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Plasticizer di(2-ethylhexyl)phthalate (DEHP) release in wet-primed extracorporeal membrane oxygenation (ECMO) circuits

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Abstract

A wet-primed ready-to-use extracorporeal membrane oxygenation (ECMO) circuit is used in some centres for rapid deployment of ECMO during cardiopulmonary resuscitation. Yet, the potential release of plasticizer di(2-ethylhexyl)phthalate (DEHP) from the polyvinyl chloride tubing in the circuit during storage is a concern. In this study, a high performance liquid chromatography method was used to determine the concentration of DEHP in the priming solution (Plasmalyte®) from an ECMO circuit stored for up to 14 days at 8 °C. No accumulation of DEHP in the circulating fluid was detected. The results provide important information for centres where ECMO circuits are kept wet-primed prior to clinical use.

Keywords: Di(2-ethylhexyl)phthalate; DEHP; Plasticizer; ECMO; Release; HPLC

Extracorporeal membrane oxygenation (ECMO) is used to support patients with critical cardiorespiratory failure that is refractory to conventional treatment. ECMO allows blood to be oxygenated extra corpus circumventing the need for gaseous exchange by the lung. Each ECMO circuit comprises a pump, a membrane oxygenator and a heater linked by plastic tubing to venoarterial cannulas. Recently, some centres have reported (Jacobs et al., 2000; Duncan et al., 1998) emergency use of ECMO during or shortly after cardiopulmonary resuscitation. For this purpose, ECMO circuits are sometimes stored pre-assembled

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and pre-primed. However little information is available regarding the durability of pre-primed ECMO circuits and the safety of such practice.

We have found (Karimova et al., 2004) that ECMO circuits (primed with Plasmalyte®, Baxter Healthcare Corporation, IL, USA) could be stored without loss of their oxygenation function and that the sterility of the circuits could be maintained for up to two weeks, suggesting a longer storage time was indeed feasible. Yet another concern was the potential release of plasticizers from the polyvinyl chloride (PVC) tubing in the circuit. The most often used plasticizer di(2-ethylhexyl)phthalate (DEHP) has been reported to cause a wide range of adverse effects on the liver and on the reproductive tract in animals (Centre for Devices and Radiological Health, 2001; Tickner et al., 2001). While the exposure of plasticizer in the parenteral route has been extensively discussed (Karle et al., 1997; Haishima et al., 2004), the release of DEHP in the wet-primed circuit during storage has not been reported. The present work reports the DEHP release in ECMO circuits primed with 1L of crystalloid (Plasmalyte®) and stored at 8 °C for up to 14 days.

Samples from ECMO circuits were collected and stored in glass containers at −18 °C until analysis. Aliquots of 1.5 ml were extracted twice with hexane (1.5 and 1.0 ml each time), the solvent being removed under a stream of nitrogen at room temperature. The residual was finally reconstituted with 0.1 ml acetonitrile and 20 μl was injected into a high performance liquid chromatography HPLC (HP1050 system, Hewlett-Packard, Waldbronn, Germany) for analysis. The column used was a Synergi 4 μm ODS C_{18} (Phenomenex, Macclesfield, UK) 150 mm × 4.6 mm. The mobile phase was acetonitrile: methanol (90/10, v/v) and the flow rate was maintained at 1.0 ml/min. The wavelength of detection was 222 nm and the retention time of DEHP was 5.8 min. Those chromatographic conditions were derived from Aignasse et al. (1995). The extraction showed a recovery yield of 100.04 ± 2.15% for added DEHP (mean ± S.D., $n = 6$). All materials used were proved to be negative of DEHP at the applied condition. The limit of detection (at signal to noise ratio, S/N = 3) was 0.05 μg/ml, equivalent to an original sample concentration of 0.0033 μg/ml. The limit of quantification (S/N = 10) was 0.15 μg/ml, equivalent to an original sample 0.01 μg/ml. Below this value, the concentration was recorded as zero. The DEHP concentration was expressed as the mean (±S.D., $n = 5$ circuits).

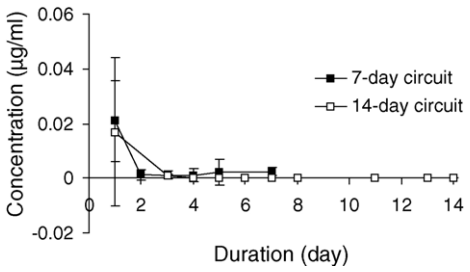

Fig. 1. DEHP concentration in μg/ml (mean ± S.D., $n = 5$ circuits) in 7- and 14-day ECMO circuits as a function of the wet-priming duration.

Fig. 1 shows the concentrations of DEHP as a function of the duration of wet-priming. The highest levels of DEHP were detected in both 7- and 14-day circuits on the first day (0.021 and 0.017 μg/ml, respectively). The concentration then dropped sharply below the lower limit of quantification from day two in the 7-days circuits. In the 14-day circuits there was no DEHP detectable after 3 days of wet priming.

The measured DEHP concentrations in the circuits were significantly lower than that of the original Plasmalyte®, a commercial parenteral solution containing multiple electrolytes used to wet prime the circuit (0.041–0.170 μg/ml, measurements on three different batches).

This suggested that the source of DEHP in the circuit was the priming solution rather than plasticizer leaching from the PVC circuit itself. As reported by Faouzi et al. (1999), lipophilic ingredients in solution cause the release of DEHP from medical PVC products and low temperatures significantly slow down the release of DEHP. Therefore, the low storage temperature of the circuit (8 °C) and the absence of lipophilic compound in Plasmalyte® minimised DEHP leaking.

The reason that the concentration dropped in the circuit after 2 or 3 days was possibly because the DEHP from the priming solution was adsorbed onto the surface of the capillaries of the oxygenator or onto the silicone bladder (both do not contain DEHP, information from the supplier) in the circuit. If this was the case, one may worry that the adsorbed DEHP could potentially be extracted by blood when the circuit is applied to a patient. However, since the concentration of DEHP was very low throughout the test period,

the short term exposure is unlikely to be of clinical relevance. In the worst case, if all the plasticizer was entrapped in the circuit and later exposed to the patient, the highest exposure would be 0.17 mg, or 0.085 mg/kg body weight for a 2 kg neonate, which is seven times lower than the parenteral tolerable daily intake of DEHP (0.6 mg/kg body weight, Centre for Devices and Radiological Health, 2001). It is also below the reported exposure of DEHP (0.708–0.721 mg/kg) in a 6-h simulation of (non-wet-primed) ECMO circuit (Haishima et al., 2004).

Although no accumulation of DEHP in the circulating fluid was detected, further experiments are needed to elucidate the fate of DEHP in the circuit. Nevertheless, as the primed circuits are for life-saving emergencies, the benefits of ready to use ECMO circuits out-weigh the risk of the potential low dose DEHP desorption. The results of this study are of value for clinicians in setting up and maintaining wet-primed ECMO circuits.

References

Aignasse, M.F., Prognon, P., Stachhowicz, M., Gheyouche, R., Pradeau, D., 1995. A new and rapid HPLC method for the determination of DEHP in PVC packaging and releasing studies. Int. J. Pharm. 113, 241–246.

Centre for Devices and Radiological Health, 2001. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Food and Drug Administration, USA (http://www.fda.gov/cdrh/ost/dehp-pvc.pdf, accessed on 06/01/05).

Duncan, B.W., Ibrahim, A.E., Hraska, V., Nido, P.J., Laussen, P.C., Wessel, D.L., Mayer, J.E., Bower, L.K., Jonas, R.A., 1998. Use of rapid-deployment extracorporeal membrane oxygenation for the resuscitation of pediatric patients with heart disease after cardiac arrest. J. Thorac. Cardiovasc. Surg. 116, 305–311.

Faouzi, M.A., Khalfi, F., Dine, T., Luyckx, M., Brunet, C., Gressier, B., Goudaliez, F., Cazin, M., Kablan, J., Belabed, A., Cazin, J.C., 1999. Stability, compatibility and plasticizer extraction of quinine injection added to infusion solutions and stored in polyvinyl chloride (PVC) containers. J. Pharmaceut. Biomed. Anal. 21, 923–930.

Haishima, Y., Matsuda, R., Hayashi, Y., Hasegawa, C., Yagami, T., Tsuchiya, T., 2004. Risk assessment of di(2-ethylhexyl)phthalate released form PVC blood circuits during hemodialysis and pump-oxygenation therapy. Int. J. Pharm. 274, 119–129.

Jacobs, J.P., Ojito, J.W., McConaghey, T.W., Boden, B.D., Chang, A.C., Aldousany, A., Zahn, E.M., Burke, R.P., 2000. Rapid cardiopulmonary support for children with complex congenital heart disease. Ann. Thorac. Surg. 70, 742–749, discussion 749–750.

Karimova, A., Robertson, A., Cross, N., Smith, L., Tuleu, C., Long, P., Beeton, A., Han, J., O'Callaghan, M., Rawn, H., Ridout, R., Goldman, A., Brown, K. A wet primed ECMO circuit with hollow fibre membrane oxygenator maintains adequate function for use during CPR after 2 weeks on stand-by. Crit. Care Med., submitted for publication.

Karle, V., Short, B., Martin, G.R., Bulas, D.I., Geston, P.R., Luban, N.L.C., O'Brien, A.M., Rubin, R.J., 1997. Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl)phthalate. Crit. Care Med. 25, 696–703.

Tickner, J.A., Schettller, T., Guidotti, T., CcCally, M., Rossi, M., 2001. Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: A critical review. Am. J. Ind. Med. 39, 100–111.