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Aluminium, cadmium and lead in large volume parenterals: contamination levels and sources

F. Pavanetto[1], I. Genta[1], B. Conti[1], T. Modena[1] and L. Montanari[2]

[1] *Department of Pharmaceutical Chemistry, University of Pavia, Pavia (Italy)*
and [2] *Department of Pharmaceutical Sciences, University of Padua, Padua (Italy)*

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Summary

Aluminium, cadmium and lead levels in large volume parenteral solutions (LVPs) produced in Italy were investigated; 135 samples of parenteral solutions of sterile water, 0.9% NaCl and 5%–10%–33% dextrose in varying volumes, taken from 25 batches and supplied by 3 different manufacturers, were examined. In order to highlight the factors contributing most significantly to the final contamination of LVPs by Al, Cd and Pb, raw material samples and extracts of rubber stoppers were analyzed. The leaching of Al and Cd from glass bottles was also evaluated before and after sterilization. Aluminium levels were in many cases found to be too high, cadmium was detected in appreciable concentrations while lead levels were quite low in all types of solutions examined. Leaching from rubber stoppers was always negligible; the contribution from glass bottles was also very low except for considerable leaching of Al from Type II glass in NaCl solutions. As far as aluminium is concerned, it would be advisable to establish official limits at least for those solutions used in total parenteral nutrition (TPN).

Introduction

Many investigations have pointed out the potential toxicity of trace elements present as contaminants in parenteral solutions. The topic was critically reviewed and discussed in the Working Conference on Parenteral Trace Elements II of 1982 (Am. Med. Assoc., 1984). Intravenous administration of aluminium and some heavy metals such as cadmium and lead, which are poorly eliminated by the body, represents a significant risk for patients undergoing total parenteral nutrition (TPN).

Recently, the accumulation of aluminium has been found to cause anemia, bone disease and encephalopathy in premature infants or babies with immature or impaired renal function (Sedman et al., 1985; D'Arcy, 1985; McGraw et al., 1986).

The toxic effects of cadmium and lead contaminating parenteral solutions have not so far been investigated and are unknown. It is, however, a fact that cadmium absorbed by the body is stored in the liver, in the kidneys and also in considerable amounts in the bones, causing osteomalacia and osteoporosis (Mahaffey, 1984). The biological damage caused by lead loading

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Correspondence: F. Pavanetto, Department of Pharmaceutical Chemistry, University of Pavia, Via Taramelli, 12-27100 Pavia, Italy.

mainly concerns the nervous system (Mahaffey, 1984): in adults the peripheral nervous system is usually affected, whereas the central nervous system is most commonly involved with children. Moreover, the toxic action of lead is also exerted on the haematopoietic organs and on the kidneys. Hence the need to reduce the amounts of cadmium and lead in intravenous parenteral solutions to a minimum.

The USP XXI, the only pharmacopoeia which considers large volume parenteral solution (LVP) requirements for heavy metals, has established a limit of 0.3 p.p.m. for some of these solutions. No official limits have yet been codified for aluminium but, in view of its proven toxicity, the need to establish contamination limits in TPN solutions is presently under discussion in the United Kingdom (McGraw et al., 1986) and in the U.S.A. (P.D.A. Annual Meeting, 1988).

Few data on aluminium can be found in the literature (Sedman et al., 1985; D'Arcy, 1985; McGraw et al., 1986; Klein et al., 1982; Winston et al., 1986; Quagliaro et al., 1988) and no data on the Cd and Pb content of intravenous solutions in general. Moreover, reliable information is still not available regarding factors responsible for this contamination (containers, raw materials and manufacturing procedures), essential when establishing effective preventive measures.

In this work we carried out a preliminary investigation on Al, Cd and Pb contamination of LVPs chosen among the most commonly used in therapeutic practice in order to assess their potential toxicity. We analyzed the following types of products in glass bottles: sterile water, 0.9% sodium chloride, 5%–10%–33% dextrose, volumes 500, 250 and 100 ml, and supplied by 3 different Italian producers. In all, 135 bottles from 25 batches were examined.

In order to assess the factors contributing most significantly to the final contamination of LVPs, the concentration of Al, Cd and Pb were determined for 10 batches including analyses of raw material samples and stopper extracts. The leaching of Al and Cd from glass bottles was also evaluated. The concentrations of these elements were compared in bottles from the same batch before and after sterilization.

The quantitative analysis of the elements was carried out using atomic absorption spectrophotometry.

Materials and Methods

Instrumentation

VARIAN mod. AA-1275 atomic absorption spectrophotometer, equipped with VARIAN mod. GTA-95 graphite furnace and a deuterium lamp for background correction; aluminium, cadmium and lead hollow-cathode lamps; VARIAN standard pyrolytic graphite-coated tubes.

Materials

135 LV parenteral solutions of different volumes (100, 250, 500 ml) from 25 batches and supplied by 3 different manufacturers (a,b,c). Rubber stoppers; NaCl and dextrose raw materials. Samples belonging to the batches examined were supplied by the manufacturers. All standard solutions and chemicals were high-purity quality (BDH, Spectrosol).

Contamination content uniformity in single LVP units

Al, Cd and Pb content uniformity was evaluated in ten 500 ml volume units of the different types of solutions considered. After shaking, the content of each bottle was divided into 10 portions; 3 of them, randomly chosen, were then analyzed.

Sample preparation

LVP solutions. A sample of about 50 ml solution was collected from each bottle, after shaking, by direct pouring into the polyethylene containers. For each batch, 5 units, randomly chosen, were analyzed.

Rubber stopper extracts. Extracts of stoppers from 10 batches were prepared following the F.U.I.IX ed. procedure; two samples from each batch were analyzed for leaching of Al, Cd and Pb. The influence of the type of product was evaluated on the most contaminating stoppers from 3 batches. Stopper extracts were prepared following the F.U.IX procedure, replacing water with NaCl 0.9% and dextrose 33% solutions as the extracting medium. Two samples were analyzed for each type of solution.

Analysis

Aluminium was analyzed as described in Halls and Fell (1985), lead as in Halliday et al. (1980) and cadmium following the standard procedure. The aluminium, cadmium and lead concentrations in the different samples were determined by the standard addition method. Each measurement was carried out at least in triplicate.

Statistical analysis

Statistical analysis consisted of univariate descriptive statistics and verification of the assumptions relating to the method of univariate analysis of variance. SPSS/PC + package procedures were used for all steps (Norusis, 1986).

Results

Contamination levels

Al, Cd and Pb contamination levels were uniform within each bottle: the concentration values for the individual portions of the bottles were always found to be between ±3% of the mean value. It is, therefore, possible to examine a single sample for each bottle.

Table 1 gives the concentrations (in μg/l) of Al, Cd and Pb in the examined batches. Sterile water contamination was found to be quite low, while 0.9% NaCl was the most highly contaminated product. Aluminium and cadmium were

TABLE 1

Concentration values (μg/l) of aluminium, cadmium and lead in different types of LVP

Solution	Batch no.	Mfg	Bottle volume (ml)	Al	Cd	Pb
Sterile water	1	a	500	6	2	5
	2	b	500	9	3	7
	3	b	250	20	< 1	3
	4	b	100	17	1	4
	5	c	500	12	1	3
0.9% NaCl	6	a	500	5 400	250	32
	7	b	500	4 300	183	30
	8	b	250	1 600	333	12
	9	b	100	1 600	417	16
	10	c	500	3 400	250	21
	11	a	500	3 484	57	–
	12	a	500	739	175	–
5% Dextrose	13	a	500	7	20	10
	14	b	500	5	21	5
	15	b	100	23	37	8
	16	c	500	24	22	7
10% Dextrose	17	a	500	43	120	9
	18	b	500	7	98	4
	19	b	250	16	85	7
	20	b	100	24	63	11
	21	c	500	27	125	2
33% Dextrose	22	a	500	81	422	37
	23	b	500	36	267	3
	24	c	500	38	308	7
	25	a	500	30	122	–

Mean values of the determinations made on 5 bottles per batch.

detectable in all the types of solutions, being present in appreciable amounts in 0.9% NaCl and 33% dextrose solutions. Pb concentrations were low in all the types of products.

The most highly contaminated batch was No. 6, with 5400 μg/l of Al, 250 μg/l of Cd and 32 μg/l of Pb; one bottle contained 8700 μg/l of Al and 1000 μg/l of Cd.

Contamination by the 3 trace elements varied considerably within the analyzed batches, even by a factor of 10 or more. Table 2 gives an example: the minimum and maximum concentrations of Al (μg/l) found in bottles belonging to the same batch. Through the statistical analysis of the data obtained for each metal the influence of the following possible sources of contamination was evaluated: type of product, container, manufacturer and raw material concentration.

Aluminium. The degree of contamination was found to depend mainly on the type of product. Al content in sterile water and dextrose solutions was usually < 50 μg/l, and thus comparable with the values reported in the literature (Sedman et al., 1985; McGraw et al., 1986; Klein et al., 1982; Winston et al., 1986). Levels in 0.9% NaCl solutions were much higher than reported in the literature (Sedman et al., 1985; McGraw et al., 1986; Winston et al., 1986).

In order to evaluate the leaching from the bottle, the ratios of volume to surface were calculated and are as follows:

Volume (ml)	V/S (ml/cm^2)
100	0.3
250	0.5
500	0.7

In all the types of products, the Al concentration was not significantly related to the corresponding ratio indicating that the container is not always the main source of contamination.

The Al contamination level varied according to the manufacturer ($P < 0.05$), such differences, however, being less marked than those relating to the type of product. For dextrose solutions, the Al content increased as the dextrose concentrations increased: no direct relationship was found. This should indicate that the raw material is one of the most important contamination sources, even though not the only one.

TABLE 2

Minimum and maximum aluminium concentrations (μg/l) in bottles from the same batch

Solution	Batch no.	Min	Max
Sterile water	1	4	11
	3	14	24
0.9% NaCl	6	600	8700
	9	140	1700
5% Dextrose	16	18	33
10% Dextrose	17	8	71
33% Dextrose	22	18	120

Cadmium. As with Al, Cd concentrations were clearly related to the type of product and, in the case of dextrose solutions, to their concentration. Furthermore, Cd concentration was not related to the ratio of volume to surface.

Unlike Al, for the same type of product no significant changes in contamination levels were found in relation to the manufacturer. Since no data can be found in the literature, at present no comparison can be made with similar products from other suppliers.

Lead. Pb content was very low in all products. For this reason, the statistical analysis of the data failed to reveal any significant difference in terms of the above mentioned variables. Further investigation of sources of contamination was limited to rubber stoppers.

Raw material contribution to contamination of LVPs

Table 3 gives the contribution of raw materials to Al and Cd content of some batches (Table 1). As far as Al contamination is concerned, the raw material is responsible for less than 60% of the total content, with the exception of Batch no. 13. The raw material contribution to Cd contamination varies from 10% to 90% and does not seem to be related to the product type.

The most contaminated NaCl raw materials contained 258 p.p.m. of Al and 15 p.p.m. of Cd. This Cd content exceeds the heavy metal limit of 10 p.p.m. stated by the European Pharmacopoeia (Eur. Pharm., 1983). This requirement is already

TABLE 3

Concentrations (μg/l) of aluminium and cadmium in some types of LVP and contribution of the various raw materials to the individual solutions

Solution	Batch no.	Al (μg/l)		Cd (μg/l)	
		LVP	Raw material [a]	LVP	Raw material [a]
0.9% NaCl	6	5400	2324	250	50
	7	4300	840	183	104
	11	3484	470	57	52
	12 [b]	739	96	175	135
Dextrose 5%	13	7	6	20	15
	14	5	3	21	3
Dextrose 10%	17	43	10	120	20
	18	7	4	98	10
Dextrose 33%	23	36	13	267	27
	25	30	9	122	65

[a] Values represent the mean of the data obtained with the analysis of two samples per batch.
[b] Sample packaged in Type I glass.

less strict than those of the USP XXI and J.P.IX, respectively 5 and 3 p.p.m.

Leaching from rubber stoppers

The extracting medium (water, 0.9% NaCl and dextrose 33%) has no detectable effect on the leaching. The minimum and maximum concentration (μg/l) of Al, Cd and Pb in the extracts examined are the following:

	Al	Cd	Pb
Min.	0.3	0	0
Max.	34	4	3

These values represent the leaching of at least 25 stoppers and therefore their contribution to final contamination of LVPs is negligible.

TABLE 4

Leaching of aluminium and cadmium from glass bottles

Solution	Batch no.	Al (μg/l)		Cd (μg/l)	
		n.s. [a]	s. [b]	n.s. [a]	s. [b]
0.9% NaCl	11 [c]	620	3484	57	57
	12 [d]	13	30	89	122
Dextrose 33%	25 [c]	555	739	157	175

Each value represents the mean of 5 bottles.
[a] Not sterilized.
[b] Sterilized.
[c] Type II glass F.U.IX ed.
[d] Type I glass F.U.IX ed.

Leaching from glass bottles

Al and Cd concentrations before and after sterilization of some batches (Table 1) are given in Table 4. The chemical attack of NaCl 0.9% solution on Type II glass led to a considerable increase in Al content after sterilization. The use of Type I glass could effectively reduce the Al contamination. The effect of sterilization is negligible in dextrose solutions.

In the products examined, leaching of Cd from both types of glass seems unaffected by sterilization.

Conclusions

This investigation revealed that Al and Cd contamination values in the LVPs examined vary and may be even quite high, depending mainly on the type of product. Pb levels are low in all types of solutions.

Generally, a patient undergoing TPN receives one litre of NaCl 0.9% and two litres of dextrose 33% daily. Considering the most contaminated solutions, the total burden over a month could be up to: 166 mg of Al plus 38 mg of Cd and 3 mg of Pb. In our view the contamination levels detected may be considered potentially toxic and should be reduced.

None of the contamination sources evaluated may be considered the main one. Release from rubber stoppers was always negligible. The contribution of bottles to final contamination is also very low, with the exception of considerable leaching of Al from Type II glass in NaCl 0.9% solutions. This product should be packaged in Type I glass bottles. The raw material is responsible for 10–90% of the Al and Cd content found in the different types of solutions.

In order to effectively prevent contamination by the above-mentioned trace elements, it would be useful to set specific limits for raw materials used in parenteral products. However, this is not a sufficient guarantee and also the finished product should be checked.

Recently, a maximum concentration of Al of 10 μg/l has been set in F.U.I.IX edn. for peritoneal dialysis and haemofiltration solutions, which contain electrolytes and dextrose (Farmacopea Ufficiale Italiana IX edn. I Supplemento 1988). Such limits might be also considered for LVPs to be used in TPN.

The subject of Cd contamination needs to be further investigated from a toxicological standpoint in order to define a suitable contamination limit.

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