# WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

**Worksheet author(s)**
Melissa Givens, Greene Shepherd

**Date Submitted for review:** 2/3/2010

## Clinical question.

In adult cardiac arrest (prehospital or in-hospital) due to beta blocker toxicity (P), does use of any specific intervention (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival)

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention

**State if this is a proposed new topic or revision of existing worksheet:** New

## Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

## Search strategy (including electronic databases searched).

**Ovid/Embase (Embase included) and Pubmed**

**Keywords:**

(P1) = 8,116

- Beta blocker OR beta antagonist
- (metoprolol, atenolol, labetalol, esmolol, acebutolol, carvedilol, propranolol, sotolol, timolol, pindolol, oxprenolol, nadelol)

(P1a) overdose OR toxicity = 210,255

(I) = 30,139

- Insulin, glucagon, calcium chloride OR calcium gluconate, lipid emulsion OR intralipid, vasopressin, aortic balloon pump, cardipulmonary bypass, atropine, amrinone OR phosphodiesterase inhibitors, cardiac pacing OR pacemaker

(P1) AND (P1a) = 165

(P1) AND every (I)

- Insulin = 9
- Glucagon = 33
- Calcium = 22
- Lipid = 5
- Vasopressin = 2
- Aortic balloon pump = 0
- Cardipulmonary bypass = 0
- Atropine = 6
- Amrinone or phosphodiesterase inhibitor = 3
- Cardiac pacing or pacemaker = 5

**All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED (Embase included)**

- (P) = Overdose AND beta-blocker OR beta antagonist = 0

**ECC EndNote X Master Library**

- (P) = betablocker AND overdose = 0

The final literature search was conducted on 8/31/2009.

Hand search of bibliographies and current toxicology textbooks to include Goldfrank’s Toxicologic Emergencies (8th ed), Medical toxicology (3rd ed), Clinical Management of Poisoning and Drug Overdose (4th ed) = 3

### State inclusion and exclusion criteria

**Inclusion:** human and animal studies, case reports, case series, abstract available

**Exclusion:** review articles, laboratory studies, animal studies involving specific tissue or organs, case reports with multiple substances ingested, pediatric cases

### Number of articles/sources meeting criteria for further review:

- 93 articles for review, 58 were excluded

- 35 articles kept after exclusion criteria were applied.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Evidence Supporting Clinical Question</th>
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<tbody>
<tr>
<td>Glick, 1968, 789 BE,</td>
<td></td>
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<tr>
<td>Kosinski, 1973, 840 BE (glucagon +)</td>
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<tr>
<td>Love 1996, 1 E (CaCl +)</td>
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<tr>
<td>Love 1992, 399 E (glucagon&gt;amrinone)</td>
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<tr>
<td>Kerns 1997, 748 BE (Insulin&gt;Glugagon&gt;Epi)</td>
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<tr>
<td>Holger 2007, 45 BE (Insulin &gt; vasopressin + Epi)</td>
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<tr>
<td>Harvey 2008, 71 E (lipid+)</td>
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<tr>
<th>Fair</th>
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<tbody>
<tr>
<td>Pertoldi 1998, 777 B,E (CaCl+)</td>
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<tr>
<td>Brimacombe 1991, 854 B,E (CaCl+)</td>
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<td>Fahed 2008, 13</td>
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<tr>
<td>Fernandes 1995, 659</td>
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<td>Frishman, 1979, 798</td>
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<td>Gabry 1985, 229</td>
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<td>Hazouard 1999, 336</td>
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<td>Khan 1985, 1062</td>
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<td>Moller 1976, 222</td>
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<tr>
<td>O’Mahoney 1990, 101</td>
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<tr>
<td>Weinstein 1985, 1123</td>
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<tr>
<td>B,E (Glucagon +)</td>
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<th>Poor</th>
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<tbody>
<tr>
<td>Page 2009, 139</td>
<td></td>
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<tr>
<td>B,E (Insulin +)</td>
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<td>Italics = Animal studies</td>
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### Evidence Neutral to Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td></td>
<td>Holger 2006, 396 BE (Glucagon = Vasopressin)</td>
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<tr>
<td>Fair</td>
<td>Kenyon 1988, 711 B,E (Glucagon +/-)</td>
<td>Freestone 1986, 343</td>
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<td>Wallin 1983, 253 B,E (Glucagon +/-)</td>
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<tr>
<td>Poor</td>
<td>Cave 2009, 449 E (Lipid +/-)</td>
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#### Level of evidence

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### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Good</td>
<td>Love 1993, 399 E (Glucagon w/ Amrinone -)</td>
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<tr>
<td></td>
<td>Sato 1995, 337 BE (Milrinone w Glucagon -)</td>
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<tr>
<td></td>
<td>Toet 1996, 120 BE (Dopamine w/ Isoproterenol -)</td>
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<tr>
<td></td>
<td>Toet 1996, 411 BE (Dopamine w/ Glucagon -)</td>
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<tr>
<td>Fair</td>
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<tr>
<td>Poor</td>
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- **A** = Return of spontaneous circulation
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**REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

In this review, articles are graded with respect to their relevance to the clinical question of cardiac arrest. Under this system, reports of animal models or human experience shy of cardiac arrest are classified as LOE 5 because they represent a different patient population. If a slightly different clinical question is considered (management of patients with severe/life-threatening cardiovascular toxicity), many of these human case reports would qualify as LOE 4.

Currently, there are no studies specifically designed to address possible beta blocker (BB) antidotes in the setting of arrest. Available data include animal models and case reports that describe utility for improving hemodynamics and preventing deaths in the setting of BB induced cardiotoxicity. Among the various antidotes that have been proposed glucagon had the most evidence available to evaluate and appears likely to offer some clinical benefit.

**GLUCAGON:** No formal studies evaluate the use of glucagon for beta blocker poisoning in humans. Animal studies using glucagon as a treatment of beta blocker poisoning date back to 1968. (Glick 1968, 789, LOE5) Previous work in the setting of heart failure demonstrated that 50-150 micrograms/kg of glucagon is an effective cardiac stimulant. In animal models of beta-blocker overdose, glucagon consistently increased the heart rate and contractility, at least transiently, but had little effect on mean arterial pressure. In many of these studies dosing was likely suboptimal. Its effect on the survival rate in animal models of beta-blocker overdose was unclear. One study that used what is felt to be appropriate dosing resulted in a significant improvement in survival and cardiac output. (Kerns 1997, 748, LOE5) One study suggests that dopamine (Toet 1996, 411, LOE5) in combination with glucagon may negatively impact survival. Another (Love 1993, 360, LOE5) demonstrated that glucagon in combination with amrinone diminished glucagon’s ability to increase hemodynamic parameters. However, given the poor efficacy of other inotropic agents based on their mechanisms of action, glucagon should be used early in the treatment of beta-blocker overdose.

Studies in the setting of heart failure demonstrated that 50 micrograms/kg of glucagon is an effective cardiac stimulant in humans. (Vander Ark 1970, 481) It’s first use in human beta blocker poisoning was reported by Kosinski in 1971 (Kosinski 1971, 1325) for the treatment of a multiple substance ingestion that included propranolol. Since then, numerous human case reports indicate that glucagon can be used safely and appears beneficial in humans with beta blocker poisoning. Sixteen cases (2 LOE4, 15 LOE5) were identified where the only substance ingested was a beta blocker and glucagon was used. The patients survived in all 16 cases and rapid improvements in cardiovascular parameters were noted in 12/16 cases. (Fahed 2008, 13, Fernandes 1995, 659, Frishman, 1979, 798, Gabry 1985, 229, Hazouard 1999, 336, Khan 1985, 1062, Moller 1976, 222, O’Mahoney 1990, 101, Weinstein 1985, 1123) In the cases where glucagon was not effective, external pacing (2 cases) and the beta selective agonist prenalterol (2 cases) resulted in improvement. (Alderfliegel, 1993, 57, Freestone 1986, 343, Kenyon 1988, 711, Wallin 1983, 253) In the Alderfliegel case, sotolol poisoning caused asystole twice despite atropine, glucadon and isoprenaline therapy but cardiopulmonart resuscitation followed by external pacing was successful. Based on available animal studies and human experience a bolus of 5–10 mg followed by an infusion of 1–5 mg/h (0.15 mg/kg followed by an infusion of 0.05–0.10 mg/kg/h) appears to be an effective regimen.

**INSULIN:** Animal studies of propranolol overdose suggests that high dose insulin with supplemental glucose and potassium may be of greater benefit in survival and improving hemodynamic variables when compared to glucagon or pressor therapy such as epienehrine and vasopressin. (Kerns 1997, 748, Holger 2007, 45) A case report of a 5 gram ingestion of metoprolol exists where high dose insulin (10 u/kg/hr) was associated with improvements in heart rate and mean arterial pressure after failure to respond to supportive measures but glucagon was not given. (Page 2009, 139) Further studies are needed to establish benefit in humans and define optimal dosing regimens of high dose insulin therapy for beta-blocker overdose.

**LIPID EMULSION:** Two small animal studies evaluate the potential for lipid rescue therapy in beta blocker toxicity but this therapy has not been evaluated against standard therapy and may have limited efficacy against water soluble agents. Optimum dosing regimens are unknown. In a rabbit model of propranolol (lipid soluble) poisoning administering 6 mL/kg of 20% lipid emulsion caused statistically significant improvements in MAP compared with administering 6 mL/kg of saline. (Harvey 2008 71) In a rabbit model of atenolol (water soluble) poisoning administering 6 mL/kg of 20% lipid emulsion did not caused statistically significant improvements in MAP compared with administering 6 mL/kg of saline. (Cave 2009, 449)

**OTHER THERAPIES:** Case reports of other therapies such as phosphodiesterase inhibitors (Kollef 1994, 626; O’Grady 2001, 224), calcium salts (Brimacome 1991, 267; Pertoldi 1998, 777), extracorporeal support (Mcvey 1991, 744), intra-aortic balloon pumps (Lane 1987, 1381), and ECMO (Rooney 1996, 760) suggest other opportunities for further investigation. Hemodialysis specifically for water soluble atenolol is another possible consideration based on successful case reports (Salhanick 2000, 224).
COMBINING MODALITIES: Combining certain therapies may be counter productive. Two animal studies suggest that dopamine may negatively impact survival in combination with glucagon or isoprenalid. (Toet 1996, 120, 1996, 411). Glucagon does not appear to work well in combination with amrinone or milrinone. (Love 1993, 399, Sato 1995, 337)

Acknowledgements:
Citations

[1-50][51-92]


   Case report of sotalol poisoning that developed asystole twice despite glucagon, atropine and isoprenaline therapy. Cardiopulmonary resuscitation and pacing in the setting of on going antidote therapy was effective. LOE 4, Good, Supportive


   LOE 5, good, supportive


   LOE 4, Fair, Supportive


   A rabbit model of atenolol poisoning comparing lipid therapy with saline. No significant difference was detected. Given that atenolol is water soluble the outcome is not surprising. LOE 5, good, neutral


   Case report of iatrogenic labetalol overdose in a 75 yo woman that responded to glucagon. Toxicity from a labetalol infusion was suspected and glucagon was ordered. The patient was given one liter of 0.9% NaCl rapidly, ephedrine 5 mg IV twice, and atropine 0.5 mg IV without result. A dopamine infusion of 10 mcg/min was also ineffective. Two doses of 10 mcg of epinephrine IV raised systolic BP to 70 mmHg and HR to 65 beats per minute. An epinephrine infusion was then started at 0.05 mcg/kg/min. The glucagon arrived 10 minutes after being ordered and 3.5 mg IV (.05 mg/kg) was given over 3 min. Blood pressure promptly recovered to 94/47 mmHg, HR to 73/min, and a CVP of 14 cm H2O. The glucagon bolus was followed by an infusion of glucagon 1 mg/hr for 27.5 hours. After the glucagon bolus the patient's blood sugar transiently reached 255 mg/dl and corrected with one dose of intravenous insulin. The epinephrine infusion was gradually discontinued over 3 hours. LOE 5, fair, supportive


   An 80 yo woman prescribed sotalol for paroxysmal atrial fibrillation presented with a heart rate of 42 beats/min and blood pressure of 122/60mmHg secondary to therapeutic use. glucagon was administered at a rate of 0.2 mg/min. After 3.5 mg was administered, the rhythm converted to a normal sinus with a rate of 60 beats/min. LOE 5, fair, supportive


This article is an early case series of propranolol poisonings that describes hemodynamic improvements associated with glucagon administration and survival in 3 cases it also review previous published cases of beta blocker poisoning. LOE 5, fair, supportive


A case report of metoprolol poisoning that displayed rapid improvement in hemodynamic parameters after the administration of glucagon. LOE 5, fair, supportive


Animal studies in dogs and cats that demonstrates glucagon can stimulate heart rate and blood pressure in the presence of beta blockade. LOE 5, good, supportive


Rabbit model of propranolol poisoning that demonstrates efficacy of lipid therapy vs a saline control. LOE 5, good, supportive


In this case report of propranolol overdose, administration of glucagon was temporally associated with improved hemodynamics and resolution of hallucinations. LOE 5, fair, supportive


A pig model that demonstrates that Insulin and glucose were superior to vasopressin plus epinephrine for treating propranolol toxicity. LOE 5, good, supportive


A pig model that demonstrates that glucagon and vasopressin offer similar hemodynamic improvements when propranolol toxicity. LOE 5, good, neutral


Propranolol overdose where glucagon was used late in the course and no benefit was seen. Pacing was successful. LOE4, fair, neutral

In a dog model of propranolol poisoning insulin > glucagon > epinephrine in terms of survival. Insulin was also superior for improving depressed hemodynamics. LOE 5, good, supportive


In 1 case glucagon administration was temporally associated with improved blood pressure and heart rate following propranolol overdose. LOE 5, fair, supportive


This study describes a case report of successful treatment of IV labetalol induced cardiovascular compromise with amrinone and alpha agonists.


Dog model of propranolol poisoning that compares glucagon and isoproterenol. Both improved hemodynamics in the setting of propranolol poisoning. LOE 5, fair, supportive


Successful use of intra-aortic balloon pump in propranolol overdose who failed medical therapy. LOE 4, fair, supportive


In a dog model of propranolol poisoning calcium chloride improved hemodynamics when compared to an equal volume of saline. LOE 5, good, supportive


In a dog model of propranolol poisoning mortality increased when glucagon was combined with amrinone. LOE 5, good, opposing


In a dog model of propranolol poisoning glucagon was more effective than amrinone. LOE 5, good, supportive


LOE 5, fair, supportive

Case report of metoprolol poisoning where by history 10,000 mg were ingested and a plasma concentration of 12,200 nanomol/mL was detected. On arrival the patient was alert with a heart rate of approximately 60 bpm and blood pressure was undetectable. Glucagon was associated improved hemodynamics and recovery.

LOE 5, fair, supportive


LOE 5, fair, supportive


Case report of oxprenolol overdose that requires continuous infusion of glucagon to maintain good blood pressure and heart rate. LOE 5, fair, supportive


A case report that describes the use of high-dose insulin (10 IU/kg per hour) to treat significant metoprolol poisoning. LOE 5, fair, supportive


The calcium doses used were three 1-gram (13.6 mEq) boluses, followed by an infusion of 125 mg (1.7 mEq)/hr. The LOE 4, fair, supportive.


LOE 4, fair, supportive


LOE 5, fair, supportive


Dog model of propranolol poisoning looking at glucagon and milrinone. Both produced improvements in hemodynamics. LOE 5, good, neutral


Dog model of propranolol poisoning looking at glucagon, milrinone and both in combination. Both worked independently to improve hemodynamics but in combination produced an excessive increase in heart rate. LOE 5, fair, opposing

Rat model of propranolol poisoning that indicates that dopamine in combination with isoproterenol decreased survival. LOE 5, fair, opposing


Rat and Rabbit models of propranolol poisoning. Glucagon alone or in combination with dopamine did not improve survival. The combination appeared worse than glucagon alone. LOE 5, fair, opposing


Propranolol intoxication with cardiovascular collapse and seizures. Failed to respond to high-dose intravenous pressor agents, but improved with IV glucagon. LOE 5, fair, supportive