC devices such as IV tubing and bags.[5] DEHP is a plasticizer that provides flexibility to soft PVC devices and makes them easier to manipulate. Temperature and exposure time affect the rate at which DEHP will leach into the fluid path and subsequently be delivered to the patient. All of the ICU devices are manufactured from exclusively DEHP-free components therefore effectively eliminating any risk of DEHP leaching.

Drug 'sorption' describes the process by which the drug components themsleves stick to or are absorped into the plastic devices.[6] This dynamic is most heavily impacted by time and surface area that the drug is exposed to. Drug sorption impacts the drug's chemical make-up and results in a loss of stability. The specific plastics that are used to manufacture the ICU devices are chosen for their resistance to drug sorption and their ability to support drug stability. The ICU compatibility validation is described below.

Antineoplastic Compatibility Protocol

To evaluate the interaction between the chemotherapy product line and the series of antineoplastic drugs which are known to react with plastics, protocols were developed at an Italian Research Facility: *STUDIO AMBIENTE S.r.l. (VR) Italy.* Antineoplastic drugs are prepared and stored in a variety of methods, and investigation work was done to determine a worst case exposure and storage procedure. Specific drugs were researched and selected to represent various therapeutic classes and chemical compositions.

Each series of devices were exposed to ten different antineoplastic drugs in their undiluted form. Drugs were diluted to three times their therapeutic value for testing with IV sets to represent the worst case exposure for the administration equipment. Three unique tests were completed including a functional integrity test, a drug stability test and a plastic migration test to verify drug compatibility with the chemotherapy devices.

To prepare test samples, each drug was infused through independent test samples, agitated and then subjected to a storage protocol. Samples were placed in refrigeration for a specified time period and then stored at room temperature for a time period. Devices were visually inspected during the storage period at various time points and then leak tested to verify functional integrity.

Following the storage period using cisplatin, etoposide and flourouracil, the drug was removed from each sample and tested for stability using the HPLC method. Next, using gaschromatography with mass detector, the drug samples were evaluated for plastic migration including concentrations of phthalate and vinyl chloride. The standard used for phthalate concentration was based on the European Directive 2005/84/EC with an acceptance level of 0.1% of mass. The standard for vinyl chloride concentration was based on the European Pharmacopeia which requires <1ppm. All results are available in Table 1.

Table 1.

Antineoplastic Agent	Spiros Male Luer 120 Days Refrigeration, and 7 Days Room Temperature			Genie Vial Access* 30 Days Refrigeration, and 10 Days Room Temperature			Vial Access Devices* 30 Days Refrigeration, and 7 Days Room Temperature			Administration Sets* 24-Hours at Room Temperature Diluted to 3x therapeutic level		
	Functional Failure	Drug Stability 120-Days	Plastic Migration Per Device	Functional Failure	Drug Stability 30-Days	Plastic Migration Per Device	Functional Failure	Drug Stability 30-Days	Plastic Migration Per Device	Functional Failure	Drug Stability 24-Hours	Plastic Migration Per Device
Bevacizumab	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Cetuximab	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Cisplatin	0/10	99.60%	P= .25µg VC= <.08µg	0/10	99.60%	P= .25µg VC= <.08µg	0/10	99.96%	P= .125µg VC= <.05µg	0/10	99.93%	P= .07µg VC= .07µg
Cyclophosphamide	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Doxorubicin	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Etoposide	0/10	99.60%	P= .05µg VC= <.05µg	0/10	99.20%	P= .05µg VC= <.05µg	0/10	99.66%	P= .014µg VC= <.05µg	0/10	99.73%	P= .25µg VC= .09µg
Flourouracil	0/10	99.60%	P= .58µg VC= <.07µg	0/10	99.20%	P= .58µg VC= <.07µg	0/10	99.52%	P= .014µg VC= <.05µg	0/10	99.73%	P= .60µg VC= .05µg
Methotrexate	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Paclitaxol	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT
Vincristine	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT	0/10	NT	NT

*Includes CLAVE Needlefree Connector in Evaluation

Conclusions

All chemotherapy preparation and delivery devices reached acceptable limits for all phases of testing. The known effects; cracking of plastic devices and leaching of DEHP plasticizer can be eliminated with proper product design and validation. ICU exclusively uses DEHP free components and evaluates all plastic components for use in its chemotherapy product line. All products which are available in the above mentioned devices or series, are validated for use with antineoplastic drugs. Test reports and further information are kept on file at ICU Medical, San Clemente, CA.[7,8,9]

References

[1] National Institute for Occupational Safety and Health (US). Prevention of Occupational Exposure to Antineoplastics and Other Hazardous Drugs in Healthcare Settings. Sep-2004.

[2] United States Pharmecopia (USP) 797. Pharmaceutical Compounding, Sterile Preparations. 2006.

[3] Paclitaxol (TAXOL®) Injection. Bristol-Myers Squibb Company, Oncology, Princeton, NJ. Package Insert. 2003.

[4] Etoposide (TOPOSAR®) Injection. Teva Sicor Pharmaceuticals, Irvine, CA. Drug Package Insert, 2005.

[5] FDA Public Health Notification: PVC Devices Containing DEHP Plasticizer. July 12, 2002.

[6] Astier, A. Compatibility with Anticancer Drug Solutions with Administering Devices. EJHPP, Vol.14, 2008/5, pg.55.

[7] ICU Medical Engineering Test Report ENG-103.

[8] ICU Medical Engineering Test Report ENG-91.

[9] ICU Medical Engineering Test Report ENG-79.