

Aluminium leaching in fluid warming devices – A Review

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Abstract

Current guidelines recommend the use of an intravenous fluid warmer to prevent perioperative hypothermia. Among the various methods of warming intravenous fluids, contact warmers are among the most effective and accurate, particularly in clinical conditions requiring rapid infusions of refrigerated blood or fluids. Contact warmers put the infusate in direct contact with a heating block. Some fluid warmers use heating blocks manufactured from aluminium. Several recent publications, however, have shown that uncoated aluminium blocks can leach potentially toxic amounts of aluminium into the body. In this review we performed a systematic literature review on aluminium leaching with contact fluid warmers and describe what manufacturer and competent authorities did in the past years to ensure patient safety. The search resulted in five articles describing the aluminium leaching. Four different devices (Level 1 Fluid Warmer from Smiths Medical, ThermaCor from Smisson-Cartledge Biomedical, Recirculator 8.0 from Eight Medical International BV, enFlow from Vyair) were shown to leach high levels of aluminium when heating certain intravenous fluids. One manufacturer (Vyair) voluntarily removed their product from the market, while three manufacturers (Eight Medical International BV, Smisson-Cartledge Biomedical, and Smiths Medical) revised the instructions for use for the affected devices. The enFlow fluid warmer was subsequently redesigned with a parylene coating over the heating block. The scientific literature shows that by using a thin parylene layer on the heating block, the leaching of aluminium can be nearly eliminated without affecting the heating performance of the device.

Background

Intravenous fluid warmers are frequently employed for the prevention of intraoperative and perioperative hypothermia. Current guidelines recommend incorporating a method of warming infused fluids during surgery.[1–4] Direct heating using heating blocks provides controlled and rapid heating, often at high flow rates, and the technology has been applied to intravenous as well as intracavitary lavage fluid systems. However, fluid warmers based on uncoated aluminium heating blocks have been troubled with aluminium leaching into the infusate, leading to concerns about aluminium toxicity.[5–9]

Aluminium is one of the most common elements in the Earth's crust, and its presence around us is almost universal. Yet in the human body, aluminium has no known biological effects and indeed is a potential toxin. Aluminium has been linked to neurodegenerative disorders such as Alzheimer's Disease[10], although it remains unclear whether elevated levels of aluminium seen in certain parts of the brain are the cause or the effect of Alzheimer's Disease.[11] There may be adverse effects of elevated aluminium levels on bone marrow, brain development[12], and kidney function. Aluminium is generally excreted in the kidneys, although small amounts do pass through the blood-brain barrier where aluminium is likely to remain for prolonged periods of time. It may also be deposited in bone and contribute to osteomalacia. [13]

We performed a systematic review of the available literature related to aluminium release into intravenous fluids due to heating units that utilize aluminium heating blocks. The aim of this review is to

see which warming devices leach how much aluminium and identify which ones are safe to use.

Methods

Using the literature search tool ProQuest Dialog®, we used the following search string:

(Aluminum OR aluminium) AND “intravenous fluid\$” AND “warmer”

Dialog searched the following databases: AdisInsight: Drugs, AdisInsight: Trials, Adis Pharmacoconomics & Outcomes News, Allied & Complementary Medicine™, Animal Behavior Abstracts, APA PsycInfo®, British Nursing Index, ClinicalTrials.gov, COVID-19 Research, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, DIOGENES® FDA Regulatory Updates, Drug Information Fulltext, Embase®, EMCare®, Entomology Abstracts, ESPICOM Pharmaceutical & Medical Device News, FDAnews, Global Health, Health Research Full Text Professional, HSELINE: Health and Safety, IMS Company Profiles, IMS New Product Focus, IMS Pharma Trademarks, IMS R&D Focus, IMS R&D Focus Drug News, King's Fund, KOSMET: Cosmetic Science, Lancet Titles, MEDLINE®, Morressier Life Science Conference Abstracts and Posters, New England Journal of Medicine, Northern Light Life Sciences Conference Abstracts, ProQuest Biological & Health Science Professional, ProQuest Dissertations and Theses Professional, ProQuest Environmental Science Professional, Publicly Available Content, and ToxFile®. Our inclusion criteria were dates 2011-2021; intravenous fluids; peer reviewed articles; and scholarly journals. Exclusion criteria included non-scientific publications, theses, and patents. No language restrictions were applied. In addition to the scientific articles, we included information regarding device recalls from the FDA and MHRA database.

Results

The literature search identified 166 unique articles which were screened initially by title search, then by review of the abstract. After exclusion of unrelated and duplicate articles, five articles were included in this report. Table 1 provides a summary of the included articles from our literature search.

<Insert Table 1 here>

Table 1
Results of literature search strategy

Set#	Searched for	# Records
S1	aluminum or aluminium	965740*
S2	intravenous fluid\$	330283*
S3	warmer	1404574*
S4	(s1 and s2 and s3)	3636°
S5	((s1 and s2 and s3)) and (dates(2010-2029))	1287°
S6	((s1 and s2 and s3)) and (dates(2010-2029) and (searchtype("Scholarly Journals")))	205°
S7	((s1 and s2 and s3)) and (dates(2010-2029) and (articletype("Article") AND searchtype("Scholarly Journals")))	169°
S8	((s1 and s2 and s3)) and (dates(2011-2021) and (articletype("Article") AND searchtype("Scholarly Journals")))	166°
* Duplicates are removed from the search but included in the result count.		

° Duplicates are removed from the search and from the result count.

A study, led by Perl et al in 2019[5], compared aluminium release between an uncoated enFlow device with the Fluido® Compact (The 37°Company, Amersfoort, the Netherlands), a device that uses a parylene coating between the aluminium blocks and the infusate. The study evaluated aluminium release into normal saline (0.9% NaCl solution) or a balanced electrolyte solution (Sterofundin 1/1E) at various infusion rates. Fluids were run through with the heating units activated, then again with the heating units off. Their results clearly showed that the uncoated device leached aluminium into the infusate at higher levels than did the coated device. The amount of leaching was higher at slow infusion rates and when the heating units were activated. Notably, there was virtually no leaching of aluminium by either device into saline, in striking contrast to the high levels seen in the balanced electrolyte solution. This suggests that the balanced electrolyte solution demonstrated a more corrosive effect on the aluminium blocks than did the saline.

In January 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) learned of research indicating that one of the uncoated fluid warming devices (enFlow®, Vyaire Medical, Mettawa, IL) was releasing unusual levels of aluminium when used to warm certain infusates. This led to a formal investigation by MHRA into the medical device concerned. Following this report, the MHRA released a Medical Device Alert[14] warning clinicians of these findings as reported by Pike.[8] Vyaire initiated a voluntary recall of all enFlow uncoated devices in March 2013.[15]

Also in 2019, Taylor et al evaluated the uncoated enFlow heating cartridge using a broad variety of fluids. Plasma-Lyte 148, compound sodium lactate solution, 4% human albumin solution, expired resuspended packed red cells, and fresh frozen plasma were pumped through the warming system at $2 \text{ ml}\cdot\text{min}^{-1}$. [9] Infusates were infused over 60 minutes and samples for analysis were collected before heating, then every 10 minutes with heating for 60 minutes. The investigators found that balanced salt solutions were associated with potentially toxic levels of aluminium leaching while saline was not. Blood products were associated with lower levels of aluminium leaching, although levels still exceeded the US Food and Drug Administration (FDA) recommended level of $25 \text{ mcg}\cdot\text{l}^{-1}$ ($0.9 \text{ }\mu\text{mol}\cdot\text{l}^{-1}$) for intravenous nutrition. [16]

The Level 1® Fast Flow Fluid Warmer (Smith Medical, Minneapolis, MN) is a rapid infusion device that utilizes a passivated anodized aluminium heat block to warm passing fluids. This device was evaluated in 2020 by Cabrera et al using normal saline, lactated Ringer's, and heparinized whole blood at a constant flow rate of $30 \text{ ml}\cdot\text{min}^{-1}$ over the course of 1 hour. [17] Samples were collected every 10 minutes and each fluid was evaluated in triplicate. The amount of aluminium released into saline was negligible, and that released into whole blood initially was high but dropped to undetectable levels after 20 minutes. Aluminium levels in lactated Ringer's solution rose steadily over the one hour of infusion but did not reach toxic levels as defined by the FDA [18] and the Agency for Toxic Substances and Disease Registry. [19] In separate Letters to the Editor, both Perl [6] and Exley [20] disagreed with the assumptions of Cabrera's study, and Exley asserted that the aluminium-based fluid warmers were not safe for use in humans. Cabrera responded by defending the assumptions and conclusions in his study. [21]

Perl et al compared aluminium elution using the uncoated enFlow warmer heating fluids including saline, with or without combinations of sodium acetate, sodium lactate, and with or without sodium hypochlorite or hydrochloric acid, infused at $4 \text{ ml}\cdot\text{min}^{-1}$ over 60 minutes. [22] There was no elution of aluminium in pure normal saline, while the addition of either acetate or lactate significantly increased aluminium leaching at a level that increased over time. In their second experiment, the Level 1® H-1025 with DI-300 disposable tubing, and the ThermoSens® (Barkey GmbH & Co. KG, Leopoldshöhe, Germany), a low flow warmer that uses a parylene coated aluminium heating chamber as a heat exchanger, were compared using alkalized lactate-spiked saline or Sterofundin®, balanced electrolyte solution. Results between the enFlow and the Level 1 device were nearly identical, while the parylene-coated ThermoSens resulted in undetectable levels of aluminium elution.

The Food and Drug Administration (FDA) subsequently issued a letter to health care providers warning that multiple fluid warmers have been restricted or recalled. [23] Included among the recalls was the uncoated enFlow® intravenous fluid warmer which was subsequently redesigned to include a parylene coating over the heating block. [7, 24] According to the FDA, Vyair performed a complete product recall in 2019. [23] Two years later, the other companies had changed their Instructions For Use (IFU).

In an analysis by Waldmann et al, the team measured the concentration of aluminium that leached into three solutions (Sterofundin ISO, Plasma-Lyte 148, and whole blood) which were continuously pumped (0.2 and $5.5 \text{ mL}\cdot\text{min}^{-1}$) and warmed to 40°C for 5 h using the parylene-coated enFlow cartridge. In

addition, prolonged quasi-static bench tests were performed that measured aluminium concentration in 16 different clinically relevant solutions which were gently rocked within the enFlow cartridge (polyethylene-coated) for 72 h at 40°C. It was determined that there was virtually no elution of aluminium resulting from the polyethylene coated enFlow, even in fluids high in lactate.[7] Despite the additional layer between the actual heating surface and the fluid, studies have found that there is no negative effect on the performance characteristics of the enFlow device.[25]

A summary of the literature search is presented in Table 2.

Table 2

Summary of literature search on aluminium elution from aluminium block intravenous fluid warmers

Author, year	Device	Fluid	Infusion rate	Duration	Findings
Perl, 2019[5]	enFlow (uncoated)	Saline	2, 4, and 8 ml.min ⁻¹	60 min	Very low aluminium elution
		Sterofundin	2, 4, and 8 ml.min ⁻¹	60 min	Very high elution of aluminium, higher at low flow, higher when warming vs. room temperature
	Fluido Compact (coated)	Saline	2, 4, and 8 ml.min ⁻¹	60 min	Very low aluminium elution
		Sterofundin	2, 4, and 8 ml.min ⁻¹	60 min	Very low aluminium elution
Taylor, 2019[9]	enFlow (uncoated)	Saline	2 ml.min ⁻¹ , heated and unheated	60 min	Very low aluminium elution
		Distilled water	2 ml.min ⁻¹ , heated and unheated	60 min	Very low aluminium elution
		Distilled water with acetic acid	2 ml.min ⁻¹ , heated and unheated	60 min	High elution of aluminium, higher when warming vs. room temperature
		Plasma-Lyte 148	2 and 16.6 ml.min ⁻¹ , heated and unheated	60 min	Very high elution of aluminium, higher at low flow, higher when warming vs. room temperature
		Compound sodium lactate	2 ml.min ⁻¹ , heated and unheated	60 min	Very high elution of aluminium, higher when warming vs. room temperature
		Expired packed red blood cells	2 ml.min ⁻¹ , heated and unheated	60 min	High elution of aluminium, higher when warming vs. room temperature

* Sterofundin ISO; Plasma-Lyte 148; single donor human whole blood; human packed cells; Ringer's lactate in 5% dextrose; human platelet lysate; human buffy coat; human plasma diabetic type 2; 5% dextrose solution; 3% sodium chloride injection; human serum albumin 25%; normal human serum off-the-clot charcoal-dextran 1; human cord blood; leukocytes; potassium chloride in 5% dextrose and 0.9% sodium chloride; and 10% dextrose and 0.45% sodium chloride.

Author, year	Device	Fluid	Infusion rate	Duration	Findings
		Fresh frozen plasma	2 ml.min ⁻¹ , heated and unheated	60 min	High elution of aluminium, higher when warming vs. room temperature
		4% human albumin solution	2 ml.min ⁻¹ , heated and unheated	60 min	High elution of aluminium, higher when warming vs. room temperature
Cabrera, 2020[17]	Level 1 Fast Flow Fluid Warmer	Saline	30 ml.min ⁻¹	60 min	Undetectable
		Lactated Ringer's	30 ml.min ⁻¹	60 min	Did not reach toxic levels as defined by FDA
		Heparinized whole blood	30 ml.min ⁻¹	60 min	Undetectable
Perl, 2021[22]	enFlow (uncoated)	Saline	4 ml.min ⁻¹	60 min	Very low aluminium elution
		Saline with sodium acetate	4 ml.min ⁻¹	60 min	High aluminium elution
		Saline with sodium lactate	4 ml.min ⁻¹	60 min	Very high aluminium elution
		Saline with sodium lactate, acidified	4 ml.min ⁻¹	60 min	High aluminium elution
		Saline with sodium lactate, alkalinized	4 ml.min ⁻¹	60 min	Very high aluminium elution
		Saline, acidified	4 ml.min ⁻¹	60 min	High aluminium elution
		Sterofundin	4 ml.min ⁻¹	60 min	Very high aluminium elution
		Level 1	Saline with sodium lactate, alkalinized	4 ml.min ⁻¹	60 min

* Sterofundin ISO; Plasma-Lyte 148; single donor human whole blood; human packed cells; Ringer's lactate in 5% dextrose; human platelet lysate; human buffy coat; human plasma diabetic type 2; 5% dextrose solution; 3% sodium chloride injection; human serum albumin 25%; normal human serum off-the-clot charcoal-dextran 1; human cord blood; leukocytes; potassium chloride in 5% dextrose and 0.9% sodium chloride; and 10% dextrose and 0.45% sodium chloride.

Author, year	Device	Fluid	Infusion rate	Duration	Findings
		Sterofundin	4 ml.min ⁻¹	60 min	Very high aluminium elution
	ThermoSens	Saline with sodium lactate, alkalized	4 ml.min ⁻¹	60 min	Very low aluminium elution
		Sterofundin	4 ml.min ⁻¹	60 min	Very low aluminium elution
Waldmann[7]	enFlow (polyethylene coated)	Plasma-lyte 148	0.2 and 5.5 ml.min ⁻¹	5 hours	Undetectable
		Sterofundin ISO	0.2 and 5.5 ml.min ⁻¹	5 hours	Undetectable
		Whole blood	0.2 and 5.5 ml.min ⁻¹	5 hours	Undetectable
		Sixteen challenge solutions*	Quasi-static soak	72 hours	All below toxic exposure levels
<p>* Sterofundin ISO; Plasma-Lyte 148; single donor human whole blood; human packed cells; Ringer's lactate in 5% dextrose; human platelet lysate; human buffy coat; human plasma diabetic type 2; 5% dextrose solution; 3% sodium chloride injection; human serum albumin 25%; normal human serum off-the-clot charcoal-dextran 1; human cord blood; leukocytes; potassium chloride in 5% dextrose and 0.9% sodium chloride; and 10% dextrose and 0.45% sodium chloride.</p>					

<Insert Table 2 here>

Discussion

According to Table 1, uncoated aluminium heating plates are more likely to be corroded by fluids containing organic acids at low flow rates and at operating temperatures. Polyethylene coating appears to eliminate aluminium elution. Even after extensive exposure including soaking the cartridge in the fluid for 3 full days, polyethylene-coated cartridges do not appear to elute clinically significant levels of aluminium.

There are a wide variety of technologies that have been used for intravenous fluid warming. In addition to the direct contact warmers reviewed here, others have utilized dry heat countercurrent flows with plastic or stainless-steel tubing over heated plates, water baths, radiant heat, and coaxial heated tubes. Numerous authors have studied the effectiveness of the different approaches.[26–34] In general, direct contact warmers (fluid in contact with the heat source) outperform other technologies particularly at high flow rates.[26, 30, 31, 34] All approaches are highly sensitive to the distance between the warmer and the patient, so techniques that allow the heating unit to be close to the patient deliver more consistent temperatures.[29, 35, 36]

The primary risk of using contact warmers for parenteral fluid administration for prevention of hypothermia is in fact hypothermia. Very rapid administration of fluids or blood products is likely to overwhelm the ability of the device to warm the fluid sufficiently to prevent or treat hypothermia. The risk of air embolism has been described, and contemporary systems have been designed specifically to eliminate that risk.[37, 38] Hemolysis of heated blood products has been described with older technologies, although contact warmers are carefully controlled by microprocessors to maintain a safe temperature.[39, 40] Because of the direct contact between the infusate and the warming device, such warmers are subject to corrosion by the passing fluid with subsequent release of elements and other chemicals into the infusate. This risk seems to have been eliminated by the layer of parylene applied to the heating blocks. Parylene coatings have long half-lives with little risk of breakdown[41], particularly since these are single-patient-use cartridges.

In their Letter to Health Care Providers, the FDA identified the four original equipment manufacturers that were impacted by the concerns of safety related to aluminium leaching.[23] Vyaire did a complete voluntary recall and redesign of the uncoated enFlow in 2019 as described in an effort to protect patients from the harmful effects of aluminum elution.[15] Three manufacturers (Eight Medical International BV, Smisson Cartledge Biomedical, and Smith Medical) have initiated changes in their IFUs, and Eight Medical initiated a complete recall of its product two years later in 2021.[42] Smisson sent warning letters and IV pole laminated cards advising evaluation of risk vs. benefit when using their device in 2021.[43] Smiths Medical has not withdrawn the Hotline™ product line. As noted above, the literature related to potential aluminum poisoning from these devices was published in 2019.

Conclusions

Discussions about aluminium leaching from aluminium-based fluid heaters continue regarding measurement methodology, experimental set-up, and result interpretation.[17, 21, 22] In the interim, the FDA and European regulatory agencies will continue to provide guidance to practitioners. Parylene-coated aluminium block heaters appear to be safe and effective in the prevention of hypothermia in adults and children. Because of aluminum elution from uncoated heating blocks, only parylene-coated heating block contact warmers should be used. Studies are ongoing regarding elution of other potentially toxic substances from these life-saving devices. Direct contact IV fluid warmers appear to be among the most effective at prevention of perioperative hypothermia, and data on aluminum elution shows that a parylene-coated direct contact warmer should be selected.

Declarations

Ethics approval and consent to participate: not applicable Consent for publication: not applicable Availability of data and materials: not applicable Competing interests: DB, DH, MP, and AW are employees of Vyaire Medical. ER is an independent contractor working with Vyaire Medical. All authors were involved in the design of the study, review of the data, interpretation of the data, and creating and editing the manuscript. Funding: none Authors' contributions: ER and AW designed the literature search and reviewed

the articles; DB, DH, and MP collaborated on data analysis; ER and AW wrote the manuscript; all authors were involved in reviewing and revising the manuscript. All authors approved the final manuscript.

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