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Original article

Barium in intravenous solutions for administration to neonates: Origins and levels of contamination

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SUMMARY

Background & aims: Barium is a glass constituent and a component of plastic additives, and may migrate from containers and devices into solutions. As barium is a toxic element, all steps involved in the preparation of intravenous solutions for premature neonates in an intensive care unit were evaluated to determine to what degree, if any, they contribute to Ba load. Commercial solutions for parenteral nutrition (PN) and medications and the apparatus used for administration were analyzed for their Ba content. Bags after compounding, medications after their preparation, infusion sets, and syringes were also evaluated.

Materials and methods: Ba concentration was determined by atomic absorption spectrometry.

Results: Bags, burettes, syringes, rubber caps, and glass containers yielded Ba in levels ranging from 0.02 to 4.38 mg/g. The highest levels among the solutions were found in multivitamins, magnesium sulfate, and calcium gluconate at 262 μg/L, 193 μg/L, and 166 μg/L, respectively. Most medications did not have measurable Ba contamination. However, after dilution in syringes, all of them became contaminated, and the highest level was reached in dexamethasone samples at 1333 μg/L Ba. Compounded PN bags ($n = 15$) had a mean of 54.6 μg/L Ba. The content of the same bags after percolating the burette had a mean level of 94.2 μg/L Ba.

Conclusion: Barium is leached from container materials into solutions parenterally administered to preterm babies. The handling processes of compounding and delivering nutrition solutions and medicines increased the Ba intake by almost 3 fold in relation to its levels in the starting products.

1. Introduction

Barium in the form of oxide is a glass constituent, and it is also present in plastics and rubbers in the form of soaps as stabilizers [2]. These materials are widely used in the pharmaceutical industry for storing solutions and drugs. Nevertheless, official concentration limits have not been established for Ba in packaging materials, except for polyvinyl chloride (PVC). The British Pharmacopoeia limits the amount of Ba in PVC bags to 5 ppm [3]. A species present in the container/closure system can go into the product via a leaching process that depends on several factors, of which the formulation composition plays a key role [4,5].

Barium is not an element essential to the body and is toxic in the form of soluble salts (the LD_{50} of $BaCl_2$ for humans, orally ingested, is 11.4 mg/kg). Reports of individuals exposed to high levels of barium suggest that the cardiovascular, nervous, and gastrointestinal systems are targets of barium toxicity. The likely cause of most of these effects is barium-induced hypokalemia [6]. Gastrointestinal disturbances are usually the first symptoms of acute barium exposure [7–11]. Hypokalemia, hypertension, and abnormalities in heart rhythm frequently occur shortly afterward [12]. About 90% of barium is absorbed in the bones [13], where it replaces calcium and is deposited in the form of phosphate or carbonate [14]. The remainder can be distributed in soft tissues such as the brain and the cardiovascular system.

Preparation of parenteral nutrition (PN) and intravenous medication involves multiple product manipulations. Although infusion solutions (NaCl, glucose, and Ringer's solution) are usually

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administered as they are furnished (ready-to-use bags), PN solutions are individually prepared from commercial products in hospital pharmacies according to the necessity of each patient [1]. Parenteral nutrition for neonates demands a particular strategy for the product and the drugs to be administered to the patients. Fig. 1 shows a simplified scheme of this process. The hospital pharmacy compounds the bags using commercial products and sends them to the neonatal intensive care unit (NICU). Drugs for administration to neonates are usually diluted in syringes and delivered to the patient via a burette, a graduated cylinder device intended to allow control over the volume of the infusion administered. These syringes are usually stored in the NICU for up to 7 days. During the course of this process, the final product administered to the patient remains in contact with different packaging materials for relatively long periods of time, which may favor an increase in contamination.

PN products contaminated by metals can lead to metal distribution in the body and metal deposition in organs, posing several risks to the patients. Previous studies have shown significant contaminations of PN solutions with metals such as barium, germanium, and manganese [15], arsenic [16], aluminum [17], chromium [18], and lead [19]. In this context, this study aimed to investigate the presence of Ba in packaging materials where pharmaceutical formulations for parenteral use are stored and to determine the level of this metal in medicines and PN solutions administered to preterm neonates.

2. Methods

2.1. Chemicals

All solutions were prepared using analytical grade reagents and ultra-pure water obtained in a Milli-Q water purification system (Millipore, Bedford, MA, USA). Reference solutions were prepared by suitable dilutions of the stock solutions containing 1000 mg/L of Ba (NIST, USA) in water. Arginine (Merck, Darmstadt, Germany), ornithine (Sigma–Aldrich, St. Louis, USA), glutamic acid (Merck), aspartic acid (Aldrich), EDTA (Merck), calcium gluconate (Sigma–Aldrich) and citric acid (Merck) solutions were prepared by suitable dissolution of their salts.

2.2. Contamination control

To avoid contamination, only plastic (polyethylene) laboratory ware (pipette tips and volumetric flasks) was used. It was immersed for at least 48 h in 10% HNO_3 in an ethanol (v/v) mixture and washed with Milli-Q purified water shortly before use. To avoid contamination from the air, all steps in the sample and reagent preparations were performed in a Class 100 clean bench.

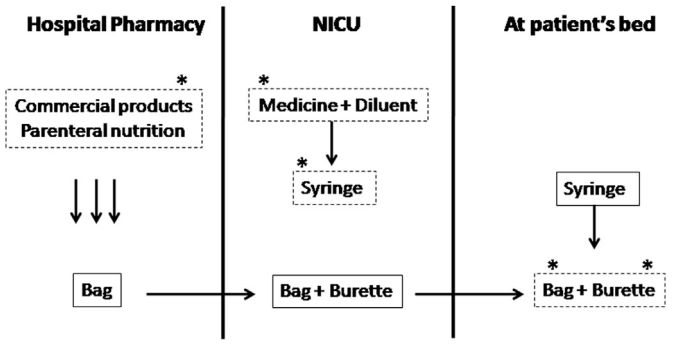

Fig. 1. Scheme of the handling process of formulations and medication at the hospital pharmacy and neonatal intensive care unit (NICU) to the patient administration. *Points at which samples were collected for analysis.

2.3. Apparatus

Barium was measured by atomic absorption spectrometry (AAS). For container materials, the measurements were carried out by flame AAS, and for all other samples by graphite furnace AAS (GF AAS). The flame AAS was a novAA 300 atomic absorption spectrometer from Analytik Jena AG (Jena, Germany). The flame used was C_2H_2/N_2O, the gas flow was 180 L/h, and the burner height was 5 mm. For these measurements, KCl (2% (m/v)) was used as an ionization suppressant. The graphite furnace atomic absorption spectrometer was a ZEEnit600 from Analytik Jena AG (Jena, Germany) with transverse Zeeman-effect background correction system and equipped with an MPE 60z auto-sampler. Calcium chloride (1% (m/v), 5 μL) was used as a chemical modifier.

2.4. Samples

Two groups of samples were collected at the University Hospital of Santa Maria. The first group, collected at the hospital pharmacy, included the commercial formulations for PN and infusion solutions used to prepare the patients' bags and the medicines administered to the patients. The second group, collected at the neonatal intensive care unit (NICU), included compounded bags with their respective administration sets (burette and lines) and the syringes containing the medications delivered to the patients. The commercial formulations and the medications were from batches identical to those used for compounding the bags and preparing the syringes. All samples from the first group had no previous manipulation. The second group consisted of the solutions left in the bags, burettes, and syringes after their administration to the patients. The asterisks in Fig. 1 represent process-handling points where samples were collected.

The commercial samples consisted of infusion solutions of sterile water for injection (SWFI), 0.9% NaCl, and 5% and 10% glucose and solutions for PN, including 10% amino acids, 20% lipids, 50% glucose, 10% calcium gluconate, 20% NaCl, 10% KCl, 10% and 50% magnesium sulfate, trace elements, and multivitamins. The medicines were aminophylline, dexamethasone, dobutamine, dopamine, gentamicin, furosemide, midazolam, morphine, and ranitidine. Three samples from the same lots were analyzed. Solutions from 15 compounded bags (used for different patients) were analyzed after collecting the fluid from both the bag itself and the burette.

Barium in these samples was measured by GF AAS. For the measurement, 50 μL HNO_3 was added to 1 mL of each sample, which was then diluted to 10 mL with water.

2.5. Container evaluation

An experiment was conducted to determine the concentration of Ba in each container/closure system and set used to store and deliver the formulations. The analyzed materials were new empty bags (Baxter, São Paulo, Brazil), clear and amber 10-mL ampoules (Schott, São Paulo, Brazil), polyethylene bottles (Fresenius, São Paulo, Brazil), burette sets (pediatric burette sets, Baxter), rubber stoppers from commercial amino acid solutions and lipid emulsions bottles, and rubber plungers removed from the syringes. For the determination of Ba, plastic and rubber samples were cut into small pieces, calcined and dissolved following the protocol established by the British Pharmacopoeia [3]. Glass samples were broken, crushed and prepared as described previously [20]. Briefly, the glass containers were crushed into fragments approximately 1 mm in size and mixed well. One hundred milligrams of the glass fragments were placed in a PTFE vessel with 5 mL of 48% (m/m) hydrofluoric acid and 5 mL of water, and heated in a domestic