Prophylaxis with Amiodarone Post General Thoracic Surgery: A Fact or A Fib

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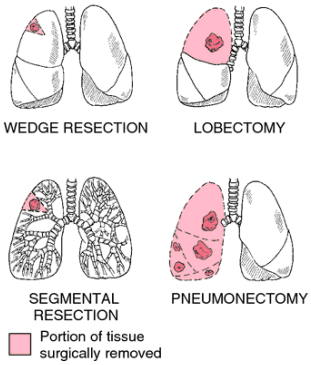
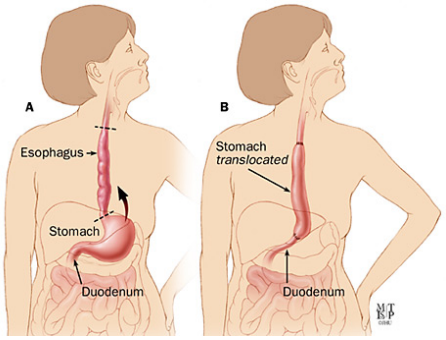
Background

- Atrial fibrillation (AF) common complication post-cardiac surgery
- Incidence of AF after major non-cardiovascular thoracic surgery:
  - Pneumonectomy: 23 – 67%
  - Pulmonary resection (lobectomy): 12 – 30%
  - Esophagectomy: 12 – 44%

Can J Surg 2002;45:264–8





Background

- Onset 2-3 days post surgery
- Risk of AF decreases over first post-operative month
  - 6 weeks post-op AF risk returns to baseline
- Mechanism of AF
  - Increased pulmonary vascular resistance (right ventricular pressure)
  - Extensive surgical stress/sympathetic activity
  - Hypoxemia
  - Perioperative fluid load

Can J Surg 2002;45:264–8

Background

- Complications of AF:
  - Triple median duration of stay in ICU
  - Increase total length of stay in hospital by 2-9 days
  - Increase cost to hospital
  - Risk of Stroke
  - Increased mortality (cardiopulmonary complications)

Can J Surg 2002;45:264–8

Background

Risk Factors:

- Age >60 years of age
- Male
- Previous history of AF event
- More invasive surgery (lobectomy > esophagectomy)

Semin Thoracic Surg 2010;22:310-20

Background

Prophylaxis

- BB
  - Studies with small sample size (all patients receiving BB prior surgery)
  - Risk of exacerbating pulmonary disease
  - High rates of hypotension
- CCB
  - Conflicting evidence (not all studies demonstrate reduction in AF) – up to 35% RR
  - No reduction in length of hospital stay, length of ICU stay, mortality, hospital cost
- Digoxin
  - No reduction in AF

Background

- Magnesium
  - Data from one small study suggest a reduction in AF
- Amiodarone
  - Interest over the last few years
  - New studies may suggest benefit

The guidelines say…

- Class IIa recommendation: Amiodarone prophylaxis is reasonable to reduce the incidence of atrial fibrillation after GTS (excluding pneumonectomy), according to strict dosing regimens.

Ann Thorac Surg 2011;92:1144–52

The guidelines say…

- For patients undergoing pulmonary lobectomy, the recommended dose is 1,050 mg by continuous infusion over the first 24 hours after surgery (43.75 mg/h), followed by 400 mg orally twice daily for 6 days. (Level of evidence B)
- For patients undergoing esophagectomy, the recommended dose is continuous intravenous (IV) infusion at a rate of 43.75 mg/h (1,050 mg daily) for 4 days. (Level of evidence B)

Ann Thorac Surg 2011;92:1144–52

P	Post-op major non-cardiac thoracic surgery -Lobectomy -Esophagectomy
I	Prophylactic Amiodarone
C	No Prophylaxis
O	Occurrence of AF Mortality Length of hospital/ICU stay Cost to healthcare system Adverse drug reactions Stroke

Search Strategy

Databases	Pubmed, Embase, Cochrane database, Google scholar
Search Terms	Atrial fibrillation, general thoracic surgery, lobectomy, esophagectomy, amiodarone
Limitations	Human, English
Results	1 retrospective pilot study 3 prospective, randomized, non-placebo-controlled trials

Low-Dose Oral Amiodarone Prophylaxis Reduces Atrial Fibrillation After Pulmonary Resection

Louis A. Lanza, MD, Antonio I. Visbal, MD, Patrick A. DeValeria, MD, Alan R. Zinsmeister, PhD, Nancy N. Diehl, and Victor F. Trastek, MD

Ann Thorac Surg 2003;75:223–30

Design	Pilot study, Retrospective, Single-center (Mayo Clinic Hospital, Phoenix, Arizona), data collection Oct 1998 – Mar 2001
Population	60 years or older who underwent pulmonary resection Exclusion: not clear
Intervention	N = 31 Amiodarone 200 mg po q8h for duration of hospitalization
Comparator	N = 52 No prophylactic treatment
Outcomes	AF identified by continuous cardiac monitoring Overall postoperative complications including AF

Ann Thorac Surg 2003;75:223–30

	LDOA (N = 31)	No Amiodarone (N = 52)	Absolute difference
Atrial Fibrillation	3 (9.7%)	17 (33%)	23.3%
Duration of AF (hours)	2.0 (0.5 – 12)	18 (8 – 168)	16 hours
Length of hospital stay (days)	6 (3 – 22)	7 (3 – 17)	1 day

Ann Thorac Surg 2003;75:223–30

Table 5. Distribution of Complications[a]

Complication	Patients Without LDOA Prophylaxis, number (N = 52)	Patients With LDOA Prophylaxis, number (N = 31)
Prolonged air leak	7	4
Pneumonia	3	0
Atelectasis requiring bronchoscopy	3	0
Respiratory failure requiring ventilatory support	2	0
Renal failure	2	1
Gastrointestinal tract bleeding	2	0
Re-exploration for bleeding	2	0
Myocardial infarction	1	1[b]
Pericarditis	1	0
Bronchopleural fistula	0	1[b]
Urinary retention	0	1
Physical deconditioning	0	1
Total events	23	9

Ann Thorac Surg 2003;75:223–30

Conclusions

- "Low dose oral amiodarone significantly reduces the incidence of AF following pulmonary resection"
- "Results of our pilot study support proceeding with a prospective randomized trial"

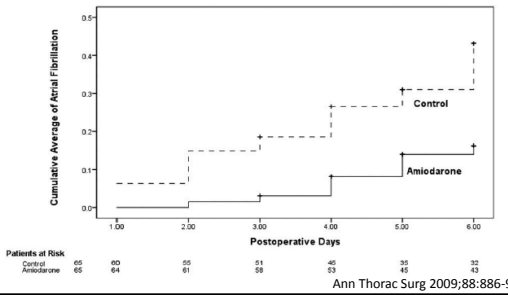
A Randomized Trial Evaluating Amiodarone for Prevention of Atrial Fibrillation After Pulmonary Resection

James E. Tisdale, PharmD, Heather A. Wroblewski, MSN, Donna S. Wall, PharmD, Karen M. Rieger, MD, Zane T. Hammoud, MD, Jerry V. Young, MD, and Kenneth A. Kesler, MD

Ann Thorac Surg 2009;88:886-95

Design	P, R, Single-center (270-bed tertiary care hospital, Indianapolis)
Population	>40 years undergoing lobectomy, bilobectomy, or pneumonectomy Exclusion: history of AF or flutter, AF requiring treatment during procedure, contraindication to amiodarone, elevated ALT and AST
Intervention	N = 65 Amiodarone 43.75 mg/hr x 24 hrs (1050 mg total daily) followed by 400 mg po/ng BID until discharge or max. 6 days Initiated at anesthesia induction
Comparator	N = 65 No Amiodarone
Outcomes	Primary Endpoint: AF requiring treatment - rapid ventricular rate, SOB or fatigue, or hemodynamic compromise Secondary Endpoint: Total post-operative hospital stay ICU stay Incidence of ADR Total cost of hospitalization

Outcome	Amiodarone N = 65	Control N = 65	RR (95% CI)	Absolute Difference (NNT)	P value
AF requiring treatment	9/65 (13.8%)	21/65 (32.3%)	0.43 (0.14 – 0.81)	18.5% (5.4)	0.02



Ann Thorac Surg 2009;88:886-95

Outcome	Amiodarone	Control	Absolute Difference	P value
Post-operative hospital stay	7 days	8 days	1 day	0.79
Post-operative ICU stay	46 hours	84 hours	38 hours	0.03
Total cost of stay	$13,453 (+/-$6,303)	$14,445 (+/-$7,623)	$992	0.46

Ann Thorac Surg 2009;88:886-95

Table 2. Postoperative Adverse Events/Morbidity/Mortality

Adverse Event	Amiodarone (n = 65)	Control (n = 65)	*p* Value
Hypotension[a]	21 (32.3%)	22 (33.8%)	> 0.99
Bradycardia[b]	4 (6.2%)	1 (1.5%)	0.36
QTc interval > 500 ms	1 (1.5%)	0 (0%)	> 0.99
Gastrointestinal	9 (13.8%)	11 (16.9%)	0.81
Respiratory complications[c]	15 (23.1%)	10 (15.4%)	0.37
ARDS	0	1 (1.5%)	> 0.99
Pneumonia	7 (10.8%)	4 (6.2%)	0.52
Atelectasis	8 (12.3%)	4 (6.2%)	0.36
Pulmonary fibrosis	0	1 (1.5%)	> 0.99
Other			
Pericarditis	1.5%	0	> 0.99
Wound dehiscence	0	1.5%	> 0.99
Mortality	2 (3%)	1 (1.5%)	> 0.99

[a] Hypotension defined as systolic pressure less than 90 mm Hg. [b] Bradycardia defined as heart rate less than 50 beats per minute. [c] Respiratory complications defined as adult respiratory distress syndrome (ARDS), pneumonia, pulmonary fibrosis, or atelectesis requiring bronchoscopy and/or reintubation.

Ann Thorac Surg 2009;88:886-95

Conclusions

- "Perioperative and postoperative administration of amiodarone reduces the incidence of AF after anatomic pulmonary resection, and is associated with a decrease in duration of ICU stay"
- "Amiodarone prophylaxis of AF should be considered in patients undergoing anatomic pulmonary resection"

Ann Thorac Surg 2009;88:886-95

Limitations

- Not placebo controlled/blinded
- Procedure completed by different surgeons (AF related to procedure technique?)
- Patients followed only until hospital discharge
- Diagnosis of AF left to discretion of physician (no standard protocol)
- Contrast in outcomes (length of ICU/hospital stay/cost of hospitalization) – protocol ICU stay
- Risk of stroke/cardiopulmonary complications

A randomized, controlled study of amiodarone for prevention of atrial fibrillation after transthoracic esophagectomy

James E. Tisdale, PharmD,[a,b] Heather A. Wroblewski, MSN,[a] Donna S. Wall, PharmD,[e] Karen M. Rieger, MD,[c] Zane T. Hammoud, MD,[c] Jerry V. Young, MD,[d] and Kenneth A. Kesler, MD[c]

J Thorac Cardiovasc Surg 2010;140:45-51

Design	P, R, Single-center (270 bed ICU Indianapolis)
Population	>40 years undergoing transthoracic esophagectomy through open or minimally invasive approach Exclusion: history of AF or flutter, AF requiring treatment during procedure, ADR to amiodarone, elevated ALT and AST
Intervention	N = 40 Amiodarone 43.75 mg/hr x 96 hrs (1050 mg total daily) Initiated at anesthesia induction
Comparator	N = 40 No Amiodarone (no placebo)
Outcomes	Primary Endpoint: AF requiring treatment - rapid ventricular rate, SOB or fatigue, or hemodynamic compromise Secondary Endpoint: Total post-operative hospital stay ICU stay Incidence of ADR Total cost of hospitalization

Outcome	Amiodarone N = 40	Control N = 40	RR (95% CI)	Absolute difference (NNT)	P value
AF requiring treatment	6/40 (15.0%)	17/40 (42.5%)	0.35 (0.16 – 0.86)	25% (4)	0.02

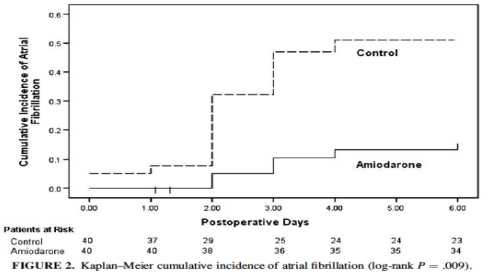


FIGURE 2. Kaplan–Meier cumulative incidence of atrial fibrillation (log-rank $P = .009$).

J Thorac Cardiovasc Surg 2010;140:45-51

Outcome	Amiodarone N = 40	No Amiodarone N = 40	Absolute Difference	P value
Post- operative hospital stay	11 days	12 days	1 day	0.31
Post-operative ICU stay	68 hours	77 hours	9 hours	0.097
Total Cost of stay	$24,153	$24,977	$824	0.93

J Thorac Cardiovasc Surg 2010;140:45-51

TABLE 2. Postoperative adverse events and morbidity

	Amiodarone (n = 40)	Control(n =40)	*P* value
Cardiovascular complications			
Hypotension*	21 (52.5%)	19 (45.0%)	.66
Bradycardia†	2 (5.0%)	1 (2.5%)	>.99
QTc interval >500 ms	1 (2.5%)	0 (0%)	>.99
Ventricular tachycardia	0 (0%)	2 (5.0%)	.49
Respiratory complications‡	9 (22.5%)	9 (22.5%)	>.99
Adult respiratory distress syndrome	0 (0%)	0 (0%)	>.99
Pneumonia	6 (15.0%)	5 (12.5%)	>.99
Atelectasis	3 (7.5%)	4 (10.0%)	>.99
Other			
Pericardial effusion	1 (2.5%)	1 (2.5%)	>.99
Anastomotic leak	1 (2.5%)	2 (5.0%)	>.99

All data represent numbers of patients. *Systolic pressure less than 90 mm Hg. †Heart rate less than 50 beats/min. ‡Respiratory complications include adult respiratory distress syndrome, pneumonia, pulmonary fibrosis, and atelectesis necessitating bronchoscopy or reintubation.

Total 2 deaths during study period – both in control group
1 MI
1 Toxic megacolon

J Thorac Cardiovasc Surg 2010;140:45-51

Conclusions

- "Prophylactic administration of IV amiodarone reduced the incidence of AF after transthoracic esophagectomy"
- "Amiodarone prophylaxis against AF should be considered for this population"

J Thorac Cardiovasc Surg 2010;140:45-51

Limitations

- Study not placebo controlled/blinded
- Procedure completed by different surgeons (AF related to procedure technique?)
- No comment of treatment success if developed AF
- Follow-up only as long as hospitalization
- Diagnosis of AF left to discretion of physician (no standard protocol)
- Contrast in outcomes (length of ICU/hospital stay/cost)
- Risk of stroke/cardiopulmonary complications

A comparative study between amiodarone and magnesium sulfate as antiarrhythmic agents for prophylaxis against atrial fibrillation following lobectomy

Mohamed A. Khalil · Ahmed E. Al-Agaty · Wael G. Ali · Mohsen S. Abdel Azeem

J Anesth DOI 10.1007/s00540-012-1478-3

Design	P, R, University hospitals in Cairo
Population	Patients with lobectomy Exclusion: permanent atrial fibrillation, previous lung resection, asthmatic patients, and patients with previous cardiac surgery, a history of thyroid disease, or coexisting cardiac or renal disease.
Intervention	Group A: 5 mg/kg amiodarone load pre-op, maintenance dose of 15 mg/kg was infused over 48 hr postoperatively.
Comparator	Group M: $MgSO_4$ 80mg IV pre-op, then 8mg/kg/hr x 48 hr Group control: No treatment (analyzed retrospectively)
Outcome	Occurrence of AF (12-lead EKG) Bradycardia and/or hypotension ICU stay (hours) Hospital stay (days)

	Amiodarone (n = 219)	Magnesium (n = 219)	Control (n = 219)	P value
Postoperative AF	21 (10%)$^{\Psi}$	27 (12.5%)$^{\phi}$	44 (20.5%)*	0.005
Bradycardia (<60/min)	133 (61%)	128 (58.5%)	129 (59%)	0.927
Hypotension (>20% reduction)	151 (69%)	142 (65%)	140 (64%)	0.498
ICU stay (hrs)	24.8 (0.86)	32.5 (0.94)	43.8 (1.2)*	<0.001
Hospital stay (days)	4.2 (0.17)	6.1 (0.19)	8.3 (0.17)*	<0.001

*Significant difference between both treatment groups
Ψ Significant difference between amiodarone and control
ϕ Significant difference between magnesium and control

J Anesth DOI 10.1007/s00540-012-1478-3

Conclusions

"Both amiodarone and magnesium sulfate are effective at preventing postoperative atrial fibrillation following lung resection in comparison to the control group."

J Anesth DOI 10.1007/s00540-012-1478-3

Limitations

- Study not placebo controlled/blinded
- Extensive exclusion criteria
- Procedure completed by different surgeons (AF related to procedure technique?)
- Follow-up for duration of hospital stay
- No comment of treatment success if AF developed
- Comparator analyzed retrospectively

In a patient post major non-cardiac surgery, does Amiodarone…

Reduce occurrence of AF	✓
Reduce length of stay hospital/ICU	= ✓
Reduce mortality	=
Reduce hospital cost	?
Adverse events were few and minor	✓
Reduce stroke	?

Recommendation

- Prophylactic amiodarone after esophagectomy or lobectomy
  - Amiodarone 43.75 mg/hr x 24 hrs (1050 mg total daily) followed by 400 mg po/ng BID until discharge or max. 6 days - lobectomy
  - Amiodarone 43.75 mg/hr x 96 hrs (1050 mg total daily) – esophagectomy
- Need results in high-risk patients
- Additional research needed to compare prophylactic effects of amiodarone to beta-blockers