Bradycardia and Desaturation: Just another day in the Life of an Extremely Premature Infant?

DR. AN SAMAEY, FELLOW NEONATOLOGY

CLINIQUES UNIVERSITAIRES SAINT-LUC, BRUXELLES

Background of the case

- Antenatal
  - Prophylactic cerclage at 12w
  - Bleeding, cervical gap and bulging pouch at 23w 2/7
  - Pulmonary maturation started at 23w 5/7
  - Chorioamnionitis with unavoidable delivery at 23w 6/7
- Birth
  - 23w 6/7, 650g
  - Vaginal delivery
  - Apgar 5/4/6
  - Intubation at 5 minutes and administration of surfactant

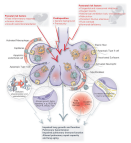
Background of the case

Birth
23w6/7

Extubation D1
NIPPV

NEC stade IIb + sepsis Citrobacter Koseri, D11
•Suspicion of meningitis

BPD
•2 times steroids
•diuretics



Full enteral D43

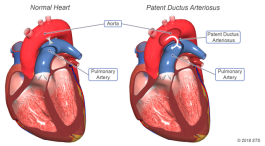
Stop cafeine D86 (36w1/7)

D151
45w3/7
Transfer pediatrics

HMD-IRDS: surfactant 1x

Re-intubation D5-D37

PDA R/ paracetamol



Extubation D37
•NIPPV
•NIV-NAVA
•nCPAP
•High flow/Optiflow

Low flow D79-D109, D145-D193

Full autonome D86

D156 46w1/7, readmission NICU

The problem

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Severe recurrent events characterized by:

- Desaturation and bradycardia
- Requiring non-invasive ventilation with rPAP or mask-balloon ventilation to recuperate

Differential diagnosis

PollEv.com/ansamaey120

What more?

Severe recurrent events characterized by:

- Desaturation and bradycardia
- Requiring non-invasive ventilation with rPAP or mask-balloon ventilation to recuperate

- Sometimes milk in the mouth with need for aspiration

Our differential diagnosis

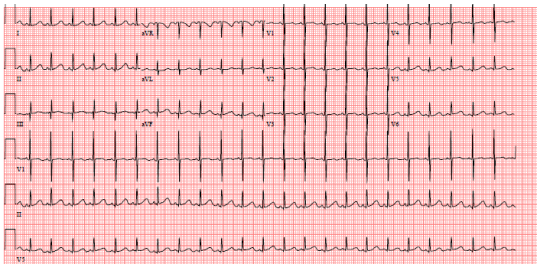
- Brady-apnea syndrome of prematurity
- Gastroesophageal reflux
- Seizures/epileptic
- Cardiac?
- …

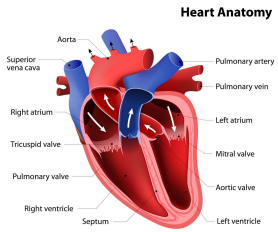
Examinations

PollEv.com/ansamaey120

Results of examinations

- Echocardiography: Bonne fonction biventriculaire. CA fermé. Petite CIA de 3mm.

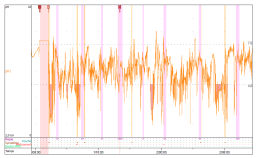




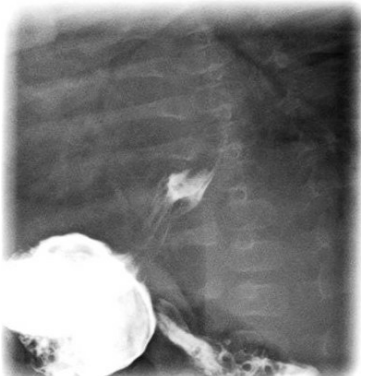
- ECG: ok, pas d'allongement du Qtc
- Holter (24h): normale
- Polysomnography:
  - Anormale
  - Épisodes obstructifs s'accompagnant de bradycardie, désaturation, d'un effort respiratoire, d'un bruit respiratoire et d'une instabilité du sommeil
  - Polypnée
  - Bruit respiratoire fréquent et discret, inspiratoire et expiratoire
  - Une instabilité de la fréquence cardiaque
  - Bradycardies à l'éveil
  - Instabilité de la SpO2 liée ou non aux événements respiratoires.
- Long vEEG: ok, no seizures/epileptic events

Results of examinations

- pH-metry and Esophageal impedance testing: Toujours de reflux malgré traitement



- Gastric emptying scintigraphy: vidange gastrique ralentie
- 3-day pH-metry: Pathologique la première journée, les autres jours ne sont pas récupérables
- ORL-Fibroscopy: Examen fibroscopique rassurant, pas de facteur obstructif mis en évidence.
- Rx OED/SMD: Pas de trouble de la déglutition. Pas de fausse route objectivée. Composante de reflux gastro-œsophagien avec petite hernie hiatale.



=> Suspicion of severe gastroesophageal reflux and secondary causing these events

Further course of the hospitalization

- Thickening of the milk with nutriton since D77
- Start Omeprazole D81
- Trial of different milks: NAN AR, Nutramigen LGG, Allernova-AR, Nutramigen Puramino and again Nutramigen LGG
- Domperidone D111-D126
- Erythromycine D126-D191
- Trial Belladone D126-D134
- Switch Nutriton to Gelilact D134
- Discussion with the parents to do a Nissen-fundoplication because of persistance of events and reflux despite treatment => refusal

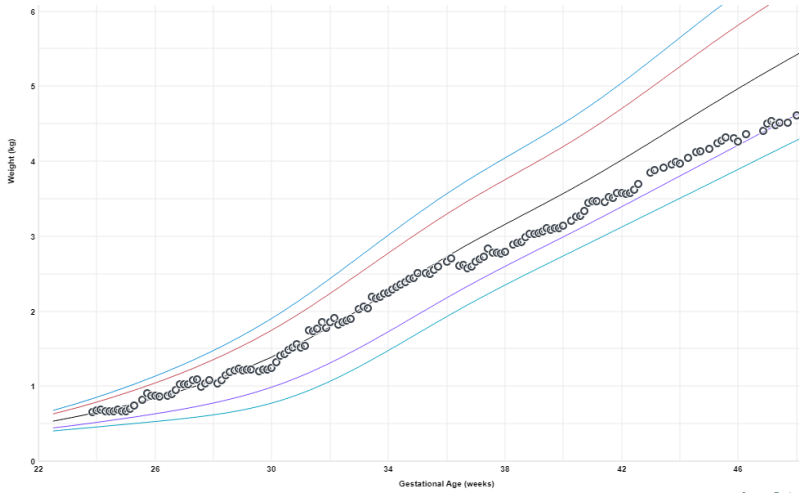
But are we missing something?

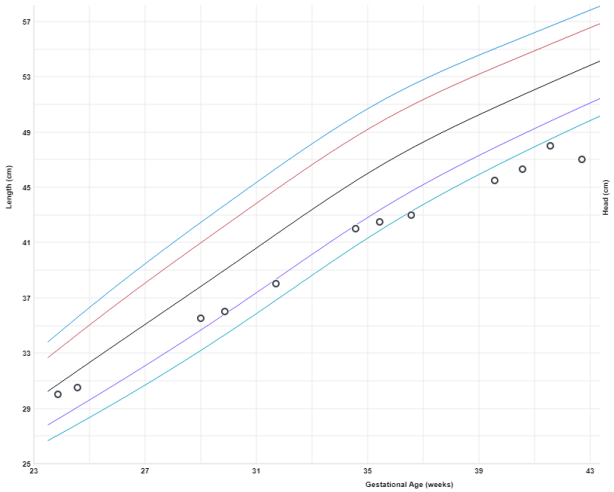
With the combination of Nutramigen-gelilact, erythromycine and omeprazole => no events for several weeks before re-admission at the NICU

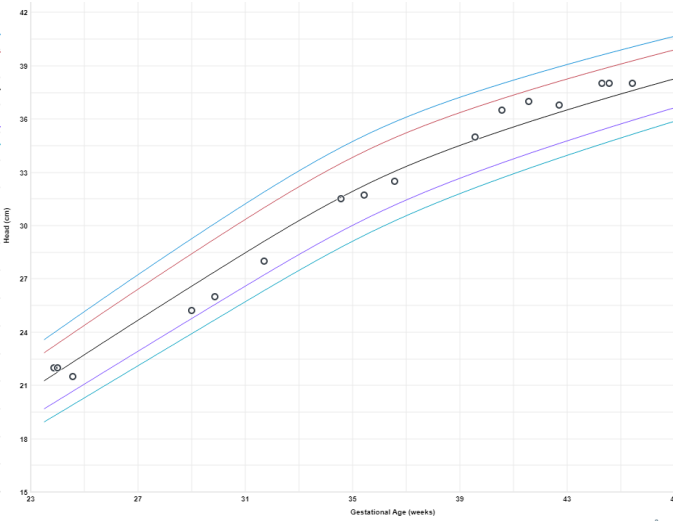
Last episodes:
- Hyperextension
- Finally hypotonia

=> EEG normal

And then…


Weight (kg)
Gestational Age (weeks)


Length (cm)
Gestational Age (weeks)


Head (cm)
Gestational Age (weeks)

And then…

pH	7,35 - 7,45	**7,29 (L)**
pCO2	41 - 51 mm Hg	**57 (H)**
pO2	41 - 51 mm Hg	**56 (H)**
Excès de base	-2,0 - 2,0 mmol/L	0,9
Bicarbonate	22 - 28 mmol/L	24

Hémoglobine totale	14,0 - 18,0 g/dL	**10,4 (L)**
Oxyhémoglobine	70,0 - 100,0 %	84,4
Carboxyhémoglobine	<=2,0 %	**2,1 (H)**
Methémoglobine	0,0 - 2,0 %	1,5
Hématocrite	38 - 54 %	**32 (L)**
Sodium	135 - 145 mmol/L	143

Potassium	3,5 - 5,0 mmol/L	3,7
Chlorures	97 - 107 mmol/L	107
Calcium ionisé	4,4 - 4,8 mg/dL	**4,1 (L)**
Glucose	60 - 90 mg/dL	**135 (H)**
Acide lactique	0,5 - 2,2 mmol/L	**2,4 (H)**

Calcium total °	2,25 - 2,75 mmol/L	**1,81 (L)**
Calcium corrigé	2,25 - 2,75 mmol/L	**1,76 (L)**
Phosphore °	0,81 - 1,45 mmol/L	**1,60 (H)**
Magnésium	0,70 - 0,95 mmol/L	**0,40 (L)**
Albumine	38 - 54 g/L	42
Vitamine A °	20 - 43 µg/dL	**15 (L)**
Vitamine E °	300 - 800 µg/dL	**215 (L)**

Fer	33 - 193 µg/dL	63
Transferrine	2,0 - 3,6 g/L	**1,9 (L)**
Coefficient de saturation de la transferrine	20,0 - 50,0 %	23,7
Capacité de fixation de la transferrine	50,0 - 95,0 µmol/L	**47,5 (L)**
Ferritine	30 - 400 µg/L	86
Ac.folique sérique	>=2,1 ng/mL	>20,0
Créatinine (IDMS) °	0,60 - 1,30 mg/dL	**0,31 (L)**
Sodium °	135 - 145 mmol/L	141
Potassium °	3,50 - 5,00 mmol/L	4,96
Chlorures °	97 - 107 mmol/L	107
Calcium total °	2,25 - 2,75 mmol/L	**1,70 (L)**
Calcium corrigé	2,25 - 2,75 mmol/L	**1,63 (L)**
Phosphore °	0,81 - 1,45 mmol/L	**1,60 (H)**
Albumine	38 - 54 g/L	43
Bilirubine totale	<=1,2 mg/dL	0,5
GOT (AST) °	9 - 80 U/L	47
GPT (ALT) °	13 - 45 U/L	25
GGT °	<=60 U/L	**408 (H)**
Phosphatases alcalines totales	122 - 469 U/L	**1.118 (H)**
PTH intacte °	15 - 80 pg/mL	**289 (H)**
25(OH) Vitamines D °	30 - 100 ng/mL	**15 (L)**

And then…


Il y a 13 m
Retour à la grille
Unité de soins intensifs - néonatologiqu…
Unité de soins i…
Unité de…
2023
1/5
1/6
1/7
1/8
1/9
1/10
GAZ DU SANG ET …
Nature du prél…
pH
pCO2
pO2
Excès de base
Bicarbonate
Saturation en …
Hémoglobine t…
Contenu en O2
Oxyhémoglobine
Carboxyhémo…
Méthémoglobine
Hématocrite
Sodium
Potassium
Chlorures
Calcium ionisé
Glucose
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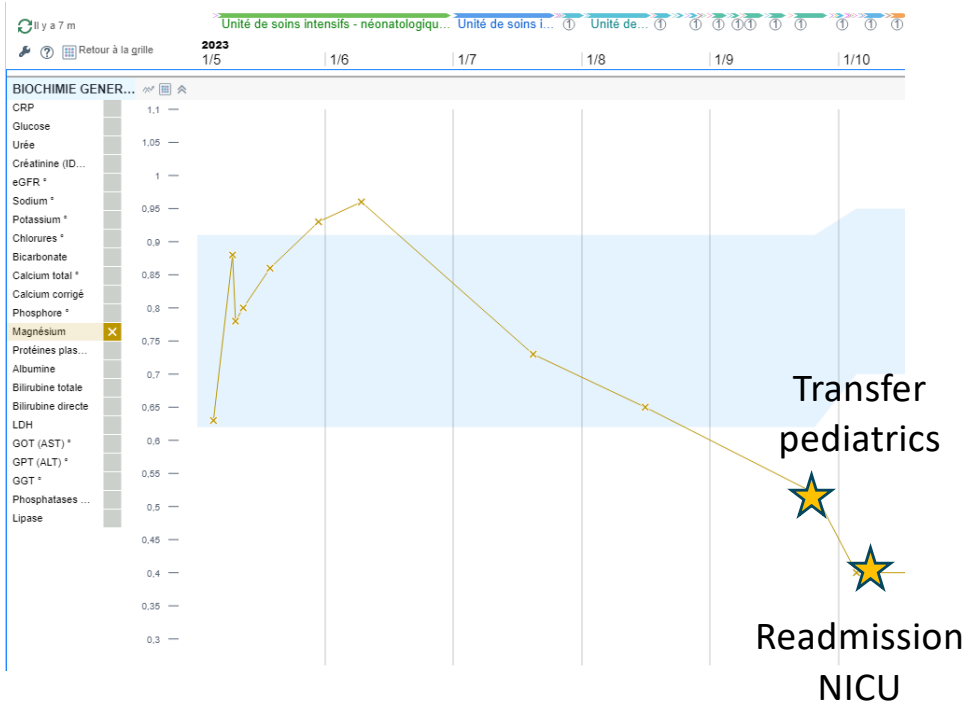
Transfer pediatrics
Readmission NICU


Il y a 7 m
Retour à la grille
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Unité de soins i…
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2023
1/5
1/6
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BIOCHIMIE GENER…
CRP
Glucose
Urée
Créatinine (ID…
eGFR *
Sodium *
Potassium *
Chlorures *
Bicarbonate
Calcium total *
Calcium corrigé
Phosphore *
Magnésium
Protéines plas…
Albumine
Bilirubine totale
Bilirubine directe
LDH
GOT (AST) *
GPT (ALT) *
GGT *
Phosphatases …
Lipase
1,1
1,05
1
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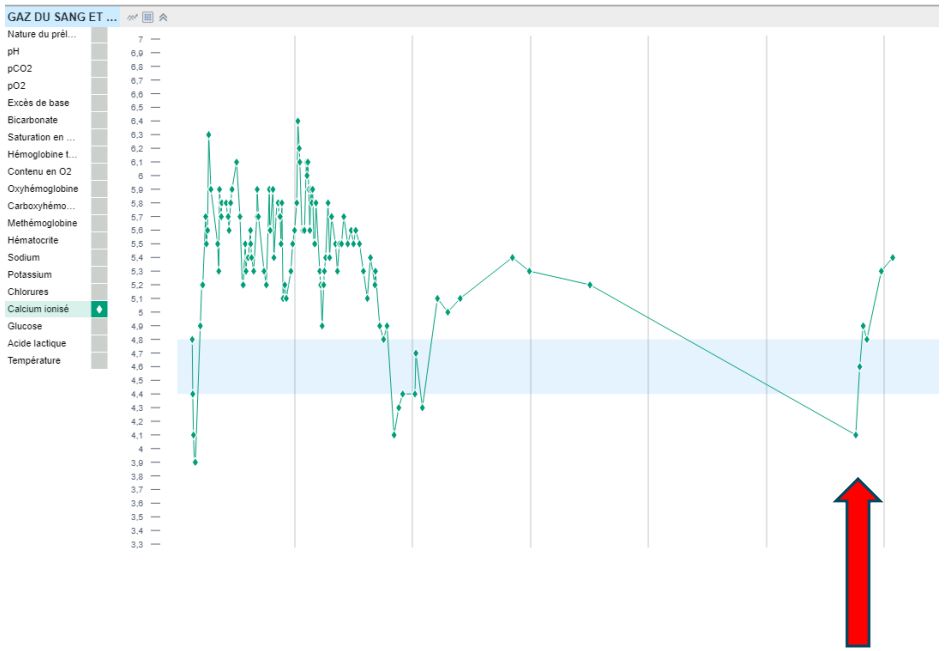
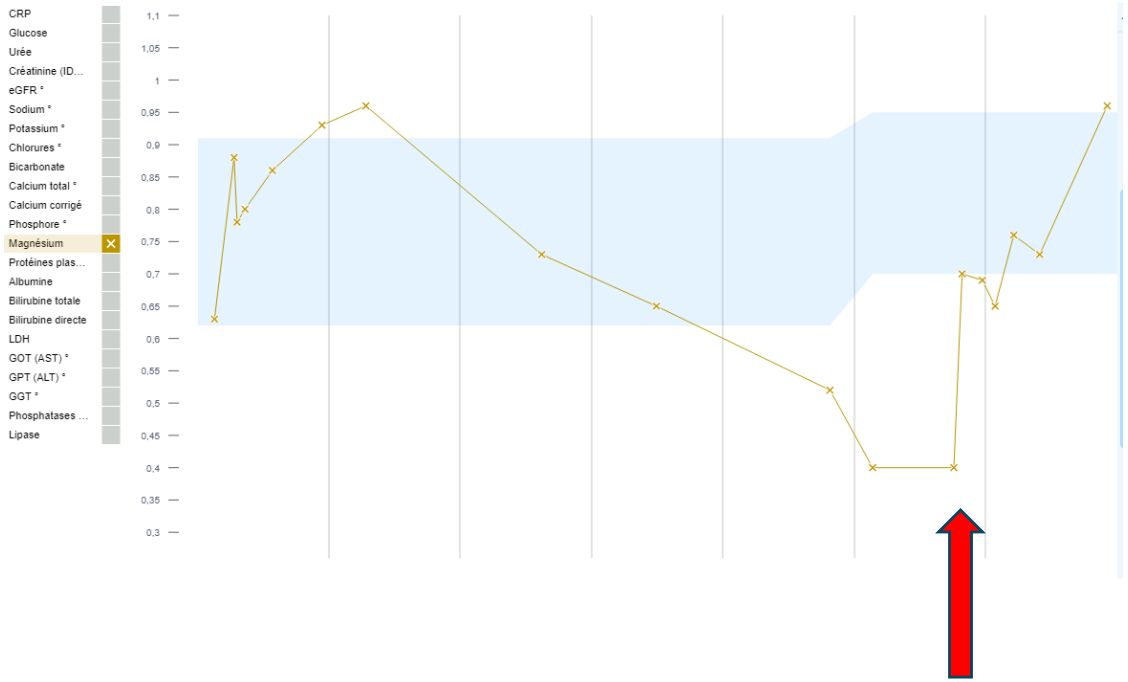
0,8
0,75
0,7
0,65
0,6
0,55
0,5
0,45
0,4
0,35
0,3
Transfer pediatrics
Readmission NICU

Treatment

- Adaptation of supplements of calcium and phosphore
- Increased dose of Dedrogyl (25-OH vitamin D; Calcifediol)
- Magnesium started
  - MgSO4 20% IM 1x/d for 2 days
  - Continuation of oral Magnesiumsupplements
- Omeprazole dose lowered

After treatment





=> Disappearance of events after normalization of ions

Theoretical background

Hypomagnesemia

→ Serum level < 1.7 mg/dL

Neuromuscular manifestations
- Tremor, tetany, seizures
- Weakness
- Apathy
- Delirium
- Coma

Cardiovascular manifestations
- Prolonged QTc
- Widening of QRS
- Atrial and ventricular dysrhythmias

Hypokalemia
- Renal potassium wasting

Abnormalities of calcium metabolism
- Hypocalcemia
- Hypoparathyroidism
- Parathyroid hormone resistance
- Decreased synthesis of calcitrol

J Am Coll Nutr. 1990 Feb;9(1):58-64. doi: 10.1080/07315724.1990.10720351.

Effects of hypomagnesemia on reactivity of bovine and ovine platelets: possible relevance to infantile apnea and sudden infant death syndrome

J K Miller [1], M D Schneider, N Ramsey, P K White, M C Bell

Magnesium deficit and sudden infant death syndrome (SIDS): SIDS due to magnesium deficiency and SIDS due to various forms of magnesium depletion: possible importance of the chronopathological form

Jean Durlach [1], Nicole Pagès, Pierre Bac, Michel Bara, Andrée Guiet-Bara

Affiliations + expand
PMID: 12635883

Abstract

Sudden Infant Death Syndrome (SIDS) might be due to the fetal
deficiency, which might be prevented by simple atoxic nutrition
stresses in the pregnant women or in the infant may transform
depletion which may not be cured by nutritional Mg supplemen
causal dysregulation. Beside the well established risk factors in
important to stress the possible role of a primary hypofunction
treated by darkness therapy; total light deprivation at night for
supplement for the pregnant women. The place in the preventic
and of the use of melatonin, L-tryptophan and taurine is now ur

PubMed Disclaimer

of hypomagnesemic ruminants was
ethers, eight Finnish-Hampshire ewes, and
by feeding vegetative spring tall fescue to
four ewes, and 18 lambs. In comparison
entrations 55% in cows, 36% in wethers,

Magnesium in perinatal care and infant health

J L Caddell [1]

Affiliations + expand
PMID: 1844556

Abstract

Magnesium, the second most abundant intracellular cation, is essential for life. The consequences of deficiency are severest in the smallest and youngest members of each species and may include sudden unexpected death. Magnesium deficiency, usually diagnosed by hypomagnesemia, may be congenital, as in premature infants, infants of magnesium-deficient mothers and infants with intrauterine growth retardation. It may be acquired or caused by low magnesium intake, the use of magnesium-wasting drugs, illness provoking gastrointestinal or renal losses of the mineral, or high metabolic demands imposed by catch-up growth or postsurgical healing. Finally, the deficiency may be conditioned, caused by excessive dietary calcium, phosphorus or protein in relation to dietary magnesium, especially during a period of rapid growth or tissue repair. Magnesium therapy is safe when a low dosage is given with monitoring of plasma or serum magnesium levels, with occasional checking of calcium and potassium levels. A parenteral dose of 0.1 ml/kg/day of 50% magnesium sulfate USP (approx. 0.2 mmol/kg/day or 0.4 mEq/kg/day) may be given for 5 dose days. An oral dose of 1.0 ml of 10% magnesium chloride solution providing 0.5 mmol/kg/day magnesium or 1.0 ml/kg/day of 10% magnesium chloride USP (0.5 mmol/kg/day) or magnesium magonate (Magonate) 1.0 ml/kg/day (0.45 mmol/kg/day) may be given for extended periods; higher doses may be required for malabsorption syndromes. Hypermagnesemia, which usually results from magnesium overdosage or inadequate renal function, is a potential threat to neonates born to magnesium-treated eclamptic mothers. Most show marked improvement after 36 h of conservative management that includes calcium salts and intravenous infusions of glucose and saline, but obtunded neonates may require dialysis.

Hypocalcemia Assessment

Neuromuscular
- Irritability
- Hallucinations
- Paresthesias
- Tetany
- Seizures
- Muscle spasms
- Chvostek's sign
- Trousseau's sign

Gastrointestinal
- Hyperactive bowel sounds
- Cramping
- Diarrhea

Other
- Weak bones
  - Increased risk of fractures
- Weak/brittle nails
- Arrhythmias
  - Ventricular tachycardia

Theoretical background

REVIEW ARTICLE

ACTA PHYSIOLOGICA

Mechanisms of proton pump inhibitor-induced hypomagnesemia

Lisanne M. M. Gommers | Joost G. J. Hoenderop | Jeroen H. F. de Baaij

Department of Physiology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

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Funding in
Nederlandse Wetenschap
Award Numb
VICI 016.13

Abstract

Proton pump inhibitors (PPIs) reliably suppress gastric acid secretion and are therefore the first-line treatment for gastric acid-related disorders. Hypomagnesemia (serum magnesium [Mg^{2+}] <0.7 mmol/L) is a commonly reported side effect of PPIs. Clinical reports demonstrate that urinary Mg^{2+} excretion is low in PPI users with hypomagnesemia, suggesting a compensatory mechanism by the kidney for malabsorption of Mg^{2+} in the intestines. However, the exact mechanism by which PPIs cause impaired Mg^{2+} absorption is still unknown. In this review, we

Case Reports > Gastroenterol Rep (Oxf). 2015 Aug;3(3):243-53. doi: 10.1093/gastro/gou054. Epub 2014 Aug 19.

Hypomagnesaemia associated with long-term use of proton pump inhibitors

James Wei Tatt Toh [1], Evonne Ong [2], Robert Wilson [3]

Affiliations + expand

PMID: 25138239 PMCID: PMC4527261 DOI: 10.1093/gastro/gou054

Abstract

Hypomagnesaemia and associated hypocalcaemia and hypoparathyroidism have been increasingly recognised as rare long-term side-effects of proton pump inhibitors (PPIs). The PPIs may inhibit active magnesium (Mg) absorption by interfering with transcellular transient receptor potential melastatin-6 and -7 (TRPM 6 and 7) channels. More recent cell culture studies have suggested concomitant inhibition of passive Mg absorption by omeprazole. After being treated with a range of PPIs, the four patients in our case series developed hypomagnesaemia, which responded to withdrawal of therapy and initiation of Mg replacement. Their clinical course and management demonstrate key aspects of hypomagnesaemia associated with long-term use of PPIs.

> Int J Med Sci. 2012;9(5):322-6. doi: 10.7150/ijms.4397. Epub 2012 Jun 13.

Omeprazole- and esomeprazole-associated hypomagnesaemia: data mining of the public version of the FDA Adverse Event Reporting System

Takao Tamura [1], Toshiyuki Sakaeda, Kaori Kadoyama, Yasushi Okuno

Affiliations + expand

PMID: 22745572 PMCID: PMC3384913 DOI: 10.7150/ijms.4397

Abstract

Objective: Case reports showing that proton-pump can cause hypomagnesaemia have been accumulatir to the Adverse Event Reporting System (AERS) of the evaluated to assess omeprazole and esomeprazole i

Methods: After a revision of arbitrary drug names ar reports involving omeprazole and esomeprazole wer pharmacovigilance tools were used for the quantitat between a drug and an adverse drug event, includin odds ratio, the information component given by a Ba and the empirical Bayes geometric mean.

Results: A total of 22,017,956 co-occurrences were f where a co-occurrence was a pair of a drug and an a drug events were listed as omeprazole- and esomep ranking 85th and 135th, respectively. Although both statistical metrics suggested that the association was

Conclusion: The data obtained in this study do not p systematic monitoring of magnesium levels in plasm severe hypomagnesaemia.

> J Res Med Sci. 2020 Nov 26:25:106. doi: 10.4103/jrms.JRMS_637_18. eCollection 2020.

Electrolyte disturbances in children receiving omeprazole for gastroesophageal reflux disease

Fatemeh Famouri [1 2 3], Forough Derakhshani [1 3], Yahya Madihi [1 2 3], Armindokht Shahsanai [4]

Affiliations + expand

PMID: 33824671 PMCID: PMC8019125 DOI: 10.4103/jrms.JRMS_637_18

Abstract

Background: Gastroesophageal reflux disease (GERD) is one of the common gastrointestinal diseases with various side effects. Proton pump inhibitor (PPI) drugs are widely used for their treatment and long-term ingestion, which results in an electrolyte imbalance. This study investigates the changes in serum magnesium, calcium, sodium, and potassium after long-term use of omeprazole in children.

Materials and methods: This cross-sectional study was conducted in 2016-2017 on 97 children and adolescents, aged 1-15 years, with GERD, in Isfahan, Iran. Enrolled were patients visiting a referral pediatric gastroenterology clinic (Imam Hossein and Amin Hospitals) examined by an academic pediatric gastroenterologist. Before and 4 weeks after omeprazole administration, clinical manifestations including lethargy, muscle spasm, dyspnea, nausea, vomiting, abnormal heartbeat and deep tendon reflexes, and Chvostek and Trousseau signs were recorded in a data-gathering form. In addition, fasting serum magnesium, calcium, sodium, and potassium were measured.

Results: The McNemar test results showed that omeprazole can reduce sodium, calcium, and magnesium levels statistically significantly ($P < 0.05$), but potassium levels do not have a meaningful reduction ($P > 0.05$).

Conclusion: Consumption of omeprazole might cause asymptomatic hypomagnesemia, hypocalcemia, and hypernatremia in children. Such side effects should be considered in the follow-up of children under treatment with this medication.

Case Reports > Clin Nephrol Case Stud. 2024 Jan 4:12:6-11. doi: 10.5414/CNCS111284. eCollection 2024.

Multiple electrolyte disorders triggered by proton pump inhibitor-induced hypomagnesemia: Case reports with a mini-review of the literature

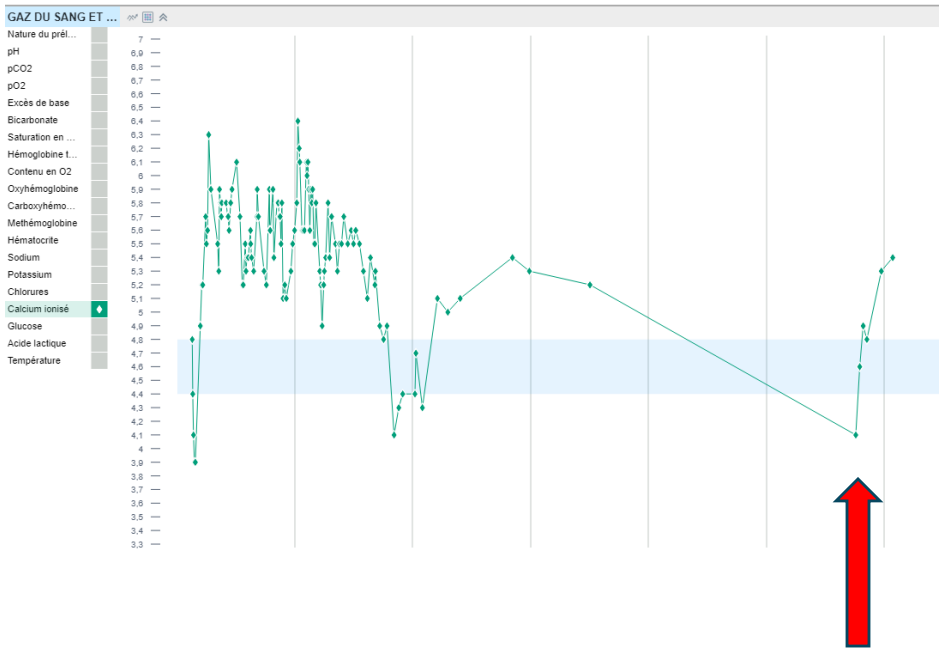
Camila Costa Souza [1], Larissa G Rigueto [1], Henrique Costa Santiago [1], Antonio Carlos Seguro [2], Adriana Castello Girardi [3], Weverton Machado Luchi [1]

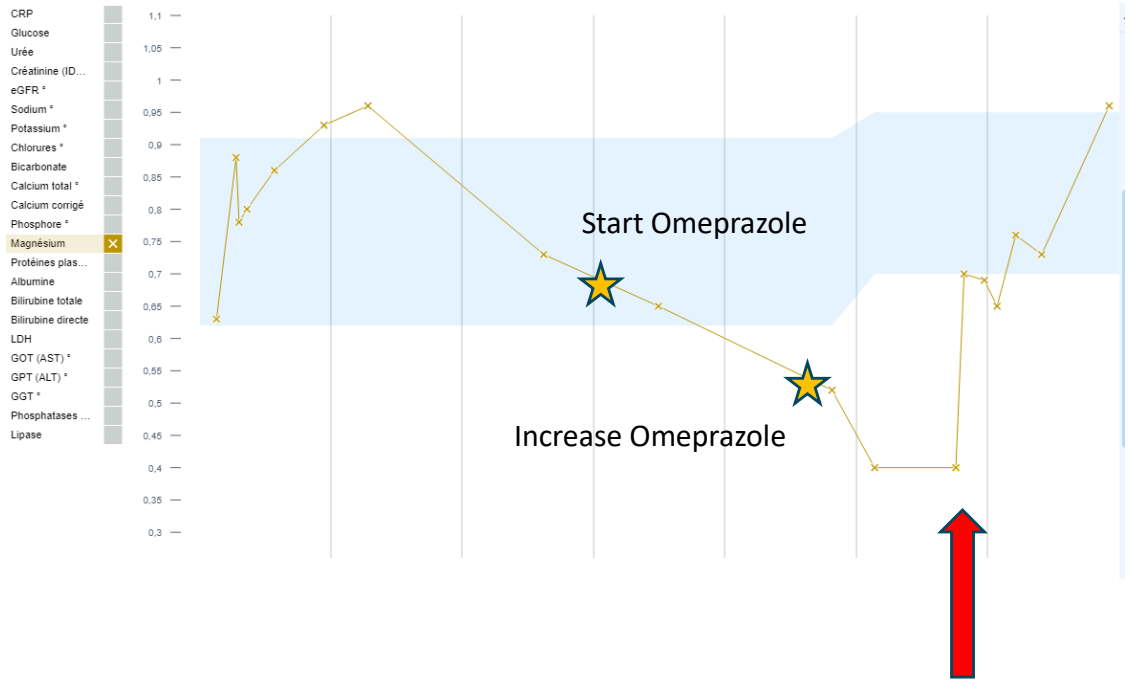
Affiliations + expand

PMID: 38222324 PMCID: PMC10783169 DOI: 10.5414/CNCS111284

n adverse effect with the potential for serious and fatal outcomes.
pump inhibitors (PPIs) can cause hypomagnesemia due to
ly attributed to reduced transcellular transport of magnesium via
in 6 (TRPM6) and 7 (TRPM7) channels. However, a reduction of
due to the downregulation of intestinal claudins has also been
mia can trigger other concomitant electrolyte derangements,
a, hypophosphatemia, and hyponatremia. Here we report two
rs associated with PPI-induced hypomagnesemia, the clinical
arrhythmia, cognitive changes, and seizure crisis. These cases
magnesium levels in patients on long-term PPI use, especially in
ptive bowel syndromes or taking loop diuretics and thiazides.

After treatment





Theoretical background

- PPI's cause an impaired Mg-absorption
- Hypomagnesemia contributes to hypocalcemia
  - Impaired secretion of PTH
  - Causes skeletal resistance to PTH
- Discussion in the literature about the role of PPI and malabsorption of vitamin D and calcium, there seems to be a correlation of PPI and bone fractures/osteoporosis
- Probably exacerbated by a pre-existing metabolic bone disease of prematurity

Lessons from this case

- Sometimes you have to restart the whole thinking-process
- Every medication can have adverse events, even when frequently used
- Less may be more
- Don’t forget the magnesium!

Thank you for your attention

Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

Questions?

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