NUEVAS ESTRATEGIAS EN LA PREVENCIÓN Y TRATAMIENTO DE LAS NÁUSEAS Y VÓMITOS POSTOPERATORIOS

Juan I. Gómez-Arnau

III WORKSHOP GATIV SISTEMAS TCI
Alicante, 2010

Hospital Universitario
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SaludMadrid
Comunidad de Madrid

Dr. JI Gómez-Arnau

Complicaciones en Anestesia

Mortalidad
Morbilidad mayor
Morbilidad menor
Insatisfacción del paciente
Aumento del gasto

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Complicaciones en Anestesia

Mortalidad
Morbilidad mayor
Morbilidad menor
Insatisfacción del paciente
Aumento del gasto

PONV UNPLUGGED

Seminars in Anesthesia, Perioperative Medicine and Pain, Vol 23, No 3 (September), 2004: pp 203-220

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Posibilidad de NVPO

	Habitantes	Cirugías	NVPO (30%)
Francia, 1996	60 mill	7.020.000	2.100.000
Alemania, 2001	80 mill	9.600.000	2.880.000
España, 2005	42 mill	5.600.000	1.680.000

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Tasas de mortalidad anestésica y NVPO

	1980	2010
Mortalidad / 10.000	**1,9-7**	**0,19-1,4**
NVPO %	**30**	**30**

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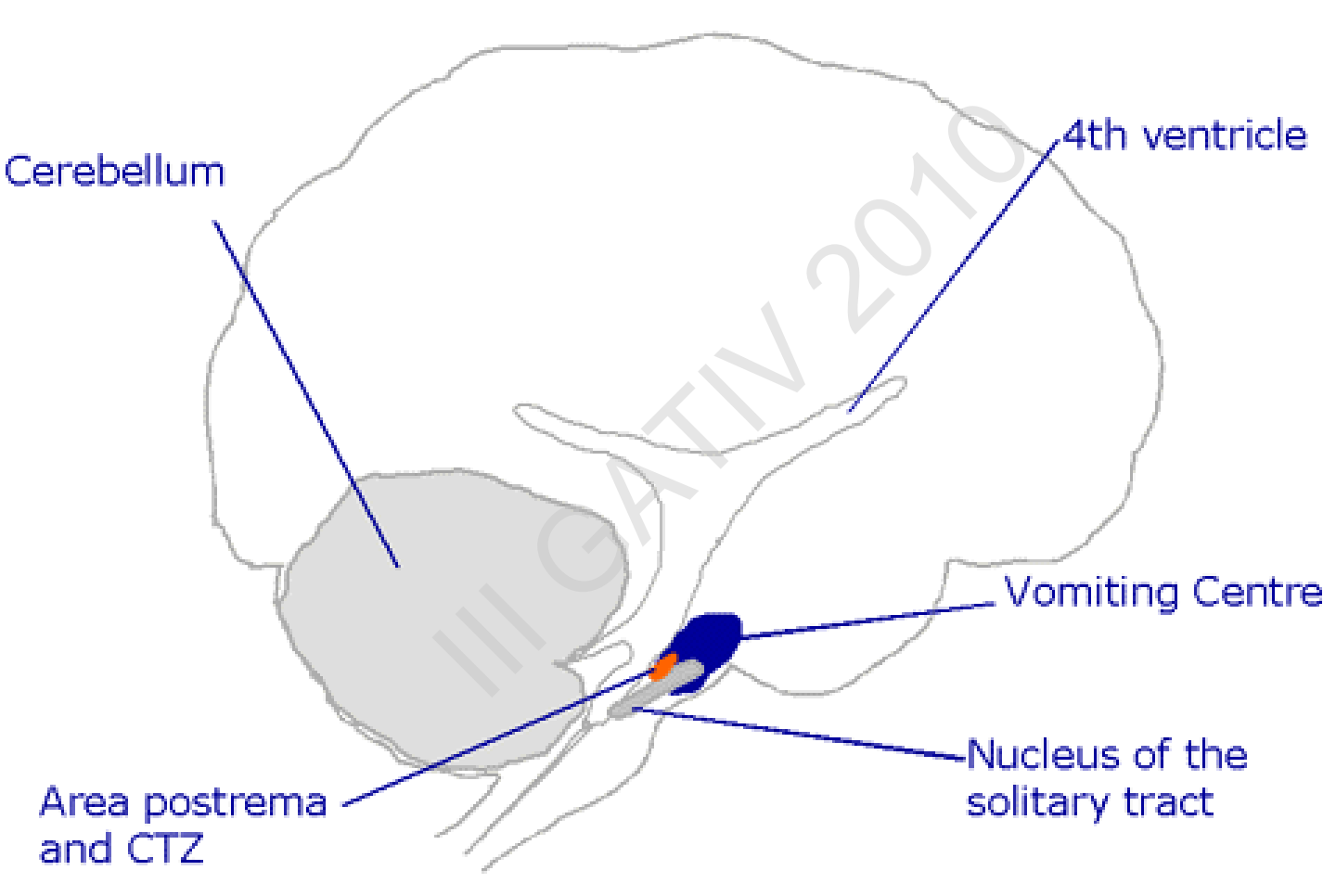
Fisiopatología de las náuseas y vómitos



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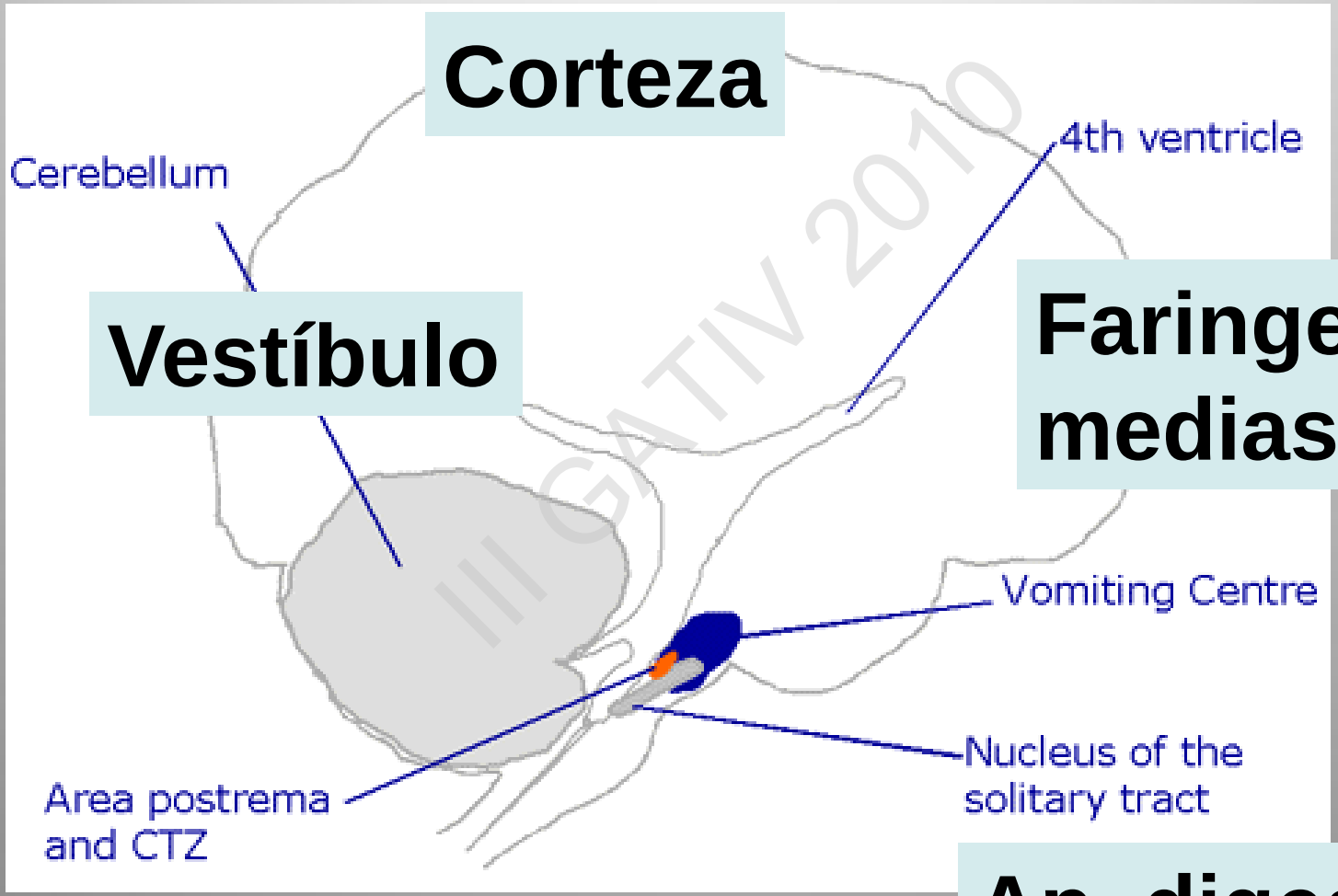
Fisiopatología: origen de los estímulos



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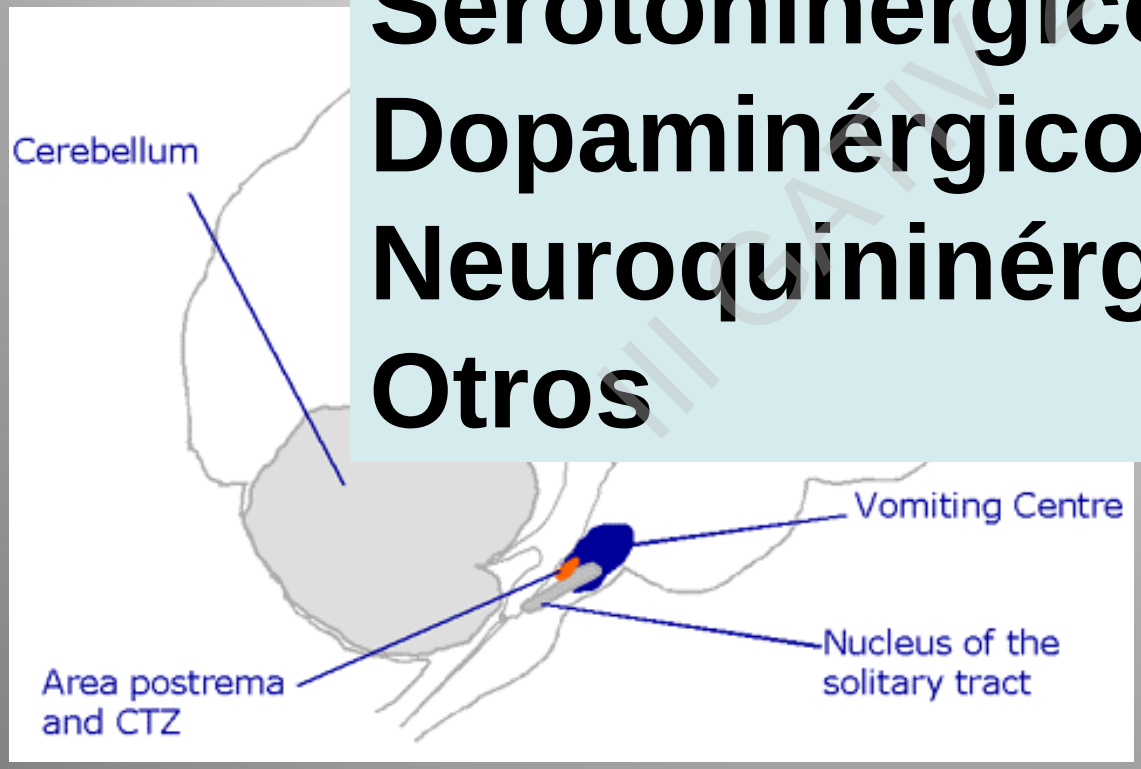
Fisiopatología: receptores involucrados

Histaminérgicos: H_1
Colinérgicos
Serotoninérgicos: $5HT_3$
Dopaminérgicos: D_2
Neuroquininérgicos: NK_1
Otros



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Recomendaciones

Escala Apfel	Riesgo	Actuación	Rescate
0	10%	“Esperar y ver”	Ondansetron
1	20%	1 Antiemético (Dx ó Dr)	Ondansetron
2	40%	2 AE (Dx + Dr)	Ondansetron
3	60%	TIVA + 2 AE (Dx + Dr)	Ondansetron
4	80%	TIVA + 3 AE (Dx + Dr + Ond)	AE no usados

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DROPERIDOL	ONDANSETRON	DEXAMETASONA
EFICACIA (NNT)		
5-6	5-7	6
EFECTOS SECUNDARIOS (%)		
S. Extrapiramidales <1.1 Vértigo 0.7 Sedación 4.2	Cefalea 3.3 Estreñimiento 3 ↑Transaminasas 3.2	Hiperglucemia Escozor perineal Otros

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Alternativas

- **Aprepitant: 40 mg po**
- **Palonosetron: 0,075 mg iv**
- **Metoclopramida : 25- 50 mg iv**
- **Prometazina: 6,25-12,50 mg iv**
- **Propofol: carga de 10 mg + infusión 10 µg/kg/min (340 ng/ml)**

Escopolamina parche: 1,5 mg
Dimenhidrinato: 1mg/kg iv

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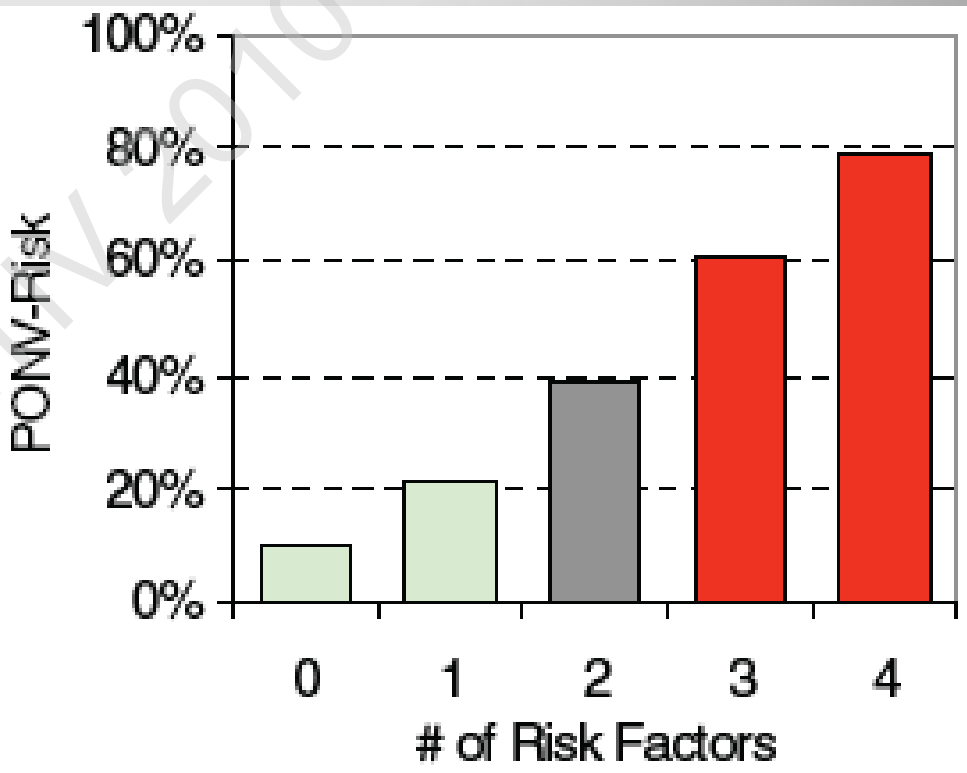
A Simplified Risk Score for Predicting Postoperative Nausea and Vomiting

Conclusions from Cross-validations between Two Centers

Christian C. Apfel, M.D.,* Esa Läärä, Ph.D.,† Merja Koivuranta, M.D., Ph.D.,‡ Clemens-A. Greim, M.D.,§

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV	1
Postoperative Opioids	1
Sum =	0 ... 4



Anesthesiology 1999;91:693–700

IIIGATIV 2010
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Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2010, **65**, pages 379–387 doi:10.1111/j.1365-2044.2010.06249.x

REVIEW ARTICLE

Association between nitrous oxide and the incidence of postoperative nausea and vomiting in adults: a systematic review and meta-analysis

J. Fernández-Guisasola,[1] J. I. Gómez-Arnau,[2] Y. Cabrera[3] and S. García del Valle[4]

1 Staff Anaesthesiologist, Anaesthesia Department, Hospital Rúber, 2 Chief, Anaesthesia and Critical Care Department, 4 Chief, Unit of Anaesthesia, Hospital Universitario Fundación Alcorcón, 3 Staff Gynaecologist, Obstetrics and Gynaecology Department, Hospital Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain

Summary

Some, but not all studies have suggested intra-operative use of nitrous oxide is correlated with postoperative nausea and vomiting. We performed a meta-analysis of randomised controlled trials

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A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting

The NEW ENGLAND JOURNAL of MEDICINE

Christian C. Apfel, M.D., Kari Korttila, F.R.C.A., Ph.D., Mona Abdalla, Ph.D., Heinz Kerger, M.D.,

Table 3. Estimated Incidence of Postoperative Nausea and Vomiting as a Function of Baseline Risk, on the Basis of the Assumption That Each Intervention Reduces the Relative Risk by 26 Percent.

Baseline Risk (No Intervention)*	Estimated Incidence of Postoperative Nausea and Vomiting			
	One Intervention	Two Interventions	Three Interventions	Four Interventions
	percent			
10%	7	5	4	3
20%	15	11	8	6
40%	29	22	16	12
60%	44	33	24	18
80%	59	44	32	24

N Engl J Med 2004;350:2441-51.

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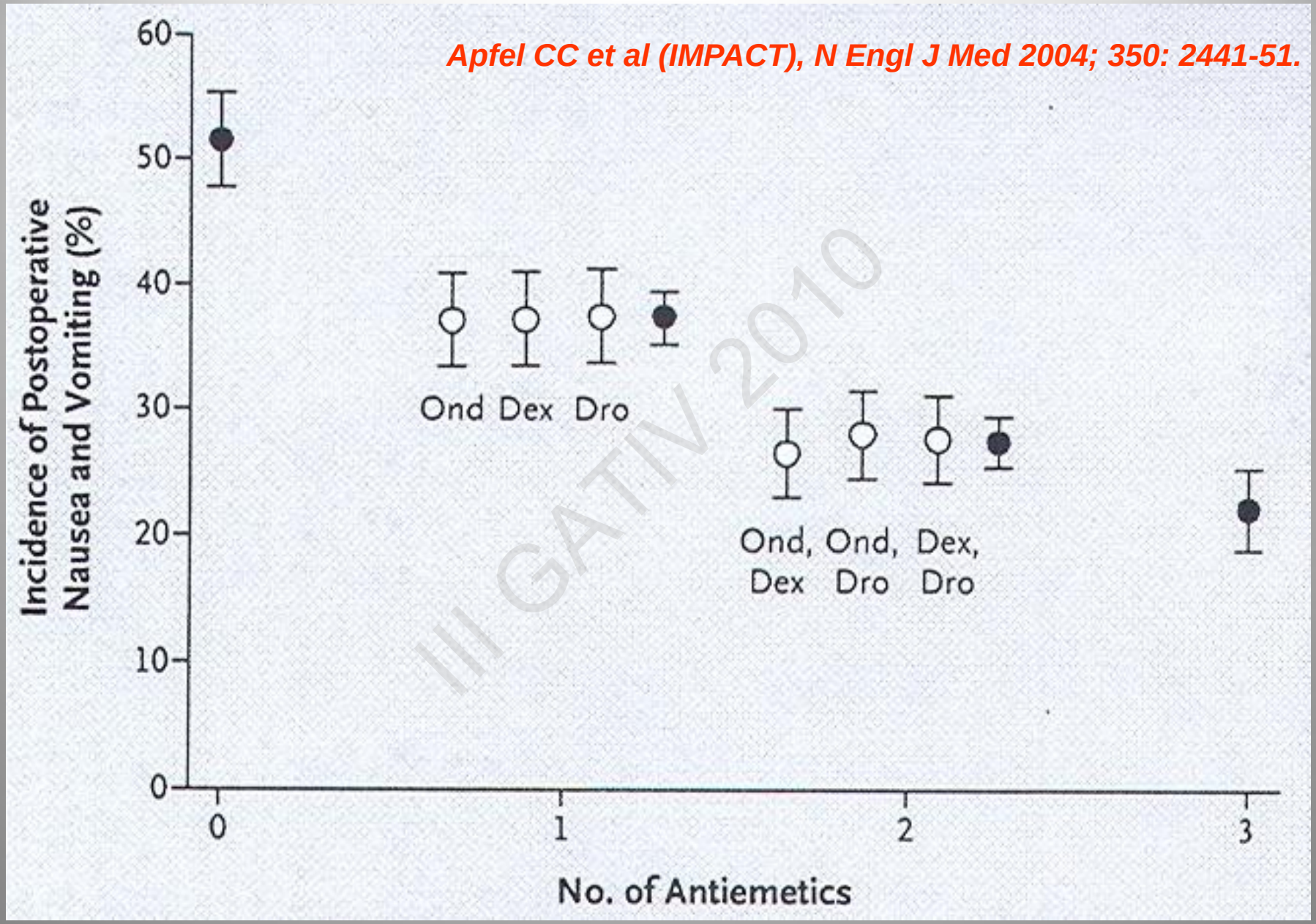
Apfel CC et al (IMPACT), N Engl J Med 2004; 350: 2441-51.



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Antagonistas 5-HT_3
Características generales

Específicos y selectivos

Perfil favorable

Variabilidad farmacogenética

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Antagonistas 5-HT_3
Farmacogenética y NVPO

Polimorfismo glicoproteína-P
Polimorfismo receptor 5HT3
Polimorfismo CYP2D6

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Antagonistas 5-HT_3
Metabolismo CYP450

	Primario	Secundario
Dolasetron	2D6	3A
Granisetron	3A	3A4
Ondansetron	3A4	2D6
		1A2
Palonosetron	2D6	3A
		1A2
Tropisetron	2D6	3A4

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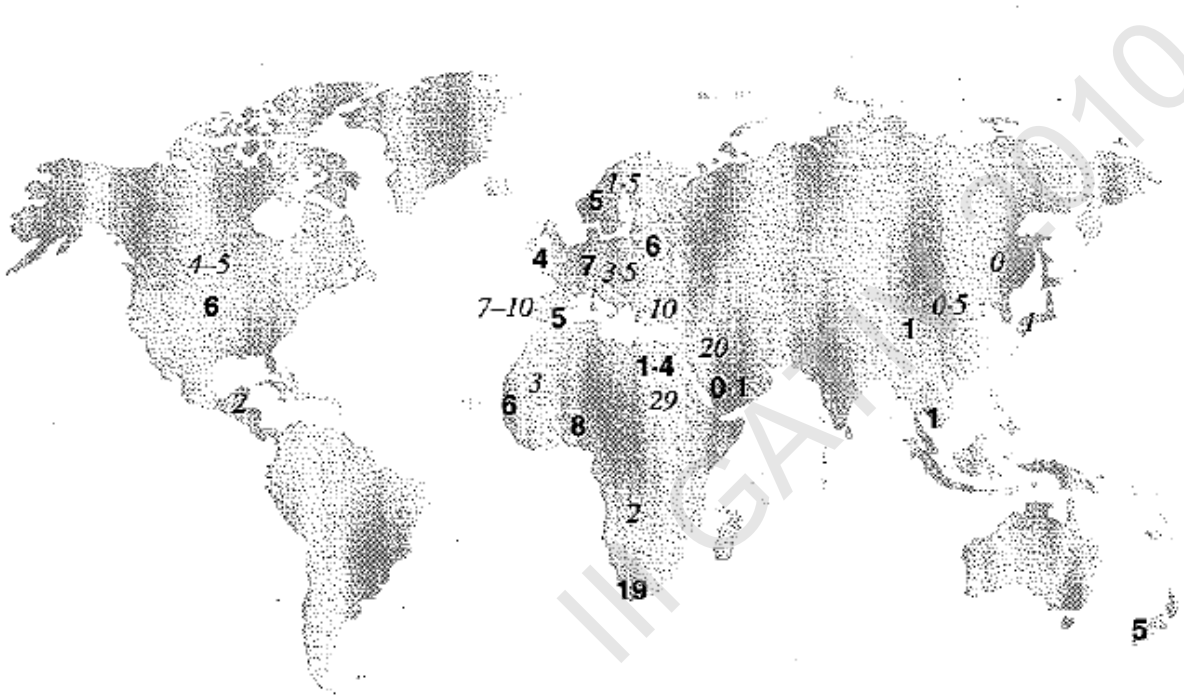

Figure 1 Frequency (%) of CYP2D6 poor metabolizers (bold) and ultrarapid metabolizers (italic) in different populations (for detailed references see 5,58)

III GAT 2010

Cascorbi I, Eur J Clin Invest 2003

Dexametasona

Efectiva
Perfil favorable
Barata

JIL GATV 2010

Droperidol
Características generales

Efectivo
Mejor antinauseoso
Duración larga
Perfil favorable (?)

JL GATIV 2010

WARNING

Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving INAPSINE at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Due to its potential for serious proarrhythmic effects and death, INAPSINE should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (see Warnings, Adverse Reactions, Contraindications, and Precautions).

Cases of QT prolongation and serious arrhythmias (e.g., torsades de pointes) have been reported in patients treated with INAPSINE. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of INAPSINE to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, INAPSINE should NOT be administered. For patients in whom the potential benefit of INAPSINE treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias.

INAPSINE is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome.

INAPSINE should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and IV opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

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USFDA, Diciembre 2001

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WARNING

Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving INAPSINE at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

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USFDA, Diciembre 2001

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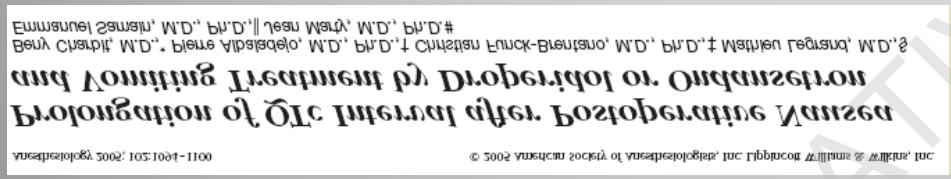
Habib AS, Gan TJ.
***Food and Drug Administration Black Box warning on the Perioperative Use of Droperidol: A Review of the Cases*.**
Anesth Analg 2003; 96: 1377-79.

III GATIV 2010

Análisis de 10 casos de arritmias severas tras droperidol < 1,25 mg:

En ninguno existía relación causa-efecto



Prolongation of QTc Interval after Postoperative Nausea and Vomiting Treatment by Droperidol or Ondansetron

Benjamin Christoph, M.D.*, Pierre Alphonsetto, M.D., PhD.†, Christian Enck-Bienfait, M.D., PhD.‡, Matthias Lagrand, M.D.§, Emmanuel Samain, M.D., PhD.‖, Jean Marty, M.D., PhD.#

Anesthesiology 2002; 105:1094–1100

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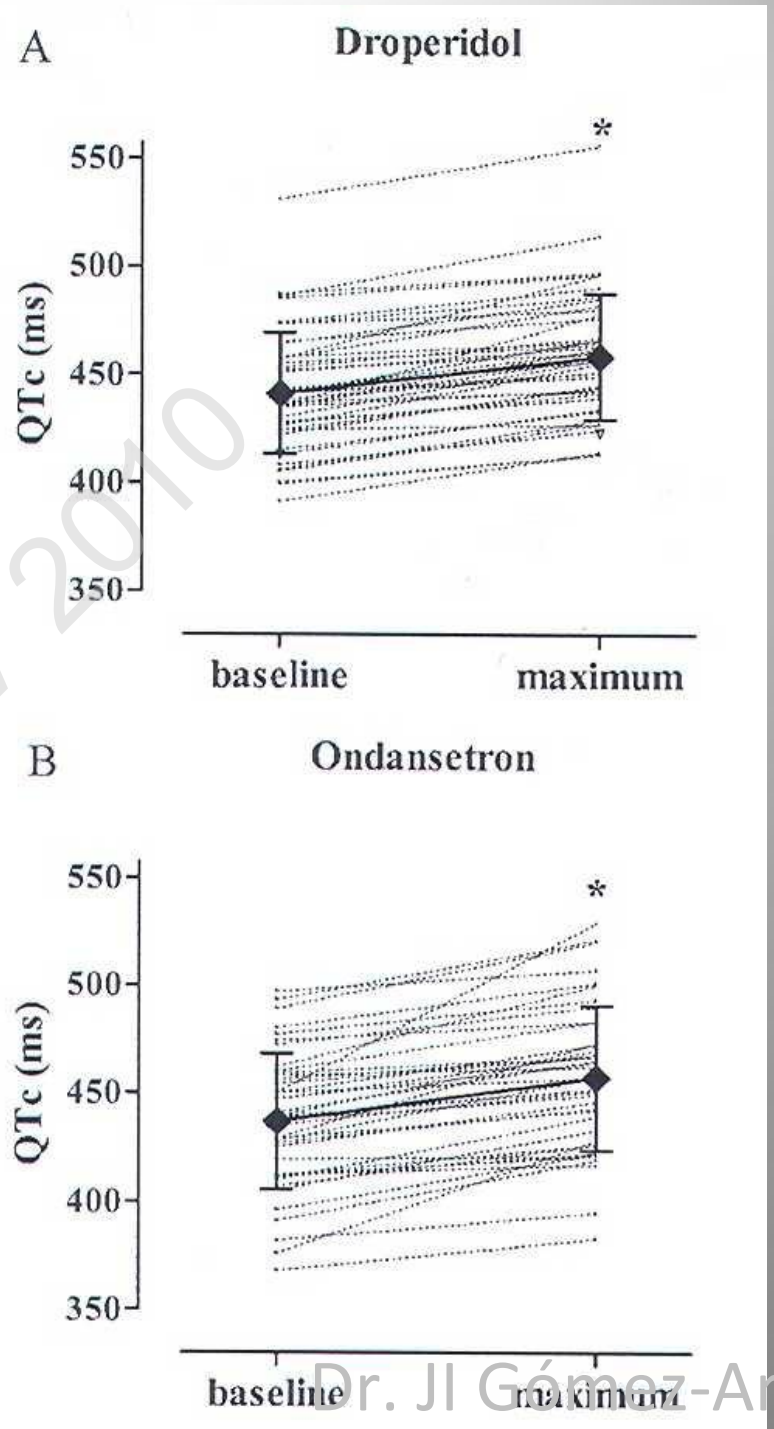

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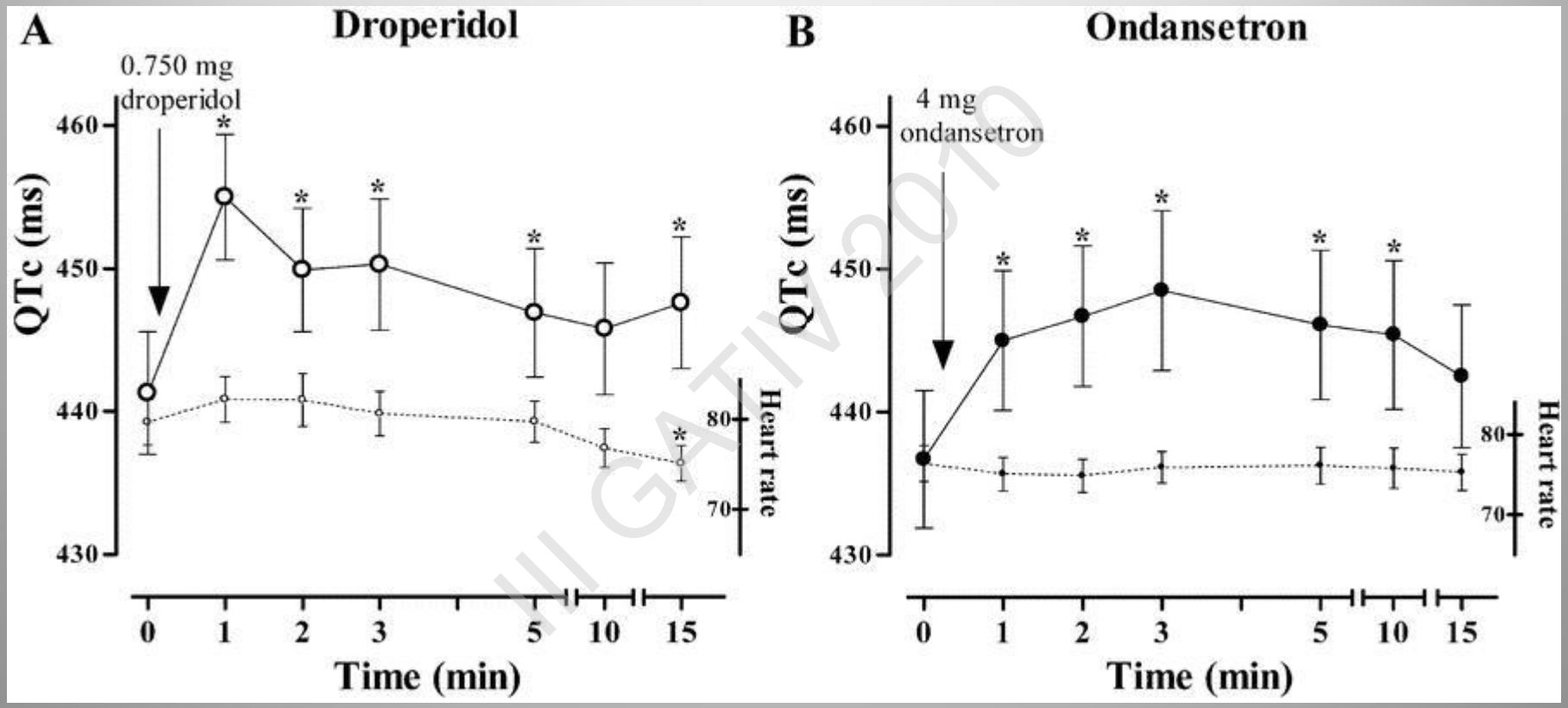

III GATIV 2010

Charbit et al, Anesthesiology 2005

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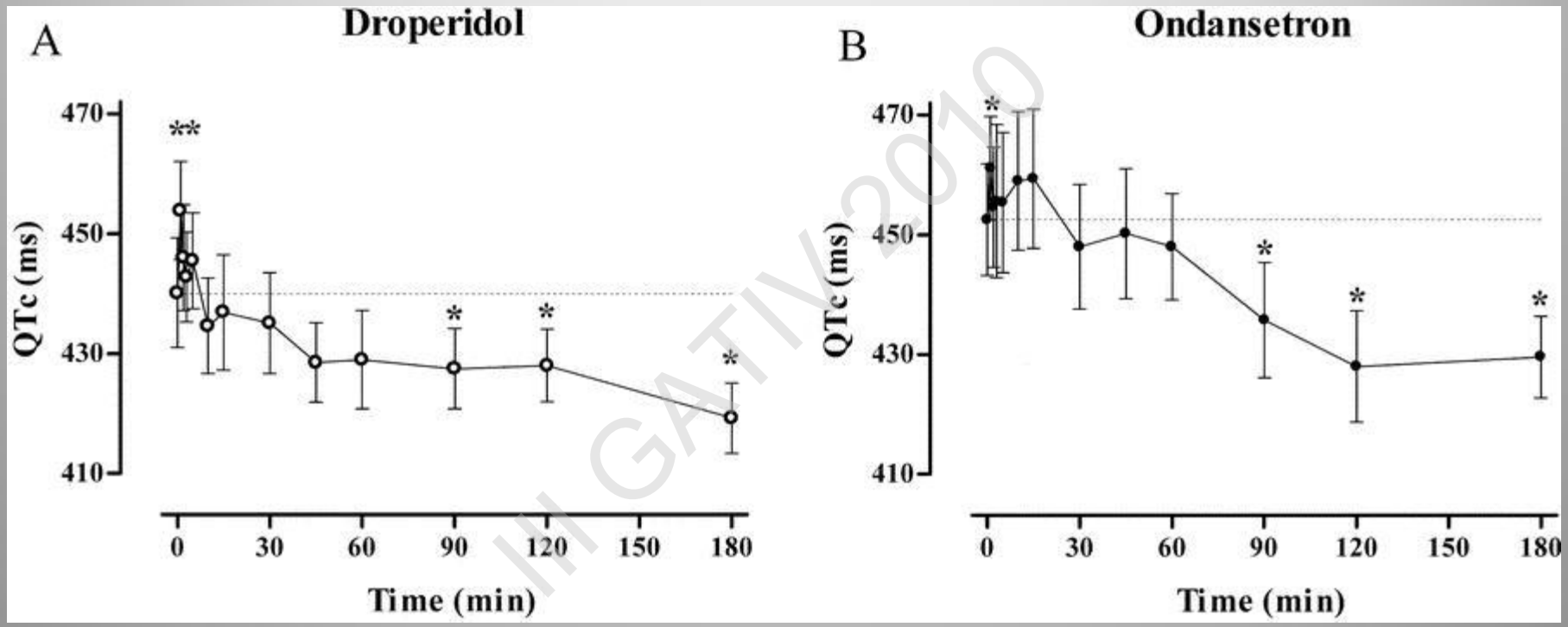

Charbit et al, Anesthesiology 2005

III GATIV 2010

Anesthesiology 2005; 102:1101–5
© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Effect of Low-dose Droperidol on the QT Interval during and after General Anesthesia

A Placebo-controlled Study

Paul F. White, Ph.D., M.D., Dajun Song, M.D., Ph.D.,† Joao Abrao, M.D., Ph.D.,‡ Kevin W. Klein, M.D.,§ Bryan Navarette, M.S.‖*

Table 2. Effects of the Study Medication on the Electrocardiographic QT Interval during the 10-min Observation Interval before the Start of Surgery in the Initial Three Treatment Groups

	Control	0.625 mg Droperidol	1.25 mg Droperidol
QT interval before injection, ms	406 ± 28	400 ± 56	396 ± 46
QTc before injection, ms	439 ± 28	435 ± 27	426 ± 47
QTc at 10 min after injection, ms	446 ± 35	449 ± 40	444 ± 52
QTc ≤ baseline at 10 min, n (%)	10 (50)	6 (30)	8 (40)
QTc prolongation 0–10% at 10 min, n (%)	8 (40)	11 (55)	10 (50)
QTc prolongation 10–25% at 10 min, n (%)	2 (10)	3 (15)	2 (10)
Mean maximum ΔQTc, ms*	12 ± 35	15 ± 40	22 ± 41

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Anesthesiology 2005; 102:1081–2 © 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

You (Still) Can't Disprove the Existence of Dragons

dol. In the doses routinely used for the prevention and treatment of PONV, its safety is unparalleled. The argument by the FDA that the minimum approved dose is 2.5 mg and the use of smaller doses is outside the jurisdiction of the FDA is clearly specious and does a tremendous disservice to the American public. The true incidence of dysrhythmias resulting from the administration of "low-dose" droperidol is likely to be vanishingly small. The number of patients necessary to establish the

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REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Drug-Induced Prolongation of the QT Interval

Dan M. Roden, M.D.

IN THE PAST DECADE, THE SINGLE MOST COMMON CAUSE OF THE WITHdrawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with polymorphic ventricular tachycardia, or torsade de pointes (Fig. 1), which can be fatal.[1] Nine structurally unrelated drugs that were marketed in the United States or elsewhere for a range of noncardiovascular indications have been removed from the market or had their availability severely restricted because of this rare form of toxicity. These drugs are terfenadine, astemizole, grepafloxicin, terodiline, droperidol, lidoflazine, sertindole, levomethadyl, and cisapride.

A convergence of data obtained from clinicians, basic electrophysiologists, and geneticists who have studied the congenital long-QT syndrome (also characterized by torsade de pointes) has resulted in some understanding of the mechanisms whereby

From the Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville. Address reprint requests to Dr. Roden at the Division of Clinical Pharmacology, Vanderbilt University School of Medicine, 532 Medical Research Bldg. I, Nashville, TN 37232, or at dan.roden@vanderbilt.edu.

N Engl J Med 2004;350:1013-22.
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Rare, poorly understood side effects occur with many highly effective drugs, and the withdrawal of these medications from the market would probably harm more patients than it would help. Our par-

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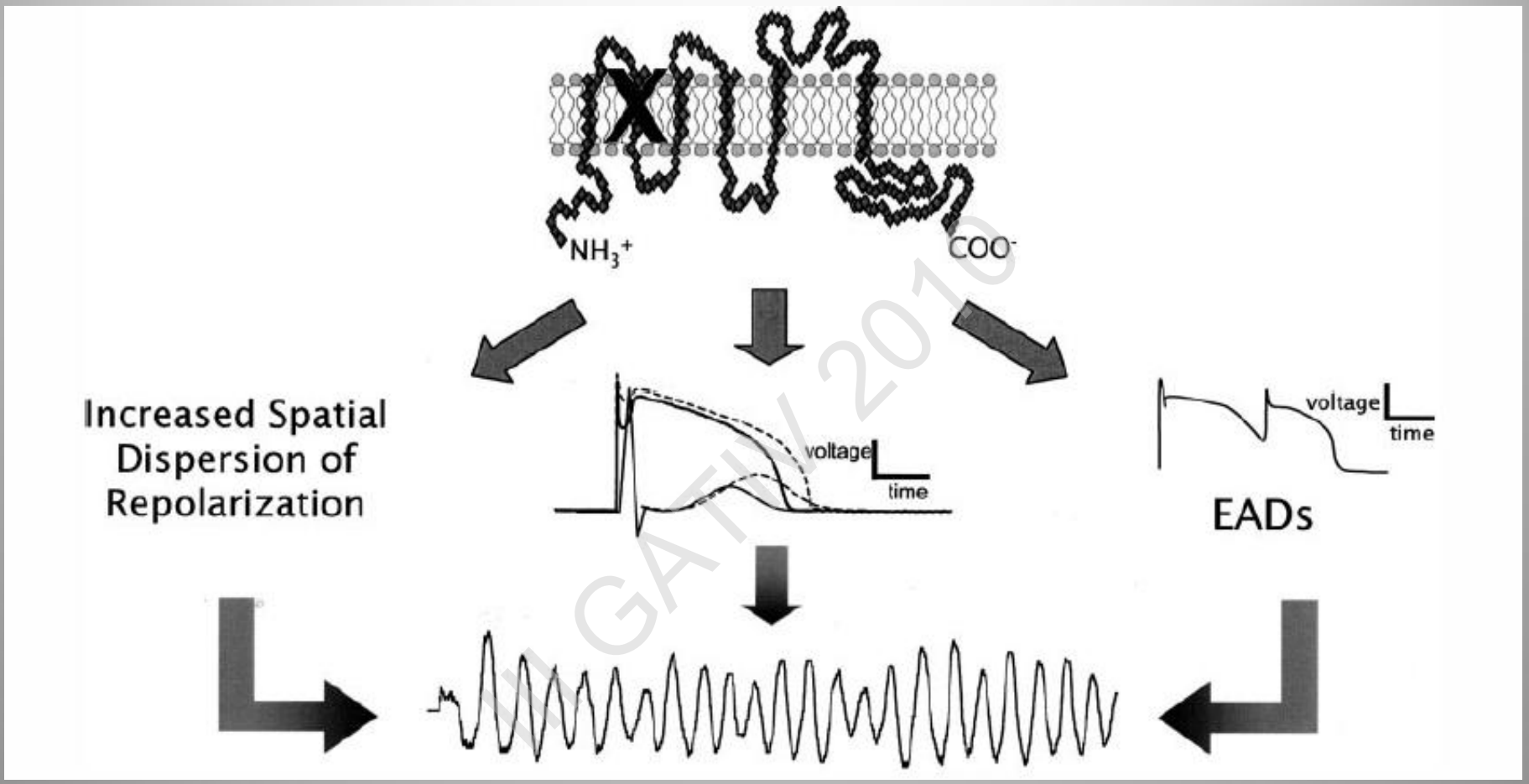

Shah M et al, Circulation 2005

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Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 1161–1167

Editorial

Droperidol: past, present and future

Droperidol, a butyrophenone derivative and dopamine D_2 receptor antagonist, was developed in the 1950s as an antipsychotic and was first approved in Denmark in 1963 for use in anaesthesia, in chronic psychiatric conditions. The injectable form was withdrawn for commercial reasons rather than safety concerns [4]. At the end of that year, the United States Food and Drug Administration (FDA) issued a 'black box' warning concerning droperidol and torsades de pointes [5]. The warn- a day surgery setting indicated that the corrected QT (QTc) changes following saline and droperidol 0.625 or 1.25 mg were modest, similar, reversible and of short duration [11]. Furthermore, when QTc changes were compared in rando- mised studies, both droperidol and ondansetron were associated with

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BMC Anesthesiology

BioMed C

Research article

Open Ac

Systematic review on the recurrence of postoperative nausea and vomiting after a first episode in the recovery room – implications for the treatment of PONV and related clinical trials

Leopold HJ Eberhart*[1], Silke Frank[2], Henning Lange[1], Astrid M Morin[1], André Scherag[3], Hinnerk Wulf[1] and Peter Kranke[4]

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Anesthesiology 2002; 96:994–1003 © 2002 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Systematic Review and Analysis of Postdischarge Symptoms after Outpatient Surgery

Christopher L. Wu, M.D., Sean M. Berenholtz, M.D.,* Peter J. Pronovost, M.D., Ph.D.,† Lee A. Fleisher, M.D.‡*

	Estudios	Pacientes	Periodo	Incidencia
Náuseas	12	5.500	3 días	17 (0-55)
Vómitos	11	5.429	2.9 días	8 (0-16)

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Incidencia de NVPA
Apfel et al, 2010

n=2170

Náuseas	**50%**
(severas 13%)	
Vómitos	**17%**
(severos 5%)	

III GATIV 2010

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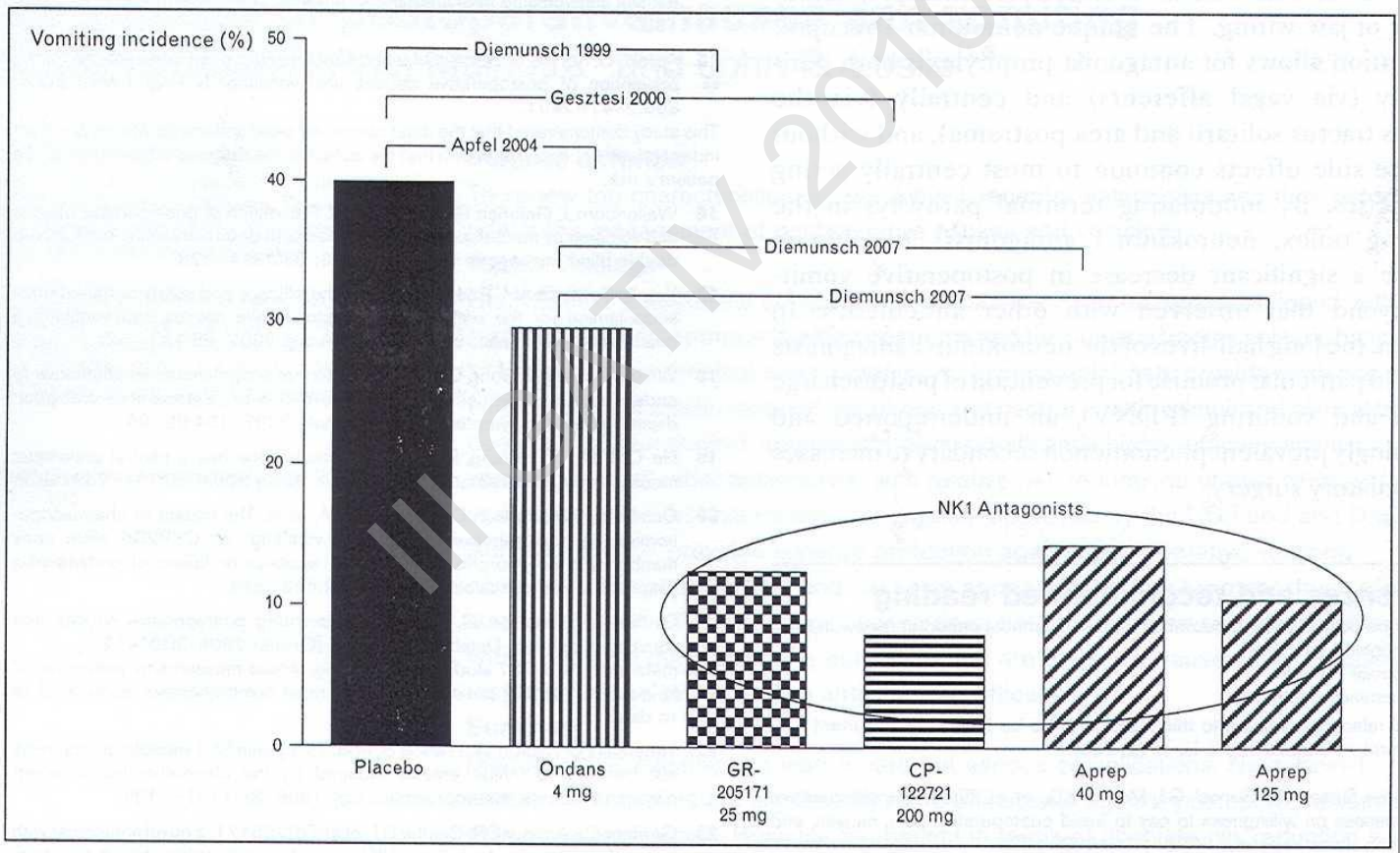
Apfel CA et al. The role of <u>neurokinin-1 receptor antagonists</u> for the management of postoperative nausea and vomiting. Curr Opin Anesthesiol 2008; 21: 427-32.



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Anesthetic Pharmacology
Preclinical Pharmacology
Section Editor: **Marcel E. Durieux**

Clinical Pharmacology
Section Editor: **Tony Gin**

Palonosetron Exhibits Unique Molecular Interactions with the 5-HT_3 Receptor

Camilo Rojas, PhD*
Marigo Stathis, MS*
Ajit G. Thomas, MSE*
Edward B. Massuda, MS*
Jesse Alt, BS*
Jie Zhang, PhD*
Ed Rubenstein, MD†
Silvia Sebastiani, PhD‡

BACKGROUND: Palonosetron is a 5-HT_3-receptor antagonist (5-HT_3-RA) that has been shown to be superior to other 5-HT_3-RAs in phase III clinical trials for the prevention of acute, delayed, and overall chemotherapy-induced nausea and vomiting. The improved clinical efficacy of palonosetron may be due, in part, to its more potent binding and longer half-life. However, these attributes alone are not sufficient to explain the results with palonosetron. We sought to elucidate additional differences among 5-HT_3-RAs that could help explain the observations in the clinic.

METHODS: Receptor site saturation binding experiments were performed with [^{3}H] palonosetron, [^{3}H] granisetron, and [^{3}H] ondansetron to obtain the corresponding Scatchard analyses and Hill coefficients. Diagnostic equilibrium binding experiments and kinetic dissociation experiments were conducted to examine competitive versus potential allosteric interactions between ondansetron, granisetron and palonosetron and the 5-HT_3 receptor. Finally, the long-term effect of the three antagonists on receptor function as measured by Ca^{2+} influx in HEK 293 cells expressing the 5-HT_3-receptor was compared.

RESULTS: Analyses of binding isotherms using both Scatchard and Hill plots

IIGA-IV 2010

Anesth Analg 2008; 469-78

Dr. JI Gómez-Arnau

Conclusiones

1. Evaluar el riesgo
2. Prevenir en casi todos
3. Regional mejor que general,
   TIVA mejor que inhalatoria
4. 1, 2 ó 3 antieméticos según el riesgo
5. Si NV, tratar siempre
6. Controlar más allá de 24 horas

II CATIV 2010

(Rev. Esp. Anestesiol. Reanim. 2010; 57: 404-412) **REVISIÓN**

Recomendaciones de prevención y tratamiento de las náuseas y vómitos postoperatorios y/o asociados a las infusiones de opioides

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Resumen

Las náuseas y los vómitos postoperatorios (NVPO) producen malestar e insatisfacción del paciente y aumen-

individuales en cada paciente; 5. El tratamiento de las NVPO establecidas debe hacerse preferentemente con un fármaco diferente al empleado en la profilaxis. El fárma-co más efectivo es el ondansetrón; 6. Debe evaluarse la

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