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REVIEW-SYSTEMATIC

The FDA Extended Warning for Intravenous Haloperidol and Torsades de Pointes: How Should Institutions Respond?

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BACKGROUND: In September 2007, the Food and Drug Administration (FDA) strengthened label warnings for intravenous (IV) haloperidol regarding QT prolongation (QTP) and torsades de pointes (TdP) in response to adverse event reports. Considering the widespread use of IV haloperidol in the management of acute delirium, the specific FDA recommendation of continuous electrocardiogram (ECG) monitoring in this setting has been associated with some controversy. We reviewed the evidence for the FDA warning and provide a potential medical center response to this warning.

METHODS: Cases of intravenous haloperidol-related QTP/TdP were identified by searching PubMed, EMBASE, and Scopus databases (January 1823 to April 2009) and all FDA MedWatch reports of haloperidol-associated adverse events (November 1997 to April 2008).

RESULTS: A total of 70 of IV haloperidol-associated QTP and/or TdP were identified. There were 54 reports of TdP; 42 of these events were reportedly preceded by QTP. When post-event QTc data were reported, QTc was prolonged >450 msec in 96% of cases. Three patients experienced sudden cardiac arrest. Sixty-eight patients (97%) had additional risk factors for TdP/prolonged QT, most commonly receipt of concomitant proarrhythmic agents. Patients experiencing TdP received a cumulative dose of 5 mg to 645 mg, patients with QTP alone received a cumulative dose of 2 mg to 1540 mg.

CONCLUSIONS: While administration of IV haloperidol can be associated with QTP/TdP, this complication most often took place in the setting of concomitant risk factors. Importantly, the available data suggest that a total cumulative dose of IV haloperidol of <2 mg can safely be administered without ongoing electrocardiographic monitoring in patients without concomitant risk factors. ***Journal of Hospital Medicine*** **2010;5:E8–E16.** © *2010 Society of Hospital Medicine.*

KEYWORDS: **antipsychotics, adverse drug reactions, cardiac adverse events, haloperidol, QT prolongation, torsades de pointes.**

Haloperidol is Food and Drug Administration (FDA)-approved in the United States for the management of acute and chronic psychotic disorders and widely used in the management of delirium-associated agitation in hospitalized patients.[1] Delirium in the hospital is an acute confusional state that frequently arises from multiple complex factors and may affect up to 30% of hospitalized patients.[2] Although the first step in the management of delirium involves identification and treatment of underlying causes and offering supportive behavioral care; medications may be needed to control severe agitation.[2] Low dose intravenous (IV) haloperidol (ie, 0.25–0.5 mg every 4 hours) is a commonly used medication in this setting as recommended by expert-groups including the Cochrane Collaboration and the American Psychiatric Association.[2,3]

Although injectable haloperidol, a butyrophenone-derived antipsychotic agent pharmacologically related to the piperazine phenothiazines,[4] is approved for IV use in many countries (Table 1), parenteral use is approved only for intramuscular (IM) administration in the US. Thus, IV administration of the drug in the US is considered an off-label use.[5]

Haloperidol is often preferred over other antipsychotics as a result of its effectiveness, low rate of anticholinergic side effects, familiarity with dosing and usage, and minimal respiratory or sedative properties.[6] Use of the IV route in patients with acute delirium has several advantages over the IM or oral route,[7] including rapid onset, immediate bioavailability, and ease and safety of administration.

Prior to September 2007, the package insert for haloperidol alerted healthcare professionals to the risk of cardiovascular side effects. Based on case reports of potentially fatal cardiac events, the FDA revised the label, warning that the QT prolongation (QTP) and risk of torsades de pointes (TdP) were increased with IV administration of haloperidol or administration of the drug at greater than recommended

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TABLE 1. Package Information of Officially Approved Haloperidol IV Products

Indication	Country					
	Canada[24]	France[29]	Germany[25]	Great Britain[37]	Italy[30]	Switzerland[31]
	Mainly delirium (schizophrenia, other psychosis, short-term management of psychomotor agitation, excitement, violent or dangerously impulsive behavior, vomiting, hiccup)	Short term treatment of agitation and aggressiveness during an acute or chronic psychotic episode, vomiting along with antimitotic post-radiotherapy treatment	Acute and chronic schizophrenia, psycho-motorical agitation of psychotic genesis	Schizophrenia, other psychosis, short-term adjunctive management if psychomotor agitation, violent or dangerous impulsive behavior	Resistant forms of psycho-motorical excitement, acute delirious and/or hallucinatory psychosis' chronic psychosis High doses restrictions: syndrome of psycho-motorical excitement, acute delirious and/or hallucinatory psychosis, chronic psychosis	Acute schizophrenic episode, mania, vomiting
IV dosing in adults	1–2 mg every 2–4 hours	The use is limited to adult patients and the drug can be administered IM or IV.	5–10 mg/day, daily max.: 30(–100) mg	2–10 mg initially, PRN every 4–8 hours, daily max. 18 mg	5–10 mg initially, PRN every hour, daily max. 60 mg	5 mg PRN every 30 minutes
IV dosing in geriatric care	0.25–0.5 mg	The IV route is restricted to the treatment of vomiting.	Single dose of 0.5–1.5 mg, daily max. 5 mg	Half adult dose	Adjust to appropriate dose	0.5 mg, than PRN
Risk factors for the development of cardiac adverse events	QT prolonging drugs, diabetes, obesity, hypokalemia, congenital long QT syndrome	Bradycardia <55 beats per minute, hypokalemia, congenital QT prolongation, other medications provoking bradycardia, deceleration of the intra-cardiac transition or prolonged QT interval	QT syndrome, hypokalemia, other electrolyte imbalance, cardiovascular diseases, QT prolongation in the family history	Cardiovalscular disease, drugs that can prolong the QTc, diabetes, obesity, hypokalemia, congenital long QT syndrome	Contraindications: recent cardiac infarction, uncompensated cardiac insufficiency, cardiac arrhythmias, antiarrhythmic drugs, pre-existing QT prolongation, cases of arrhythmia or torsades de pointes in the family history, untreated potassium imbalance, QTc prolonging drugs	QT syndrome, hypokalemia, hypomagnesemia, other electrolyte imbalances, cardiovascular diseases, hypothyreosis, QT prolongation in the family history
Monitoring recommendations	Electrolytes	ECG monitoring at admission time, electrolytes	ECG monitoring, electrolytes	Metabolic parameters	ECG at baseline and regular ECG monitoring, electrolytes	Close ECG monitoring, electrolytes
General recommendations	Regular reevaluation in long-term use	Apply the lowest effective dose	Apply the lowest effective dose	Application per mouth is the route of choice	Decrease dose if QTc >500 msec	Switch to PO as soon as possible

Abbreviations: ECG, electrocardiogram; IV, intravenous; max, maximum; PO, by mouth; PRN, medication as needed; TdP, torsades de pointes; VT, ventricular tachycardia.

doses. Unfortunately, neither the "typical" dosing range nor the minimum dose associated with these cardiac side effects were specified in this recommendation.[5]

It is well-established that haloperidol may prolong the QT interval by blocking the repolarizing potassium I_{Kr} current.[8] Although drugs that block the I_{Kr} channel can produce arrhythmia in healthy individuals, additional risk factors, such as underlying heart conditions, electrolyte imbalances (ie, hypokalemia and hypomagnesemia), concomitant proarrhythmic drug use, and mechanical ventilation may increase this risk.[9] Prolongation of the QT interval has been associated with subsequent malignant cardiac arrhythmias including ventricular fibrillation and TdP.[10] Prolongation of the QT interval is considered the strongest risk factor for TdP, particularly with a baseline QTc $>$ 450 msec.[9]

Based on the increased risk for QTP and TdP and the case reports of cardiac events, the FDA advisory recommended continuous electrocardiogram (ECG) monitoring in patients receiving IV haloperidol.[5] However, such monitoring may be impractical and costly in hospitalized patients who require low doses of IV haloperidol to manage acute delirium and who are not in telemetry or intensive care units.

The aim of this review was to evaluate the case reports leading to the recent FDA warning for IV haloperidol,

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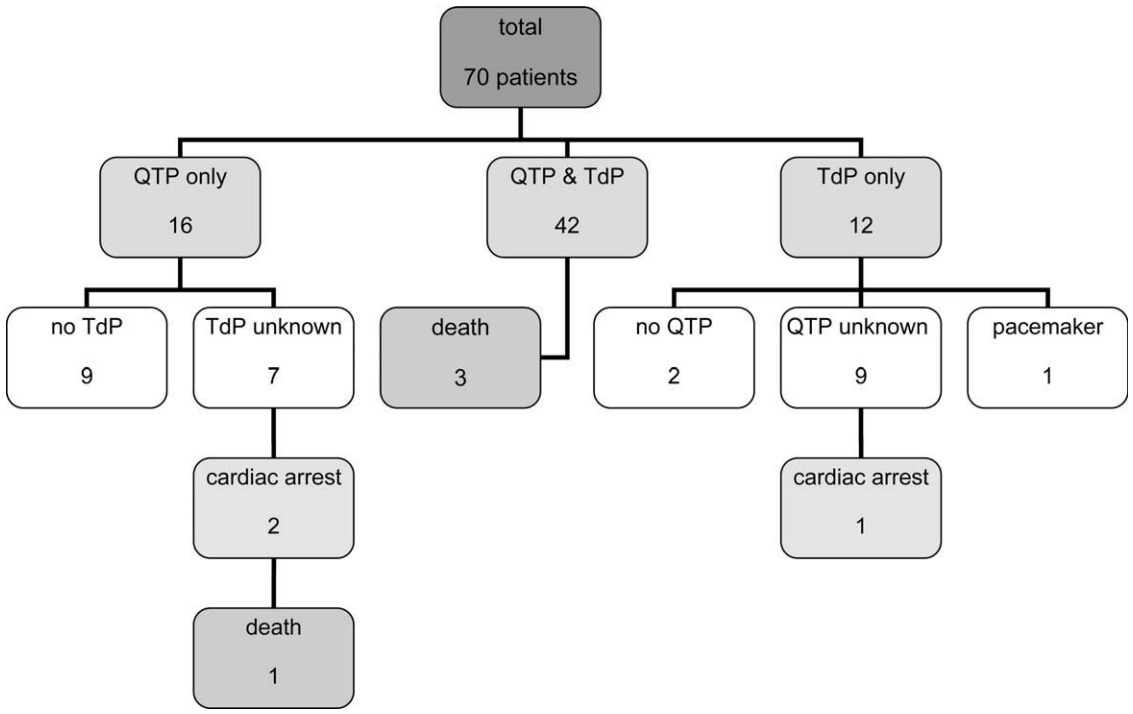

FIGURE 1. Distribution of cardiac adverse events among unpublished and published case reports of intravenous haloperidol-associated QTP/TdP, 1997–2008.

specifically focusing on the presence of risk factors for arrhythmias. Based upon the evidence, an additional aim was to provide an institutional response to this warning toward the optimal use of this agent.

Method

Two search pathways were used to evaluate reports of haloperidol-associated TdP and/or QT prolongation:

Literature Review

We searched for published literature in humans indexed in Pubmed (1966–April 2009), EMBASE (1972–April 2009), and Scopus (1823–April 2009) using the search terms haloperidol or Haldol combined with intravenous or infusion and at least one of the following terms: QT prolongation, TdP, torsades de pointes, torsades with a specific focus on case reports.

References from the retrieved articles were also reviewed to search for additional case reports.

In addition to cases reported in English journals, several of our reports originated from Japan[11] (translation provided by the FDA), Spain[12] and Germany[13] (translated by the primary author).

Search of the FDA Database

We reviewed all adverse drug events reported through MedWatch or those submitted by the manufacturer from November 1997 to April 2008 through the Freedom of Information Act (FOIA) request. The FDA provided a full-text summary of 5944 reports involving oral, intramuscular and IV use of haloperidol. The FDA data were transferred to a Microsoft Access database and screened for the key terms torsade, QT, prolongation, wave. Incident report number, date of report, age, gender, origin of report, medication name, role of drug as categorized by the FDA (suspect, concomitant, primary suspect, secondary suspect), route, dose, units, duration, symptoms and FDA outcome category (death, life-threatening, hospitalization initial or prolonged, disability, congenital anomaly, required intervention to prevent permanent damage, other) were recorded. Only those reports in which IV haloperidol was considered by the reporter to be the primary causative agent for the adverse event were reviewed. Available information included diagnosis, laboratory parameters, QTc measurement, cardiac symptoms, outcomes and a description of recovery. No peer review was applied to the MedWatch reports and the data reported in this publication reflect the original information from the FDA MedWatch database. Baseline QTc was either the value defined as such in the original report or the lowest QTc reported. Haloperidol doses administered were defined as cumulative dose at event, encompassing all doses administered during the hospital stay until the occurrence of the adverse cardiac event.

The drugs listed in the case reports were assessed for proarrhythmic potential using 2 references: the individual package insert and the website of the Arizona Center for Education and Research on Therapeutics.[14]

The drugs were only considered proarrhythmic when the 2 resources were in agreement.

Duplicates and/or previously published cases, as well as reports involving adverse cardiac effects not associated with QTP or TdP, were identified and excluded.

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In their advisory, the FDA does not state the exact origin of the reports, their specific search strategy to identify haloperidol-associated adverse events, or the role IV haloperidol played in the individual events included in the extended warning. Consequently, the number of events identified in this review may differ from that published in the FDA extended warning.

Results

A total of 70 reported cases of IV haloperidol associated TdP and/or QTP were identified. Of these 70, 41 were identified through the PubMed/EMBASE/Scopus review, while an additional 29 cases were identified through the FDA database search.

Of the 29 cases in the FDA database, 21 were reported by health care professionals and 8 by manufacturers.

A total of 35 publications described cases originating from the US. Three cases took place in Japan and 1 case each in Canada, Germany and Spain. Several cases in the MedWatch database were reported outside the US: 1 case each originated from Austria, Canada, France, Japan, Spain, Switzerland and the United Kingdom. A summary of the published case reports is displayed in Table 2 and the FDA cases are summarized in Table 3.

Of the 70 cases, 54 cases of TdP were reported. The remaining 16 of 70 cases involved cases of QTP, 9 of which did not progress to TdP and 7 of which the progression to TdP was unclear. Of note, 42 of 54 of the cases of TdP were reported as preceded by documented QTP. Presence of QTP was unknown in the other 12 original reports. Three out of 70 patients experienced sudden cardiac arrest, 1 of which was fatal. One arrest was preceded by TdP and 2 by QTP (Figure 1).

The patient ages ranged from 18 years to 86 years. Of note, 17 patients experiencing TdP and/or QTP were <40 years old, and 2 of those patients were <30 years old.

Haloperidol-associated QTP and/or TdP were observed in 27 female and 42 male patients; the gender was not stated in one report. Of the 54 patients experiencing TdP (with or without report of previous QTP), 22 were female and 31 were male (1 gender unknown).

A total of 68 of 70 patients were determined to have associated risk factors[15] for QTP/TdP (see Table 4). The circumstances of the remaining 2 patients were not described in sufficient detail to identify associated risk factors.

Overall, 32 patients had underlying heart conditions. Electrolyte imbalances, including hypokalemia, hypomagnesemia, and hypocalcemia, were present in 17 patients. At least 39 patients were receiving potentially proarrhythmic agents (1-8 proarrhythmic drugs per patient) in addition to IV haloperidol. At least 23 patients were receiving additional drugs with a potential for other cardiac adverse events than QTP and TdP.

A wide range of other disease states previously reported to be associated with QTP[15] were identified in these patients: asthma (5 patients), diabetes (5 patients), obesity (3 patients), impaired renal and/or liver function (3 patients each), human immunodeficiency virus (HIV) (2 patients); chronic obstructive pulmonary disease (COPD), pancreatitis and hypothyroidism (1 patient each). A total of 22 patients had a history of substance abuse (alcohol and/or drugs), and 4 patients were smokers.

The administered doses of IV haloperidol varied widely. Considering that information regarding the maximal daily dose was missing in 22 reports and ambiguous in another 20 cases, the results have been presented using cumulative IV haloperidol doses. Patients experiencing TdP without preceding QTP received a cumulative dose (= total dose at event) ranging from 5 mg to 645 mg. Patients with both confirmed QTP and TdP were administered a cumulative dose of 2 mg to 1700 mg. Patients who experienced QTP without TdP received a cumulative dose of 2 mg to 1540 mg of IV haloperidol.

Sudden cardiac arrest following administration of IV haloperidol was observed in cumulative doses ranging from 6 mg to 35 mg. The cardiac arrest leading to a fatal outcome was preceded by an administration of at least 6 mg of IV haloperidol. Overall, 14 out of 70 patients received cumulative doses of $\leq$10 mg IV haloperidol.

The time from administration to documentation of QTP and/or TdP ranged from immediately post administration to 8 hours after administration of the last dose of IV haloperidol.

Baseline QTc was known in 44 patients. Baseline QTc was >450 msec in 18 of these 44 patients.

The change from baseline QTc varied widely from 20 msec to 286 msec; 36 patients demonstrated a prolongation of >50 msec.

In those patients with reported haloperidol-associated QTP, 25 patients demonstrated a QTc >600 msec and 38 patients >520 msec.[9] Of the cases with known specific QTc values, the QTc was prolonged >450 msec in 48 out of 50 cases. The lowest reported QTc leading to TdP was 413 msec.

A total of 20 patients were reported as having a "normalization of QTc" (as defined by the original reports) within several hours to 8 days; minimal QTP was reported as persisting in 2 patients. The specifics of the other patients were unknown, although 25 patients were categorized as "recovered", 13 were stated as having an uneventful remainder of hospitalization, and 5 patients were discharged to a rehabilitation facility or a nursing home.

Discussion

The current review was performed in response to the FDA warning recommending the use of continuous ECG monitoring associated with the administration of intravenous haloperiodol.[5] This warning has resulted in substantial dilemmas for health care organizations, additional resource allocation, and increased scrutiny from regulatory agencies. The results

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TABLE 2. Summary of Case Reports of Intravenous Haloperidol-associated QTP/TdP Published in Pubmed, Embase and/or Scopus (1823–04/2009)

Case	Source (reference#)	Date	Age, Years	Gender	Drugs Pro-arrhyth.	Venti-lated	Max. Daily Dose (mg)	Total Dose at Event (mg)	Time to Event	Prolonged QT	QTc Maximal (baseline), msec	Change in QTc (msec)	TdP	ECG Normalization, *Outcome*
1	35	1991	56	m	No	Yes	1200	≥1540	NR	Yes	584 (400)	184	NR	NR, *uneventful*
2	13	1992	36	m	Yes	No	≥11.5	≥11.5	20 hours after start	Yes	714 (428)†	286	Yes	QTc normalization (440 msec), *NR*
3	38	1993	39	f	Yes	Yes	NR	580	Max. QTc 72 hours after start	Yes	650 (420)	230	Yes	QTc normalization after 6 days, *uneventful*
4	38	1993	19	f	Yes	No	170	≥170	Max. QT 12 hours after start	Yes	600 (480)	120	Yes	QTc normalization after 8 days, *uneventful*
5	38	1993	63	f	Yes	No	NR	489	Max. QT 48 hours after start	Yes	670 (520)	150	Yes	QTc normalization after 8 days, *uneventful*
6	38	1993	74	f	Yes	Yes	NR	10	NR	No	430 (410)	20	Yes	QTc unchanged after 8 days, *uneventful*
7	17	1993	39	m	Yes	Yes	NR	>490	NR	Yes	457 (348)	109	Yes	QTc normalization within 2 to 3 days, no further TdP, *NR*
8	17	1993	61	m	Yes	Yes	115	≥211	NR	Yes	500 (390)	110	NR	QTc normalization within 2 days, *death*
9	17	1993	48	m	Yes	Yes	825	≥825	NR	Yes	538 (441)	97	NR	QTc normalization in 3 days, *rehabilitation*
10	39	1994	23	f	Yes	Yes	120	300	12 hours after dose increase	Yes	NR (550)	NR	Yes	NR, *uneventful, extubation after 5 days, discharge after 10 days*
11	39	1994	28	m	Yes	Yes	300	>300	24 hours after dose increase	Yes	NR (>520)	NR	Yes	No recurrence of arrhythmia, *patient death (multi-organ failure)*
12	40	1994	65	m	Yes	NR	230	≥410	Worsening from day 2 to day 5	Yes	594 (490)	104	Yes	QTc normalization (406 msec), *no cardiac problems at discharge*
13	40	1994	65	f	Yes	NR	500	≥980	After the last 60mg	Yes	628 (403)	225	Yes	QTc normalization (<400 msec), recurrence with oral haloperidol, *rehabilitation*
14	40	1994	76	f	Yes	NR	≥21	≥26	Day 2 after several boluses	Yes	670 (450)	220	Yes	QTc normalization within several days (412 msec), *rehabilitation*
15	41	1994	59	m	NR	Yes	865	≥1013	NR	Yes	640 (480)	160	NR	QTc normalization in 24 hours, *survived*
16	16	1995	76	f	Yes	No	NR	44.5 plus 1 PO	15 minutes	Yes	670 (409)	261	Yes	ECG normalized the next morning, *no further events*
17	16	1995	49	m	Yes	No	NR	1150 plus 20 IM	45 minutes	Yes	648 (380)	268	Yes	QTc normalization in 24 hours, *anoxic brain insult/rehabilitation*
18	16	1995	65	f	Yes	No	600	965	30 minutes	Yes	628 (403)	225	Yes	3 more episodes of TdP in 3 hours, QTc normalization in 2 days, no recurrence with further haloperidol, *NR*
19	42	1995	42	m	Yes	No	28	28	20 minutes	Yes	610 (533)	77	Yes	QTc normalization in 5 days, *uneventful, ECG normal*
20	42	1995	39	m	Yes	No	45	45	5 minutes	Yes	654 (NR)	NR	Yes	QTc normalization after 24 hours, *uneventful*
21	11	1997	56	f	No	No	10	10	Shortly after	NR	NR (NR)	NR	Yes	TdP resolved after 8 hours, *NR*
22	11	1997	82	f	NR	No	10	10	Shortly after	Yes	680 (NR)	NR	Yes	QTc normalization on day 6 after admission (470 msec), *NR*
23	11	1997	35	m	NR	No	NR	90	After 20 mg	Yes	520 (NR)	NR	Yes	TdP disappeared 12 hours later, *NR*
24	43,44	1998	45	m	NR	Yes*	NR	9	203 minutes	Yes	638 (560)	78	Yes	NR, *overall survival 100%, significantly prolonged hospital stay*
25	43,44	1998	64	f	NR		NR	115	220 minutes	Yes	605 (424)	181	Yes	
26	43,44	1998	75	f	NR		NR	85	60 minutes	Yes	567 (508)	59	Yes	
27	43,44	1998	71	f	NR		NR	55	120 minutes	Paced	Paced	Paced	Yes	
28	43,44	1998	58	f	NR		NR	75	38 minutes	Yes	657 (542)	115	Yes	
29	43,44	1998	40	m	NR		NR	35	15 minutes	Yes	679 (475)	204	Yes	
30	43,44	1998	71	m	NR		NR	70	58 minutes	Yes	521 (478)	43	Yes	
31	43,44	1998	47	m	NR		400	400	79 minutes	Yes	574 (444)	130	Yes	
32	21	1999	41	f	Yes	Yes	320	915	55 minutes	Yes	610 (426)	184	Yes	QTc normalization after 5 day, *uneventful*
33	21	1999	31	m	Yes	Yes	480	1700	40 minutes	Yes	599 (491)	108	Yes	QTc normalized in 4 days, *NR*
34	18	2000	64	f	Yes	Yes	175	175	NR	No	413 (418)	(-5)	Yes	QTc remained unchanged, *uneventful*
35	8	2000	75	m	No	NR	>2	>2	NR	Yes	615 (435)	180	No	QTc normalization in 48 hours, *uneventful*
36	8	2000	68	m	Yes	Yes	>2	>2	NR	Yes	650 (407)	243	No	QTc normalization after 4 day, *uneventful after extubation*
37	8	2000	77	m	NR	NR	(4)	2	NR	Yes	550 (393)	157	No	QTc normalization in 24 to 36 hours, *NR*
38	12	2004	34	m	Yes	NR	≥24.5	≥24.5	20 minutes	Yes	560 (420)	140	Yes	QTc normalization (440 msec), *ECG normal*
39	23	2004	58	f	Yes	NR	340	1010	NR	Yes	533 (460)	73	Yes	QTc normalization 7 days later *discharge after 27days*
40	45	2008	86	f	Yes	No	≥2 mg	≥2 mg	8 hours after last dose	Yes	524 (NR)	Probably 79	No	QTc normalization (445 msec), *NR*
41	46	2009	74	m	Yes	No	2	2	Shortly after	Yes	NR (579)	NR	Yes	Pre-existing heart block and fibrillation resolved, *nursing home/rehabilitation*

Abbreviations: ECG, electrocardiogram; IM: intramuscular; IV, intravenous; max, maximum; PO, per os; PRN, medication as needed; QTP, QT prolongation; TdP, torsades de pointes, VT, ventricular tachycardia.

*Five of 8 patients in this case series received concomitant proarrhythmic drugs. The individual patients were unspecified.

†Estimated.

TABLE 3. Summary of FDA MedWatch Reports of Intravenous Haloperidol-associated QTP/TdP, 11/1997–04/2008

Report	MedWatch Identifier	Report Date	Age, Years	Gender	Drugs Pro-arrh.	Maximum Daily Dose (mg)	Total Dose at Event (mg)	Prolonged QT	QTc Maximal (baseline), msec	Change in QTc (msec)	TdP	Outcome; *Recovery*
1	3122988-1	1998	61	m	No	48	48	Yes	NR	NR	Yes	Intervention; NR
2	3157827-6	1998	44	f	No	160	160	Yes	550 (440)	110	Yes	Intervention; uneventful
3	3178715-5	1999	60	m	NR	415	645	Yes	NR	NR	Yes	Life-threatening; QTc normalization in 1 day, no recurrence
4	3271261-X	1999	56	m	NR	NR	≥20	Yes	NR	NR	Yes	Life-threatening; QTc normalization
5	3271080-4	1999	35	m	Yes	≥7	≥7	NR	NR	NR	Yes	NR; event abated after dose stopped/reduced, hospitalization prolonged
6	3325391-4	1999	55	f	Yes	75	≥75	NR	NR	NR	Yes	Life-threatening; event abated after dose stopped/reduced
7	3381921-8	1999	52	m	No	320	634	Yes	458 (430)	28	Yes	Death; NA
8	3483869-7	2000	18	m	No	>200	>310	Yes	NR	NR	Yes	Intervention; no recurrence after haloperidol reinstitution
9	3516342-8	2000	NR	NR	NR	NR	NR	NR	NR	NR	Yes	NR; NR
10	3516320-9	2000	34	m	Yes	≥5	≥5	Yes	NR	NR	No	Life-threatening; event abated after dose stopped
11	3552263-2	2000	46	f	Yes	NR	97.5	Yes	NR	NR	Yes	Life-threatening; event abated after dose stopped/reduced
12	3574705-9	2000	78	m	Yes	NR	160	Yes	603 (453)	50	Yes	Intervention; event abated after dose stopped/reduced
13	3703871-7	2001	27	m	NR	530	530	Yes	NR	NR	Yes	Death, NA
14	3724567-1	2001	31	m	Yes	≥6	≥6	Yes	496 (449)	47	No	Life-threatening; ECG returned to baseline
15	3851984-1	2002	72	f	NR	18	18	NR	NR	NR	Yes	Hospitalization; NR
16	3942407-2	2002	51	m	Yes	14	14	Yes	461 (444)	17	Yes	Life-threatening; no recurrence
17	4066580-3	2003	>60	f	NR	50	50	Yes	>600 (480)	>120	No	Hospitalization; QTc normalization, patient recovered
18	4126280-8	2003	47	f	NR	60	180	Yes	550 (450)	100	No (bradycardia)	Hospitalization; patient recovered
19	4150700-6	2003	NR	m	NR	5	5	NR	NR	NR	Yes	NR; event abated after dose stopped/reduced
20	4340092-1	2004	52	m	Yes	≥5	≥5	Yes	>500 (490)	>10	NR (polymorphous VT)	Life-threatening; NR
21	4714692-0	2005	NR	m	NR	NR	NR	Yes	NR	NR	Yes	Hospitalization; event abated after dose stopped/reduced
22	4881813-9	2006	NR	m	NR	NR	40	NR	NR	NR	Yes	Hospitalization; event abated after dose stopped/reduced
23	4892225-6	2006	NR	f	Yes	≥10	>10	Yes	493 (300)	193	No	Hospitalization; QTc normalization (403 msec)
24	4911873-8	2006	69	m	Yes	≥6	≥6	NR	NR	NR	Yes	Cardiac arrest, death; NA
25	5366448-6	2007	53	m	Yes	NR	35	Yes	NR	NR	NR	Cardiac arrest, life-threatening; patient recovered
26	5563440-3	2007	58	m	Possible	≥5	≥5	Yes	NR	NR	Yes	Life-threatening; event abated after dose stopped/reduced
27	5642929-2	2008	42	m	Yes	165	165	Yes	640 (350)	290	Yes	Death; NA
28	5697758-0	2008	38	m	Yes	NR	620	NR	NR	NR	Yes	Hospitalization; patient recovered
29	5254840-X	2008	19	f	Possible	15	25	Yes	461	NR	NR	Cardiac arrest, hospitalization; patient recovered

Abbreviations: FDA, Food and Drug Administration; f, female; m, male; NA, not applicable, NR, not reported; QTP, QT prolongation; VT, ventricular tachycardia.

of our review reveal that intravenous haloperidol-associated QTP and TdP almost uniformly take place in patients with concomitant risk factors and with cumulative doses ≥2 mg. In light of these findings, it is possible that hospitals may be able to administer intravenous haloperidol in patients without risk factors without continuous ECG monitoring. In reviewing these published reports, it is important to note that the FDA identified 28 published cases of haloperidol-associated QTP and TdP, while our review yielded a total of 41 published case reports.

The FDA database included 73 cases of haloperidol-associated TdP in their database. However, these cases included

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TABLE 4. Presence of Risk Factors Associated With QTP and/or TdP in the Published Case Reports and the FDA MedWatch Database

Risk Factor	Patients, n (%)
Any risk factor	68/70 (97)
Unknown	2/70 (3)
Specific risk factors	
Electrolyte imbalance	27/68 (40)
Underlying cardiac disease	32/68 (47)
Concomitant proarrhythmic agents	39/68 (57)
Other drugs influencing cardiac function	23/68 (34)
Baseline QTc >450 msec	18/68 (26)
QTc known: 44 patients	18/44 (41)

Abbreviations: FDA, Food and Drug Administration; QTc, ; QT, QT prolongation; TdP, torsades de pointes.

both oral as well as IV administration; using our methodology, we identified 29 additional case reports associated with intravenous haloperidol from this database. Consequently, our review included 41 published case reports and 29 FDA database cases, resulting in the total of 70 patients.

Our review revealed a number of practical findings. First, our summary demonstrated that neither QTP nor TdP has been documented with a cumulative dose of IV haloperidol of <2 mg. The majority of patients (80%) received cumulative IV doses ≥10 mg. The lowest dose associated with sudden cardiac arrest was 6 mg and this took place in a 69-year-old male patient. Second, the majority (97%) of our patients had additional risk factors for QTP and/or TdP. Preexisting heart disease,[16–19] electrolyte imbalance,[17,19–21] concomitant proarrhythmic drugs[16,17,19–22] and mechanical ventilation[17,23] were identified as the most commonly observed risk factors (Table 4). Lastly, in those cases in which the data were reported, baseline QTc was >450 msec in 41% of the patients, and 96% had a QTc at the time of the event >450 msec. Therefore, we conclude that patients: (1) receiving low cumulative doses (<2 mg) with (2) no risk factors for prolonged QTc or TdP, and (3) with a normal QTc on baseline EKG can safely be given IV haloperidol in the hospital setting.

This dosage range is consistent with the labelling for IV haloperidol dosing in Canada[24] and Germany[25] (Table 1), where single doses of 0.25 mg to 1.5 mg are recommended for the treatment of delirium or acute agitation in the geriatric population.[24,25]

In a recent Cochrane review, low-dose IV haloperidol (<3 mg per day) was concluded to be as safe and effective as atypical antipsychotics in the treatment of acute delirium with respect to extrapyramidal adverse effects.[2]

The American Psychiatric Association recommends an initial IV dose of "1–2 mg every 2–4 hours as needed (0.25–0.50 mg every 4 hours as needed for elderly patients)," with titration to higher doses for patients who continue to be agitated for the treatment of patients with delirium (issued 1999, updated 2004).[3]

While several expert-groups and investigators currently consider IV haloperidol as an important therapeutic option for treating acute delirium and agitation in the dose range presented above, less consensus exists regarding monitoring requirements.[2,3,26,27]

The American Psychiatric Association recommends IV haloperidol only after a baseline ECG is obtained. These guidelines have not been updated since the release of the FDA extended warning.[3] In their recent review, Morandi et al.[28] support the dosage recommendation of the 1999 American Psychiatric Association's practice guidelines for treatment of delirium,[3] ie, administration of IV haloperidol in single doses of 0.5 mg to 2 mg in elderly patients, however, only after a baseline ECG is obtained.[28] While the package insert of IV haloperidol in France[29] recommends a baseline ECG, Germany,[25] Italy[30] and Switzerland's[31] package information states the need for regular ECG monitoring. Guidelines for the treatment of delirium in the intensive care unit published by the American College of Critical Care Medicine and the Society of Critical Care Medicine in collaboration with the American Society of Health-System Pharmacists consider IV haloperidol as the preferred agent for the treatment of delirium in critically ill patients (grade of recommendation = C). These expert groups recommend that patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol (Grade of recommendation = B).[32]

Nevertheless, continuous ECG monitoring (ie, telemetry) is expensive, labor-intensive and, potentially overutilized.[33,34] Requiring clinicians to place all patients receiving intravenous haloperidol on telemetry is impractical and potentially costly. Mandating telemetry could also lead to unintended harm, ie, use of a less effective or less safe drug to avoid compliance with the telemetry mandate.

Based on our findings and the current recommendations in the literature, inpatient providers should be thoughtful and deliberate in the use of haloperidol to treat acute delirium with agitation. Patients requiring pharmacologic management of their delirium should be screened for risk factors for QTP and TdP (Table 4) and a baseline ECG should be obtained prior to haloperidol administration. If significant risk factors exist or the baseline ECG reveals a prolonged QTc, then the patient should receive continuous ECG monitoring. Similarly, if cumulative doses of ≥2 mg are needed, the patient should be placed on telemetry.

There are some limitations to our study design. Our findings are based upon previously published case reports or data submitted to the FDA MedWatch. While the content of the FDA's MedWatch database is accessible to the public via the Freedom of Information Act (FOIA), the events are neither categorized nor peer-reviewed upon entry into the database. Consequently, information may be incomplete or inaccurate. In addition, the denominator representing the overall use of IV haloperidol is unknown, thus a rate of

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event cannot be assigned and the true scope of the problem cannot be determined. Despite these limitations, this summary represents the most comprehensive review of the literature to date, expanding on the analysis performed by the FDA. Of note, in our review of the FDA database, we noted several cases of haloperidol-associated QTP or TdP associated with other routes of administration. Thus, it is unknown whether this complication is any greater with IV vs. the IM or per os (PO) routes of administration.

Conclusion

Although the proarrhythmic potential of haloperidol and other antipsychotics has been well established in the literature, IV haloperidol has been considered relatively safe with respect to this complication from the time of its approval in 1967.[5,17–22,35,36] In reviewing all reported cases of cardiac complications associated with IV haloperidol, as well as the current literature, an association with QTP and TdP is likely. However, the case reports reveal that QTP and TdP generally occur in the setting of concomitant risk factors, and no cases have been reported utilizing a cumulative IV dose of <2 mg. It may therefore be safe to administer a cumulative dose of IV haloperidol of <2 mg without ECG monitoring in patients without risk factors for QTP. However, ECG monitoring should take place with IV haloperidol doses ≥ 2 mg and/or in those patients with additional risk factors of developing QTP and/or TdP.

Based on the findings of this review complemented by the guidelines of various expert-groups and the official labelling information of different countries, the Pharmacy & Therapeutics Committee of the UCSF Medical Center revised the IV haloperidol policy: administration of a total dose of <2 mg IV haloperidol without concurrent telemetry is allowed in a noncritical care setting in patients without risk factors for QTP and TdP.

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