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Haloperidol and sudden death in first acute myocardial infarction

Haloperidol is one of the oldest drugs still being used today. It is mainly prescribed for the treatment of delirium, schizophrenia, manic phase of bipolar disorder, and acute psychomotor agitation. Haloperidol was introduced as an antipsychotic and anti-emetic compound by Janssen Pharmaceutica, Belgium, in 1957. Twenty-two years later, the first clinical case was published connecting the sudden demise of a 35-year-old woman to acute treatment with haloperidol (no details on QT interval or arrhythmia were provided) [1]. Since then various studies reported the association between haloperidol and the increased risk of ventricular tachyarrhythmias and sudden cardiac death (SCD), see Table 1. In general, elevated arrhythmia susceptibility was only accompanied by mild QTc prolongation [2–4], but examples of severe QTc prolongation [5,6] or its overt absence are available in the literature [7,8]. In one case-cross over study [9] that accounted for the SCD risk associated with schizophrenia itself [10], the risk of SCD related to haloperidol remained significantly elevated. Especially patients in whom treatment lasted only shortly (<28 days), the risk of SCD was higher [9].

The metabolism of haloperidol is complex. It is degraded by CYP3A4 activity, with lesser contributions by 2D6 [19]. Some of haloperidol's metabolites inhibit 2D6, affecting other drug levels. Haloperidol can contribute to increased anticholinergic and central nervous system depressant effects of opiates, anesthetics, and alcohol. Multiple drugs interact with haloperidol [20]. Haloperidol acts as a nonspecific drug with affinity to dopamine D_2 receptors, serotonin $5HT_2$ receptors, α_1-adrenergic receptors, σ_1/σ_2 receptors, and muscarinic M_1 receptors. Besides these neural modulatory pathways, haloperidol blocks the rapidly-activating delayed-rectifier potassium current (I_{Kr}), a major contributor to cardiac repolarization [21,22]. In rat retinal ganglion cells [23] and Xenopus oocytes expressing hERG channels [24], the slowly-activating delayed-rectifier I_{Ks} (-like) is inhibited by this antipsychotic drug by a limited degree. Haloperidol exerts minor effects on the arrhythmogenic late sodium current [25]. Moreover, via stimulation of σ_2 receptors, haloperidol is involved in additional inhibition of the hERG potassium current [26] and transient outward potassium current [27]. Acute and chronic exposure to haloperidol results in increased QT intervals in rats [28], guinea pigs [28,29], and rabbits [30]. In isolated rabbit hearts, it led to a marked increase in spatiotemporal dispersion of repolarization, early afterdepolarizations, and polymorphic ventricular tachycardia [31].

An elevated arrhythmia risk during an acute coronary event in the presence of antipsychotic drug therapy, including haloperidol, has been suggested by Honkola et al [17]. Here, the treatment with antipsychotic drugs was paralleled by a significant and independent risk factor for the occurrence of SCD (odds ratio 3.4, 95% C.I. 1.8–6.5, $P < 0.001$). This risk was even more evident when phenothiazines or any other antidepressants were co-administered (odds ratio 18.3, 95% C.I. 2.5–135.2, $P < 0.001$). The latter study constitutes one of the few in which investigators focused on the risk of haloperidol in acute ischemia/infarction.

In this issue of the journal; *IJC Heart & Vasculature*, [39] Sattler and coworkers postulate that the surplus mortality observed in patients with psychiatric illnesses treated with haloperidol could be explained by a higher incidence of acute myocardial infarction-related ventricular tachyarrhythmia including ventricular fibrillation (VF) and torsades de pointes (TdP). In their pig model of mid-LAD occlusion, Sattler observed primary VF in 64% of the control animals, compared to 27 and 33% (within 30 min) in the low and high haloperidol treatment arms, respectively. Catecholamine-sensitive phase-1b arrhythmias were less present in the high-dose haloperidol group. This observation seems counterintuitive at first glance as it occurred despite significant global QTc prolongation and dispersion of repolarization prior to, during and after the ischemic trigger. However, ischemia-induced changes of the myocardium, largely driven by an increase in extracellular potassium concentration and elevated sympathetic input, result in regional depolarization of the resting membrane potential, slowed conduction, and action-potential shortening. It could be hypothesized that haloperidol's inhibitory effects on I_{Kr}, and to a lesser extent on I_{Ks}, may have counterbalanced local repolarization heterogeneities, thus exerting some antiarrhythmic action. The latter is supported by the observation by Sattler [39] et al that phase-1b ectopy was suppressed. Besides, the authors report a reduced dominant frequency of VF in the presence of haloperidol suggesting prolongation of ventricular repolarization, slowed cardiac conduction properties, or a combination of both. An increased threshold for the induction of VF was also observed in a healthy pig model pretreated with haloperidol [32]. Similar to the findings by Sattler, intracardiac conduction velocity was reduced during intravenous haloperidol infusion in an anesthetized guinea pig model [33]. As potential explanation, one may consider the pleiomorphic effects that haloperidol has on various receptors. Haloperidol-related σ_1/σ_2 receptor stimulation concurrently modulates various cardiac voltage-gated potassium, calcium, but also sodium channels, significantly reducing the I_{Na} in HEK-293 cells, COS-7 cells, and neonatal mouse cardiac myocytes [34]. The slower

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Table 1
Studies and case reports on relation between haloperidol and arrhythmia susceptibility.

Ref.	Year	Type of study	Nr. of patients	Administration	Duration of treatment	QTc (ms)	QT risk factor	Cardiac disease/structural abnormalities	(Risk of) arrhythmias
Ketai [1]	1979	Case	1	Intravenous	4 days	N.A.	Female gender	N.A.	SCD
Kriwisky [5]	1990	Case	1	Oral	7 days	720	No	Mitral-valve prolapse	TdP
Douglas [6]	2000	Case series	3	Intravenous	2–5 days	509–648	No	Acute coronary syndrome (day 2–13), ischemic cardiomyopathy	VF (1 case), no arrhythmia (2 cases)
Perrault [7]	2000	Case	1	Intravenous	3 days	413	Female gender	Post coronary bypass surgery, moderate LV dysfunction	Premature ventricular complexes, R-on-T, TdP
Hatta [3]	2001	Cross-sectional cohort	307	Intravenous	N.A.	454	Hypokalemia (47%)	Not specified	No arrhythmias
Ray [11]	2001	Cohort	481,744	Haloperidol in 21%	N.A.	N.A.	N.A.	CV disease score: if diagnosed or treated for cardiovascular disease, including medications, outpatient encounters, or hospitalizations	SCD risk (no CV disease): 2.4 (95% C.I. 1.8–3.2) SCD risk (severe CV disease): 3.5 (95% C.I. 1.7–7.5)
Remijnse [12]	2002	Case	1	Oral	Single	460 prior to haloperidol	Hypokalemia, hypomagnesemia	Alcoholic cardiomyopathy	SCD
Hennessy [2]	2002	Cohort	41,295	Oral	30 days	N.A.	N.A.	N.A.	Cardiac arrest/ventricular arrhythmias:4.2 (95% C.I. 3.5–5.0) per 1000 person years
Akers [13]	2004	Case	1	Intravenous	5 days	533	Levofloxacin	Pneumonia	TdP
Bush [4]	2008	Cases	57	Oral or intravenous	3 days	+ 9.8 (95% C.I. 0.6–19.0)	28% had $\geq$ 1 other QT-prolonging drug; 25% electrolyte abnormalities	Congestive heart failure (12%), cardiomyopathy (6%), ischemic heart disease (18%)	No arrhythmias
Jolly [14]	2009	Case-control	1010 cases; 3030 controls	Oral	N.A.	N.A.	Hypokalemia (3%), hypocalcemia (1%), bradycardia/AV block (2%)	Previous myocardial infarction (11%), heart failure (10%),	SCD: + CV disease: 7.8 (95% C.I. 0.8–72.8) − CV disease: 2.6 (95% C.I. 0.1–48.3)
Ginwalla [15]	2009	Case	1	Intravenous	Single injection	N.A.	Pre-existing QTc prolongation 579 ms	Complete AV block	TdP
Muzyk [16]	2012	Cohort	175	Intravenous	Not specified	>50% had prolonged QTc before haloperidol	86% $\geq$ 1 risk factor; $\geq$ 2 in 58%; LQT-prolonging drugs in 43%; electrolyte abnormalities in 30%	80% $\geq$ 1 CV risk factor	N.A.
Honkola [17]	2012	Case-control	1814 (SCD), 1171 (AMI)	Oral	N.A.	N.A.	N.A.	Acute coronary syndrome	SCD risk Antipsych.: 4.4 (95% C.I. 2.9–6.6) Antipsych. + antidepressant 5.1 (95% C.I. 2.2–11.2)
Wu [9]	2015	Case-cross over	17,718	Oral	High risk <28 days	N.A.	Adjusted for risk factors	No modifier	SCD/ventricular arrhythmia: 1.5 (95% C.I. 1.2–1.8)
Salvo [18]	2016	Meta-analysis	740,306 person-years and 2557 cases, 17,670 controls	N.A.	N.A.	N.A.	Mean hERG blockade potency	N.A.	SCD risk haloperidol: 3.0 (95% C.I. 1.6–5.5)
Naksuk [8]	2017	Prospective, observational	244	Not specified	1.0–10.0	454 ± 49	N.A.	Acute coronary syndrome (61%), heart failure (65%)	No difference for in-hospital mortality, ventricular arrythmias of 1-year mortality

AMI indicates acute myocardial infarction; antipsych., antipsychotic; AV, atrioventricular; C.I., confidence interval; CV, cardiovascular; LQT, long QT; N.A., not available; SCD, sudden cardiac death; TdP, torsades de pointes; VF, ventricular fibrillation.

heart rates during the high-dose regimen may be indicative of the indirect ionic effects brought about by $\sigma 1/\sigma 2$ receptors stimulation.

The authors are to be complimented for their comprehensive approach to investigate proarrhythmic side-effects of haloperidol taking both electrics and mechanics into account in their intact pig model. Most contemporary arrhythmia studies still focus merely on electrical denominators of arrhythmogenesis, despite the increasing recognition of the importance of mechano-electric and autonomic triggers/modulators of arrhythmia. This holds true for acquired arrhythmia syndromes, and particularly when studying prolonged-repolarization ventricular tachyarrhythmias like TdP. Both in long-QT syndrome patients and in a drug-induced LQTS dog model, electromechanical heterogeneities and a negative electromechanical window (defined as timeframe between end of contraction minus end of repolarization) consistently preluded

these deadly events [35,36]. While the (mini)pig has a high susceptibility to the development of VF, it appeared refractory to torsades-de-pointes arrhythmias despite extensive QT prolongation [37]. As clinical documentation of the type of life-threatening arrhythmias in patients with haloperidol during an acute ischemic event is currently lacking, we are left in the dark as to the underlying arrhythmic mechanisms: primary VF or TdP/polymorphic ventricular tachycardia precipitating VF. Conversely, it is well-known that patients who develop QT prolongation in the subacute phase after myocardial infarction (day 2–11) are more prone to deadly arrhythmias [38]. Treatment with haloperidol during such electromechanical and autonomic dynamic phase can easily aggravate patient's arrhythmia susceptibility.

In conclusion, this comprehensive report by Sattler further adds to our understanding of the complex actions of haloperidol on the arrhythmogenic substrate and triggers in the setting of an acute myocardial infarction. The observation that haloperidol is associated with less phase-1b premature ventricular complexes in the presence of obvious global QT prolongation renders the important insights that this multifaceted drug may stabilize the arrhythmogenic substrate under specific conditions and that global repolarization abnormalities may not suffice for arrhythmia induction. Extending to this, it remains to be determined by mechanistic studies whether haloperidol harbors torsadogenic potency in the *sub*acute phase of myocardial infarction (days to weeks after coronary occlusion; when spontaneous QT prolongation is frequently observed), and which determinants aggravate arrhythmia susceptibility in individual patients, as the diversity in arrhythmia responses is significant.

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