

Serious Cardiovascular Adverse Events Reported with Intravenous Sedatives: A Retrospective Analysis of the MEDWATCH Adverse Event Reporting System

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‘Drugs-Real World Outcomes’

Electronic Supplemental Table 1. Summary of MedDRA terms used

Disorder category	High level group term	Low level group term	All terms
Cardiac disorders	Arrhythmias	Bradycardia	Bradycardia, Atrioventricular block, complete AV block, 1 st degree AV block, heart block, bradyarrhythmia, sinus arrest, sinus bradycardia
		Brugada	Brugada
		Tachycardia (undefined)	Tachycardia, sinus tachycardia
		Ventricular tachycardia	Ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, Torsades
		A fib	A fib, a flutter
		Supraventricular tachycardia	Supraventricular tachycardia
		Cardiac arrest (undefined)	Cardiac arrest
		Pulseless electrical activity	Pulseless electrical activity, electromechanical disassociation, pulse absent

Cardiac disorders	Cardiac and vascular investigations	Hypertension (undefined)	Hypertension, BP increased
		Hypotension (undefined)	circulatory collapse, hemodynamic instability, shock, BP decreased
		QT prolongation	

Cardiac disorders	Heart failures	Heart failure	Heart failure, left sided heart failure, cardiac failure, myocardial failure
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Vascular disorders	Atherosclerosis, stenosis, vascular insufficiency, necrosis	Myocardial infarction	MI, coronary artery occlusion, enzymes increased, troponin T increased, chest pain, ST elevation
		Cerebrovascular accident	CVA, stroke, cerebral infarct
		Possible coronary Ischemic events	Ischemia, myocardial ischemia

Associate with other causes: syncope, dizziness,

Electronic Supplemental Table 2. Distribution of cases with a serious cardiovascular event reported by serious cardiovascular event type for each IV sedative over the 8 year evaluation period*

	Benzodiazepines				Dexmedetomidine	Propofol	All Agents
	All	Diazepam	Lorazepam	Midazolam			
1. Cardiac arrest	46 (49)	9 (69)	10 (48)	27 (46)	17 (52)^	77 (29)	140 (36)
2. Ventricular arrhythmia	16 (17)	1 (8)	2 (10)	13 (22)	3 (9)	77 (29)^	96 (24)
3. Supraventricular arrhythmia	5 (5)	2 (15)	1 (5)	2 (3)	1 (3)	5 (2)	11 (3)
4. Bradyarrhythmia	7 (8)	0 (0)	3 (14)	4 (7)	2 (6)	30 (11)	39 (10)
5. Brugada ECG pattern	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (3)	8 (2)
6. QTc-interval prolongation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
7. Myocardial infarction	7 (8)	1 (6)	2 (10)	4 (7)	3 (9)	23 (9)	33 (8)
8. Stroke	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (4)	10 (3)
9. Cardiac failure	4 (4)	0 (0)	0 (0)	4 (7)	4 (12)^	19 (7)	27 (7)
10. Possible coronary ischemic event	8 (9)	0 (0)	3 (14)	5 (8)	3 (9)	17 (6)	28 (7)
Total SCAEs[#]	93 (100)	13 (100)	21 (100)	59 (100)	33 (100)	268 (100)	394 (100)

*Not adjusted for sedative exposure. [#]Percentages may not sum to 100 due to rounding. ^p<0.05 across groups

[Data presented as N (% of reported CV ADEs for that sedative class)]

Electronic Supplemental Table 3. Total annual sales of each IV sedative in the United States across each of the 8 study years

	Benzodiazepines				Dexmedetomidine	Propofol
	All Agents	Diazepam	Lorazepam	Midazolam		
2004 (g x 10⁶)	1.258	0.065	0.470	0.723	0.065	478.490
2005 (g x 10⁶)	1.003	0.060	0.469	0.474	0.090	460.655
2006 (g x 10⁶)	1.515	0.108	0.458	0.949	0.074	347.653
2007 (g x 10⁶)	1.366	0.055	0.372	0.939	0.236	284.912
2008 (g x 10⁶)	1.332	0.054	0.366	0.912	0.373	449.174
2009 (g x 10⁶)	1.373	0.056	0.421	0.896	0.571	430.147
2010 (g x 10⁶)	1.321	0.055	0.375	0.891	0.852	93.640
2011 (g x 10⁶)	1.074	0.044	0.365	0.665	1.016	13.783
Cumulative total sales 2004-2011 (g x 10⁶)	10.243	0.500	3.295	6.448	3.277	2,558.455
Hourly sedative infusion equivalence dose (not weight adjusted)^A	*	0.07 mg/kg/hr	0.04 mg/kg/hr	0.07 mg/kg/hr	1.06 mcg/kg/hr	48 mcg/kg/min = 2.86 mg/kg/hr
Hourly sedative infusion equivalence dose (weight adjusted)^{A,B}	*	5 mg/hr	3 mg/hr	5 mg/hr	74 mcg/hr	200 mg/hr
Daily sedative total dose (g)^C	*	120mg = 0.12 g	216 mg = 0.216 g	120 mg = 0.12g	131,424 mcg = 131.42 mg = 0.13 g	4,800 mg = 4.8 g
Cumulative total sedation days (2004- 2011)	73, 149, 291	4,162,700	15,253,083	53,733,508	25,210,423	533,011,507

^A (MacLaren 2005¹, Riker 2009²), ^B Based on a 70kg patient, ^CBased on a 24 hour IV infusion at the hourly equivalent IV infusion rate *Information for all benzodiazepines is a composite of the three individual agents (diazepam, lorazepam, midazolam) and these is no set equivalent dose for the class as a whole.

References:

1. MacLaren R, Sullivan PW. Pharmacoeconomic modeling of lorazepam, midazolam, and propofol for continuous sedation in critically ill patients. *Pharmacotherapy*. 2005;25(10):1319-28.
2. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-99.