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Essay

The hidden world of drug interactions in anesthesia[☆]

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ABSTRACT

Drug interactions represent the cornerstone in the basic anesthetic triangle and knowledge about such interactions contributes to a solid foundation for administering medications.

This article dwells on the anesthetic drug interactions: pharmaceutical (mixing or not mixing), pharmacokinetic (alterations in distribution, metabolism, or clearance), pharmacodynamics (synergism, additive effect) and thermodynamic (affinity and intrinsic activity).

The basic anesthetic triangle is a current concept and drug interactions are the cornerstone for safe anesthesia. These interactions are currently neglected and hence the anesthetist should recognize any drug interactions for a safer practice of anesthesia.

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El mundo oculto de las interacciones farmacológicas en anestesia

RESUMEN

Las interacciones farmacológicas constituyen los pilares de la tríada básica de la anestesia y su conocimiento contribuye a tener unas bases sólidas en la administración de medicamentos.

El presente artículo tiene como objetivo hacer una reflexión sobre las interacciones farmacológicas en anestesia: Farmacéuticas (mezclar o no mezclar), farmacocinéticas (alteración en la distribución, metabolismo o eliminación), farmacodinámicas (sinergismo, adición) y termodinámicas (afinidad y actividad intrínseca).

Palabras clave:

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La tríada básica de la anestesia es un concepto vigente y sus interacciones farmacológicas son los pilares de una anestesia segura. En la actualidad estas interacciones no se tienen en cuenta, razón por la cual es pertinente que el anestesiólogo las tenga presente para hacer un ejercicio más seguro de los medicamentos que administra.

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Introduction

We are living through an unprecedented event in anesthesiology, leaving the dark ages behind – when opening or closing a vaporizer was decided on a whim, where an intravenous drug was administered on a “little bit” or “a fair amount” or “not too much” basis, and the teaching of anesthesia depended on the expertise of the professor with many years of experience, who would finally have found the magic formula to administer a cocktail of drugs to meet the surgeon’s needs.¹ Now we speak in terms of concentrations, targets, probability of non-response (PNR), synergism, etc. These are all terms supported by scientific trials that are the basis for teaching anesthesia and are repeated generation after generation. However, in order to understand those terms, it is essential to know the foundations of administering safe anesthesia, which basically can be summarized into “INTERACTIONS”.

The concept of anesthesia with three basic components as described by Gray, is essential for a sound anesthetic technique.^{2,3} These components have been expanded through the years^{4,5}; nevertheless, they continue to revolve around the three fundamental components: hypnosis, analgesia, and relaxation. Understanding the interaction among these basic components paves the way to a clear understanding of the range of responses elicited when administering anesthetic agents.

The concept of the anesthesia triangle (AT) goes beyond a triangle representing the key components of anesthesia and according to the initial model was represented by a prism with each side representing one component and the barycenter of the triangle exemplified the interactions among those components.⁶

The primary interaction submitted among the three components of anesthesia was pharmacodynamics, that entailed recording the ventilation depression associated to the interaction of the opioid, the hypnotic agent and the relaxant.

Five decades later, the AT continues to be valid and the principle of interactions resulting from the triangle has been expanding.

Today we still have the three basic components, but the range of interactions among them has grown beyond pharmacodynamics to include four interactions: pharmaceutical, pharmacokinetics, pharmacodynamics, and thermodynamics.

In sum, we have three components – opioid, hypnotic, and relaxant – that when present in the body may interact in four different ways: pharmaceutical, pharmacokinetics, pharmacodynamics, and thermodynamics.

These interactions are the foundation for the current triad and being clear about what each one involves will enable a safe administration of anesthesia with a multimodal approach that is safer and reproducible (Fig. 1).

Drug interactions

Currently, few drugs are available to build the AT: remifentanyl, propofol, rocuronium, inter alia. Getting to know the interactions of this small group of drugs is critical for administering a multimodal safe, target controlled anesthesia – TACAN.⁷ In addition to these drugs, there are others that while are not part of the AT, are commonly used in the OR (i.e. dexamethasone, midazolam, etc.); hence being familiar with their potential interactions is a guarantee for preventing adverse drug-related events.

Following is a description of drug interactions (DI) associated with physical-chemical incompatibilities that preclude mixing two or more drugs into one solution: pharmacokinetics (PKI), drug interactions involving distribution volume, clearance and metabolism; pharmacodynamics (PDI), additive, over-additive, and under-additive; and thermodynamic (TDI), affinity and intrinsic activity.

Pharmaceutical interactions

PIs are changes in the physical-chemical structure of a drug due to the action of a second drug when combined in the same solution, whether in a bag, a syringe, or in a Y-infusion system.^{8,9} This type of interactions provide information about drug stability and compatibility. The classical tests to identify stability are chromatography and the main source of information about such interactions is the *Handbook on Injectable Drugs*.¹⁰ Interactions not reported in the book may be looked-up in Internet under the terms: *Stability analysis*, *Mixture*, *compatibility*.

Whenever two or more drugs are mixed for anesthesia purposes or when these agents share the same infusion route, the question about the compatibility of such agents must be asked. Hypnotics are usually combined with opioids or with other hypnotics with no consideration as to their compatibility or potential instability when combining them. Let us consider two examples:

The combination of remifentanyl and propofol is usual in some medical institutions.^{11,12} However, is it appropriate to mix these two agents? The *Handbook on Injectable Drugs*, gives little information about this topic, but a search using the terms

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