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Hazards of mechanical ventilation—therapeutic implications

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The side effects and adverse reactions associated with the use of positive pressure volume cycle ventilators are described with a focus on information the pharmacist needs to know to monitor patient drug therapy.

Mechanical ventilation is discussed with regard to pulmonary and blood gases, infections, cardiovascular effects, renal-fluid status, metabolic considerations, central nervous system effects, gastrointestinal effects, musculo-skeletal reactions, discontinuance of mechanical ventilation and the use of inhalation drugs.

Key Words: Equipment; Inhalation therapy; Pharmacists, hospital; Toxicity

The intent of this article is to review a nondrug treatment—mechanical ventilation—which has grown in importance, sophistication and frequency in the last 10 years. The introduction of the volume cycle positive pressure ventilator has significantly changed the treatment of respiratory failure. While bringing life to some patients, it has also been controversial in its ability to prolong life.

The pharmacist must realize that a ventilator is like a drug. This "drug" is involved with the lungs, oxygen and carbon dioxide components of body physiology. Alteration of oxygen and carbon dioxide concentrations may be therapeutic or dangerous (side effects). Positive pressure ventilation also produces changes in body physiology that are independent of blood gas alterations (adverse reactions).

Ventilators work by either forcing air into the lungs (positive pressure) or creating a negative (subatmospheric) pressure around the thorax and letting normal intrathoracic

pressure expand the lungs. The classic negative pressure ventilator is the "iron lung."

Positive pressure machines require that the patient have an artificial airway (endotracheal or tracheostomy) in place for use. The negative pressure machines do not require intubation.

There are two major types of positive pressure ventilator. Pressure cycle ventilators were the first available.^a These ventilators respond to a preset pressure, such as 20 cm water. When this pressure is achieved in the lungs the ventilator stops and allows the patient to exhale. This means that in certain disease states which are accentuated by high or changing intrapulmonary pressures, these ventilators may deliver inadequate or variable volumes of air. Intermittent positive pressure breathing is usually done with pressure cycle ventilators.

Volume cycle ventilators^b deliver a preset volume. This preset volume can be accomplished despite an increase in resistance to air flow or expansion of lungs. These ventilators deliver a relatively constant volume and percentage of oxygen per minute. They are easy to control and maintain, and can be equipped with alarm systems.

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^a Bennett, PR. 1 and PR. 2; and Bird, Mark 7 and Mark 8.

^b MA-1, Emerson, OH.

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Toxicological Aspects of DEHP

Studies have shown a wide variation regarding both animal toxicogenicity and teratogenicity of a number of phthalic acid esters used in PVC plastics. An excellent review of phthalate ester toxicity has been done by Autian.³⁴

The oral and parenteral toxicity of DEHP appears to be of a low order following both acute and long-term studies. However, under appropriate conditions, DEHP has been demonstrated to have significant effects on a number of biological systems.³⁵ Perhaps the most interesting is the sensitivity of embryonic heart cells to DEHP. At DEHP levels obtained in human blood stored in vinyl plastic bags, 97-98% of these cells were killed in culture medium.

DEHP has been shown to either modify or abolish vascular response to physiological stimuli.³⁶ High doses of DEHP have caused early fetal deaths and semisterility in mice.³⁷ DEHP has been demonstrated in the developing rat fetus from early embryogenesis to birth.³⁸

One study was unable to correlate the tissue content of DEHP with the transfusion histories in the dog and rat as well as man.³⁹ The investigators suggested that environmental or possibly endogenous sources of DEHP are of greater consequence than the low-level parenteral administration of administered blood products stored in PVC blood bags. They concluded that PVC stored blood is not a significant source of tissue DEHP in humans probably because of its rapid metabolism and excretion in vivo.

A recent study evaluated the effects of DEHP on hepatic function and histology in the rhesus monkey undergoing chronic transfusion.⁴⁰ DEHP was solubilized resulting from leaching by platelets or plasma stored in PVC blood bags. The average cumulative amount of DEHP infused in one year was 21.3 mg/kg. Four of the seven PVC transfused monkeys had abnormal ^{99m}Tc liver-spleen scan ratios, four of the seven demonstrated abnormal BSP clearance and six of the seven had abnormal liver histopathology upon completion of transfusion therapy.

Cost

As with other pharmaceuticals, the quantity purchased of large-volume parenterals is the determining factor as to cost. In general, plastic containers have now been priced competitively with glass.

Conclusion

From an administrative and financial standpoint, it would appear that if plastic containers were not priced competitively with glass, there would be no compelling justification to purchase them. There are advantages and disadvantages to both plastic and glass containers. The lack of particulate matter in plastic containers, as suggested by some investigators, may be medically outweighed or equal to the presence of plasticizers in the solutions found in plastic containers. Thus from a medical point of view, various justifications can be presented for both glass and plastic containers.

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WARNING: Do not use plastic container in series connections. Such use could result in air embolism due to residual air (approximately 15 ml) being drawn from the primary container before administration of the fluid from the secondary container is completed. Certain solutions should not be administered simultaneously with blood through the same infusion set because of the possibility of pseudoagglutination.

Leaching and Adsorption Considerations

A major concern regarding the use of plastic i.v. solution containers is the possible diffusion of toxic stabilizers and plasticizers from the plastic into the i.v. solution as well as sorption of additives from the solution by the plastic.

The soft plastic containers are composed of PVC and various plasticizers, stabilizers and catalysts. One plasticizer used is di-2-ethylhexyl phthalate ester (DEHP), also known as dioctyl phthalate.¹⁸

Studies demonstrating the leaching of plasticizers from bags used to store blood and from hemodialysis equipment were published several years prior to the introduction of plastic bags for large-volume parenteral solutions. In 1967 Guess et al¹⁹ studied the alteration or contamination of anticoagulant citrate dextrose (ACD) solutions stored in PVC blood bag assemblies. Infrared analysis revealed DEHP as the main contaminant.

In a subsequent report Marcel and Noel²⁰ reported what they thought to be dihexyl phthalate as a contaminant of blood stored in plastic packs using infrared spectrophotometry and gas-liquid chromatography. They found concentrations up to 11.5 mg/100 ml after storage for 21 days. In a follow-up report, Gesler and Kartinos¹⁸ identified dioctyl phthalate in the extracts of plasma stored in plastic packs using thin layer chromatography.

Jaeger and Rubin^{21,22} found DEHP in concentrations of 5 to 7 mg/100 ml of blood stored for 21 days. The rate of migration was found to be 2.5 ppm/day. Furthermore, tissues from two patients who had been transfused were found to contain quantities of DEHP ranging from 69 to 200 µg/g dry-weight. In another report Jaeger and Rubin rejected the contention of Gesler and Kartinos that the margin of safety of DEHP is equivalent to water.²³ In this study they further reported the extraction of two phthalate plasticizers by blood used in hemodialysis and heart-lung bypass systems.

It was these communications during 1970 that stimulated the controversy on the extraction of DEHP. The studies of Jaeger and Rubin were published in their entirety later that year.²⁴

In 1971 Eubanks and Autian²⁵ reported on their evaluation of polyethylene blood bags. The blood bags were tested for leaching when partially filled with ACD solution for up to 12 months at 5 C and room temperature. They found that a chemical contaminant (residue) was found in all storage conditions, but it was found to be nontoxic in biological systems using tissue culture, intradermal and mouse toxicity tests.

A Danish report by Neergaard et al²⁶ suggested that diethyl phthalate migrated from hemodialysis tubing and

found concentrations of 10–20 mg/liter in the perfusate.

Up until this point we have reviewed the work done on the extraction of DEHP from PVC contaminating blood bags and hemodialysis equipment. The first report on investigation of the possible migration of DEHP into i.v. solutions from plastic containers was made by Rubin in 1972.²⁷ No levels greater than the control in excess of 0.24 ppm would be detected in normal saline, dextrose 5% water and 5% protein hydrolysate after storage for more than a year after manufacture. Further work by one of us (S.P.L.) using normal saline revealed the presence of foreign components when examined by ultraviolet spectrophotometry as evidenced by the appearance of distinct absorption bands at 280 nm and 225 nm. Kartinos agreed that these data represented trace amounts of leached plasticizers, the main component being DEHP.²⁸

The next series of events on DEHP came when Chiou and Moorhatch²⁹ reported on the sorption of vitamin A by plastic containers. They found 78% of 200 ml aqueous solution containing vitamin A (in the form of retinol acetate) was retained by the plastic containers after 24 hours of storage at room temperature. The amount sorbed is a function of time, with 10% sorbed after two hours of storage. They attributed the problem to the polysorbate 80 used as a solubilizer.

The work of Chiou and Moorhatch prompted Nedich to conduct a similar series of experiments. He found a rubber-stoppered glass bottle plus set delivered 77% of the available 10,000 units of vitamin A/liter over a 10-hour period while the plastic system delivered 71% over the same period of time. The solutions had been protected from light as Chiou and Moorhatch had done. In another set of experiments in which the solutions were not protected from light, data showed a 61% delivery from the glass system and 49% from the plastic system.²⁹

Additional work by Chiou and Moorhatch corroborated the subject of extractables from plastic containers.³¹ The ultraviolet absorption spectra of distilled water, normal saline and 5% dextrose solutions showed only a slight increase after an unstated storage period at room temperature as compared with the negative findings of Rubin. Results on surfactant solutions (usually fat soluble vitamins) showed that chemicals were leached out after storage for up to 48 hours. Although the identity and concentrations of the leached chemicals were not firmly established, they estimated that 2.5 mg of DEHP leached out to the 200 ml of 0.04% polysorbate 80 solution in 48 hours. It was their opinion that the manufacturer should disclose to the public the names and amounts of the plasticizers, stabilizers and other chemicals added to the PVC and their acute and chronic toxicity data if available.

It has been reported that insulin is adsorbed to glass infusion bottles, plastic i.v. tubing and plastic i.v. containers.³² A follow-up study by Petty et al³³ reported that 55% of insulin is adsorbed from solution by both glass and PVC containers within 15 seconds. In the presence of 5% dextrose there appeared to be less adsorption by both the glass and PVC systems.

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PLASTIC INTRAVENOUS FLUID CONTAINERS

should be less than the labeled maximum of 5 ppm. In light of the above, further research is needed to elucidate the role of agitation in the shedding of particles encountered during the course of shipping.

Water Vapor Transmission and Osmolarity

The current USP permeation specifications state: "A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution."¹ A container is defined as tight "if the moisture permeability exceeds 100 mg/day/liter in not more than one of the 10 test containers and exceeds 200 mg/day/liter in none of them."¹

A comparative study of PVC and polypropylene bags was done in England by MacDonald.¹¹ Results showed that the polypropylene bag, which has been used in the Scandinavian countries for about 10 years, served as a far better protective barrier than the PVC bag manufactured by Smith and Nephew. Without the outer protective wrapper, Vialflex lost 1.6-4% of its nominal volume when stored at 25 C and 33-55% relative humidity after 12 months as contrasted to 2-6% for Steriflex and 1-3.5% for the Smith and Nephew systems. Less than 1% water vapor transmission was noted with the polypropylene bags under the same storage conditions. The solutions employed in the study were not identified. One must remember, however, that a bag is usually not stored without its overwrap for a long time. The permeability of the plastic to moisture transfer has been pointed out by others.¹² In view of these findings, it appears that plastic containers do not satisfy the USP definition of a hermetic container. The results more closely approximate the definition of a tight container. Although this loss would not appear to be clinically significant insofar as concentration changes leading to a hypertonic solution, these studies do point out that the unit is not a truly closed system and a potential exists for gaseous entry into the system.

Drug Additives

A recent survey has shown that about 30% of hospital pharmacies have instituted an i.v. admixture service.¹³ A number of parameters should be considered in the use of nonrigid plastic parenteral fluid containers as far as drug additives are concerned.

Generally poor mixing of drug additives is perhaps an inherent property of flexible plastic containers because of the positioning and length of injection site. The experiments of Williams¹⁴ indicated that when potassium chloride was added to 500 ml of normal saline in a plastic container, the added solution was pooled at the injection site leading to a hyperkalemic bolus. Two cases of potassium overdosage were reported by the author. A third case of potassium overdosage was reported by Lankton et al.¹⁵ They attributed the overdosage to poor mixing because of the design of the injection port. The degree of mixing was dependent upon the distance the needle was introduced into the injection port when hanging in the infusion position.

A more recent study reported on comparative mixing of additives in i.v. solutions in glass bottles and PVC bags.¹⁶ The additives studied were chlorothiazide sodium, potassium chloride and phenytoin sodium. Results showed there was adequate mixing when the additives were injected into an upright glass container or a plastic bag which was subsequently hung in the infusion position and into a glass container in the infusion position. Poor mixing resulted when the injections were made into a plastic bag hanging in the infusion position.

Based on the reported data, Table 1 illustrates the dramatic pooling phenomenon.

The following statement appears in the manufacturer's directions for adding medication:

NOTE: When adding Potassium Chloride or substances of similar density to the Vialflex[®] container, the initial contents of both ports should be evacuated by squeezing them while the bag is in the upright position, followed by the usual mixing procedure.

The manufacturer has attempted to reduce the hazard of pooling by shortening the length of the entry port. Apparently this does not reduce the hazard of pooling of the additive but serves to reduce the accumulation of additive at the port of entry, hence mixing is still required.

Breakage and Puncturability

Plastic containers are susceptible to accidental puncture which can create a point of entry for bacteria or other contaminants.¹⁷ Care must be exercised when adding a drug through the additive port because of the possibility of puncturing the plastic with a needle.¹² It is questionable whether the overwrap protects against such punctures. Such punctures may not be evident unless the bag and its contents are squeezed as recommended prior to leaving the pharmacy.

Series Connections

Plastic containers should not be used in series connections. A warning statement by the manufacturer^c appears in the directions for use. It states:

^b See footnote a.

^c See footnote a.

Table 1. Recoveries of Additives from First 100-ml aliquots from Glass and Plastic Parenteral Containers^a

Additives	Theoretical	Inverted		Upright	
		Glass	Bag	Glass	Bag
Potassium chloride (mEq) ^b	2	1.40	15.05	1.80	2.55
Phenytoin sodium (mg) ^b	10	8.72	44.88	9.15	9.19
Chlorothiazide (mg) ^c	10	34.21	366.88	—	—

^a Recalculated data of Bighley et al.¹⁶ by the authors.

^b In dextrose 5% in water.

^c In Sodium Chloride Injection, USP.

space requirement and the handling ease. The plastic container, being less rigid than glass, requires support by virtue of shelf trays or boxes to allow for ease of identification and inventory control.

In reference to handling, the plastic container is easier to hold and will not break on falling, but it does present difficulty if an additive must be placed into the solution because of its lack of rigidity on standing.

Although the currently available plastic containers offer advantages in reference to decreased weight and storage space as opposed to glass, the lack of rigidity presents problems in handling when manipulation is required.

Environmental Contamination

The single most important advantage claimed for plastic containers is that they require no air venting and, therefore, airborne contamination of sterile solutions is reduced.

Hansen and Hepler² reported on the contamination of intravenous solutions using the closed Cutter system, the open MacBick systems, the open system with air vent tube represented by the Baxter system and the Viaflex system. They compared the extent of contamination from airborne microbes during the opening of the containers in unsterile air. The number of bacteria per cubic foot of air was determined with an air sampler and the number of bacteria which had entered the solution systems was determined by filtration. The investigators concluded that the Cutter closed system and Viaflex system offered significantly better protection against contamination by airborne microbes than did the open and open with tube systems.

Human Touch Contamination

Plastic containers^a of large-volume parenteral solutions have a separate entry port which allows for the administration set to be inserted within a closed sealed compartment. When the administration set spike is inserted, the outer part of the entry port is occluded before the internal membrane is penetrated. Because of this feature, someone cannot inadvertently touch and contaminate the internal point of puncture. It is suggested that the rubber diaphragm of glass containers should be swabbed with an antiseptic solution before entry of the administration set spike. Even so, it is conceivable that someone may touch, and thereby contaminate, the rubber diaphragm.

Poretz et al³ reported on the microbial contamination of glass bottle and plastic bag parenteral delivery systems. The frequency and potential for contamination of both systems were determined from data derived in studies simulating work and centralized admixture conditions. The plastic bags were associated with a higher frequency of contamination than the glass bottles. The incidence of contamination of the plastic bags was 6.9%, compared with 1.3% for glass containers. While the source of the contaminant was uncertain,

they concluded that human touch was an important factor. Other studies by Kundson et al found a lower contaminant incidence (0.88%) with plastic bags than with glass containers.⁴

Letcher et al⁵ determined the rate of contamination of solutions in plastic containers and administration sets under actual use conditions when the solutions and admixtures were prepared for administration and administered by nurses. Of 366 solutions sampled over a three-month period, 4.9% were found to be contaminated. The investigators concluded that this was a relatively low contamination rate with the plastic i.v. solution containers when compared to previously reported studies of other systems.

Duma et al⁶ reported that clinically significant contamination occurred while changing volume-control devices during the introduction of additives into the container or tubing, stemming from the hands of personnel or from heavily contaminated environmental surfaces. While this study shows the problems of contamination using administration devices for a glass system, no studies have been reported with the plastic containers under similar conditions.

Particulate Matter

Turco and Davis⁷ compared the particulate matter contamination of i.v. solutions manufactured by four firms during 1972. They found that solutions in plastic containers were least contaminated. The average number of particles greater than 5 μm from plastic containers was 76/liter, whereas the glass containers had averages of 204-488 particles. Specifically, plastic containers had averages of 70-96 particles greater than 5 μm in size, whereas normal saline in glass containers had averages of 217-803 particles/liter. Dextrose 5% in water in plastic containers had an average of 80 particles/liter greater than 5 μm , whereas for glass containers the range was 98-577. Although the investigators did not offer an explanation why the plastic containers had significantly less particulate matter than the glass containers, they concluded that plastic containers may have offered less potential for particulate matter contamination at that time.

A subsequent study by Whitlow et al⁸ generated particulate matter as colloidal-sized globules from polyvinyl chloride (PVC) i.v. bags containing normal saline using gyrorotatory agitation simulating conditions of a truck going over a bumpy road. After studying more than 600 bags they found that over 75% contained in excess of 20,000 particles/ml with a diameter of 2.3 to 5.0 μm . Characterization studies done previously by Needham and Luzzi identified the particulates as di-2-ethylhexyl phthalate (DEHP).⁹

Subsequent correspondence by Darby and Ausman¹⁰ regarding the conditions of agitation used by Needham and Luzzi indicated low particulate counts before shaking while drastic shaking produced microspheres of liquid plasticizer described as "pseudoparticles." On the basis of 20,000 particles/ml and an assumed diameter of 2 μm , the investigators attributed particulate levels in the order of 0.1 ppm which

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Review of current knowledge of plastic intravenous fluid containers

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A review of the features of plastic intravenous fluid containers is presented.

The following topics are discussed: (1) handling and storage; (2) environmental and human contamination; (3) particulate matter; (4) water vapor transmission; (5) drug additives; (6) leaching and adsorption; (7) possible toxicity; and (8) cost.

It is concluded that various justifications can be presented for both glass and plastic containers.

Key Words: Additives; Adsorption; Containers; Contamination; Costs; Glass; Injections; Leaching; Particles; Plastics; Storage; Toxicity

Major characteristics of the ideal plastic container for the storage and administration of large-volume parenterals should include the following:

1. Allow visual inspection of its contents prior to administration,
2. Be chemically inert to minimize changes in the properties of the solution,
3. Not contribute to particulate contamination,
4. Not interact with additives,
5. Act as a barrier to diffusional fluid loss, and
6. Maintain sterility of its contents in the presence or absence of drug additives prior to and during administration.

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The packaging and storage recommendations for large volume parenterals found in the current *United States Pharmacopeia* are stated as follows: "Preserve in single-dose containers, preferably of Type I or Type II glass."¹ Large-volume parenteral solutions have been available in plastic containers since 1971. Because plastic containers for these solutions deviate from what is preferred by the USP we felt it would be valuable to discuss the advantages and disadvantages of plastic containers for large-volume parenteral solutions. The purpose of this paper is to aid hospital pharmacists in evaluating a plastic parenteral delivery system.

Handling and Storage

The physical handling and storage of large-volume parenterals present problems both in the required space and the movement of these products.

Although the weight of a glass container is more than that of a plastic container, perhaps of equal significance is the