

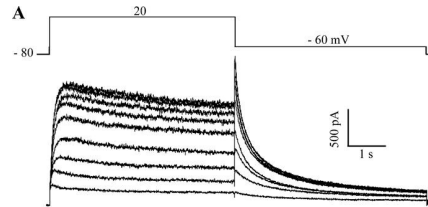
Reports of Torsades de Pointes (TdP) Associated with Intravenous (IV) Drug Formulations that Contain the Preservative Chlorobutanol (CB)

R. David Woosley, Klaus Romero, Will Heise, Tyler Gallo, Jared Tate, Raymond L. Woosley

INTRODUCTION

Torsades de Pointes polymorphic ventricular tachycardia

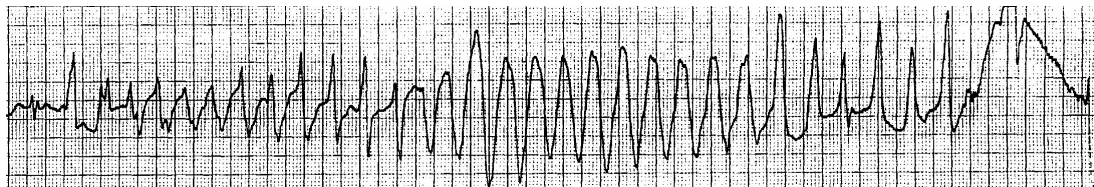
HERG
Current
Block



QT prolongation

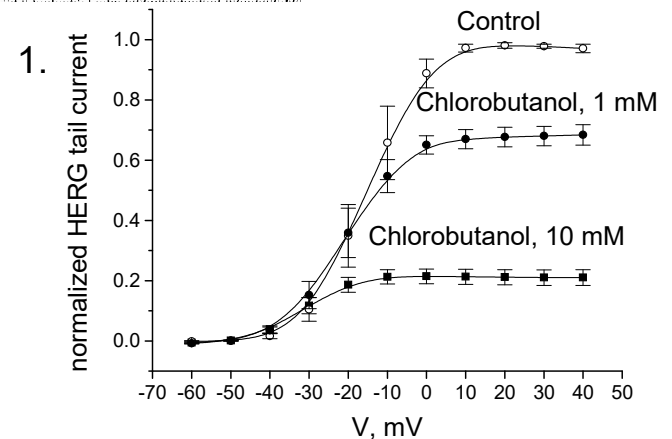
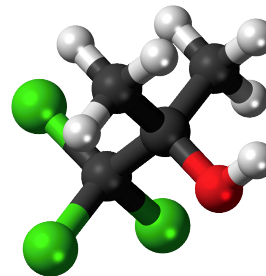


Torsades de
Pointes (TdP)



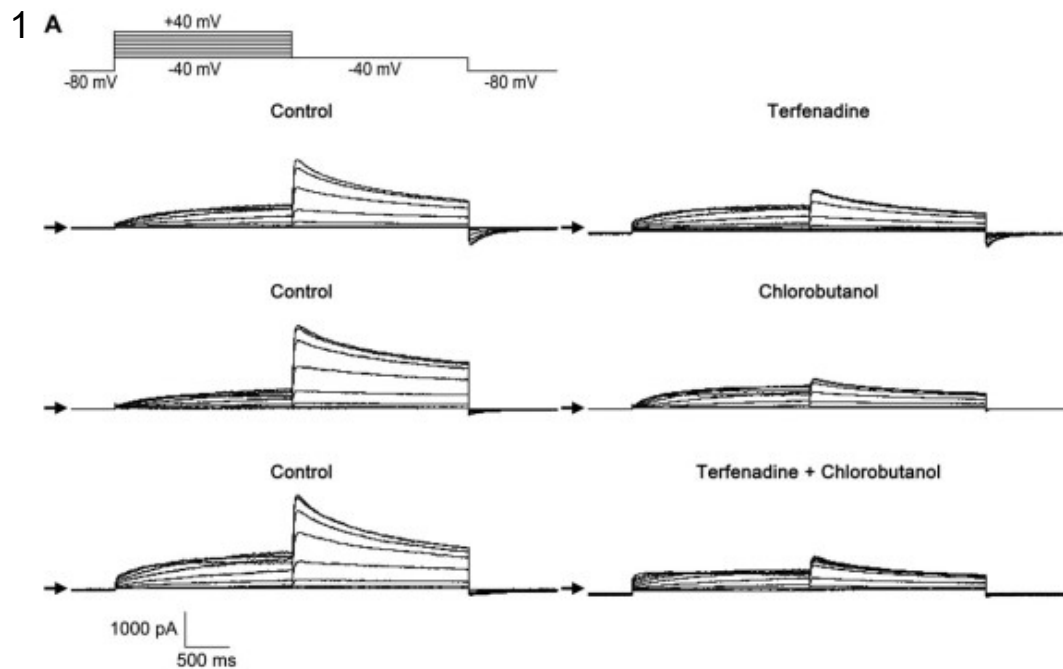
Chlorobutanol: a chemical preservative used in many IV drug and vitamin formulations

- Weak inhibitor of K⁺ ion channels

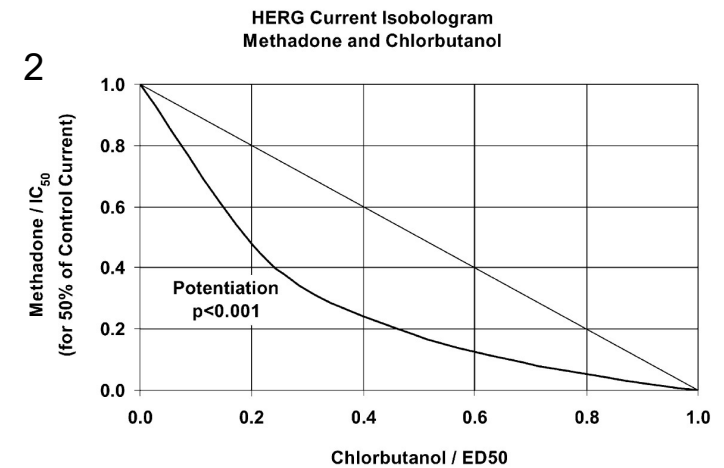


Synergistic CB-Drug Interactions

CB has been found to potentiate the HERG inhibition caused by Terfenadine and Methadone



Chlorbutanol and Terfenadine



Chlorbutanol and Methadone

1. Friemel, A and Zunkler B. Toxical Sci 114:346-55, 2013
2. Kornick, CA, et al. Pain 105:499-506, 2003

PURPOSE



To examine the association between use of CB containing drug formulations and the occurrence of QT prolongation and TDP

METHODS



- Drugs with injectable formulations containing CB were identified using dailymed.nlm.nih.gov
- A PubMed search was performed
 - Thorough QT studies
 - Case studies
 - Clinical trials
- The FDA's adverse event report system (FAERS) was queried (using Oracle's Empirica Signal) for relevant case reports
- Individual reports were reviewed
 - Route of administration
 - Confounding factors
 - Duplicate cases

RESULTS



Dailymed lists 9 drugs currently on the US market that contain CB in their IV formulation (listed below)

Drug Name	FAERS DATA				LITERATURE SEARCH RESULTS			
	QT N	QT EB05	TdP N	TdP EB05	QT prolongation in literature	TdP in literature	HERG IC50	Dose of CB received @ usual drug dose (mg)
Methadone	504	9.11***	367	23.1***	•	•	•	25-500
Epinephrine	56	1.49	37	3.08***	•	•		1.5
Estradiol	54	.532	9	.151	•		•	10
Vasopressin	5	.812	7	1.92	•	•		2.5 mg q 3 hr.
Testosterone	17	.237			•	•		10
Isoniazid	14	.432			•			7.5 – 22.5
Desmopressin	11	.548						35
Papaverine	8	1.87			•	•	•	1.5
Oxytocin					•			20

EB05: Lower bound of Bayesian risk estimate (relevant signal = >2)

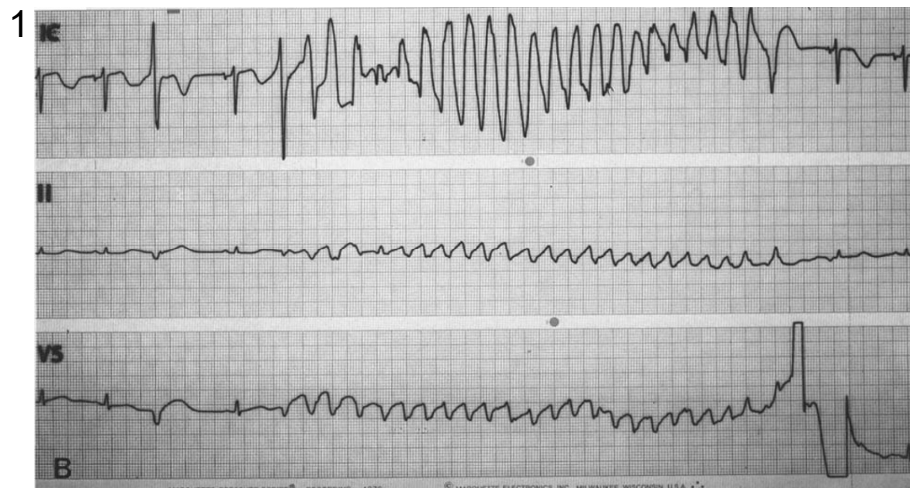
***denotes relevant result

RESULTS: Papaverine

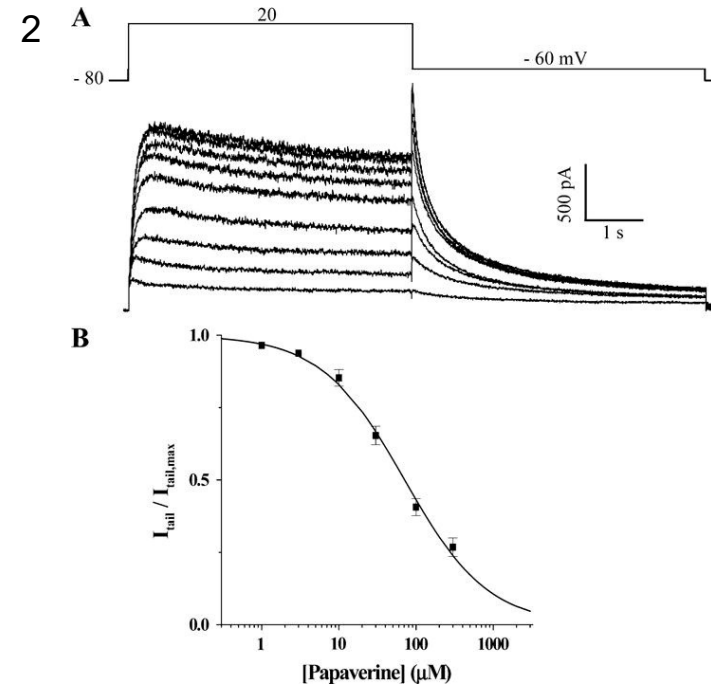
QT N	QT EB05	TdP N	TdP EB05	QT prolongation in lit.	TdP in literature	HERG inhibition in lit.
8	1.87			•	•	•

Intracoronary Papaverine in published literature

- Documented QT prolongation
- 21 cases of TdP
- 1.2% of patients treated with Papaverine developed TdP



10 mg IC Papaverine

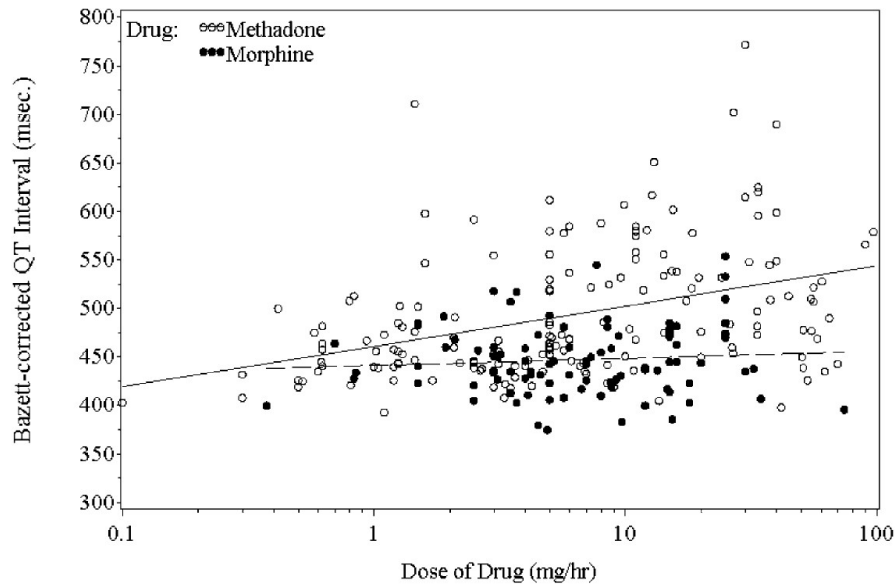


Papaverine block of HERG in HEK293 cells

RESULTS: Methadone

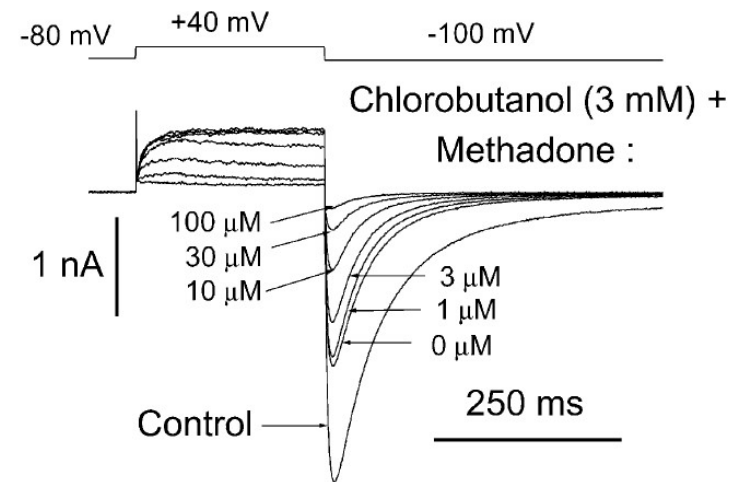
QT N	QT EB05	TdP N	TdP EB05	QT prolongation in lit.	TdP in literature	HERG inhibition in lit.
504	9.11*	367	23.1*	•	•	•

1



Methadone prolongs the QT interval

2



Methadone's QT prolongation with CB synergistically blocks HERG

LIMITATIONS



FAERS

- FAERS queries using Empirica lack route specificity

Literature

- Laboratory experiment information is incomplete regarding CB as an ingredient

CONCLUSIONS & RECCOMENDATIONS



- CB is a preservative used in injectable formulations of 9 drugs
- CB is an inhibitor of HERG current
- CB potentiates the HERG block of Terfenadine and Methadone
- Clinical reports of QT prolongation and TdP with other CB containing drug formulations indicates that CB could be potentiating the HERG block of those drugs
- CB is not in the formulations of these drugs in Europe
- CB was used in morphine formulations, now removed
- CB poses a potential risk, and its inclusion in IV formulations is unnecessary