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CLINICAL CASE

Association of benzocaine and acetaminophen with neonatal-acquired methemoglobinemia

José L. Lepe-Zúñiga[a], Luis E. Aguilar-Gómez[b], Noemí C. Godínez-Téllez[b]

[a] *Subdirector de Servicios Clínicos, Hospital de Especialidades Pediátricas, Tuxtla Gutiérrez, Chiapas, México*
[b] *Unidad de Cuidados Intensivos Neonatales, Hospital de Especialidades Pediátricas, Tuxtla Gutiérrez, Chiapas, México*

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Drug induced

Abstract
Background: Drug-induced acquired methemoglobinemia in the newborn is a rare event; however, when it develops, early diagnosis and proper treatment become paramount because it can evolve rapidly into a particularly serious disease causing permanent brain damage or death.
Case report: We report a unique case of severe methemoglobinemia that developed in a newborn associated with a minimal application of a benzocaine healing cream to an anal surgical wound while on acetaminophen. In addition to benzocaine as the primary cause in this case, we raise the possibility that acetaminophen—a mild oxidant—increased the susceptibility of the patient to benzocaine, leading to severe clinical methemoglobinemia based on the known immaturity of the enzymatic systems involved in caines and acetaminophen clearance in the newborn. Treatment of methemoglobinemia is reviewed.
Conclusions: Methemoglobinemia is a serious condition that can be easily induced by the use of oxidant medications in the newborn like local anesthetics. The possibility of unexpected drug to drug interactions, particularly between commonly used medications such as acetaminophen with other methemoglobin-causing agents, must always be kept in mind. Because of the possible deleterious consequences, mandatory labelling of caine-containing local anesthetic creams, gels and sprays with a warning for the likelihood of causing severe methemoglobinemia in children is recommended. Also, prohibiting their use in the newborn becomes mandatory.

* Corresponding author.
E-mail: joselepe36@hotmail.com (J.L. Lepe-Zúñiga).

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PALABRAS CLAVE
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Efectos adversos

Metahemoglobinemia adquirida en el recién nacido asociada con benzocaína y paracetamol

Resumen
Introducción: La metahemoglobinemia adquirida inducida por medicamentos es un trastorno raro en el recién nacido que, de no diagnosticarse y tratarse oportuna y adecuadamente, puede ser particularmente grave y determinar daño cerebral permanente o la muerte del paciente.
Caso clínico: Se reporta un caso metahemoglobinemia clínica severa que desarrolló un recién nacido después de la aplicación de una cantidad mínima de crema con benzocaína en una herida quirúrgica anal cuando al mismo tiempo recibía paracetamol. Además de considerar la benzocaína como agente causal primario de la metahemoglobinemia, se analiza y sustenta la posibilidad de que el paracetamol haya aumentado la susceptibilidad del paciente a las caínas debido a la inmadurez enzimática de los sistemas involucrados en la depuración de los agentes oxidantes, en particular de caínas y de paracetamol.
Conclusiones: Se alerta sobre la posibilidad de metahemoglobinemia en el recién nacido al emplear caínas solas o junto con otros medicamentos oxidantes en esta época del desarrollo humano, cuando es más susceptible a los efectos oxidantes de químicos incluyendo medicamentos. Se revisa el tratamiento y se propone etiquetar debidamente los productos farmacológicos que contienen caínas, prohibiendo su empleo en recién nacidos para evitar la metahemoglobinemia iatrogénica.

1. Introduction

Methemoglobinemia is a clinical syndrome with variable severity characterized by the presence in the blood of oxidized hemoglobin (methemoglobin), which is unable to transport and release oxygen in the tissues, resulting in cyanosis and proportional tissue hypoxia that can lead to death. In newborns, hypoxia as a result of methemoglobinemia may also have important consequences on brain development.

This disorder can be acquired or hereditary. The hereditary form can be associated with abnormalities in primary/tertiary structure such as those referred to as hemoglobin M or with molecular or functional defects of cytochrome reductase, the enzyme that reduces methemoglobinemia to functional hemoglobin. These cases manifest from birth. Acquired cases are more frequent and are associated with the ingestion or contact with a variety of oxidant chemical agents whether in the industrial, chemical, food, agricultural, or pharmaceutical forms or acquired naturally in the environment.[1]

1.1. Acquired methemoglobinemia

Cases of acquired methemoglobinemia in newborns were at one time relatively frequent and were associated with the use of well-water (with excess nitrates) in food preparation.[1,2] Once the source was recognized, acquired cases in infants were no longer common and today are rare.

In the present study we report of a unique case of acquired methemoglobinemia in a newborn in which a sole application of a small amount of cream with benzocaine applied to the surgical wound induced significant clinical methemoglobinemia that placed the life of the patient at risk. In the case reported, at the same time, acetaminophen was the usual postoperative medication—a mild oxidant—contributing in an additive form with benzocaine to the important development of methemoglobinemia. We reviewed treatment and propose measures to avoid caine-associated methemoglobinemia in the newborn.

2. Clinical case

We present the case of a term male newborn who was the product of a first gestation. No family or personal history was reported of cyanosis. Anorectal malformation with recto-perineal fistula was diagnosed at birth without any other malformations or functional alterations. The fundus of the rectal pouch was located 1 cm from the skin. During the second day of hospitalization, after prior evaluation by the anesthesiologist, posterior primary sagittal anorectoplasty was carried out (without derivative colostomy). Treatment was initiated with ampicillin, amikacin and acetaminophen (10 mg/kg/dose/8 h orally) on the same day. Immediate postoperative evolution including arterial gases was satisfactory. On the third postoperative (PO) day, dehiscence of two suture points was observed and the patient cried continually. Fentanyl was added (2 μg/day orally for 2 days). During the night of the fifth PO day, local application of a cream containing 20% benzocaine and 2% ketaserine (Sufrexal P®, Janssen-Cilag, México) was indicated for the surgical wound. During the night, nursing reported the application of two doses to the wound the size of half of a pea. During the morning shift, the patient was in a very poor general status with polypnea, irritability and with generalized cyanosis, with 4-sec capillary refill, pulse 151/min, blood pressure 107/61 mmHg, and pulse oximetry with 75% O_2 saturation. Arterial gases showed pH 7.54, PaO_2 156 mmHg, $PaCO_2$ 14 mmHg, HCO_3 12 mEq/l and lactate 7.0 mmol/l. Hemoglobin was 13.2 g. Intubation was decided

upon to verify permeability of the airways and assisted breathing was inititaed with FiO_2 ventilator to 100%. Pulse oximetry showed an increase to 81% O_2 saturation. New arterial gases during ventilation showed pH 7.41-7.42, PaO_2 178-405 mmHg and $PaCO_2$ 30-32 mmHg; HCO_3 19-21 mEq/l and lactate 1.7-2.1 mmol/l. Blood was observed with a chocolate color in all determinations.

As a result of the dissociation between pulse oximetry and pO_2 with lactic acidosis, deep cyanosis without evidence of airway obstruction, color of the blood, absence of cardiopathy or pneumopathy that would explain the cyanosis and history of use of a benzocaine-containing cream—a known hemoglobin oxidant—at the same time that the patient received acetaminophen among other medications, clinical diagnosis of methemoglobinemia was made. Determination of methemoglobin by the laboratory was not available in the short term and it was decided to suspend all medications and to apply methylene blue without delay. The patient received a sole dose of methylene blue (1.5 mg/kg IV) followed by 200 mg of ascorbic acid (IV) for the remainder of the day. Cyanosis rapidly disappeared. One hour after the application of methylene blue, pulse oximetry showed 100% oxygen saturation and arterial gases returned to normal values. The patient was extubated on the seventh PO day in good general condition and was followed-up in the outpatient clinic with satisfactory evolution and without presenting cyanosis.

3. Discussion

Red blood cells have an enzymatic machinery that constantly reduces oxidized hemoglobin (methemoglobin), maintaining its concentration at about 1% in constant form at any age.[3] The principal enzyme that intervenes in this process is cytochrome reductase 5b (previously referred to as methemoglobin reductase).

In newborns and infants <4 months of age there are physiological conditions that facilitate the formation of methemoglobin. On one hand, cytochrome 5b reductase activity is less than in other ages.[3] On the other hand, fetal hemoglobin—the dominant form of hemoglobin during this age—is more susceptible to oxidation than adult hemoglobin and possesses the same oxidizing capacity that pressures reduction of the red blood cell.[4,5] Because of this, overload of exogenous oxidizing agents in the newborn easily produces methemoglobin in quantities that exceed the physiological capacity of reversal, giving rise to the clinical picture of methemoglobinemia.[3] The reality is that the prescription of caines (in any presentation) constitutes a risk for the newborn and that the use of creams or aerosols that contain benzocaine, lidocaine or other caines (alone or in combination with other medications) is widely associated with methemoglobinemia in children as well as in adults.[1,6-10] However, given their high efficiency, local anesthetics are widely used in pediatric practice even though technical information is provided about the possibility of methemoglobinemia in infants.

In the present case, use of an analgesic cream with 20% benzocaine explains, *per se,* the greatest part of the clinical picture, probably due to the immaturity of cytochrome 5b reductase at this age. However, the rapidity and intensity of the development of methemoglobinema after application of a relatively small amount of cream was remarkable. This led us to suspect that additional factors may have contributed to this scenario.

From the list of additional medications administered to this patient, only acetaminophen—a mild anti-oxidant—has the potential to produce methemoglobinemia. Oral administration of this medication is rapidly absorbed in the duodenum and is glycosylated or sulfated in the liver and later excreted in the urine.[11] A small fraction (5-15%) is eliminated by the cytochrome 450 oxidative system, forming N-acetyl-p-benzoquinone-imine (NAPQI), a highly reactive molecule that binds to glutathione reductase and is excreted in the bile.[12] NAPQI is a molecule attributed to liver damage produced by acetaminophen as a result of oxidative stress of mitochondria.[12] In humans, acetaminophen shows further a "maturation effect" and newborns eliminate about half of what humans eliminate from lactancy until adulthood. This fact determines that, in the newborn, the half-life of acetaminophen in plasma is double that at other ages, increasing the possibility of adverse effects at a critical age.[13]

Case reports have been published of methemoglobinemia in adults directly attributed to acetaminophen as a sole agent or in combination with other oxidants, e.g., sodium nitrate added as a meat preservative.[14-16] On the other hand, dogs, cats and other mammals are especially susceptible to methemoglobinemia due to acetaminophen. It has been proposed that this susceptibility depends on the metabolic accumulation of p-aminophenol—a minor metabolite of acetaminophen—due to the low activity in these species of arylamine N-acetyl-transferases (NAT) that form in the enzyme system responsible for clearance of p-aminophenol.[17] Two isoenzymes exist in humans of the same system (NAT1 and NAT2). Both acetylene systems clear p-aminophenol and other medications and amine carcinogens.[18] These systems exhibit high polymorphism (NAT2 > NAT1), which determines that there are at least three human acetylator phenotypes (slow, medium and rapid), and thus three patterns of clearance and susceptibility to the toxic effects of those amine chemicals eliminated in this manner.[18-20] The NAT system also presents immaturity at birth that decreases in older age, increasing in newborns the susceptibility to these medications.[21] These facts and the pharmacogenetic variations observed in the general population such as those related to heredity, nutritional status and other factors are added elements to the possibility of abnormally low tolerance to the usually mild oxidizing action of acetaminophen.[22] Further studies may elucidate if the present case has some deficiency, quantitative or function, of some of the enzymes involved in the reduction of methemoglobin—hereditary in nature—or in the clearance of acetaminophen that facilitated the clinical picture or if acetaminophen induces, in general, subclinical levels of methemoglobinemia in newborns that can be exacerbated when associated with other oxidants such as caines. Before the possibility of severe methemoglobinemia in a newborn, prompt action is required because acute hypoxia can present significant neurological consequences. Ideally, in order to make timely decisions, pulse "co-oximetry" with the capacity to determine methemoglobin in real time in NICUs should be available and pulse "oximetry" should be routinely used. There is a tendency to overestimate O_2 saturation in the presence of methemoglobin ("co-oximetry" measures light absorption at

four different wavelengths to detect oxy-, deoxy-, carboxy- and methemoglobin whereas "oximetry" uses only wavelengths corresponding to oxy- and deoxyhemoglobin[23]). Alternatively, the hospital laboratory has an array of techniques to produce methemoglobin results in minutes. Unfortunately, the majority of hospital laboratories in Mexico have not implemented a rapid diagnostic test for diagnosis of methemoglobinemia and these hospitals do not have cooximeters capable of determining this diagnosis in real-time in intensive care units. For this reason, diagnostic presumption and therapeutic decisions are primarily based on clinical characteristics. In all well-oxygenated newborns without a previous diagnosis of cardiopathy or pneumopathy and who suddenly develop cyanosis while receiving some type of medication, airway permeability should first be ensured followed by secure administration of oxygen, direct or through an intubation cannula connected to a ventilator. If improvement is not quickly shown, methemoglobinemia should be suspected secondary to any medications administered and which should be suspended. Arterial gases should be carried out as an emergency procedure. The discordant pattern of normal or elevated pO_2 with pulse oximetry lower than normal and progressive metabolic acidosis is suggestive of lack of delivery of oxygen to the tissues due to a malfunction of hemoglobin, strongly contributing to the diagnosis of methemoglobinemia. Additionally, if there is a reported association of methemoglobinema with some type of medication administered, along with earlier data, this allows establishing the diagnosis and making a timely and adequate therapeutic decision.

Fortunately, methemoglobinemia has been treated safely and effectively since 1939 by using a single dose of methylene blue 1-2 mg/kg IV and its effect is almost immediate. The dose can be repeated one time, 24 h later, if methemoglobin at the time is >5%.[24] Methylene blue allows using nicotinamide adenine dinucleotide phosphate (NADPH)—generated in glucose metabolism by way of hexose monophosphate—as an electron donor to reduce iron in methemoglobin and regenerate hemoglobin. Without methylene blue as an intermediary, NADPH cannot efficiently interact with cytochrome reductase 5b.[1,25,26] Patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency do not efficiently produce NADPH and, in those patients, methylene blue is not used and in fact may aggravate the clinical picture.[26] For these cases, the use of ascorbic acid is proposed as a reasonable alternative.[27] Depending on the local prevalence of G6PD deficiency, ascorbic acid can be added to the initial treatment. Ascorbic acid was provided to this patient to cover this possibility. Cases of methemoglobinemia always need to be addressed as an emergency because levels that reach methemoglobinemia are unknown beforehand and thus hypoxia can ensue and can result in the death of the patient or permanent brain damage. For this reason, it is recommended that medical units always have the availability of three vials of 10 ml of methylene blue 1% on reserve.

The present case emphasizes the need to be alert to the presence of secondary effects of commonly used medications in the newborn such as acetaminophen and caines that can interact in unpredictable ways during this age due to enzymatic immaturity.

This case supports the need of the necessity to place a warning on all medication labels containing caines, indicating that they can cause methemoglobinemia at any age and to consider prohibiting its use in the newborn.

Ethical disclosure

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflict of interest

The authors declare that there are no conflicts of interest.

References

1. Beutler E. Methemoglobinemia and other causes of cyanosis. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, eds. Williams Hematology. New York: McGraw Hill; 2001. pp. 611-8.
2. Lukens JN. Landmark perspective: the legacy of well-water methemoglobinemia. JAMA. 1987;257:2793-5.
3. Lo SC, Agar NS. NADH-methemoglobin reductase activity in the erythrocytes of newborn and adult mammals. Experientia. 1986;42:1264-5.
4. Wind M, Stern A. Comparison of human adult and fetal hemoglobin: aminophenol-induced methemoglobin formation. Experientia. 1977;33:1500-1.
5. Valenzuela A, Guerra R, Lazcano L, Cañas P. Differential prooxidative effect of adult and fetal hemoglobin. FEBS Lett. 1986;196:353-6.
6. Afzal A, Collazo R, Fenves AZ, Schwartz J. Methemoglobinemia precipitated by benzocaine during intubation. Proc (Bayl Univ Med Cent). 2014;27:133-5.
7. Moos DD, Cuddeford JD. Methemoglobinemia and benzocaine. Gastroenterol Nurs. 2007;30:342-5;quiz 346-7.
8. Kane GC, Hoehn SM, Behrenbeck TR, Mulvagh SL. Benzocaine-induced methemoglobinemia based on the Mayo Clinic experience from 28,478 transesophageal echocardiograms: incidence, outcomes, and predisposing factors. Arch Intern Med. 2007;167:1977-82.
9. Chowdhary S, Bukoye B, Bhansali AM, Carbo AR, Adra M, Barnett S, et al. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. JAMA Intern Med. 2013;173:771-6. doi:10.1001/jamainternmed.2013.75.
10. Bouziri A, Khaldi A, Menif K, Ben Jaballah N. Unusual cause of severe toxic methemoglobinemia in an infant: a case report. Int J Emerg Med. 2010;27:57-9. doi: 10.1007/s12245-009-0149-0.

11. McGill MR, Jaeschke H. Metabolism and disposition of acetaminophen: recent advances in relation to hepatotoxicity and diagnosis. Pharm Res. 2013;30:2174-87. doi:10.1007/s11095-013-1007-6.
12. Jaeschke H, McGill MR, Ramachandran A. Oxidant stress, mitochondria, and cell death mechanisms in drug-induced liver injury: lessons learned from acetaminophen hepatotoxicity. Drug Metab Rev. 2012;44:88-106. doi: 10.3109/03602532.2011.602688.
13. Zuppa AF, Hammer GB, Barrett JS, Kenney BF, Kassir N, Mouksassi S, et al. Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. J Pediatr Pharmacol Ther. 2011;16:246-61. doi: 10.5863/1551-6776-16.4.246.
14. Kanji HD, Mithani S, Boucher P, Dias VC, Yarema MC. Coma, metabolic acidosis, and methemoglobinemia in a patient with acetaminophen toxicity. J Popul Ther Clin Pharmacol. 2013;20:e207-11.
15. MacLean D, Robertson PGC, Bain S. Methaemoglobinaemia and paracetamol. Br Med J. 1968;4:390.
16. Kobayashi T, Kawabata M, Tanaka S, Maehara M, Mishima A, Murase T. Methemoglobinemia induced by combined use of sodium nitrate and acetaminophen. Intern Med. 2000;39:860.
17. McConkey SE, Grant DM, Cribb AE. The role of para-aminophenol in acetaminophen-induced methemoglobinemia in dogs and cats. J Vet Pharmacol Ther. 2009;32:585-95. doi:10.1111/j.1365-2885.2009.01080.x
18. Butcher NJ, Boukouvala S, Sim E, Minchin RF. Pharmacogenetics of the arylamine *N*-acetyltransferases. Pharmacogenomics J. 2002;2:30-42.
19. Walker K, Ginsberg G, Hattis D, Johns DO, Guyton KZ, Sonawane B. Genetic polymorphism in N-acetyltransferase (NAT): population distribution of NAT1 and NAT2 activity. J Toxicol Environ Health B Crit Rev. 2009;12(5-6):440-72. doi: 10.1080/10937400903158383.
20. Sim E, Abuhammad A, Ryan A. Arylamine N-acetyltransferases: from drug metabolism and pharmacogenetics to drug discovery. Br J Pharmacol. 2014;171:2705-25. doi: 10.1111/bph.12598.
21. Hein DW, McQueen CA, Grant DM, Goodfellow GH, Kadlubar FF, Weber WW. Pharmacogenetics of the arylamine N-acetyltransferases: a symposium in honor of Wendell W. Weber. Drug Metab Dispos. 2000;28:1425-32.
22. Krasniak AE, Knipp GT, Svensson CK, Liu W. Pharmacogenomics of acetaminophen in pediatric populations: a moving target. Front Genet. 2014;5:314. doi: 10.3389/fgene.2014.00314.
23. Ashurst J, Wasson M. Methemoglobinemia: a systematic review of the pathophysiology, detection, and treatment. Del Med J. 2011;83:203-8.
24. Wendel WB. The control of methemoglobinemia with methylene blue. J Clin Invest. 1939;18:179-85.
25. Bradberry SM. Occupational methaemoglobinaemia. Mechanisms of production, features, diagnosis and management including the use of methylene blue. Toxicol Rev. 2003;22:13-27.
26. McDonagh EM, Bautista JM, Youngster I, Altman RB, Kleina TE. PharmGKB summary: methylene blue pathway. Pharmacogenet Genomics. 2013;23:498-508. doi:10.1097/FPC.0b013e32836498f4.
27. Topal H, Topal Y. Toxic methemoglobinemia treated with ascorbic acid: case report. Iran Red Crescent Med J. 2013;15:e12718. doi:10.5812/ircmj.12718.