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Review Article

LIPIDS IN LOCAL ANESTHETIC TOXICITY

Lipídeos nas intoxicações por anestésicos locais

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ABSTRACT – ***Introduction*** - With the advent of long-lasting local anesthetics, local and regional anesthesia gained considerable impetus and the use of these techniques has become increasingly widespread. New block techniques have been described and regional anesthesia is frequently associated with general anesthesia to provide postoperative analgesia. In contrast, large doses of local anesthetics are required with the risk of accidents due to inadvertent intravascular injection, which is a severe complication without a specific treatment until a few years ago. In 1998, the use of lipid emulsions was proposed in animals. Since 2006, many studies have demonstrated an interest in these solutions in cases of local anesthetic-induced toxicity with a decrease in morbidity and mortality. The aim of this review article was to research the methodology, reviewing mechanisms, interests, limitations and currently recommended treatment. ***Method*** - Some historical references on local anesthetics, articles published during the last 30 years in journals indexed in Medline and in two textbooks were reviewed. Articles on local anesthetic toxicity, lipid emulsion therapy, review articles on the topic and treatment adopted in diverse services and countries were selected, producing a summary. **Conclusions** - It is no longer necessary to show the effectiveness and interest in lipid emulsion therapy for local anesthetic toxicity. Various specialty societies have already published their guidelines and advice about stocking these products in any setting in which local and regional anesthetic techniques are practiced.

HEADINGS - Anesthesia , local. Toxicity. Lipids.

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RESUMO – ***Introdução*** - Com o advento dos anestésicos locais de longa duração, a anestesia locorregional ganhou grande impulso sendo cada vez mais utilizada. Novas técnicas de bloqueios foram descritas e a técnica é frequentemente associada à anestesia geral com o objetivo de proporcionar analgesia pós-operatória. A contra-partida é a necessidade da utilização de grandes doses com risco de acidentes por injeção intravascular inadvertida; trata-se de complicação grave sem tratamento específico até há alguns anos. Em 1998 foi proposta a utilização de emulsões lipídicas em animais e a partir de 2006 vários trabalhos demonstraram o interesse dessas soluções nos casos de intoxicações por anestésicos locais com diminuição da morbi-mortalidade. O objetivo desta revisão foi fazer um levantamento da metodologia, revisando os mecanismos, interesses, limites e as condutas preconizadas atualmente. ***Método*** - Foram revistas algumas referências históricas sobre anestésicos locais, artigos publicados nos últimos 30 anos em revistas indexadas no Medline e em dois livros-texto. Foram selecionados os artigos que tratavam da intoxicação por anestésicos locais, da terapia com emulsões lipídicas, os de revisão sobre o assunto e as condutas adotadas em diversos serviços e países, sendo realizada uma síntese. ***Conclusões*** - A eficiência e interesse da terapia com emulsões lipídicas nas intoxicações por anestésicos locais não é mais a demonstrar; várias sociedades da especialidade já publicaram suas diretrizes e aconselham que se disponha desses produtos nos locais onde se pratica a anestesia locorregional.

DESCRITORES - Anestesia local. Toxicidade. Lipídeos.

INTRODUCTION

Local anesthetic toxicity has been recognized long before the introduction of cocaine in clinical practice. In 1868, a Peruvian physician named Moreno y Maiz in pursuit a doctorate degree in Paris described the first signs and symptoms of cocaine toxicity in an animal study[22]. This occurred 16 years before cocaine was used for the first time by Karl Köller in ophthalmic anesthesia in 1884[14]. Afterwards, the use of the local

anesthetic was rapidly disseminated. In the following years, it began to be administered in nerve trunk injections, as well as in spinal and epidural blocks[10]. Reports describing cocaine toxicity rapidly appeared[5] and included various deaths[19]. It soon became clear that it was necessary to synthesize less toxic drugs. A number of agents slowly emerged, e.g. synthetic procaine in 1905, tetracaine in 1930, lidocaine in 1944, chloroprocaine in 1955, mepivacaine in 1957, prilocaine in 1960 and bupivacaine in 1963. The discovery of the latter, which is the most frequently used local anesthetic to date, was a major step forward in local and regional anesthesia because of the quality of anesthesia provided and also its duration of action. As expected, descriptions of its adverse effects soon began to be reported. In 1979, Albright highlighted the severe toxic complications of bupivacaine and etidocaine in a seminal editorial of the journal Anesthesiology[3]. Since then, a number of cases of refractory cardiac arrest with seizures have been notified[8]. Initially, there were attempts to find agents with similar but less toxic characteristics. In 1996, ropivacaine emerged, followed by levobupivacaine[29] in 1999. Other authors were dedicated to find an antidote for local anesthetic toxicity. In 1998, Weinberg et al. demonstrated that lipid emulsions used in parenteral nutrition since 1961 were efficient in the combat of local anesthetic cardiotoxicity, increasing by 50% the mean lethal dose[31]. Rosenblatt et al. and later Litz et al. were the first authors to publish the successful use of lipid emulsions in the treatment of cardiac arrest due to local anesthetics, when conventional resuscitation had failed[16,25]. Since then, successful cases of lipid emulsion use have been reported for management of these toxicity reactions[9,30]. However, before acceptance by the medical community, new therapies must always meet certain requirements and overcome an initial reluctance until scientific and clinical evidence appears to confirm therapy efficiency. Lipid therapy in the reversal of local anesthetic toxicity, however, seems to be in accordance with the recommendations of the medical societies of Anesthesiology[1,18,23]. It is worth mentioning that lipid emulsions have also been applied in Anesthesiology for a long time. As an example, propofol is a hypnotic used in routine practice for more than 25 years and its vehicle for solution is a lipid agent[21]!

Local Anesthetic toxicity

In case of local anesthetic toxicity, the attention of the physician should be focused mainly on the central nervous system and the cardiovascular system. In the brain, inhibiting pathways are the first to be suppressed and initially produce patient complaints such as a metallic taste in the mouth that may progress to seizures as concentrations of the anesthetic rise. When the excitatory pathways are also affected, apnea and coma occur. With the exception of bupivacaine, cardiovascular toxicity becomes evident after plasma levels have compromised the central nervous system. Cardiovascular toxicity is manifested by arrhythmias and refractory myocardial depression, especially when the agent used is bupivacaine[28]. Toxic doses are capable of inhibiting sinoatrial and atrioventricular node conduction, prolonging the PR space, widening the QRS complex, generating atrioventricular blocks of varying degrees and arrhythmias, both bradycardias and reentrant tachyarrhythmias with ventricular tachycardia or fibrillation[11]. Therapeutic activity and local anesthetic toxicity is attributed to Na+ channel block, although the flow of K+ and Ca++ is also altered. Bupivacaine is bound predominantly to open and inactive Na+ channels, which may justify the severity of toxicity. Myocardial depression occurs because of several factors: inhibition of Ca++ release in the sarcoplasmic reticulum by blockade of β-adrenergic receptors, decreasing adenylate cyclase activity by reducing the synthesis of cyclic adenosine monophosphate and the conversion of ADP into ATP[28].

Lipid therapy

Until recently, cardiopulmonary bypass was the only method known to be effective in the treatment of refractory cardiac arrest from local anesthetic overdose[17]. It is easy to imagine the difficulty encountered with this methodology in daily practice. Fortunately, nowadays the efficiency of lipid therapy in local anesthetic toxicity is no longer a questionable debate. The use and interest in these solutions, even in toxicity due to a number of other drugs have been demonstrated both in animals and in humans. Lipid emulsions have already been used in the treatment of toxicity due to cyclic antidepressants, verapamil, β-blockers, barbiturates among others[7]. Local anesthetics are hydrophobic molecules and their lipid solubility is related to potency and toxicity. The higher the lipid solubility of the agent, the easier it is transported through the cell membrane to reach its site of action. Three non-excluding hypothetical mechanisms of action of lipid emulsions have been proposed.

The first and most widely accepted mechanism is the creation of an expanded plasma lipid phase, into which local anesthetic molecules are sequestered. Lipophilic local anesthetic molecules are chelated, reducing the concentration of the free-base form of the local anesthetic, thus making local anesthetics unavailable to tissues and resulting in decreased toxicity. In the Anglo-Saxon literature this theory is termed 'lipid sink'. This schematic representation is based on three facts: the speed of functional recovery of the cardiac tissue after the use of lipid emulsion is important and consistent with a physical phenomenon. Local anesthetics are sequestered in vitro by lipids. Sequestration is greater with increasing lipid solubility. Finally, in an isolated heart preparation submitted to toxic concentrations of local anesthetics, lipids accelerate the elimination of these agents[4].

The second mechanism is based upon the

concept of inhibition of fatty acid transport at the inner mitochondrial membrane, particularly by bupivacaine. The hypothesis formulated is that lipid emulsions would counteract the reduction in the main source of myocardial energy[4].

Finally, the third mechanism originates from evidence that lipid emulsions have a positive inotropic effect on the isolated heart and may reverse myocardial depression due to bupivacaine at lipid levels lower than those needed to reduce the aqueous bupivacaine concentration[26], occurring with increased levels of intracellular Ca++. Thus, physiologic, metabolic or inotropic pathways may all contribute to antagonize local anesthetic toxicity[32].

Various lipid preparations are available in the market. With respect to the nature of the lipid source, these solutions differ greatly. The most widely used preparations are derived from soybean oil with long-chain triglycerides, soybean oil and coconut oil with medium-chain and long-chain triglycerides and those incorporating olive oil and fish oil. Each of these solutions is of specific interest to parenteral nutrition. According to some authors, emulsions based on long-chained triglycerides were shown to be 2.5 times more efficient in the treatment of local anesthetic toxicity[20], while others consider that their efficiency is equivalent[6]. Preparations that incorporate olive oil and fish oil are still less frequently used.

Limitations of lipid therapy

Experimental and clinical studies have demonstrated an unquestionable interest in lipid emulsions for the treatment of local anesthetic-induced toxicity. However, interference with other eventual drug treatments in patients must be considered. Although lipid emulsions are predicted to be slowly infused for nutrition, tolerance to large-dose and bolus administration should still be confirmed. Furthermore, recent studies have demonstrated that in the event of hypoxia lipid emulsions could have deleterious effects[12] and acidosis could reduce lipid affinity for local anesthetics[20]. This may imply an interest in the early administration of these emulsions in cases of toxic accidents, before acidosis or hypoxia can limit their therapeutic effect.

Guidelines

Lipid emulsions may be infused into peripheral veins because these solutions have a low osmolarity (between 270 and 345 mOsm/l-1 in 20% solutions). In parenteral nutrition, the recommended dose is 0.7 to 1.3 g of triglycerides/kg-1/day. Triglyceride levels should be monitored. The infusion must be reduced if levels reach 400 mg/dl-1 and discontinued if levels of 1000 mg/dl-1 are obtained[2]. Despite the respect for these recommendations, however, doses have been adapted for acute cases of severe local anesthetic toxicity. Currently, it seems unreasonable to wait until asystole develops to start to administer a bolus of lipid emulsion[32]. In 2007, the Association of Anaesthetists of Great Britain and Ireland published the guidelines currently accepted for the treatment of local anesthetic toxicity. These guidelines were rapidly followed by other specialty societies such as the American Society of Regional Anesthesia and Pain Medicine[23]. The recommended guidelines are:

1. Secure the airway and maintain oxygenation.
2. Treat seizures with benzodiazepines.
3. Inject a 1.5 ml/kg-1 bolus of 20% lipid emulsion over 1 minute.
4. Start an infusion at a rate of 0.25 ml/kg-1/min of 20% lipid emulsion.
5. Repeat the bolus twice with 5-minute intervals, if adequate circulation is not restored.
6. After five more minutes, increase the infusion to 0.50 ml/kg-1/min.
7. Respect the superior dose limit recommended for 20% lipid emulsion, which is 10 ml/kg-1 over 30 minutes.

CONCLUSION

Local and regional anesthetic techniques are currently comfortable and safe procedures. However, they are not totally devoid of risks, even in capable hands. In the past few years, substantial progress has been made. Nevertheless, recent estimates still report a rate of 7.5 to 20 cases of local anesthetic toxicity per 10,000 peripheral blockades performed. Data also indicate that four out of 10,000 epidural blocks result in systemic local anesthetic toxicity[18]. Lipid emulsion therapy is no longer a matter of controversy because its benefit and low risk are evident. Lipid emulsions should always be stocked in any setting where patients receive large doses of local anesthetics as occurs in operating rooms[15]. Since surgeons frequently perform procedures with large doses of local anesthetics[24,27], it is wise for them to know these recommendations too.

REFERENCES

1. AAGBI Safety Guideline. Management of Severe Local Anaesthetic Toxicity 2. Disponível em: http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf. Acessado 27/06/2011.
2. Adolph M, Heller AR, Koch T, Koletzko B, Kreymann KG, Krohn K, Pscheidl E, Senkal M. Lipid emulsions. Guidelines on Parenteral Nutrition. Ger Med Sci 2009;18:7-23.
3. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285-7.
4. Aya AGM, Ripart J, Sebbane MA, de La Coussaye JE. Les émulsions lipidiques dans le traitement de la toxicité systémique des anesthésiques locaux: efficacité et limites. Ann Fr Anesth Reanim 2010;29 :464-9.
5. Brown DL. Local anesthetic toxicity. Em: Finucane BT. Complications of regional anesthesia; 2nd ed., New York, Springer,2007:61-73.

6. Candela D, Louart G, Bousquet PJ, Muller L, Nguyen M, Boyer JC, Peray PA, Goret L, Ripart J, Lefrant JY, de La Coussaye JE. Reversal of bupivacaine-induced cardiac eletrophysiologic changes by two lipid emulsions in anesthetizes and mechanically ventilated piglets. Anesth Analg 2010;10 Michels1473-9.
7. Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: a systematic review. Acad Emerg Med 2009;16:815-24.
8. Cuvillon P, Nouvellon M, Ripart J, Boyer JC, Dehour L, Mahamat A, L'Hermite J, Boisson C, Vialles N, Lefrant JY, La Coussaye JE de. A comparison of pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double blind randomized study. Anesth Analg 2009;108:641-9 .
9. Dix SK, Rosner GF, Nayar M, Harris JJ, Guglin ME, Winterfield JR, Xiong Z, Mudge GH Jr.. Intractable cardiac arrest due to lidocaine successfully resuscitated with lipid emulsion. Crit Care Med 2011;39:872-74.
10. Feldman HS. Toxicity of local anesthetics agents. Em: Rice SA, Fish KJ eds.. Anesthetic Toxicity, New York, Raven-Press, 1994:107-33.
11. Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intac animal model. Reg Anesth Pain Med 2003;28:3-11.
12. Harvey M, Cave G, Kazemi A. Intralipid infusion diminishes return of spontaneous circulation following hypoxic cardiac arrest in rabbits. Anesth Analg 2009;108:1163-8.
13. Harvey M. Bupivacaine-induced cardiac arrest. Anesthesiology 2009;11:467-9.
14. Köller K. On the use of cocaine for producing anaesthesia on the eye. Lancet 1884;2:990-2.
15. Kosch MC, Miller AD, Michels JE. Intravenous lipid emulsion for treatment of local anesthetic toxicity. Ther Clin Risk Manag 2010;6:449-51.
16. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axilary plexus block using lipid emulsion. Anaesthesia 2006;61:800-1.
17. Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary by-pass. Anesth Analg 1999;69:403-6.
18. Manavi MV. Lipid infusion as a treatment for local anesthetic toxicity: a literature review. AANA J 2010;78:69-78.
19. Mattison JB. Cocaine poisoning. Med Surg Rep 1891;60:645-50.
20. Mazoit JX, Le Guen R, Beloeil H, Benhamou D. Binding of long-lasting local anesthetics to lipid emulsions. Anesthesiology 2009;110:380-6.
21. Mirtallo JM, Dasta JF, Kleinschmidt KC, Varon J. State of the art review: Intravenous fat emulsions: current applications, safety profile, and clinical implications. Ann Pharmacother 2010;44:688-700.
22. Moréno y Maiz T. Recherches chimiques et physiologiques sur l'erythroxylum coca du Pérou et la cocaine. Paris, Louis Lecter Libraire Editeur,1868;76-9.
23. Neal JM, Bernards CM, Butterworth JF 4th, Di Gregorio G, Drasner K, Hejtmanek MR, Mulroy MF, Rosenquist RW, Weinberg GL. ASRA practice advisory on local anesthetic systemic toxicity. Reg Anesth Pain Med 2010;35:152-61.
24. Ribeiro FAZ, Padron F, Castro TDM, Torres Filho LCA, Fernandes BA. Herniorrafia inguinal com anestesia local em regime ambulatorial. Rev Col Bras Cir 2010;37:397-402.
25. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate after a presumed bupivacaine-related cardiac arrest. Anesthesiology 2006;105:217-18.
26. Shen X, Wang F, Xu S, Qiang Y, Liu Y, Yuan H, Zhao Q, Feng S, Guo X, Xu J, Yang J. A Cardiolipina é o Alvo da Cardiotoxicidade dos Anestésicos Locais? Rev Bras Anestesiol 2010; 60:445-54.
27. Skinovsky J, Sigwalt MF, Bertinato LP, Chibata M, Moreira LMS, GranzottoCD. Herniorrafia inguinal com anestesia locorregional. (uso de ropivacaína). Rev Col Bras Cir 2006;33:224.
28. Tasch MD, Butterworth JF. Toxicity of local anesthetics. ASA Refresher Courses in Anesthesiology 2006;34:165-79.
29. Udelsmann A, Silva WA, Moraes AC de, Dreyer E. Hemodynamic effects of ropivacaine and levobupivacaine intravenous injection in swines. Acta Cir Bras 2009;24:296-302.
30. Warren JA, Thoma RB, Georgescu A, Shah SJ. Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. Anesth Analg 2008; 106:1578–80.
31. Weinberg GL, VadeBoncouer T. Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. Anesthesiology 1998;88:1071-5.
32. Weinberg GL. Lipid infusion therapy: translation to clinical practice. Anesth Analg 2008;106:1340-2.