REV COLOMB ANESTESIOL. 2016;xxx(xx):xxx–xxx

Revista Colombiana de Anestesiología
Colombian Journal of Anesthesiology
www.revcolanest.com.co

Scientific and Technological Research

Developmental pharmacokinetics and pharmacodynamics of parenteral opioids and nonsteroidal anti-nflammatory drugs in neonates and infants☆

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ARTICLE INFO

Article history:
Received 9 June 2016
Accepted 21 October 2016
Available online xxx

Keywords:
Infant
Infant care
Analgesics, opioid
Pharmacokinetics
Pharmacology

ABSTRACT

Introduction: Pharmacology of infants is understudied and different from other populations.
Objective: To review the unique features of neonatal and infant physiology that impact drug handling and the pharmacokinetics of analgesics, including opioids, ketorolac and acetaminophen.
Materials and methods: This article is a narrative review of the literature that constitutes a summary of the information presented at the annual Colombian Society for Anesthesia meeting in Cali, Colombia June 2015.
Conclusions: Pharmacology in neonates and infants is unique and must be considered in this vulnerable population. Recommendations for administration of these analgesics are presented based on their unique pharmacokinetic properties. Individual patient variation and clinical response must also be taken into account.

Farmacocinética y farmacodinámica del desarrollo en neonatos y lactantes de opioides parenterales y anti inflamatorios no esteroideos

Palabras clave:
Lactante
Cuidado del lactante
Analgésicos opióides
Farmacocinética
Farmacología

RESUMEN

Introducción: La farmacología de los lactantes es poco estudiada y difiere de la farmacología de otras poblaciones.
Objetivo: Revisar las características únicas de la fisiología de los neonatos e lactantes que afectan el manejo del fármaco y la farmacocinética de los anestésicos, incluyendo opioides, ketorolaco y acetaminofén.

☆ Please cite this article as: Martin L, Jimenez N, Lynn AM. Farmacocinética y farmacodinámica del desarrollo en neonatos y lactantes de opioides parenterales y anti inflamatorios no esteroideos. Rev Colomb Anestesiol. http://dx.doi.org/10.1016/j.rca.2016.10.005

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Materiales y métodos: Este artículo es una revisión narrativa de la literatura y constituye un resumen de la información presentada en la reunión anual de la Sociedad Colombiana de Anestesiología y Reanimación en Cali, Colombia, en junio de 2015.
Conclusiones: La farmacología en neonatos e lactantes es única y debe ser considerada en esta población vulnerable. Las recomendaciones presentadas para la administración de esos analgésicos están basadas en sus propiedades farmacocinéticas únicas. También deben tenerse en cuenta las variaciones individuales y la respuesta clínica.

Introduction

Perioperative pain control and selection of analgesic medications is particularly important in infants and neonates. Emerging data suggest that adverse experiences including exposure to painful stimuli in the perinatal period may negatively impact long term emotional and behavioral well-being.[1] This must be carefully weighed with the increased side-effect profile of analgesic medications in this age group.

This narrative review of the literature describes some of the features of neonatal and infant physiology that differ from adults and impact drug handling. Definitions of pharmacokinetic terms and a brief introduction to models for drug metabolism will be presented. Morphine and remifentanil will be used as examples to compare and contrast pharmacokinetics in infants and the pharmacodynamics particularly of respiratory effects in this vulnerable group. The kinetics of acetaminophen and of ketorolac (as examples of parenteral non-steroidal analgesics) in infants will be reviewed.

The article is a summation of information presented at the annual Colombian Society for Anesthesia meeting in Cali, Colombia June, 2015. It is a selection from the literature rather than a comprehensive review of all literature of these drugs or drug classes. References to the authors' own work is used for convenience and knowledge of study performance details, not to suggest other work is not equally important.

Physiology

The physiology of the neonate and infant differs in many aspects from the adult; some of these differences are important factors for drug handling. Total body water is a higher percentage of body weight in infants, reaching adult values by age 8–10 years (Fig. 1). Liver and kidney function is not fully developed at birth which affects handling of many drugs. The maturation of function occurs over several months during the first year of life.[2] Drug development in the past 10–20 years has focused on agents whose metabolism is less dependent on normal renal and/or liver function as aging populations of adults have compromise in these organs. This is beneficial for infants who also have immature function. Remifentanil is the obvious example of this process in action.

Hepatic enzymes, including both the P450 system and the glucuronidation pathways, are immature at birth. Maturation occurs over the first few months of postnatal life, at different rates for different P450 variants. Drugs that are metabolized by

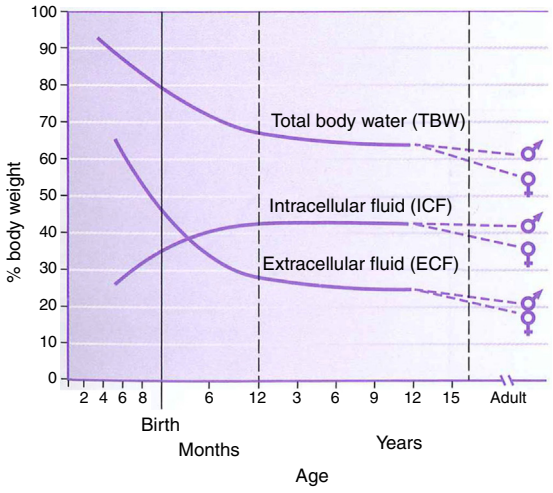

Fig. 1 – Total body water, intracellular fluid and extracellular fluid percent body weight for age in children. This figure was published in *Nelson Textbook of Pediatrics 17th edition*. Richard E. Behrman, Robert M. Kliegman, H.B. Jenson. Pathophysiology of Body Fluids and Fluid Therapy, Chapter 45, Page 191, Copyright Elsevier (2004). Source: (2) Reproduced with permission.

glucuronidation (solubility increased for excretion) will have delayed removal in the first months of life. Sulfation then becomes more important as a metabolic pathway. There are also inherited variants for the CYP (P450) system that may impact drug handling. An example of this is seen with codeine, where conversion to the active morphine can occur faster, slower, or not at all, resulting in an unpredictable effect.[3] Reports of excessive effect in ultrarapid metabolizers have been associated with respiratory calamities.[4,5]

The kidney is important for eliminating drugs or their metabolites. In infants, glomerular filtration rates (GFR) start at approximately 10% of adult normal values, reaching these by 12 months of age. Renal tubular function also matures over the first 6 months. This decreased function can result in the accumulation of metabolites, and is particularly problematic with those metabolites that have active effects.

Pharmacokinetics

Pharmacokinetics is defined as the study of drug disposition by patients; it is affected by absorption (important for non-intravenous routes of administration), distribution,