REVIEW ARTICLE

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Aluminium in Over-the-Counter Drugs

Risks Outweigh Benefits?

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Abstract

In the early 1970s, aluminium toxicity was first implicated in the pathogenesis of clinical disorders in patients with chronic renal failure involving bone (renal osteomalacia) or brain tissue (dialysis encephalopathy). Before that time the toxic effects of aluminium ingestion were not considered to be a major concern because absorption seemed unlikely to occur. Meanwhile, aluminium toxicity has been investigated in countless epidemiological and clinical studies as well as in animal experiments and many papers have been published on the subject.

It is now commonly acknowledged that aluminium toxicity can be induced by infusion of aluminium-contaminated dialysis fluids, by parenteral nutrition solutions, and by oral exposure as a result of aluminium-containing pharmaceutical products such as aluminium-based phosphate binders or antacid intake.

Over-the-counter antacids are the most important source for human aluminium exposure from a quantitative point of view. However, aluminium can act as a powerful neurological toxicant and provoke embryonic and fetal toxic effects in animals and humans after gestational exposure. Despite these facts, the patient information leaflets from European antacids that are available OTC show substantial differences regarding warnings from aluminium toxicity.

It seems advisable that all patients should receive the same information on aluminium toxicity from patient information leaflets, in particular with regard to the increased absorption through concomitant administration with citrate-containing beverages and the use of such antacids during pregnancy.

1. Aluminium Exposure and Metabolism

Aluminium is the most abundant metal (comprising 8%) of the earth's crust and is widespread in the human environment. Although aluminium predominantly exists as insoluble aluminosilicates and oxides, human exposure can occur through drinking water (content 0.001–1 mg/L),[1] food and food additives, aluminium utensils and containers, antiperspirants and airborne contaminants. Daily aluminium intake in humans is estimated to be 2–100mg[2] and blood serum levels of aluminium do not normally exceed 10 μg/L (0.37 μmol/L) in healthy people.[3] However, while the average quantities of aluminium consumed in foods and beverages can be considered negligible, quantities of up to several grams a day can be consumed in aluminium-containing pharmaceutical products, such as buffered analgesics and antacids.

1.1 Aluminium Exposure Through Pharmaceutical Products

Despite the limited understanding of aluminium toxicology, aluminium salts are widely used as drugs. Many aluminium-containing drugs such as antacids and some buffered analgesics are ingested over a long period of time and are considered to be sufficiently safe for sale over-the-counter (OTC). Aluminium salts are also used as pharmaceutical excipients or as adjuvants in the preparation of a number of vaccines, toxoids and allergen injectants.

1.1.1 Antacids

Antacids are widely used without prescription as first-line therapy against mild gastro-oesophageal reflux and heartburn.[4,5] Significant amounts of aluminium can be found in antacids and table I provides a list of the aluminium compounds most commonly found in antacids together with the percentage of

Table I. Aluminium content of different aluminium compounds used in antacids

Compound	Chemical formula	Aluminium content in % (weight/weight)
Aluminium oxide	Al_2O_3	52.9
Aluminium hydroxide	$Al(OH)_3$	34.6
Dihydroxyaluminium sodium carbonate	CH_2AlNaO_5	18.7
Magaldrate	$Al_5Mg_{10}(OH)_{31}(SO_4)_2$	12.3
Hydrotalcite	$Mg_6Al_2(OH)_{16}CO_3 \times 4H_2O$	8.9
Almagate	$AlMg_3(CO_3)(OH)_7 \times 2H_2O$	8.6

aluminium content. When taken at the maximum recommended daily dosage these products can increase aluminium intake by between 277 and 3809 mg/day (see table II) depending on which product is consumed.

Aluminium hydroxide is the most commonly used aluminium salt in antacids, as well as in other aluminium-containing medications. Although it has the greatest acid-neutralising capacity of all other aluminium salts, aluminium hydroxide is reported to be less effective compared with other available antacid compounds such as magnesium hydroxide, calcium carbonate and sodium bicarbonate.[6]

Another important group of aluminium salts used in antacids is the 'lattice-layer' magnesium-aluminium hydroxide complexes, magaldrate and hydrotalcite.[7]

1.1.2 Buffered Analgesics

Aluminium compounds, such as aluminium hydroxide and aluminium hydroxide distearate, are included in various drugs to improve the dissolution of the active substance from a solid formulation. NSAIDs such as diclofenac, aspirin (acetylsalicylic acid) or ibuprofen, are organic acids that are poorly soluble in the acidic environment of the stomach. This means that when acid penetrates into the formulation, precipitation of the drug occurs and the rate of release is diminished. By including aluminium compounds into the dosage form, a neutral micro-environment can be maintained over a longer period of time, which enables the drug to be released in the stomach faster and to a larger extent. This is of major importance if the drug substance is to reach the systemic circulation as fast as possible, such as in the case of analgesics. Aluminium salts are also included in NSAID formulations to reduce gastric acidity, in an attempt to limit the local adverse effects of NSAIDs on the gastrointestinal mucosa.[8]

1.1.3 Vaccine Adjuvants

Aluminium compounds are widely used as adjuvants for human and veterinary vaccines[9] or hyposensitisation treatment of allergies. The adsorption of antigens on to the surface of adjuvant compounds like aluminium hydroxide and aluminium phosphate improves the vaccine properties by prolongation of antibody responses, particularly following primary immunisation. The advantages of aluminium adjuvants have been clearly demonstrated for various vaccines, especially those for tetanus and diphtheria toxoids.[10] However, the amount of aluminium remaining in the body after immunisation with a single injection of vaccine is obviously very small and cannot be related to human chronic diseases.

1.2 Aluminium Absorption

Until the 1970s, there was relatively little concern about the toxic consequences of aluminium ingestion, because it was assumed that aluminium was not orally bioavailable. This perception changed when Berlyne et al.[11,12] first investigated aluminium accumulation in uraemic patients and a possible involvement of aluminium in Newcastle bone disease was suggested, and aluminium salts were no longer considered to be non-absorbable. In 1977, Kaehny et al.[13] first showed elevated plasma and urinary levels of aluminium in humans with normal renal function after oral ingestion of various aluminium-containing antacids. An increase in plasma aluminium levels was also demonstrated by

Table II. Overview of the content in patient information leaflets (PIL) for leading European antacids and alginic acids containing aluminium

Country	Medication brand[a]	Aluminium compound	Aluminium content per tablet or 10mL (mg)	Maximum daily dosage of medication	Maximum daily aluminium intake as per PIL (mg)	Last update of PIL
Austria	Riopan® chewable tablets	Magaldrate	98.4	No upper limit (1 tablet on demand)	No upper limit	Apr 1998
	Talcid® chewable tablets	Hydrotalcite	44.5	No upper limit (1–2 tablets after meals, before bed – more, if required)	No upper limit	Jul 1995
Belgium	Gaviscon® tablets	Aluminium hydroxide	34.6	No upper limit (2 tablets after meals, before bed)	No upper limit	Apr 2000
	Maalox® 220/380 suspension[b]	Aluminium oxide	116.4	140mL	1629.6	Jul 2000
	Maalox® 200/400 tablets	Aluminium oxide	105.8	14 tablets	1481.2	Jul 2000
	Maalox® Forte 900/600 suspension[b]	Aluminium oxide	476.1	70mL	3332.7	Jul 2000
	Maalox® Forte 600/400 tablets	Aluminium oxide	317.4	10 tablets	3174	Jul 2000
France	Maalox® chewable tablets	Aluminium hydroxide	138.4	12 tablets	1660.8	Jun 1998
	Maalox® suspension	Aluminium oxide	121.7 per sachet (4.3mL)	12 sachets	1460.4	Jul 2000
	Riopan® chewable tablets	Magaldrate	98.4	12 tablets	1180.8	Jul 1998
	Riopan® suspension	Magaldrate	98.4	12 sachets	1180.8	Aug 2000
Germany	Maaloxan® 25 mVal chewable tablets	Aluminium oxide	105.8	8 tablets	846.4	Oct 2000
	Maaloxan® 25 mVal suspension[b]	Aluminium oxide	121.7	8 sachets	973.6	Oct 2000
	Magaldrat-ratiopharm®	Magaldrate	98.4	8 tablets	787.2	Mar 2000
	Megalac® chewable tablets	Hydrotalcite	44.5	12 tablets	534	Jul 2000
	Riopan® tablets	Magaldrate	98.4	8 tablets	787.2	Mar 2000
	Talcid® mint	Hydrotalcite	44.5	12 tablets	534	Apr 2000
	Trigastril® tablets	Aluminium oxide	170.9	14 tablets	2392.6	Nov 2000
Italy	Maalox® TC chewable tablets	Aluminium hydroxide	207.6	9 tablets	1868.4	Jul 2001
	Maalox® TC suspension[b]	Aluminium hydroxide	415.2	45mL	1868.4	Jul 2001
	Maalox® tablets	Aluminium hydroxide	138.4	8 tablets	1107.2	Sep 1998

Continued next page

Table II. Contd

Country	Medication brand[a]	Aluminium compound	Aluminium content per tablet or 10mL (mg)	Maximum daily dosage of medication	Maximum daily aluminium intake as per PIL (mg)	Last update of PIL
The Netherlands	Gaviscon® 250 chewable tablets	Aluminium hydroxide	17.3	16 tablets	276.8	Feb 1995
	Gaviscon® Forte chewable tablets	Aluminium hydroxide	34.6	8 tablets	276.8	Feb 1995
	Maalox® chewable tablets	Aluminium oxide	105.8	8 tablets	846.4	NI
	Maalox® Forte suspension	Aluminium oxide	476.1	8 sachets	3808.8	NI
Portugal	Kompensan® tablets	Dihydroxy aluminium sodium carbonate	63.6	18 tablets	1144.8	Apr 1996
	Maalox® Plus tablets	Aluminium hydroxide	69.2	16 tablets	1107.2	Mar 2001
Spain	Almax® tablets	Almagate	43	No upper limit (1–2 tablets after meals, before bed – more, if required)	No upper limit	Dec 1995
	Almax® Forte suspension	Almagate	129 (per 15mL)	No upper limit (1–2 tablets after meals, before bed – more, if required)	No upper limit	Dec 1995
	Bemolan® tablets	Magaldrate	49.2	20 tablets	984	NI
	Minoton® gel	Magaldrate	98.4	10 sachets	984	NI
Switzerland	Alucol® tablets	Aluminium hydroxide	186.8	8 tablets	1494	Sep 1995
	Alucol® gel	Aluminium hydroxide	259.5	80 mL	2076.0	Sep 1995
	Riopan® 800 tablets	Magaldrate	98.4	No limitation (1 tablet on demand)	No upper limit	Apr 1998
UK	Gaviscon® 250 tablets	Aluminium hydroxide	17.3	No limitation (2 tablets on demand)	No upper limit	Mar 2001

a Use of tradenames is for product identification purposes only and does not imply endorsement.

b The product contains citric acid as an excipient, which is reported to increase aluminium absorption.

NI = not indicated.

Tsou et al.[14] in infants (mean age of 6 months) after the ingestion of aluminium-containing antacids.

Today it is well established that aluminium is absorbed via the gastrointestinal tract. Its absorption is strongly determined by the chemical form and the doses of aluminium administered as well as the physico-chemical environment in the gastrointestinal tract and the presence of dietary constituents.[15] Accordingly, the amount of systemically absorbed aluminium is subject to large variation. The data vary from 0.06–27% in animals and 0.001–24% in humans depending on the aluminium intake,[15] although in general the absorption rate is likely to be towards the lower part of this range. For antacids, after the reaction of the ingested aluminium hydroxide with gastric acid, between 17% and 30% of the resulting aluminium chloride can be systemically absorbed.[16] Although aluminium hydroxide is known to be one of the least soluble aluminium salts, it can serve as a source of bioavailable aluminium. As an amphoteric compound it is, to a certain extent, soluble in both acidic and basic solutions so that aluminium absorption may occur.[6]

In addition, aluminium from the lattice-layer antacid, magaldrate, has been shown to be absorbed in individuals with normal renal function. After four single doses given at 4-hourly intervals, serum aluminium levels were significantly increased after 24 hours compared with baseline.[17]

Investigations have shown that giving aluminium with beverages such as fruit juices, coffee, tomato juice, ethanol and wine may significantly enhance the absorption of the element.[18-20] In particular, concomitant citrate ingestion greatly increases aluminium uptake.[21-23] As Weberg and Berstad reported,[24] blood aluminium levels rise 50-fold in individuals with normal renal function when a commercial aluminium hydroxide antacid preparation is taken with citric acid solution, compared with water.

1.3 Aluminium Retention

In healthy people, approximately 90% of the aluminium transferred from the gastrointestinal tract to the blood is rapidly eliminated, primarily by the kidneys or via the bile.[25] However, as animals and humans accumulate aluminium in tissues with continued exposure, Greger[20] considers the assumption that all absorbed aluminium is excreted in the urine is likely to be false. Furthermore, Greger[20] expects that the relative percentage of aluminium that is retained and not excreted in the urine could vary with kidney function, age and disease state.

Aluminium is able to make use of transferrin, a plasma protein that is normally utilised by iron, to access brain cells.[26] Specific transferrin receptors that are only present in the capillaries of the brain[26,27] may facilitate the uptake of transferrin-bound aluminium across the blood-brain barrier into the brain tissue.

In cases when aluminium is parenterally administered and the protective barrier of the gut is bypassed or renal elimination is decreased, the metal is easily deposited and will accumulate in different tissues, especially in bone, liver, spleen and kidneys, as well as in the brain and other nervous tissue.[20] Consistent with these findings, Zumkley et al.[28] showed considerably elevated aluminium concentrations in bone and brain tissue in patients with healthy kidneys who had received an aluminium-rich antacid (470mg elemental aluminium/dose) seven times daily over a period of 10 days (brain) or 4 weeks (bone).

Interestingly, citric acid and a variety of other organic acids including lactic acid, tartaric acid and oxalic acid are not only known to increase aluminium absorption, but may also enhance the retention of aluminium in tissues.[15,20]

2. Aluminium Toxicity in Adults

Aluminium has no known biological or physiological role; however, due to its size and electrical charge the metal ion may act as a competitive inhibitor of several essential elements, such as magnesium, calcium and iron. Aluminium's capability of making use of transferrin illustrates that aluminium is able to utilise plasma proteins that normally enable iron to access cells. In addition, aluminium can replace magnesium in many biological systems and seems to compete with calcium for phosphate and small ligands.[29] Meiri et al.[29] also reported that aluminium not only affects many key processes within the cell but may also produce toxic effects at the cell membrane in several ways including the alteration of the physical properties of the membrane or the secretion of transmitters. Regarding the potential role of aluminium in Alzheimer's disease, McLachlan[30] summarises the potential pathological mechanism of aluminium related to Alzheimer's disease in his detailed review.

2.1 Classic Aluminium-Related Human Health Disorders in Kidney Patients

Most of the documented cases of aluminium-related health disorders are due to iatrogenic exposure to aluminium[31] including various sources such as high aluminium haemodialysis solutions, the administration of aluminium-containing antacids and phosphate binders, and aluminium-contaminated parenteral nutrition.

Kidney patients undergoing routine haemodialysis were the first patient group to display symptoms of aluminium toxicity. Significantly elevated exposure to aluminium has occurred from dialysis for the following reasons:[25]

- the use of untreated water and the circumvention of the usual gut-blood barrier during dialysis caused increased aluminium levels;
- aluminium hydroxide containing phosphate binders were the main oral aluminium source affecting long-term dialysis patients;
- renal failure reduces renal excretion of aluminium.

As a result of this aluminium loading, uraemic patients have developed a triad of dialysis-related conditions; renal osteodystrophy, hypochromic microcytic anaemia and dialysis encephalopathy.

2.1.1 Renal Osteodystrophy

Renal osteodystrophy is a unique vitamin D-resistant osteomalacia, characterised by highly elevated amounts of aluminium in the bone, which impairs the mineralisation process as well as the proliferation and activity of bone cells. The aluminium acts directly on bone by inducing a state of phosphate deficiency or by indirectly inhibiting parathyroid hormone (PTH) function.[6,32-36]

2.1.2 Hypochromic Microcytic Anaemia

Microcytic anaemia is associated with elevated aluminium plasma levels. It has been postulated that this condition may result from the plasma binding of aluminium with transferrin leading to competition with iron transfer and metabolism.[6,37]

2.1.3 Dialysis Encephalopathy

Dialysis encephalopathy (which is characterised by severe mental disorders), observed in renal dialysis patients, was first related to aluminium intoxication by Alfrey et al. in 1976.[38] Haemodialysis with aluminium-containing solutions has been identified as the cause of an increasing aluminium content in various tissues including the brain, ultimately leading to this progressive and lethal mental disease. With the introduction of reverse osmosis as the purification technique for water used during dialysis and the availability of aluminium-free phosphate binders, dialysis encephalopathy has essentially disappeared. Nevertheless, chronic dialysis patients are still subject to subclinical aluminium neurotoxicity as reported by Cannata-Andia.[39] It should be kept

in mind that increased serum aluminium levels may have significant impact on mortality among patients undergoing long-term haemodialysis as reported by Chazan et al.[40] In their study of 10 646 dialysis patients, serum aluminium level proved to be an important predictor of survival: mortality rates were 18% higher for patients with serum aluminium levels of 1.52–2.22 μmol/L compared with lower plasma levels (normal levels: up to 0.37 μmol/L). Although the mechanism of this toxicity is still unknown, these data may indicate that elevated aluminium concentrations have adverse effects on enzyme activities and cell metabolism.

2.2 Long-Term Exposure Through Aluminium-Containing Medications

As research work over the last 3 decades has shown, ingestion of aluminium-containing antacids, for even a relatively short period of time, increases aluminium plasma levels.[13,14,17,22-24] Furthermore, it was strongly suggested that the consumption of these medications may lead to an elevated concentration of aluminium in various organs and to the deposition of aluminium in bone and brain tissue.[28] Compared with the wide range of literature on renal patients, these findings were obtained from adults and infants with healthy kidneys. Nevertheless, currently available data suggest that, in healthy individuals, the absorbed amounts of systemic aluminium after using aluminium-containing antacids for a relatively short amount of time will, under normal circumstances, be eliminated mainly via the kidneys.[20,41]

In contrast to short-term consumption, long-term antacid therapy, even when used by patients with normal renal function and within the manufacturer's label recommendations, can lead to severe phosphate depletion, osteomalacia and toxic accumulation of aluminium.[42] Recker et al.[43] described one suspected case of aluminium associated osteodystrophy in a patient with normal renal function. The patient in question had consumed aluminium-containing antacids for a period of 25 years and had an elevated aluminium bone content. Direct toxicity of the bone rather than phosphate depletion was suggested. These findings have been reported for high aluminium-containing antacids (aluminium hydroxide). Nevertheless, possible subtle toxicity should be taken into account when low aluminium-containing lattice-layer antacids (magaldrate, hydrotalcite) are administered in critically ill patients and patients with renal failure over a longer period.[17] It still remains unclear whether long-term exposure to even small amounts of aluminium in patients with normal renal function may slowly lead to accumulation, leading to clinically inapparent toxic effects over time, as reported for dialysis patients in recent years.[39,44,45] In this context, data published by Chazan et al.[40] should be noted, which suggested that increased aluminium plasma levels have significant adverse effects on survival rates of patients receiving long-term dialysis even in the absence of overt aluminium toxic reactions.

2.3 Aluminium and Alzheimer's Dementia

Flaten[46] indicated in his informative review that there are several reports of elevated aluminium concentrations in samples of neurofibrillary tangles and senile plaques, as well as in the brain of patients with Alzheimer's dementia. Some epidemiological studies indicate a relationship between aluminium exposure through drinking water and Alzheimer's dementia. In addition, it has been documented that many pathological and clinical aspects similar to those of Alzheimer's dementia can be induced in experimental animals depending on aluminium dose, type of compound and application procedure.[47] Elevated aluminium levels have also been detected in brains of patients with a variety of chronic encephalopathies such as amyotropic lateral sclerosis (ALS) and Parkinsonism-related dementia.[41,48] Interestingly, ALS and Parkinsonism-relat-

ed dementia have been described as a consequence of environmentally-induced aluminium intoxication on the island of Guam in the western Pacific.[49] Although these findings may suggest that there is some association between aluminium and Alzheimer's dementia, they are not adequate to prove any aetiological relationship. Flaten[46] believes that if aluminium has any role in Alzheimer's dementia it may probably contribute to the disease as a co-factor by accelerating the neurodegeneration process. There are still many unanswered questions remaining. So far, epidemiological studies of aluminium-containing medication exposure and Alzheimer's dementia have been largely negative.[50,51]

3. Aluminium Toxicity in Pregnancy, Lactation and Neonates

3.1 Animal Studies

A large number of experiments carried out on animals have shown that aluminium can penetrate the placenta and accumulate in the fetal tissue, particularly in the bones.[52] The majority of studies have investigated the effects of prenatal aluminium exposure on postnatal development and the behaviour of the offspring. Common findings included reduced weight of offspring, lower rate of weight gain during the period of lactation, abnormal skeletal growth, and impairment of neurological functions, as well as increased rates of stillbirths and perinatal mortality.[53-63] In addition, aluminium has been found to be present in the milk of aluminium-exposed dams for a long period of time.[64]

3.1.1 Effects of Systemically Administered Aluminium Salts

When administered systemically, aluminium salts (e.g. aluminium lactate) at doses of 10.8 mg/kg/injection lead to embryo and neurotoxic effects in rabbit does and their offspring. Rabbit does showed a reduced litter size following subcutaneous doses of aluminium lactate during gestation. Rates of stillbirth and postnatal mortality of the offspring were slightly increased, even at lower dosages (2.7 mg/kg/injection). Young animals displayed a lower weight gain during the lactation period.[62,65]

In rat fetuses and sucklings, increased aluminium levels were found in the brain and the nuclear fraction (brain cell nuclei) after maternal subcutaneous injections. Yumoto et al.[66] concludes that aluminium passes the blood-brain barrier, enters the placental passage and reaches the maternal milk.

Muller et al.[64] documented damaging effects of aluminium on young rats through lactational transfer of aluminium. When female rats received aluminium chloride (10mg aluminium/kg/day) intraperitoneally during the first 12 days after delivery, the aluminium plasma values rose 30-fold compared with the control group. Furthermore, the milk/plasma ratio had increased to 6.6 in the aluminium-treated dams, compared with 2.0 in the control group. In addition, offspring of the intoxicated dams showed growth retardation after postnatal day 7.

3.1.2 Effects of Orally Administered Aluminium Salts

Experiments on rats and mice have confirmed that embryo/fetal toxicity also occurs following oral administration of a variety of aluminium salts (aluminium-nitrate, aluminium-lactate, aluminium-chloride, aluminium-hydroxide) via drinking water, food or by gavage. Increased postnatal mortality in rats has been reported following the administration of aluminium during gestation,[54] as well as an increased number of cleft palates and skeletal malformations following the administration of aluminium nitrate,[67] aluminium lactate and aluminium hydroxide concurrent with lactic acid.[58]

A study by Golub et al.[57] indicated that high maternal aluminium dietary levels (250 mg/kg/day) may lead to growth retardation in offspring. Further investigations by Clayton et al.[60] examined the

long-term effects of aluminium exposure in pregnant mice on the foetal mouse brain. Significant effects on the cholinergic system in the brains of offspring up to the age of 44 weeks were detected by measuring choline acetyl transferase. This implies sufficient access of aluminium to the fetal brain in order to induce neurotoxic effects. A number of other studies have also shown neurotoxic effects in rats and mice where maternal oral aluminium exposure leads to impaired negative geotaxis, and reduced forelimb or hind limb grip strength.[57,63]

3.1.3 Aluminium Hydroxide and the Influence of Citrate

As mentioned, aluminium hydroxide is commonly used in aluminium-containing antacids. While aluminium salts such as aluminium chloride or aluminium nitrate proved to be embryotoxic when administered to pregnant rats and mice, no developmental effects were observed when aluminium hydroxide in dosages up to 260mg aluminium/kg/day were given orally to rats and mice during gestation.[56,68] However, when citric acid (62 mg/kg/day) was orally administered concomitantly with aluminium hydroxide (133mg aluminium/kg/day) to rats during organogenesis, the incidence of skeletal variations increased significantly.[69] Similar results were obtained with aluminium hydroxide and concurrent ingestion of lactic acid.[58]

3.2 Aluminium Toxicity in Human Pregnancy and Lactation

Gastro-oesophageal reflux with the typical symptom of heartburn is a common complaint during pregnancy affecting up to 85% of pregnant women, with the prevalence of heartburn increasing with gestational age and parity.[5,70] Although between 30–50% of pregnant women use antacids to relieve dyspeptic symptoms,[5] little is known about the impact of aluminium-containing antacids in human pregnancy. In a case study by Gilbert-Barness et al.,[71] a mother disclosed that she had taken an average of 75 antacid tablets daily during her entire pregnancy, corresponding to a daily intake of 15g aluminium hydroxide or 5200mg elemental aluminium. Her daughter was diagnosed as having a neurodegenerative disorder with profound mental retardation, multifocal seizures, spastic tetraplegia, growth retardation, and spasticity. The girl died at the age of 9 years.

A study by Mandic et al.[72] found extraordinarily high aluminium concentrations in human breast milk. This would suggest that aluminium may generally reach breast-fed newborns, but toxicity data are lacking. At usual dosages, however, no cases of toxicity in fetuses or newborns have been reported although encephalopathies in preterm infants, severe adverse reactions in patients with renal failure, as well as the results of recent investigations on embryo/fetal toxicity of aluminium in mammals, act as a reminder of caution.[38,39,44,52,73,74]

3.3 Aluminium Toxicity in Preterm Infants and Neonates

Bishop et al.[73] investigated the effects of perinatal exposure to intravenous aluminium on the neurological development of 227 infants born prematurely. One group of premature infants received standard feeding solutions and the other group received aluminium-depleted intravenous feeding solutions. They were evaluated using the Bayley scales of infant development at 18 months of age. The authors found significant differences between the two groups, especially for subgroups with longer duration of feeding, indicating that the children who received the non-aluminium-depleted feed had a lower Bayley index and hence an increased risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminium exposure was associated with a reduction in the index; an adjusted loss of one point per day was noted with intravenous feeding.

With the exception of new borns with renal failure, the risk of aluminium toxicity through oral iatrogenic aluminium exposure seems to be low in neonates. Nevertheless aluminium-containing solutions should be avoided in the intravenous feeding of preterm infants and neonates.

4. Implications of Aluminium Toxicity Data on European Regulatory Practice for Over-the-Counter Antacids

4.1 Aluminium-Containing Antacids in Selected European Countries

Aluminium consumed in foods and beverages amounts to <1% of the quantities that can be consumed by ingestion of pharmaceutical products such as aluminium-containing antacids. Antacids are widely used as first-line therapy for mild gastro-oesophageal reflux and heartburn,[4] and are administered in substantial amounts. Investigations in selected European countries (Austria, Belgium, France, Germany, Italy, The Netherlands, Portugal, Spain, Switzerland, and the UK) shows that aluminium-containing antacids are available OTC, which means that they can be administered over a longer period of time without the need for a medical prescription.

An overview of the aluminium content of these pharmaceutical products (see table II) reveals considerable differences in the aluminium content per dose and in the maximum recommended daily dosage, leading to variations in the maximum daily aluminium intake which may range from 277 to 3809 mg/day of aluminium depending on which product is consumed. Aluminium hydroxide and the magnesium-aluminium-hydroxide complex, magaldrate, are the most commonly used aluminium salts in these European antacids. Interestingly, several of these antacids even contain the absorption-enhancing agent, citric acid, as an excipient (see footnote b in table II).

4.2 European Patient Information Leaflets of Aluminium-Containing Antacids

Registration dossiers of medical products, as well as professional and patient information leaflets (PILs), are provided by pharmaceutical companies in their role as marketing authorisation holders, and these leaflets are controlled and approved by national regulatory authorities. A comparative survey of current PILs for aluminium-containing antacids sold in selected European countries shows some common information, but also certain discrepancies.

In all PILs that were examined (see table II), a warning against the administration of these products in cases of existing renal disease or kidney problems is present. Concerning pregnancy, Dutch and Belgian leaflets do not warn against the use of aluminium-containing antacids during pregnancy, but, in some cases, patients are advised against their use during breast-feeding. Portuguese patients are clearly advised against the administration of these products during the lactation period. In most cases, Austrian, French, Italian, Spanish and Swiss PILs advise patients to use these products in pregnancy and lactation only on the basis of advice from a medical practitioner or pharmacist. However, the professional information (Summary of Product Characteristics) in Switzerland and Austria merely contain general statements concerning pregnancy and lactation periods, for example, antacids containing aluminium should only be administered if 'the potential benefit exceeds any health risk for the fetus'. In the UK, PILs contain no special limitations concerning pregnancy and lactation.

Interestingly, the PILs mentioned above in this section contain no indication that the concurrent use of aluminium-containing antacids with other acidic beverages such as fruit juices, wine, or with citrate-containing beverages, should be avoided. Advice to this effect is, however, of some importance as these fluids can increase the intestinal absorption of aluminium as mentioned above.

In addition, the information that aluminium can be absorbed via the gastrointestinal tract and be retained in human brain and bone tissue, if consumed over the long-term in patients with normal renal function, is not provided in any European PILs except for those issued in Germany. The latter are indeed the most detailed and contain important information on the possible properties of aluminium, which consumers of an OTC drug should take into account. The following are of particular note (from German PILs of aluminium-containing antacids):[75]

- "The concurrent administration of the drug with acidic beverages like fruit juices or wine leads to an unwanted increase in aluminium absorption from the intestine;"
- "In order to avoid an aluminium overload of the child during pregnancy, the drug may only be consumed short-term. Aluminium compounds are transferred into mother's milk."

5. Discussion

It is now commonly acknowledged that aluminium toxicity can be induced by infusion of aluminium-contaminated dialysis fluids, by parenteral nutrition solutions, and by oral exposure as a result of aluminium-containing pharmaceutical products such as aluminium-based phosphate binders or antacid intake. This so-called aluminium toxicity syndrome includes neurotoxic effects, osteomalacia and microcytic anaemia, and mainly affects patients with chronic renal failure and patients on dialysis. The discovery of orally-administered aluminium as an aetiological agent of this toxicity syndrome finally brought about a general consensus that aluminium is absorbed via the gastrointestinal tract. Although today, aluminium toxicity is widely considered as a problem of the past, subclinical aluminium toxicity with more or less clinically inapparent aluminium accumulation is still seen in renally-impaired patients on chronic dialysis as a result of continued exposure to low but non-negligible amounts of aluminium via dialysis fluids and through oral sources.[39,44]

Animal studies indicate that, once absorbed, maternally administered aluminium crosses the placenta and accumulates in fetal tissues causing a developmental syndrome that includes *in utero* death, malformation, delayed ossification, growth restriction and developmental retardation.[52,76] The developmental toxicity of orally-administered aluminium appears to be highly dependent on the bioavailability of the aluminium compound and the presence of dietary components that promote aluminium uptake.

Recent data on human fetal exposure seem to confirm the findings from animal studies. Gilbert-Barness et al.[71] reported the death of a child at the end of progressively deteriorating neurodegeneration following daily ingestion of very high amounts of aluminium hydroxide by the mother. Although these findings should be queried on account of the extreme and unusually high doses of aluminium-containing antacids consumed by the mother, this clinical case makes it difficult to further deny a causal relationship between aluminium exposure during pregnancy and developmental neurotoxicity. Nevertheless, it is evident, that this study does not lend itself to the assessment of the actual health risks of aluminium-containing medication administered during pregnancy. It does, however, confirm that a critical and yet to be determined threshold value exists (as for any other active agent) where the effectiveness and tolerability of the medication is superseded by its toxicity and adverse effects begin to be clinically apparent. The determination of such a threshold is likely to be a slow and gradual process, possibly involving a large number of unreported cases.

As indicated by the German regulatory authority, Bundesamt für Arzneimittel und Medizinprodukte (BfArM), in a written statement on the subject submitted on request of the authors of this article, "it is surely assumed that less serious neurotoxic impair-

ments in children prenatally exposed to aluminium are unlikely to be spontaneously reported as such" (U. Heier, personal communication). This assumption may have contributed to the decision to insist on detailed information/warnings in the German PILs on aluminium-containing antacids.

The critical threshold value for oral aluminium consumption may be particularly difficult to identify because aluminium toxicity is largely determined by its bioavailability. Additionally, most metabolic processes through which aluminium can exert its toxic properties are still unknown.

It is clear from the above that there are still many gaps and inconsistencies in the epidemiological and toxicological data concerning aluminium. However, in the absence of detailed understanding of the effects of aluminium *in vivo* and its influence on physiological processes as well as its toxicology, it appears prudent to recommend that the needless intake of aluminium salts from foods and OTC drugs, especially during pregnancy, should be avoided whenever possible. In a recently published paper, an expert panel on gastroenterology and obstetrics – chaired by Professor Tytgat – agreed that high-dose aluminium antacids should not be recommended for the treatment of reflux in pregnancy.[77]

The discrepancies in the information content of the various European PILs of aluminium-containing antacids (mentioned in section 4.2) may be due to the fact that antacids have been available on the market as OTC medications for several decades, and yet, the available scientific data on aluminium toxicity have, to date, not been considered by all national regulatory authorities to an equal degree.

The findings of the numerous and most recent experimental studies and clinical reports discussed in this article clearly indicate that there is a need to re-assess the PILs of aluminium-containing antacids as already undertaken by some of the regulatory bodies included in this review.

6. Conclusions

OTC antacids are the most important source for human aluminium exposure from a quantitative point of view. Aluminium can act as a powerful neurological toxicant and provoke embryonic and fetal toxic effects in animals and humans after gestational exposure as evidenced by the presented toxicological data. Bearing these data in mind and the fact that OTC antacids can be consumed without professional medical control over a long time period, there is justification for the recommendation that the PILs of such pharmaceuticals should provide an equal degree of information for the patient regarding aluminium toxicity in all countries. In particular, warnings regarding the concurrent ingestion with acidic beverages such as those containing citrate that can cause a marked augmentation of intestinal aluminium absorption should always be given, and a general contraindication for use during pregnancy should be considered.

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