

Avoiding Carcinogen Exposure With Intraperitoneal Paclitaxel

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Purpose/Objectives: Diethylhexylphthalate (DEHP) is a lipid-soluble plasticizer commonly used in the manufacture of polyvinyl chloride- (PVC-) based plastics. Previous studies have documented the leaching of DEHP from PVC-based containers and extension sets during the IV administration of paclitaxel.

Design: Study of the leaching of DEHP from infusion bags and peritoneal dialysis solution transfer sets and clinical study of DEHP was proposed.

Setting: The experiments were performed in a laboratory with plastic ware normally used for intraperitoneal chemotherapy delivery.

Sample: Samples were taken from fluids that had been in contact with the plastic ware. Also, blood, peritoneal fluid, and urine were collected from a patient.

Methods: In a controlled laboratory environment, the authors used an established high-performance liquid chromatography assay to determine the rate and extent of DEHP leaching from infusion bags and in the solution transfer set used for early postoperative intraperitoneal chemotherapy (EPIC) administration of paclitaxel. Paclitaxel was tested at a concentration of 40 mg/L to simulate the median dose used for EPIC. In a single patient receiving 34 mg paclitaxel in 1 liter of 1.5% dextrose peritoneal dialysis solution (Dianeal®), the presence and concentration of DEHP in samples of peritoneal fluid and urine were determined during the first 24-hour EPIC administration.

Main Research Variables: DEHP levels in fluids exposed to plastic ware and in the patient's blood, peritoneal fluid, and urine were determined.

Findings: The in vitro studies showed that a solution of 40 mg paclitaxel dissolved in a 1 liter bag of Dianeal resulted in the extraction of approximately 26 mg DEHP over 24 hours. Approximately 2 mg DEHP was leached during the first hour and approximately 1 mg per hour over the following 23 hours. Equivalent results were obtained when 20 mg paclitaxel was dissolved in a 500 ml bag of 6% hetastarch (Hespan®) with a leaching of approximately 13 mg DEHP in 24 hours. Using the same paclitaxel concentration, the chronic ambulatory peritoneal dialysis solution transfer tubing with a total capacity of 10 ml produced approximately 2 mg DEHP over 24 hours, of which approximately 0.5 mg was produced during the first four hours. Samples from a single patient showed that immediately prior to administration, a 1 liter bag of Dianeal containing 34 mg paclitaxel had about 3.3 mg DEHP. Approximately 3% (110 mcg) of unchanged DEHP was recovered from the peritoneal fluid at 24 hours. Total DEHP excreted in urine over the 24-hour period was approximately 900 mcg (27%).

Conclusion: This study showed that the carcinogen DEHP is leached after preparation of paclitaxel from PVC-based containers and DEHP constantly accumulates in the solution transfer tubing.

Implications for Nursing: Unless precautionary steps are taken, DEHP can be transferred to patients receiving intraperitoneal paclitaxel. Steps to minimize patient exposure to DEHP during EPIC with paclitaxel are necessary. In the ideal situation, no DEHP-containing plastic should be used for chemotherapy delivery. If that is not possible, (a) paclitaxel solution should be administered as soon as possible after preparation by the pharmacy, (b) infusion should proceed as rapidly as possible via the Tenckhoff catheter, and (c) the Tenckhoff catheter and extension tubing should be cleared by draining ascites fluid through these tubes prior to subsequent intraperitoneal infusions.

Key Points . . .

- ▶ Diethylhexylphthalate is present in all soft plastic.
- ▶ Polyvinyl chloride in its "soft form" contains diethylhexylphthalate as a softener.
- ▶ This can be leached from the soft plastic with lipid, taxane chemotherapy such as paclitaxel and docetaxel and may transfer the carcinogen to patients unless the appropriate precautions are taken.

Diethylhexylphthalate (DEHP) is a common lipid-soluble plasticizer found in polyvinyl chloride- (PVC-) based plastics. When added to PVC, the plastic product remains soft and pliable, a characteristic that is essential to the function of many plastic items. Animal studies have shown DEHP to be a hepatotoxin, carcinogen, and teratogen (Gray, Beamand, Lake, Foster, & Gangolli, 1982; Kevy & Jacobson, 1982; Singh, Lawrence, & Autian, 1972; Warren, Lalwani, & Ready, 1982). Mono(2-ethylhexyl)phthalate (MEHP), a plasma metabolite of DEHP, has caused hypotension and cardiac arrest in rats (Rock, Labow, Franklin, Burnett, & Tocchi, 1987) and has had cardiotoxic effects on human myocardium (Barry, Labow, Rock, & Keon, 1988).

Paclitaxel is formulated in Cremophor EL® (BASF Corporation, Florham Park, NJ), a vehicle that is an admixture by volume of polyoxyethylated castor oil in 49.7% dehydrated alcohol (Bedford Laboratories, 2001). Previous studies have shown that this admixture caused leaching of DEHP from IV administration bags and extension sets used in IV administration of paclitaxel (Maas, Huber, & Kramer, 1996; Mazzo, Nguyen-Huu, Pagniez, & Denis, 1997; Trissel, Xu, Kwan, & Martinez, 1994; Waugh, Trissel, & Stella, 1991).

The purpose of this study was to determine the rate and extent of DEHP loss from infusion bags and solution transfer

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tubing made of PVC plastic used in the intraperitoneal administration of paclitaxel in either Hespan® (Abbott Laboratories, Chicago, IL) or Dianeal® (Baxter Healthcare, Deerfield, IL) solution (Mohamed, Marchettini, Stuart, Yoo, & Sugarbaker, 2003). The goal was to establish specific guidelines to minimize the amount of DEHP delivered into the peritoneal cavity of a patient receiving intraperitoneal chemotherapy. The authors also determined the amount of DEHP transferred to a patient receiving standard treatment with intraperitoneal paclitaxel in 1 liter of peritoneal dialysis solution before the initiation of precautionary procedures.

Materials and Methods

Leaching of DEHP From Infusion Bags

The rate and extent of leaching of DEHP was determined using paclitaxel at a concentration of 40 mcg/ml. This dosage was selected because it was the median dosage used in intraperitoneal administration in 1.5% dextrose peritoneal dialysis solution and 6% hetastarch. Peritoneal dialysis solution with 1.5% dextrose was supplied in 1 liter bags as Dianeal PD-2. Six percent hetastarch in 0.9% sodium chloride solution was supplied in 0.5 liter bags as Hespan. Samples (0.25 ml) were taken at 0, 0.25, 0.5, 1, 2, 4, 6, 12, and 24 hours from the chemotherapy solution, and DEHP concentrations were assayed by high-performance liquid chromatography (HPLC). The experiment was performed at room temperature.

Leaching of DEHP From Chronic Ambulatory Peritoneal Dialysis Solution Transfer Set

A chronic ambulatory peritoneal dialysis solution transfer set with locking connector (obtained from Baxter Healthcare) was used for testing because this set was used exclusively in the administration of chemotherapy solution to patients. Solutions of paclitaxel in Dianeal or Hespan at a concentration of 40 mcg/ml were used. The total capacity of the chronic ambulatory peritoneal dialysis solution transfer set with locking connector set was 10 ml. A syringe containing 12 ml of the solution to be tested was attached to one end of the tubing. At the other end was placed a three-way stop-cock with one opening permanently stopped. The entire tubing was filled with the paclitaxel solution, leaving a 2 ml reservoir in the syringe. Samples of 0.25 ml were taken from the stop-cock end of the tubing at similar time intervals as previously indicated and assayed for DEHP.

Determination of DEHP Concentrations From Clinical Study

DEHP concentrations were evaluated in a single patient before the initiation of precautionary measures. Samples were obtained during the first 24-hour dwell of intraperitoneal chemotherapy with 34 mg paclitaxel in 1 liter of Dianeal (see Figure 1). Samples of the peritoneal fluid and blood were taken at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours. Urine samples were collected at 0, 1, 2, 4, 6, 8, 10, 12, and 24 hours. At each collection, the total volume of urine voided was recorded.

Samples of peritoneal fluid and urine were stored at -4°C until HPLC analysis was performed. Blood samples taken in tubes containing ethylenediaminetetra-acetic acid were centrifuged at 3,000 rotations per minute for 10 minutes, and the separated plasma was stored at -4°C until HPLC analysis.

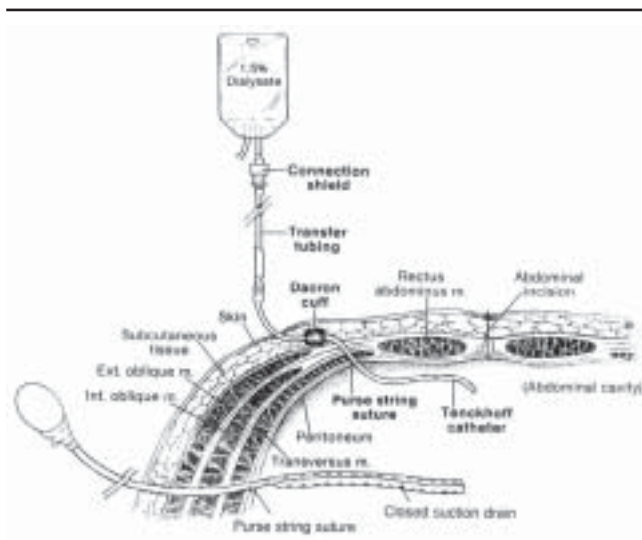


Figure 1. Intraperitoneal Infusion and Drainage for Treatment With Paclitaxel

High-Performance Liquid Chromatography Analysis

DEHP concentrations were determined using a modification of the HPLC procedures described by Mazur, Stennett, and Egging (1989). The HPLC system consisted of a Shimadzu LC-7A (Shimadzu Corporation, Columbia, MD) instrument equipped with an SPD-6AV (UV-VIS) detector set at 254 nm and a C-R6A Chromatopac data processor (Shimadzu Corporation). A 150 x 4.6 mm reversed phase column of Dynamax 100A 5 micron silica (Varian Associates, Walnut Creek, CA) was used coupled to a guard column of the same chemical consistency. The mobile phase was an isocratic mixture of acetonitrile and 0.1% phosphoric acid in deionized water (85:15v/v) run at a flow rate of 2 ml per minute. All solvents used were HPLC grade and obtained from Fisher Scientific in Suwanee, GA. DEHP used in preparation of HPLC standards was obtained from Aldrich Chemicals in Milwaukee, WI.

Sample Preparation for High-Performance Liquid Chromatography Analysis

Samples from in vitro experiments were diluted in the mobile phase solution as required and injected onto the HPLC column. Peritoneal fluid and urine samples also were diluted with mobile phase solution and filtered through 0.45 micron nylon syringe filters before HPLC injection. Plasma samples were processed for HPLC analysis using the same procedure described by Mohamed et al. (2003) for extraction of paclitaxel.

Results

Leaching of DEHP From Infusion Bags

The study of the rate and extent of DEHP leaching from the 1 liter soft plastic bag of Dianeal containing 40 mg of paclitaxel and from the bag containing 20 mg paclitaxel in 500 ml Hespan produced very similar results (see Table 1 and Figure 2). In the first 15 minutes, the average concentration of DEHP was 0.4 mcg/ml, which is equivalent to 0.4 mg total DEHP in 1 liter of solution. The average DEHP concentration was 2.7 mcg/ml after two hours and 5.8 mcg/ml after four hours.

Table 1. Summary of the Rate of Diethylhexylphthalate (DEHP) Leaching From Infusion Bags

Time (hours)	DEHP-Dianeal® (mcg/ml)	DEHP-Hespan® (mcg/ml)	Average (mcg/ml)	Average Total DEHP (mg)
0.25	0.45	0.35	0.4	0.4
0.5	1.70	1.36	1.5	1.5
1	2.26	2.26	2.3	2.3
2	2.83	2.59	2.7	2.7
4	6.25	5.40	5.8	5.8
6	7.81	7.10	7.5	7.5
12	11.36	10.73	11.0	11.0
24	25.56	26.27	25.9	25.9

Note. Total volume = 1 liter

After 24 hours, an average of 25.9 mg DEHP accumulated in 1 liter of solution. The average concentration of DEHP was 25.9 mcg/ml after a 24-hour incubation of paclitaxel solution in a soft plastic bag.

Leaching of DEHP From Chronic Ambulatory Peritoneal Dialysis Solution Transfer Set

Leaching of DEHP from the chronic ambulatory peritoneal dialysis solution transfer tubing was similar when paclitaxel (at a concentration of 40 mcg/ml) in either Dianeal or Hespan was introduced (see Table 2). The average concentration of DEHP after 15 minutes was 2.5 mcg/ml (equivalent to 25 mcg total DEHP). After 30 minutes, the average concentration of DEHP within the transfer tubing had increased almost fivefold to 10.9 mcg/ml (equivalent to 109 mcg DEHP). At 24 hours, an average of 1.74 mg DEHP accumulated in the chronic ambulatory peritoneal dialysis tubing.

Results From a Clinical Study

At time 0, a sample for DEHP analysis was removed from a 1 liter plastic bag containing 34 mg paclitaxel in Dianeal. The sample was taken immediately prior to intraperitoneal administration. The elapsed time between preparation in the pharmacy and the initiation of intraperitoneal administration was 2.5 hours. The time taken to complete the infusion was 15 minutes. The concentration of DEHP in the time 0 sample was 3.3 mcg/ml (equivalent to a total of 3.3 mg of DEHP). At 24 hours, a total of 180 ml was drained from the peritoneal cavity. The DEHP concentration was 0.6 mcg/ml

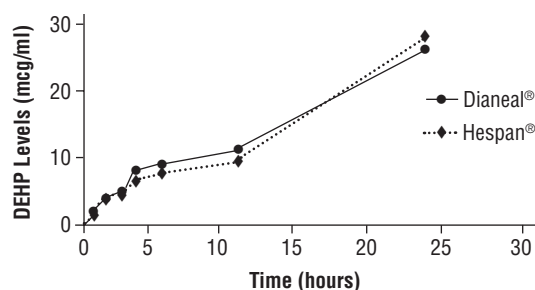


Figure 2. Comparison of the Rate of Diethylhexylphthalate (DEHP) Leaching From Infusion Bags Containing Paclitaxel (40 mcg/ml) in 1.5% Dextrose Peritoneal Dialysis Solution (Dianeal®) Versus 6% Hetastarch Solution (Hespan®)

for a total of 108 mcg of unchanged DEHP. This represents approximately 3% of the total DEHP introduced into the peritoneal cavity (see Figure 3). A total of 930 mcg of unchanged DEHP in the 800 ml urine was excreted during the 24-hour dwell.

Discussion

The extraction of the plasticizer DEHP from PVC infusion materials containing paclitaxel solutions has been well documented for IV administrations of paclitaxel (Maas et al., 1996; Mazzo et al., 1997; Trissel et al., 1994; Waugh et al., 1991). The acute toxicity of DEHP and other phthalate esters in animal studies is relatively low. The reported LD₅₀ (i.e., the dose [D] of the drug that was lethal [L] for 50% of the animals tested at that dose level) for intraperitoneal administration of DEHP is 14.2 mg/kg for mice and 50 mg/kg in rats (Autian, 1973). However, the degree of toxicity in humans during prolonged exposure to DEHP has not been well defined. The novel use of paclitaxel for prolonged intraperitoneal installations during a phase I clinical study presented some concerns about the rate and extent of DEHP leaching from the PVC infusion bags and solution transfer sets (Mohamed et al., 2003). The concern for patient safety is magnified in that the complete treatment required 24-hour intraperitoneal installations of paclitaxel at 20 mg/m² in 1 liter of either hetastarch solution or peritoneal dialysis solution for five consecutive days. Additional five-day cycles of intraperitoneal paclitaxel was possible up to a total of six.

In vitro studies with 40 mg paclitaxel in 1 liter of solution showed that approximately 2 mg of DEHP was leached from the bag during the first hour after preparation followed by a more constant rate of approximately 1 mg per hour over the following 24 hours. This data was consistent with the amount of DEHP (3.3 mg) found in the infusion bag of the patient who was studied. The elapsed time between preparation in the pharmacy and completion of intraperitoneal administration was approximately three hours. This time period controlled the quantity of DEHP accumulation in the chemotherapy solution. The quantity of DEHP infused in the patient could be reduced considerably with efficient coordination between pharmacy and nursing staff. This information needs to be appreciated by all members of the oncology teams involved in intraperitoneal paclitaxel administration.

Table 2. Summary of the Rate of Diethylhexylphthalate (DEHP) Leaching From the Chronic Ambulatory Peritoneal Dialysis Solution Transfer Tubing

Time (hours)	DEHP-Dianeal® (mcg/ml)	DEHP-Hespan® (mcg/ml)	Average (mcg/ml)	Average Total DEHP (mcg)
0.25	3.3	1.6	2.5	25
0.5	11.9	9.8	10.9	109
1	13.5	11.1	12.3	123
2	30.3	38.4	34.4	344
4	54.5	46.5	50.5	505
6	80.1	56.6	68.4	684
12	113.1	97.0	105.1	1,051
24	161.6	185.8	173.7	1,737

Note. Total volume = 10 ml

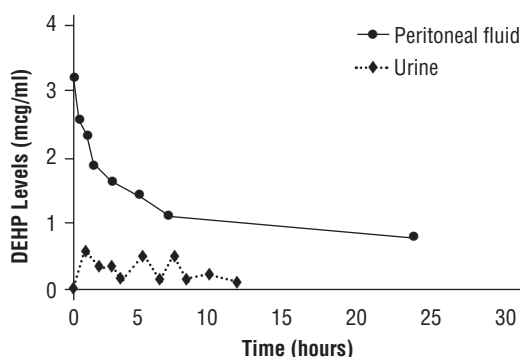


Figure 3. Diethylhexylphthalate (DEHP) Levels in Peritoneal Fluid and Urine in a Single Patient During the First 24-Hour Intraperitoneal Administration of Paclitaxel (34 mg) in 1 Liter of 1.5% Dextrose Peritoneal Dialysis Solution (Dianeal®)

The study by Mohamed et al. (2003) showed that 6% hetastarch was a more efficient carrier solution for intraperitoneal administration of paclitaxel. Hetastarch, a high-molecular-weight solution, showed reduced clearance from the peritoneal cavity when compared with peritoneal dialysis solution. This resulted in greater exposure of residual cancer cells or minute tumor nodules on peritoneal surfaces to the chemotherapy solution. Based on these findings, the hetastarch solution will be used as the carrier solution for all future patients receiving intraperitoneal paclitaxel. It does not present an increased risk over 1.5% dextrose peritoneal dialysis solution for DEHP exposure.

A hetastarch solution packaged in an EXCEL® container (B. Braun Medical Inc., Bethlehem, PA) currently is recommended for intraperitoneal paclitaxel. This container is not composed of PVC-based plastic and does not contain any phthalate ester plasticizers. The use of the Braun-formulated hetastarch has eliminated any further concerns for DEHP accumulation in the infusion bag and may significantly reduce the threat of DEHP toxicity. General use of non-PVC tubing and infusion bags for intraperitoneal chemotherapy would be an optimal nurse-management goal. However, logistical and cost considerations are important. Plastic bags and plastic tubes with DEHP can be used if precautions are taken.

Certainly, all efforts to reduce DEHP contamination of taxane chemotherapy treatments should be taken. After the chemotherapy is mixed in the pharmacy, it should be hand carried to an oncology nurse for immediate infusion. The shorter this time interval, the less DEHP contamination. Also, the rate of chemotherapy infusion should be as rapid as possible without causing high levels of patient discomfort. Chemotherapy solution that remains stagnant between infusions within the chronic ambulatory peritoneal dialysis tubing should be flushed from this tubing before instillation of another liter of paclitaxel solution. This can be accomplished by draining residual ascites fluid from the peritoneal cavity through the chronic ambulatory peritoneal dialysis infusion tubing prior to attaching the new bag of chemotherapy.

In a review article, Doull et al. (1999) contested the current U.S. Environmental Protection Agency (EPA) classifica-

tion of DEHP as a possible human carcinogen. The authors argued that the mechanisms that resulted in a hepatocarcinogenic response to DEHP in rats and mice are unique to rodents and could not be translated to humans. However, no definitive information about the chronic effects of DEHP in humans currently exists. The current EPA reference dose (RfD) for DEHP in humans is 0.02 mg/kg per day. The RfD is an estimate of a safe daily oral intake of DEHP for humans and is based on increased relative liver weights in guinea pigs (EPA, 1999). Intensive intraperitoneal use of taxane chemotherapy over a short period of time in an immunologically compromised patient with cancer with altered metabolism most likely will increase any chronic effects of DEHP exposure. If the approximate DEHP exposure per treatment is 3 mg and 30 treatments are possible during a six-month period, the total amount of DEHP could exceed EPA standards.

The survival expected with peritoneal carcinomatosis from gastric cancer is extremely poor (four to six months), and this has been well documented in the oncology literature (Sadeghi et al., 2000). In a study of induction intraperitoneal docetaxel and systemic chemotherapy, patients, especially those who had minimal carcinomatosis, benefited from treatment (Yonemura et al., 2004). The median survival of 14.4 months and one-year survival of 57% may represent the longest survivals recorded in this group of patients with gastric cancer and carcinomatosis. This combined approach of systemic and intraperitoneal chemotherapy was associated with no mortality and a very reasonable morbidity of 16%. Also, the disappearance of ascites in a majority of patients who showed this symptom was remarkable. This combination of systemic chemotherapy and intraperitoneal docetaxel should be considered in patients with carcinomatosis from gastric cancer, especially those who have small volumes of disease and symptomatic ascites.

Many oncologists who have used intraperitoneal chemotherapy extensively in the past have stopped pursuing this treatment modality. Although benefits have been demonstrated, the logistical problems that were associated with long-term intraperitoneal chemotherapy delivery were thought to outweigh the limited benefits. In patients who receive the intraperitoneal taxane chemotherapy in the perioperative period, these logistical problems do not exist. The tubes and drains are always open, and adhesions in the peritoneal cavity have not yet formed. In patients with peritoneal mesothelioma, cytoreductive surgery plus intraperitoneal chemotherapy using paclitaxel has extended the median survival from less than one year to more than five years (Feldman et al., 2003; Sugarbaker et al., 2002). The dosimetry for these treatments was established by Markman et al. (1992) in a study of patients with ovarian cancer. De Bree et al. (2003) used heated intraperitoneal docetaxel with good results in the surgical treatment of primary ovarian cancer. Intraperitoneal taxane chemotherapy may be a new, very helpful treatment strategy for abdominal and pelvic malignancy worthy of further exploration.

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