NUEVAS FORMULACIONES DE PROPOFOL

GATIV Septiembre 2010

Dra. S. Telletxea

EVOLUCION HISTORICA

NUEVAS FORMULACIONES DEL PROPOFOL

FORMULACIONES DE PROPOFOL CON DIFERENTE VEHICULO O DIFERENCIAS EN EL EXCIPIENTE

PROFARMACOS DEL PROPOFOL: FOSPROPOFOL

HOCATIV 2010

EVOLUCION HISTORICA

Cremofor EL(aceite de castor): dolor a la inyección, R. anafilactoide

Diprivan (10 % aceite de soja y 1,25% lecitina de **yema de huevo**). Los efectos indeseables que presenta son: crecimiento bacteriano, hiperlipidemia y dolor a la inyección.

Propofol EDTA (Astra-Zéneca) 1996

Perdida de la patente

Nuevas genéricos de propofol

HIGATA 2010

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- LOS GENÉRICOS PRESENTAN LOS MISMOS PROBLEMAS O EFECTOS SECUNDARIOS QUE LA FORMULACION ORIGINAL POR TRATARSE DE LA MISMA MOLECULA E IR VEHICULIZADA EN EL MISMO EXCIPIENTE.
  - PROPOFOL ROVI, RECOFOL, IVOFOL, PROPOFOL FRESENIUS, PROPOFOL ABBOTT, FRESOFOL, DISOPROFOL…
- EFECTOS SECUNDARIOS:
  - Dolor a la inyección
  - Hiperlipidemia
  - Sobreinfección microbiana

!!! CATIVADO

EVOLUCION HISTORICA

Cremofor EL(aceite de castor): dolor a la inyección, R. anafilactoide

Diprivan (10 % aceite de soja y 1,25% lecitina de **yema de huevo**)

Propofol EDTA (Astra-Zéneca) 1996

Perdida de la patente

Nuevas genéricos de propofol

Nuevas formulaciones de propofol

III GATIV 2010

NUEVAS FORMULACIONES DE PROPOFOL

III CMV 2010

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Anesthesiology 2005; 103:860–76

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Propofol

The Challenges of Formulation

Max T. Baker, Ph.D., Mohamed Naguib, M.B., B.Ch., M.Sc., F.F.A.R.C.S.I., M.D.†*

Development of a new generation of propofol

Haibo Wang, Randall Cork and Ashock Rao

Purpose of review

The current advance in development of a new generation of propofol and its clinical implications are reviewed.

Recent findings

All currently available formulations of propofol have side effects related to propofol itself, as well as to the emulsion delivery systems. A search for better and safer propofol continues. Improvement of the emulsion delivery systems is one of approaches, which can be achieved by identifying better inactive components, enhancing stability, and applying new technologies such as nanotechnology. Modification of chemical structure is another approach, particularly with the development of propofol prodrugs.

Summary

There is a continuous need to develop a better and safer propofol. The development of a new propofol should be focused on minimizing the unwanted side effects, while preserving the beneficial profiles. Hopefully, just such a new propofol will be available in the near future for clinical use.

Keywords

emulsion, microemulsion, nanoemulsion, prodrug, propofol

Curr Opin Anaesthesiol 20:311–315. © 2007 Lippincott Williams & Wilkins.

Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA

Introduction

Since its introduction to clinical use in the late 1980s, propofol has been widely accepted by the anesthesia community. Structurally, propofol is an alkylphenol derivative named 2,6-diisopropylphenol. It is highly lipid-soluble. It readily permeates biomembranes, such as the blood–brain barrier, so it rapidly gets to the target sites in the brain. Thus, its onset of anesthetic effect is rapid, equal to one arm-to-brain circulation time. Further, it can be rapidly redistributed from the brain into other tissues so that patients can be rapidly recovered from the anesthetic state. Its fast onset and fast-offset features make propofol ideal for ambulatory surgeries. In comparison with other currently used intravenous anesthetics, propofol also has some antiemetic and euphoric effects [1,2].

In spite of its multiple advantages, propofol is also associated with some anesthetic challenges, such as the difficulty in development of an injectable formulation, significant blood-pressure drop at a normal induction dose, and notable pain at the peripheral intravenous injection sites [3]. Those problems associated with the currently used formulations, however, may provide further pharmaceutical opportunity to develop a newer and better generation of propofol.

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FORMULACIONES DE PROPOFOL CON DIFERENTE VEHICULO O DIFERENCIAS EN EL EXCIPIENTE

III GATIV 2012

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PROPOFOL CON METABISULFITO (Baxter)

Efecto: evitar colonización bacteriana

Produce menor dolor a la inyección

Problemas:

- Sulfito: *reacciones alérgicas
  *broncospasmo

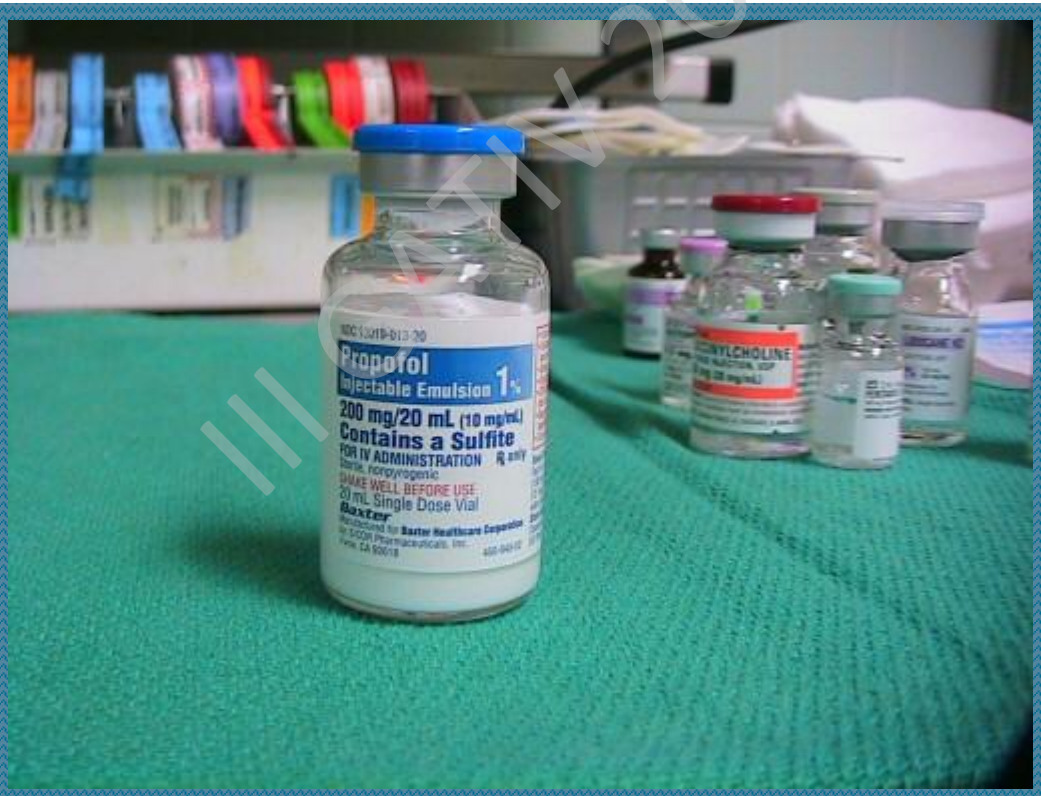
PH mas bajo 6,4: inestabilidad de la formulación (aumento de radicales libres y peroxidación de lípidos)

III GAIV 2016

Bisulfite-Containing Propofol: Is it a Cost-Effective Alternative to Diprivan™ for Induction of Anesthesia?

Xinli Shao, MD, PhD, Hong Li, MD, Paul F. White, PhD, MD, FANZCA, Kevin W. Klein, MD, Christine Kulstad, MS, and Andrew Owens, MS

Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas



IIIC CTIV 2010

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PROPOFOL CON BENCIL ALCOHOL (Bedford)

Efecto: evitar colonización bacteriana

PH mas fisiológico de 7

Problemas:

- Reacciones alérgicas
- Sind Gasping

IIIGATIV 2010

PROPOFOL EN EMULSION C/ALBUMINA

Emulsionan lípidos con albúmina sérica y propofol o unicamente albúmina con propofol

Se encuentra en estudios pre-clínicos pero la actividad anestésica parece similar al original.

III CATIV 2010

PROPOFOL LIPURO (Braun)

Sustituir el Intralipid por cadenas de TG de media y larga longitud.

Efecto: menor dolor a la inyección

Baxter alerta por 1º vez sobre
" Sind de infusión de propofol"

INGATIV 2010

IDD PROPOFOL
(Insoluble Drug Delivery)

Utilizan Nanoparticulas
Presenta apariencia transparente
Se forman MICROEMULSIONES:
MICROEMULSION MICELAR 5%
MICROEMULSION 1%
Efecto: disminuye trigliceridemia y el sobrecrecimiento bacteriano.
Problemas:
dolor a la inyección
FC/FD: diferencias entre hombres y mujeres en las conc. Plasmaticas y en el tiempo de despertar.

ITCAM 2010

PROPOFOL EN CICLODEXTRINA

- Carbohidrato ciclico soluble en agua que contiene una cavidad hidrofóbica tridimensional que acomoda al propofol.
- Beneficios potenciales:
  - Dismución del dolor a la inyección
  - Disminución del trigliceridemia
  - Disminución del crecimiento bacteriano

  - ENSAYOS EN ANIMALES

HGATIV 2010

AMPOFOL

- Emulsion baja en lipidos (50% menos)
- Alta incidencia de dolor a la inyección.
- Disminuido el sobrecreciento bacteriano.
- No diferencias FD.

III CATIV2010

AM149

- Formulación sin aceite de soja.
- No diferencias FC ni FD.
- Suspensión del ensayo clínico por alta incidencia de TROMBOFLEBITIS.

IIICATIV 2010

CLEOFOL

- Formulación libre de lecitina de huevo.
- Se manufactura y se utiliza en la India por razones religiosas.
- No se conoce la composición exacta.
- No ensayos clínicos ni estudios en animales.
- Muy irritativo incluso tromboflebitis descritas.

IIGAIV 2010

AQUAFOL(Daewon Ph)

- Microemulsión libre de lípidos.
- Libre de infecciones y de hipertrigliceridemia.
- No diferencias FC ni FD con el original.
- Según algunos autores mas dolor de inyección.
- Actualmente en ensayos en fase III (seguridad y eficacia).

III CATIV 2010

PROFARMACOS DEL PROPOFOL: FOSPROPOFOL

III GRIV 2010

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PROFARMACO:

SUSTANCIA SIN ACTIVIDAD FARMACOLOGICA QUE DENTRO DEL ORGANISMO MEDIANTE REACCIONES METABOLICAS O ENZIMATICAS SE TRANSFORMA EN UN FARMACO QUE REALIZA UNA DETERMINADA ACCION FARMACOLOGICA

MAY 2010

PROFARMACOS DE PROPOFOL

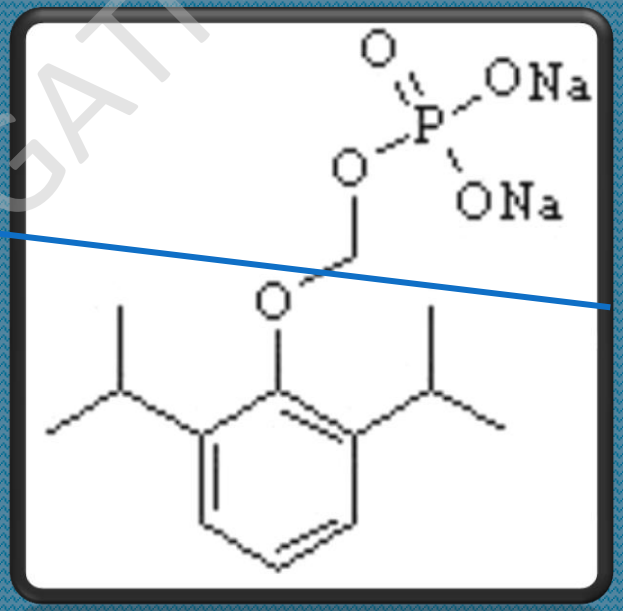
- 1. PROPOFOL FOSFATO (PP)
- 2. ETILDIOXIFOSFATO PROPOFOL
- 3.PROPOFOL HEMISUCCINATO SODICO
- 4. GPI15715 o FOSPROPOFOL

III CATI 2010

FOSPROPOFOL (LUSEDRA)

Fospropofol disodio es un ester fosfato de propofol soluble en agua.

FDA lo aprueba en Dic de 2008 para sedacion en CAM



Ester fosfato

III GATIV 2010

FOSPROPOFOL

Fosfatasa alcalina (higado y endotelio vascular)

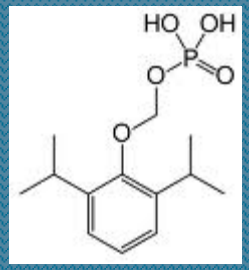
FOSFATO + PROPOFOL + FORMALDEHIDO

aldehido deshidrogenasa (higado, eritrocitos)

Acido Fórmico

10 formiltetrahidrofolato deshidrogenasa

$CO_2 + H_2O$



III GATIV 2010

Dra. S. Telletxea

PROBLEMAS CON LOS ENSAYOS CLINICOS

- LAS MUESTRAS DE ENSAYOS PUBLICADOS ENTRE EL 2003-2005
- RETIRADOS POR ERRORES EN EL MODELING PK-PD
- PROBLEMAS EN LA RECOLECCION DE LAS MUESTRAS

III GATIV 2012

Anesthesiology 2008; 109:937

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Fospropofol Assay Issues and Impact on Pharmacokinetic and Pharmacodynamic Evaluation

To the Editor:—Fospropofol disodium (GPI 15715 or Aquavan® Injection; MGI Pharma, Inc., Bloomington, MN) is a water-soluble, phosphono-*O*-methyl prodrug of propofol for intravenous injection. It has been evaluated for sedation during diagnostic and routine therapeutic procedures. The early evaluation studies were published mostly in ANESTHESIOLOGY between 2003 and 2005.

After intravenous administration, fospropofol is rapidly metabolized by alkaline phosphatase enzymes, releasing $propofol_{FP}$. Several pharmacokinetic and pharmacodynamic studies have shown that $propofol_{FP}$ demonstrated differences in pharmacokinetic and pharmacodynamic profiles compared with propofol in a lipid solution.[1–5] We have recently discovered an assay problem that may have affected the measurement of $propofol_{FP}$ plasma concentrations in previously published studies. In the earlier studies,[1–4,6] blood samples were collected in tubes containing sodium orthovanadate (SOV; 60 mg added as a solid problems were developed and validated. Additional studies were then conducted using an appropriate assay to assess the pharmacokinetics and pharmacodynamics of fospropofol in healthy volunteers and patients. We plan to publish these results shortly, along with an estimate of the degree of error from the previously published studies that reported results using the old assay. We very much regret the magnitude of the originally published incorrect information and the confusion that it has and will cause in the pharmacokinetics of propofol from the use of fospropofol.

Ajit Shah, Ph.D.,* Bipin Mistry, Ph.D., Ekaterina Gibiansky, Ph.D., Leonid Gibiansky, Ph.D. *MGI Pharma, Inc., Bloomington, Minnesota. ajit.shah@mgipharma.com

IWGATIV 2010

Dra. S. Telletxea

Erroneously Published Fospropofol Pharmacokinetic–Pharmacodynamic Data and Retraction of the Affected Publications

To the Editor:

As described in a letter to the editor, published in ANESTHESIOLOGY, *Anesthesia and Analgesia*, and the *European Journal of Anaesthesiology*,[1–3] an analytical propofol assay inaccuracy was discovered after all six initial studies on the pharmacokinetic–pharmacodynamic and tolerability of fospropofol had been published.[4–9] This assay inaccuracy makes the measured propofol plasma concentrations in these previously published studies unreliable.

propofol in human volunteers within the deadline of 12 months given by the editors-in-chief. As such, we, the undersigned corresponding and senior authors from the six original articles, in the name of all coauthors, request that the articles in question that provide flawed pharmacokinetic–pharmacodynamic data be retracted. We regret that we are unable to successfully resolve the problem within the given timeframe. *(See a list of retracted articles from ANESTHESIOLOGY on page 1058 of this issue.)*

Michel M. R. F. Struys, M.D., Ph.D.,* Jörg Fechner, M.D.,† Jürgen Schüttler, M.D.,† Helmut Schwilden, M.D., Ph.D.†
*University of Groningen, Groningen, The Netherlands, and University of Ghent, Gent, Belgium. m.m.r.f.struys@anest.umcg.nl.
†University of Erlangen-Nuremberg, Erlangen, Germany.

III GATV 2019

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FARMACOCINETICA

- MODELO DE 2 COMPARTIMENTOS PARA EL FOSPROPOFOL Y 3 PARA EL PROPOFOL

III GAIV 2010

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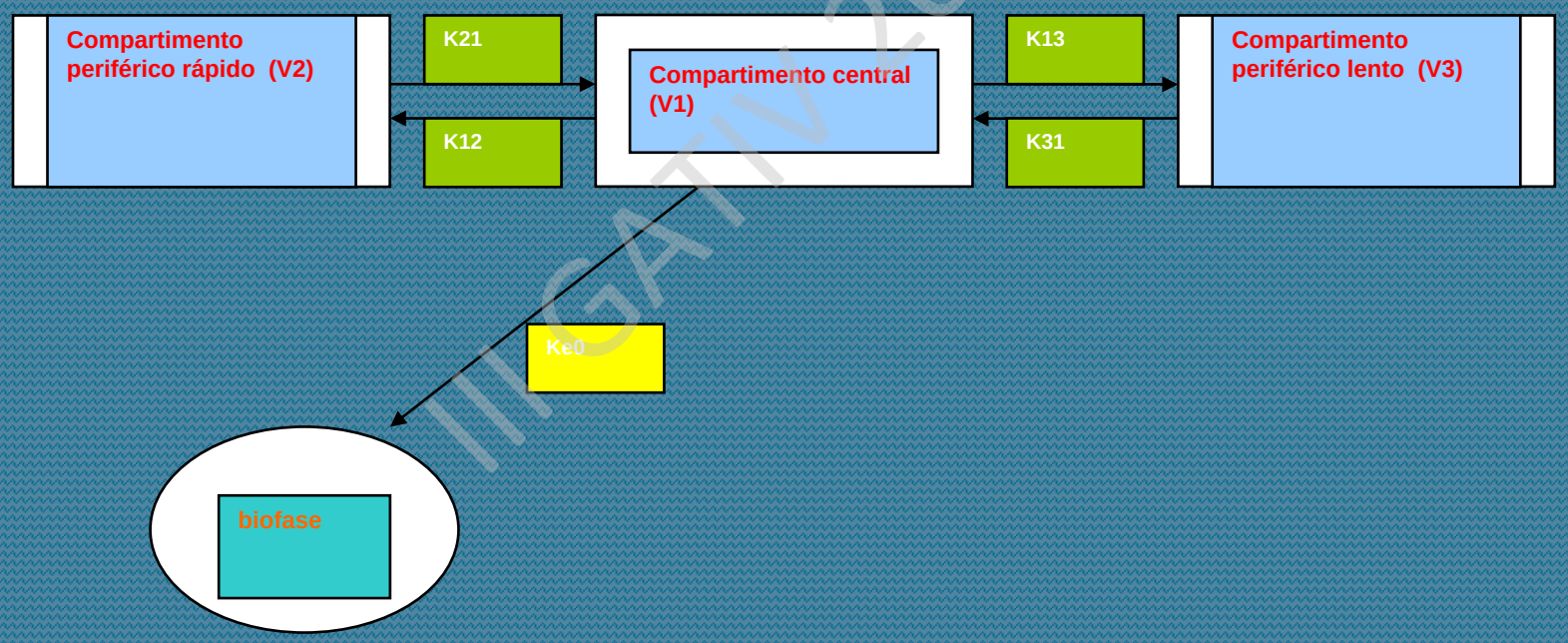

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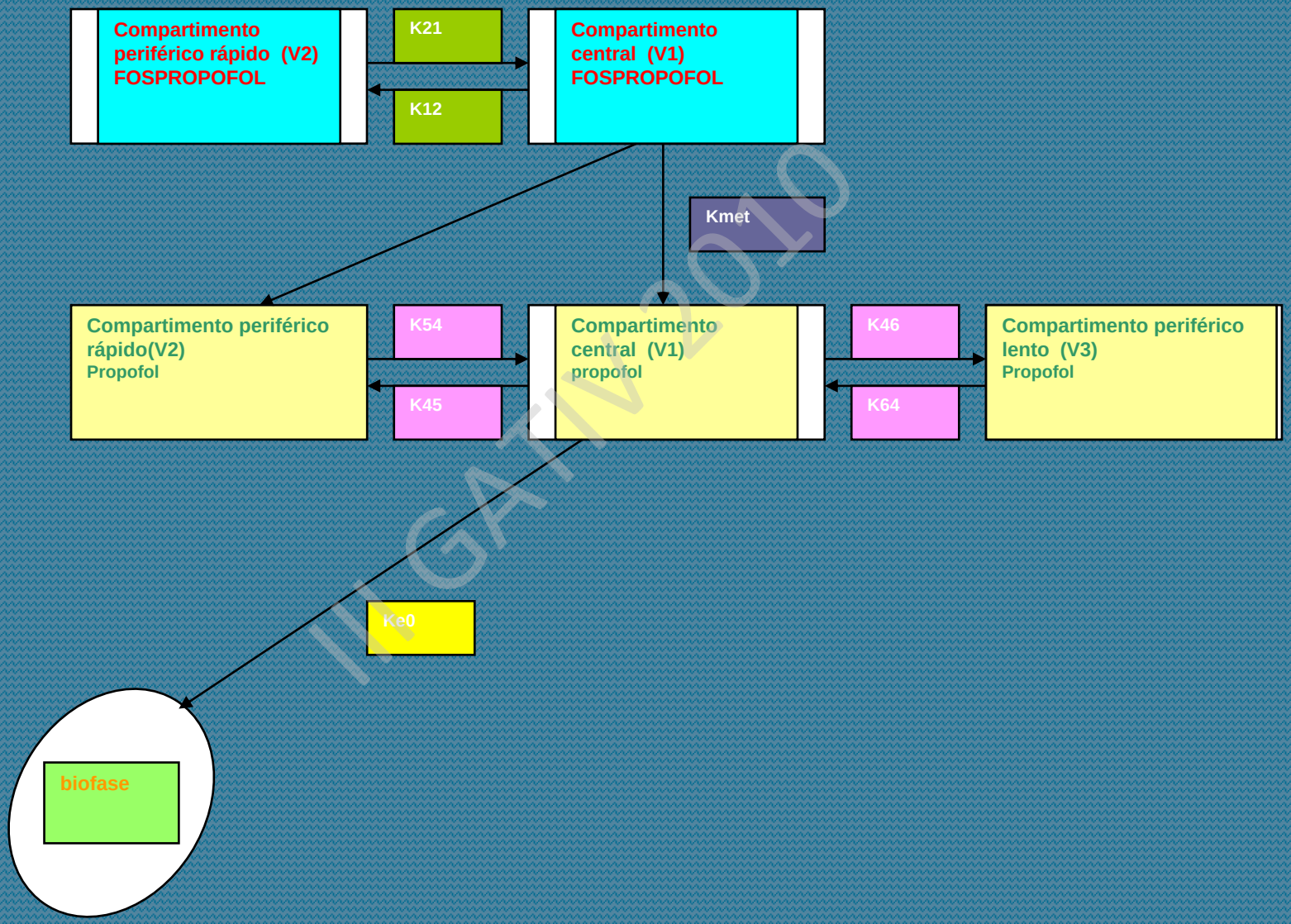

III GATIV 2010

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Interactive Web Simulation for Propofol and Fospropofol, a New Propofol Prodrug

Sinan Yavas, MD
David Lizdas
Nikolaus Gravenstein, MD
Samsun Lampotang, PhD

Using pharmacokinetic and pharmacodynamic data published in the scientific literature, we have developed interactive on-line simulations to model administration of propofol and fospropofol, a new water-soluble prodrug formulation of propofol. The prodrug formulation of fospropofol leads to a delayed onset to peak concentrations of propofol. A comparison simulation that overlays administration of fospropofol and propofol allows clinicians to understand the differences of administering fospropofol and traditional propofol. The simulations have the added advantage of allowing for differences among patients documented in test studies and the use of different models.

(Anesth Analg 2008;106:880–3)

IWGATIV 2010

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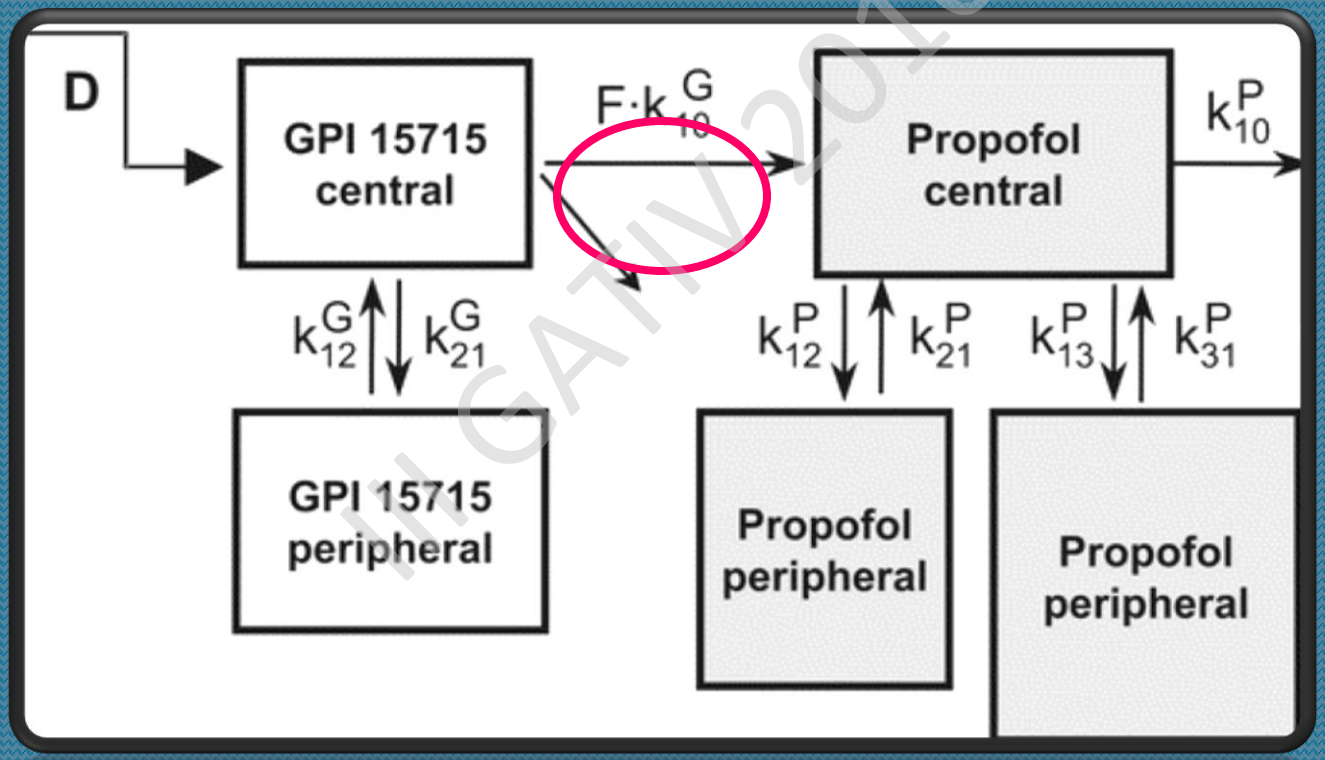
F: FACTOR DE CONVERSIÓN DE FOSPROPOFOL A PROPOFOL



III GATIV 2010

FARMACODINAMIA

- El propofol (FP) se comporta de diferente manera que el propofol original
  - Las moléculas de propofol (FP) parecen ser mas potentes farmacológicamente que el propofol original ya que a las mismas concentraciones de propofol en plasma presenta mayor efecto sedante.
  - El efecto farmacológico se obtiene antes y con menores concentraciones.
  - HISTERESIS diferente

III GATIV 2010

El propofol derivado del fospropofol es mas potente que propofol base

Table 2. Pharmacodynamic Parameters for Median Frequency

	$Propofol_D$	$Propofol_{GPI}$
E_0 (Hz)	9.1 ± 0.8	9.7 ± 1.1
E_{max} (Hz)	7.8 ± 1.0	8.4 ± 0.8
EC_{50} (μg/ml)	3.0 ± 0.7	2.1 ± 0.5*
γ	5.6 ± 3.6	7.2 ± 3.6
K_{e0} (min^{-1})	0.21 ± 0.07	–
E_β (Hz)	3.5 ± 3.4	–
EC_β (μg/ml)	0.72 ± 0.20	–
κ	3.6 ± 1.4	–
MR (%)	1.1 ± 0.8	0.1 ± 1.7
MAR (%)	3.8 ± 1.6	7.0 ± 2.7

Values are mean ± SD.

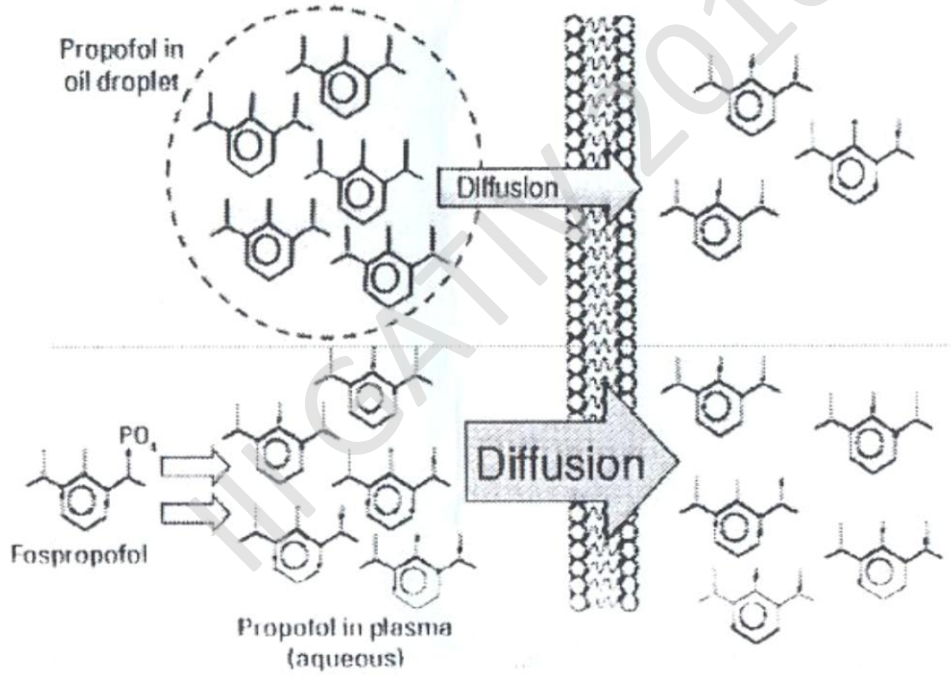
E_0 = baseline effect; E_β = maximum β activation; EC_β = effect site concentration at half-maximum β activation; EC_{50} = effect site concentration at half-maximum effect; E_{max} = maximum effect; γ = steepness of the concentration-effect curve; K_{e0} = equilibration rate constant between central and effect compartment; κ = steepness of the concentration-effect curve for β activation; MAR = median absolute residual; MR = median residual expressed as percent of pharmacodynamic range.

* $P < 0.05$ $Propofol_{GPI}$ *versus* $Propofol_D$.

III GATIV 2010

- Estructuralmente las moléculas de propofol son similares en ambas formulaciones, la única diferencia esta en la formulación en la que están vehiculizadas.

III CATI 2010



HCSATIV2010

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EFECTOS BENEFICIOSOS

- NO DOLOR A LA INYECCION
- NO PRODUCE HIPERLIPIDEMIA
- NO SOBRECRECIMIENTO BACTERIANO
- INDICADO EN ALERGICOS AL HUEVO

HCAFIV2010

EFECTOS NO DESEABLES

- PARESTESIAS TRANSITORIAS EN ZONA PERINEAL (70%)
- PRURITO (16%)

III GATIV 2010

A Phase 3, Randomized, Double-Blind Study To Assess the Efficacy and Safety of Fospropofol Disodium Injection for Moderate Sedation in Patients Undergoing Flexible Bronchoscopy*

Gerard A. Silvestri, MD, FCCP; Brad D. Vincent, MD, FCCP; Momen M. Wahidi, MD, FCCP; Emory Robinette, MD, FCCP; James R. Hansbrough, MD, FCCP; and Gordon H. Downie, MD, PhD, FCCP

A Randomized, Double-blind, Phase 3 Study of Fospropofol Disodium for Sedation During Colonoscopy

Lawrence B. Cohen, MD, Edward Cattau, MD,† Allen Goetsch, MD, CCTI,‡ Atul Shah, MD,§ John R. Weber, MD,‖ Douglas K. Rex, MD,¶ and Jacqueline M. Kline, PhD#*

HGATV 2010

Dra. S. Telletxea

BJA

"I would have everie man write what he knowes and no more." – Montaigne

BRITISH JOURNAL OF ANAESTHESIA

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Editorial I

Exploring the frontiers of propofol formulation strategy: is there life beyond the milky way?

From clinical, scientific, and commercial perspectives, propofol is a fabulous success. In addition to its popularity as an i.v. induction agent, propofol is widely used internationally for the maintenance of general anaesthesia. Coupled with target-controlled infusion technology, the introduction of propofol launched the total i.v. anaesthesia (TIVA) revolution that must be regarded as one of the most significant innovations in anaesthesia practice of the last half century. And propofol's popularity is not limited to the operating theatre. Propofol is also commonly used for the provision of sedation in procedural suites and intensive care units around the world.

Despite its success, however, propofol's current formulation has a number of undesirable properties that are in part a function of the lipid emulsion formulation approach. This lipid-based formulation frequently produces pain on injection[1] and has also been associated with serious allergic reactions.[2 3] In addition, because the lipid formulation supports rapid microbial growth,[4] inadvertent contamination of the formulation can be a cause of postoperative sepsis,[5] a problem that persists despite antimicrobial additives. Finally, hyperlipidaemia may be a risk factor in the development of the propofol infusion syndrome, an often lethal metabolic disorder typically associated with prolonged propofol administration in the intensive care unit.[6] For this reason, there is substantial interest in the development of new formulations of propofol that are devoid of some or all of the undesirable

as a lipid-based macroemulsion containing soybean oil, egg yolk lecithin, and glycerol (Diprivan®, AstraZeneca, London, UK). In this formulation, resembling Intralipid® (Fresenius Kabi, Homburg, Germany), the oil droplets containing most of the propofol are large enough to reflect and refract white light significantly.[7] Thus, the lipid-based macroemulsion looks a lot like milk (i.e. this formulation can be thought of as the 'milky way').

Given the problems associated with the current lipid-based formulation (and propofol's commercial success), it is not surprising to learn that a number of propofol formulations utilizing a wide variety of pharmaceutical technologies have been investigated. These include an array of lipid-based emulsions (typically attempting to reduce the total lipid content),[9 10] non-lipid excipients (e.g. surfactants–co-surfactants, nano-particle carriers, cyclodextrins),[11–15] and a prodrug.[16]

A substantial challenge associated with the reformulation of propofol is that reformulation may alter propofol's pharmacokinetic and pharmacodynamic characteristics.[17 18] On the basis of information from animal studies, it appears that at least some of propofol's rapid-onset, rapid-offset clinical pharmacologic profile is dependent on the formulation.[19] Thus, for propofol, a simple and important maxim for pharmaceutical chemists is that changing propofol's formulation may change its clinical pharmacology.

This issue of the *British Journal of Anaesthesia* includes

Dr. S. Telletxea

GRACIAS POR VUESTRA ATENCION

III GAIV 2010