MHRA PUBLIC ASSESSMENT REPORT

Calcium gluconate injection 10% in 10 ml glass containers: risk of aluminium exposure

September 2010

PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports we discuss safety issues associated with a particular medicine or group of medicines. The following report discusses the risk of exposure to high aluminium levels which occur in a medicine called calcium gluconate injection when stored in glass containers.

Calcium gluconate is a medicine licensed for use in several conditions such as acute hypocalcaemia[a], cardiac resuscitation[b], and some cases of neonatal tetany[c], and is given by injection or intravenous infusion[d]. Calcium gluconate injection is also used in total parenteral nutrition[e] (TPN) solutions, although this is not a licensed use. Calcium gluconate solution is stored in small containers made of either glass or plastic. It has been found that calcium gluconate solution in glass containers contains almost 200 times more aluminium[f] than calcium gluconate in plastic containers, due to the solution leaching aluminium from the glass. Increased aluminium levels can lead to risks associated with aluminium toxicity, such as adverse effects on bone mineralisation[g] and neurological (brain and nervous system) development, particularly in vulnerable patients such as those with renal impairment (where kidneys do not work properly), and children.

The Paediatric Medicines Expert Advisory Group (which advises the Commission on Human Medicines[h]) considered the available scientific evidence on the content of aluminium in calcium gluconate injection solution in glass containers, and the risks associated with aluminium accumulation, particularly in patients with renal impairment and children. On the basis of the evidence, the Group recommended that these products should no longer be used for repeated or prolonged treatment of children or those with impaired renal function, and have issued the following advice for healthcare professionals:

- Do not use calcium gluconate injection packed in small-volume (10 mL) glass containers for repeated or prolonged treatment, including as an intravenous infusion, in children aged younger than 18 years, or in patients with renal impairment

- Do not use calcium gluconate injection in small-volume glass containers in the preparation of TPN solutions

- Use calcium gluconate injection packed in plastic containers to reduce the aluminium burden in vulnerable patients

[a] Abnormally low levels of calcium in the blood, which can cause muscle cramps over short periods, and dry skin, chronic tiredness and visual problems over long periods
[b] An emergency procedure to restore blood circulation in a person who has collapsed and has no pulse, for example, due to a heart attack
[c] Long-lasting abnormal muscle contractions in a newborn baby
[d] Continuously administered into a vein
[e] Intravenous feeding of a patient (bypassing the digestive system)
[f] A metal found naturally, and in several man-made materials such as glass
[g] Acquiring vital substances such as calcium and other minerals required to maintain healthy bones
[h] An independent body who give advice to government Ministers about the safety, quality, and efficacy of medicines

Product information for all licensed calcium gluconate 10% injection in glass ampoules will be updated with the new advice.

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports we discuss safety issues associated with a particular medicine or group of medicines. The following report discusses the risk of aluminium exposure associated with calcium gluconate packed in glass containers.

Calcium gluconate 10% injection in glass ampoules is currently licensed in the UK for the treatment of hypocalcaemia, fluoride or lead poisoning, neonatal tetany and for cardiac resuscitation. There are concerns over the level of aluminium in this medicine, as aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium.

At the Congress of the European Association of Hospital Pharmacists in 2010, a poster by Beaney and Smeaton[1] was presented which discussed the aluminium content of calcium gluconate ampoules, and specifically referred to the product which is filled in clear glass ampoules. The authors analysed the aluminium content of calcium gluconate injection 10% packed in 10 mL (type 1) glass ampoules, compared to those packed in 10ml plastic ampoules. The results showed there is around 200 times more aluminium in calcium gluconate injection packed in glass ampoules than in that packed in plastic ampoules. Type 1 glass ampoules contain a significant amount of aluminium which may be leached into calcium gluconate solution during autoclaving and storage. Storage time, however, was found to have little effect on aluminium levels in plastic ampoules.

When calcium gluconate injection packed in 10 mL glass ampoules is used in the preparation of total parenteral nutrition (TPN), the aluminium content of the bag from the ampoule could be up to 220 µg/L. No current UK or EU guidelines are available on the daily limit for aluminium exposure or aluminium content in parenterals. However, in the US, to limit patients' exposure to aluminium, the Food and Drug Administration (FDA) has restricted the aluminium content of large-volume parenterals for TPN to 25 µg/L (but no limits currently exists for small-volume parenterals, although labelling of the aluminium content is required)[2].

Other publications refer to aluminium toxicity following parenteral nutrition, particularly in neonates.[3, 4] This was found to occur following the use of calcium gluconate filled in glass ampoules in the preparation of the parenteral nutrition.

Aluminium toxicity is more likely to occur in patients with impaired kidney function, including premature infants, who receive parenteral levels of aluminium at greater than 4 – 5 µg/kg/day[4]. The aluminium content in a TPN bag is likely to exceed this level if the calcium in the preparation is obtained from calcium gluconate 10% injection filled in glass ampoules. Vulnerable groups are potentially at risk of aluminium toxicity if their condition requires daily or continuous administration of calcium gluconate.

2. ASSESSMENT OF EVIDENCE

2.1 ALUMINIUM CONTENT OF CALCIUM GLUCONATE INJECTION 10% IN 10 ML GLASS AMPOULES

Calcium gluconate injection is available as 10 mL of 10% (weight/volume percentage solution [w/v]) calcium gluconate in type I clear glass ampoules. The excipients are 0.36% w/v calcium D saccharate and water for injections.

There are several literature publications on the interaction between glass and calcium gluconate. A recent poster publication by Beaney and Smeaton[1] described analysis of the aluminium content of calcium gluconate 10% injection packed in both plastic and glass 10ml containers, which was performed using inductively-coupled plasma mass spectrometry (ICP-MS). The samples from glass ampoules were pre-diluted with 18 MOhm water (100-fold) so that they were within the same range as the samples from the plastic ampoules. The average aluminium levels in calcium gluconate were as follows (µg/L):

- glass ampoules (long storage): 6135
- plastic ampoules (long storage): 31
- glass ampoules (short storage): 4890
- plastic ampoules (short storage): 27

The authors concluded that calcium gluconate from glass ampoules contain significant levels of aluminium oxide. There was little effect in aluminium content over storage time in plastic containers, although in glass it seemed that there were increased aluminium levels in old ampoules compared to new. Due to its high aluminium content, the authors recommended that calcium gluconate injection packed in glass ampoules should not be used for the preparation of parenteral nutrition solutions, particularly for neonatal use.

With this assessment, a publication in the literature was reviewed which investigated the interaction of chemicals with container materials during heating for sterilisation (Bohrer et al, 2003)[5]. Different commercial solutions for preparation of parenteral nutrition solutions, including calcium gluconate packed in glass, were assayed. The types of glass were not specified. The results showed a higher level of aluminium was measured from products packed in glass (1.57%) and rubber (4.54%), compared to plastic (0.05%).

Bohrer et al, 2003[5] also noted that aluminium release is enhanced from glass ampoules when containing solutions with calcium and phosphorus salts. In a previous study (Frey and Maier, 2000)[6], aluminium contamination was found to be less in calcium gluconate packaged in polyethylene containers (calcium gluconate Mini-Plasco, Braun 10%, 10 mL: 195 µg/L aluminium) compared to those packed in glass vials (calcium gluconate 10%, 10 mL: 5000 µg/L aluminium).

2.2 EFFECTS OF ALUMINIUM EXPOSURE

Aluminium is a polyvalent cation and is found in its ionic form in almost every animal and plant tissue. It is the third most abundant material within the earth's crust and is found in soil, water and air. The general population is exposed to aluminium from a variety of sources including food, water, beverages, canned products, containers and cooking utensils. Humans can additionally be exposed to aluminium through medication such as antacids, buffered analgesics and through intravenous pharmaceutical preparations such as parenteral nutrition (PN).

Due to the constant exposure to aluminium, estimating the minimum level of daily exposure is very difficult, but conservative estimates range between 3–5 mg/day from dietary sources. Aluminium is present in drinking water (due to the use of aluminium salts in the treatment of surface waters [eg, aluminium sulphate, aluminium polychloride]) at concentrations of less than 0.2 mg/L. Corresponding to an estimated daily consumption of 2 L of water per day, the exposure to aluminium from drinking water may be up to 0.4 mg/day.

In the 1970s, aluminium toxicity was first reported in patients with chronic renal failure receiving dialysis[7]. Aluminium toxicity associated with PN use has also been well known since the early 1980s, and steps to limit aluminium exposure in patients has been discussed ever since.

The body has a natural protective barrier to prevent systemic absorption of aluminium. Both the lung and skin are effective in limiting aluminium exposure, as is the gastrointestinal tract. Typically, <1% of ingested aluminium is absorbed systemically, however these protective mechanisms are bypassed when solutions are administered parenterally. As a result aluminium may be deposited in bone, kidney, liver, spleen, brain and other tissues.

Approximately 40% of intravenously infused aluminium is retained by adults, and up to 75% in neonates[8]; once absorbed, aluminium can remain in the body for a long time. The majority of aluminium elimination takes place via the kidneys; as such, patients at greater risk of aluminium toxicity are those with reduced renal function, particularly premature infants who have immature kidneys. In addition to their immature renal function, premature infants are more prone to aluminium toxicity due to their increased calcium and phosphorus requirements by TPN, and thus are exposed to more contaminants such as aluminium that are present in these solutions[8].

Aluminium competes with essential trace elements that are required for rapid growth and development, at times such as the last trimester in pregnancy or in early infancy. In animal studies, once aluminium is absorbed maternally it can cross the placenta and can accumulate in fetal tissue (ASCN/ASPEN, 1991)[9]. In-utero death, malformations, delayed ossification and growth and development retardation can also occur (Golub and Domingo, 1998)[10].

Exposure to aluminium from parenteral nutrition (PN)

A number of other diseases can be induced by aluminium toxicity following PN administration:

- *Metabolic bone disease:* this is a well-known complication of prolonged PN use. Aluminium affects bone development leading to decreased bone mineralisation, osteopenia and accumulation. A recent paper (Fewtrell 2009)[3] examined the significance of early aluminium exposure to bone health. In a 15-year follow-up study of premature infants exposed to PN formulations containing different aluminium concentrations, it was reported that exposure to aluminium from PN solutions impaired long-term bone mineralisation.

- *Anaemia:* aluminium appears to inhibit erythropoiesis and iron metabolism by hindering haemoglobin synthesis and erythroid cell maturation.

- *Neurological conditions:* aluminium is a neurotoxin and has been associated with dialysis encephalopathy. A paper by Bishop at al, 1997[4] reported that infants receiving TPN solutions rich in aluminium (45 µg/kg/day) for 10 days had

a 10 point deficit in Mental Development Index scores[a]. Development scores were compared to age-matched infants receiving 4–5 µg/kg/day in a similar time .

Many factors can influence the extent of aluminium contamination in a parenteral.There can be batch to batch variation of the raw material. The container design plays a significant role, glass and rubber stoppers have considerably more aluminium than plastic. Glass containers are also well known to be a source of contamination due to leaching.

In an effort to limit patient's exposure to aluminium and to prevent cases of aluminium toxicity, the US FDA implemented a requirement to include the aluminium content in a product's label, or to limit it (Code of Federal Regulations, 2009)[2]. Large-volume parenterals for TPN must state that the product does not contain more than 25 µg/L of aluminium. For small-volume parenterals no upper limit was specified, though maximum aluminium content at the product's expiry must be labelled.

The same publication also states that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminium at greater than 4–5 µg/kg/day accumulate aluminium at levels associated with central nervous system and bone toxicity.

A study assessing the aluminium content of parenteral nutrition in the USA in the paediatric population by Poole et al, 2008[11] found that available parenteral solutions contain amounts of aluminium which may lead to patients being exposed to a higher level of aluminium than that set by the FDA. It was considered that the amount of aluminium allowable in small-volume parenterals may be very high and maximum aluminium content was not set for these by the FDA.

A study by Frey and Maier, 2000[6] assessed the aluminium concentration of more than 40 products used for the preparation of TPN solutions to be administered to paediatric patients. They found high levels of aluminium especially in small glass ampoules containing complex-forming anions or glucose.

[a] Part of the Bayley Scales of Infant Development which measure the mental, motor and behavioural development of infants aged 1–42 months

3. CONCLUSIONS AND RECOMMENDATIONS

There is evidence to support that calcium gluconate is susceptible to aluminium leaching from glass containers. This is not seen in calcium gluconate solution contained in plastic ampoules.

An increased risk of aluminium toxicity therefore exists in patients who are likely to accumulate aluminium, if calcium gluconate packed in glass containers is used for prolonged or repeated treatment or in the preparation of TPN for these vulnerable patient groups. Any circumstance where continuous use is warranted could potentially put patients at an increased risk of aluminium toxicity. This is however more likely in patients with impaired renal function, including preterm infants.

The effects of aluminium toxicity are well known. These are associated with damage to the central nervous system, bone and liver, as well as haematological disorders. Aluminium toxicity is more likely to occur in patients with chronic renal failure as this may lead to decreased aluminium excretion and hence accumulation. Preterm infants are also at risk and are likely to develop aluminium-induced neurotoxicity and metabolic bone disease.

The Paediatric Medicines Expert Advisory Group (who advise the Commission on Human Medicines[a]) considered the evidence summarised in this report on the content of aluminium in calcium gluconate injection solution in glass containers, and the risks associated with aluminium accumulation, particularly in patients with renal impairment and children. On the basis of the evidence, the Group recommended that calcium gluconate injection 10% packed in 10 mL glass containers should no longer be used for repeated or prolonged treatment of children or those with impaired renal function, and have issued the following advice for healthcare professionals:

- Do not use calcium gluconate injection packed in small-volume (10 mL) glass containers for repeated or prolonged treatment, including as an intravenous infusion, in children aged younger than 18 years, or in patients with renal impairment

- Do not use calcium gluconate injection in small-volume glass containers in the preparation of TPN solutions

- Use calcium gluconate injection packed in plastic containers to reduce the aluminium burden in vulnerable patients

Product information for all licensed calcium gluconate 10% injection in glass ampoules will be updated with the new advice. The MHRA are in discussion with relevant parties within the NHS and other sectors to encourage a transition to the use of calcium gluconate injection packed in containers other than glass.

[a] An independent body who gives advice to government Ministers about the safety, quality, and efficacy of medicines

4. REFERENCES

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5. GLOSSARY

Acute colic
Severe abdominal pain of short duration

Adjunct
An additional drug used to treat a medical condition that provides benefits to the main drug used for treatment

Aluminium
A metal that occurs naturally in the Earth's crust. Aluminium compounds are found in man-made substances such as glass.

Ambulatory
Capable of walking

Ampoule
A small glass vial that is most commonly used as a container for injection solutions

Analgesic
Pain-reliever

Anion
A negatively-charged **ion**

Antacid
Drug that relieves pain and discomfort in disorders of the digestive system

Assay
An analysis that determines the presence and amount of a substance, or how powerful a drug is

Autoclaving
Sterilisation of medical or scientific equipment in a device called an autoclave, using high-pressure steam.

Bone mineralisation
The process by which the body uses substances called minerals to build bone structure

Calcium gluconate
A drug used for the treatment of conditions such as **hypocalcaemia**, fluoride or lead poisoning, **neonatal tetany**, and **cardiac resuscitation**

Cardiac resuscitation
An emergency procedure to restore blood circulation in a person who has collapsed and has no pulse, for example, due to a heart attack

Dextrose
An older name for glucose, a carbohydrate-based source of energy for the brain and body

Dialysis
The process of cleansing and filtering blood by passing it through a special machine. This process is necessary when a patient's kidneys (which naturally perform this process) do not work properly

Dialysis encephalopathy

A brain disease that occurs in some individuals receiving long-term dialysis, characterised by loss of intellect, personality changes and involuntary muscular jerks

Emulsion
A preparation of a medicine in which fine droplets of the liquid medicine are suspended in another liquid

Erythroid cell
Cells contained in bone marrow that eventually become red blood cells

Erythropoiesis
The process of red blood cell production

Excipient
An inactive substance that is combined with an active drug so that it is in a form that is suitable for a patient to take

Fetal tissue
Body tissue that is part of a fetus (unborn child)

Haemodiafiltration
Where **haemofiltration** and **haemodialysis** are used in combination

Haemodialysis
A technique of removing waste materials from the blood using the principles of **dialysis**. The technique is performed on patients whose kidneys no longer work properly (kidneys perform this process naturally)

Haemofiltration
A process that is similar to **haemodialysis,** used almost exclusively in intensive care for acute **renal failure**

Haemoglobin
Substance contained in red blood cells that binds to oxygen and transports it around the body

Heavy metals
Substances which exhibit metallic properties and may be toxic in large amounts

Hydrolytic resistance
Resistance to hydrolysis (the decomposition of a chemical compound by reaction with water)

Hypocalcaemia
Abnormally low levels of calcium in the blood

Ion
An atom or molecule that is electrically charged through gaining or losing electrons

In utero
A Latin term meaning ‘in the uterus or womb’

Inductively-coupled plasma mass spectrometry
A scientific method of determining the concentration of metals contained in a substance

Intravenous
Into, or within, a vein

Large-volume and small-volume parenterals
Different-sized containers used to hold a solution that is given to a patient through a **parenteral** route

Lumbar spine
The part of the spine located in the lower back region

Neonatal tetany
Long-lasting abnormal muscle contractions in a newborn baby

Neonate
A newborn baby aged 0–28 days

Ossification
Formation of bone

Osteopenia
Reduced bone mass

Osteoporosis
A condition involving loss of bone mass, making them more likely to break after a fall

Paediatric
Relating to children

Parenteral
Given to, or taken into the body, through a route outside the digestive system, eg, by injection

Peritoneal
Related to, or in the area of, the peritoneum (a membrane that lines the walls of the abdominal cavity)

Placenta
An organ within the uterus (womb) to which a developing embryo/fetus attaches during pregnancy. It provides the fetus with nourishment, oxygen and eliminates its waste

Polyethylene
A lightweight plastic especially used for containers and packaging

Polypropylene
A tough plastic used to make moulded articles

Polyvalent cation
A positively-charged **ion** that has more than one valency (the capacity of an ion to combine with another, based on the number of electrons it can lose, acquire or share)

Renal impairment
Failure of the kidneys to work properly

Sodium glycerophosphate
A drug used as a source of phosphate to treat imbalances of phosphate metabolism

Spleen

An organ located on the left-hand side of the body behind the stomach, which produces cells involved in immune responses, destroys old red blood cells, and acts as a reservoir of blood

Total parenteral nutrition (TPN)
Intravenously feeding a nutritionally adequate solution to a patient when they are unable to feed themselves by mouth

Trace metals
Metals that are present in animal and plant cells and tissue in very small quantities

Trimester
One of three 3-month periods that a human 9-month pregnancy can be divided by