

Update on recent advances in treating beta-blocker and calcium channel blocker overdose

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Hong Kong Poison Information Centre: Annual Report 2014

Table 4. The HKPIC annual reports important figures in latest five years

Year	2010	2011	2012	2013	2014 (current)	5 years average
Number of cases	4,418	4,331	4,184	3,783	3,609	4,065
Death (%)	1	1	0.6	0.9	0.9	0.9
Major outcome (%)	5.3	4.8	4.7	4.3	5.0	4.8
GI decontamination (%)	10.2	12.1	15.7	14.5	14.9	13.5
Antidote use (%)	9.7	8.5	11.9	13.4	15.0	11.7

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- 100 – 150 cases of CCB or/and BB poisoning per year
- 19 / 88 (22%) poisoning deaths in HK from 2013-2015



Treatment for CCB / BB Poisoning

- Supportive care
- Gastrointestinal decontamination
- Antidote
 - “Standard” (calcium, glucagon, and vasopressor)
 - “Others” (HIE, ILE)
- Extracorporeal life support (ECLS)
- Enhanced elimination

GI Decontamination

- May be life saving in cases of severe CCB/BB overdose
 - Five human case series reported sequelae-free survival of all patients who underwent GI decontamination
- GL and AC 1g/kg within 1-2 hours
- Consider WBI and MDAC in sustained release preparation or large amount overdose
 - Beware of the risk if ischemic bowel

Calcium

- Supported by
 - Animals studies
 - Case series and reports
- Dose
 - 1g CaCl₂ or 3g Ca gluconate as initial bolus
 - Repeat at 10-20mins +/- infusion
- Adverse effects such as hypercalcemia were rare
- Animal study and human experience
 - Can tolerate ionized Ca²⁺ ~ 2 mmol/L or 2 x ULN

Glucagon

- Supported by animal studies / human case series
- Dose
 - 3-5mg bolus
 - Infusion at response dose/hr
- Common concern
 - Vomiting, hyper glycaemia
 - Availability

Inotropes / Vasopressor

- Noradrenaline + Dopamine
 - ↑ survival and haemodynamic in animal studies
 - Inconsistent results in human case series / reports
- Adrenaline
 - ↑ CO in animal studies
- Isoproterenol
 - ↑ haemodynamic in case reports
- Vasopressin
 - ↑ BP in case reports
 - Reported to be harmful in a swine model

Hyperinsulinemia euglycemia (HIE)

- Also known as
 - High Dose Insulin (HDI)
- Proposed mechanisms
 - ↑ inotropy
 - ↑ glucose transportation into myocyte
 - Overcome insulin resistance/deficiency
 - Improve local microcirculation
 - Accelerates oxidation of myocardial lactate and reversal of metabolic acidosis
 -

Supporting Evidence

- In CCB/BB poisoning animal models, HDI was found to be superior to calcium, glucagon, adrenaline, and vasopressin in terms of survival
- 1st human case report in about 20 years ago
- ↑ haemodynamic in human observational study, case series of CCB/BB poisoning
- No clinical trials comparing the use of HDI to other treatments in humans

How to give?

- Dosage reported
 - Insulin boluses from 0.1 to 10 U/kg
 - Continuous insulin infusion rates from 0.015 to 22 U/kg/h
 - Most between 0.5 and 2 U/kg/h
- Majority recommend an initial bolus of 1 U/kg followed by a infusion of 0.5–1 U/kg/h
 - The infusion rate may be increased by 2 U/kg/h every 10 min to a maximum of 10 U/kg/h if no increase in cardiac output or clinical improvement is seen
- Onset of action stated as 15–45 min

Examples of IV fluid in non-PVC containers:



Goal

- Maintain perfusion of essential organs
 - Clinical parameters
 - BP/P alone may be misleading
 - Biochemical parameters
 - Non-invasive / invasive monitoring of cardiac output
- No studies illustrating the best way to decrease HDI therapy after cardiac function has improved.
- Once the hemodynamic parameters have stabilized, the insulin infusion may be gradually tapered and discontinued
 - Cases of worsening and HIE re-use after abrupt cessation of HIE were reported

Adverse Effects

- Hypoglycemia
 - Reported incidence 0-80%
 - 0/46, 1/7, 2/4/, 4/5 (Espinoza, Greene, Holger, Yuan)
 - Recommendation
 - Frequent glucose check (Q10-30min initially, Q1H if stable)
 - Dextrose (5-10%) infusion to keep >5.6mmol/L
- Hypokalemia
 - Reported incidence: 28-50%
 - 2/7, 2/4 (Greene, Holger)
 - Recommendation
 - Potassium check (Q1H initially, Q6H if stable)
 - Replace if below 2.8-3.0mmol/L

Intravenous lipid emulsion (ILE)

- Also known as
 - Lipid Rescue/Resuscitation Therapy (LRT)
 - Intravenous Fat Emulsion (IFE)
- Proposed mechanisms
 - Lipid sink theory
 - Direct cardiotoxic effect
 - ↑cardiac myocyte calcium levels

Supporting Evidence

- Promising results in experimental animal models of poisoning by lipid-soluble cardiotoxic medications
- 1st human case report in 2006
- Established antidote for LA poisoning
- List of drugs with ILE human case report(s)

Local anaesthetics	Lignocaine, prilocaine, bupivacaine, levobupivacaine, mepivacaine, ropivacaine
Non-local-anaesthetics drugs	Amitriptyline, amlodipine, atenolol, bupropion, carvedilol, diltiazem, doxepin, haloperidol, imipramine, lamotrigine, nebivolol, propranolol, quetiapine, Roundup® (active ingredient glyphosate), sertaline, venlafaxine, verampamil.

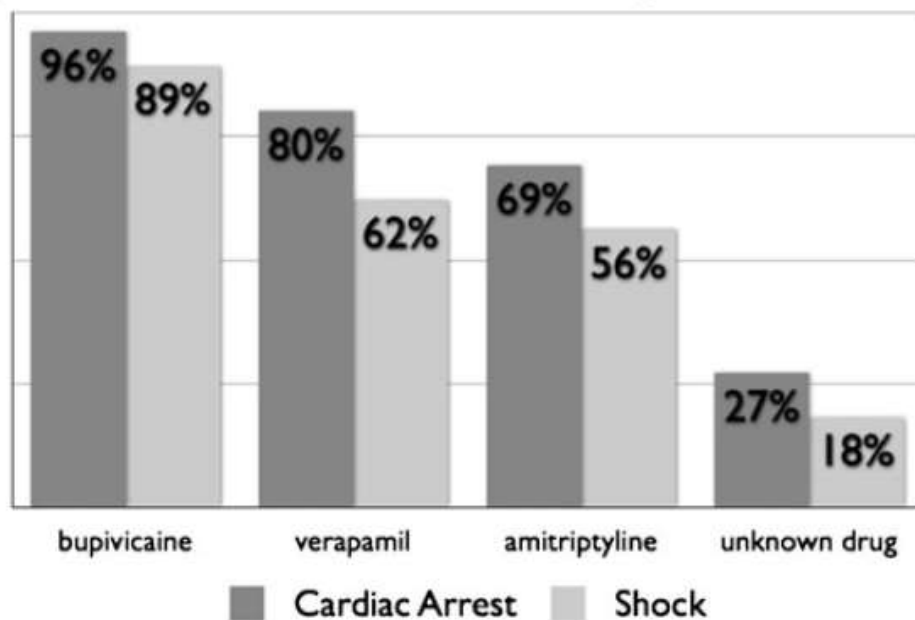
ILE in CCB/BB

- ↑ haemodynamic and survival in animal models of intravenous verapamil poisoning, animal models of propranolol poisoning
- A review in 2010 stated that available data suggest some benefits of ILE in verapamil and beta-blockers toxicity (*Jamaty 2010*)
- A case series in 2013 stated the 12/15 of CCB/BB poisoning with cardiogenic shock were given ILE, 14/15 survived (*Sebe 2015*)
- Case reports of ROSC after ILE administration in verapamil/atenolol poisoning (*Dolcourt 2008*) and propranolol poisoning (*Dean 2010*)

Lipid Rescue 911: Are Poison Centers Recommending Intravenous Fat Emulsion Therapy for Severe Poisoning?

Michael R. Christian · Erin M. Pallasch · Michael Wahl ·
Mark B. Mycyk

Percentage of PCC medical directors who would “always” or “often” recommend IFE



How to give?



- Reported dosage (20% intralipid)
 - Boluses from 1-3 ml/kg
 - Infusion from 0.2 to 0.5 mL/kg/min.
 - Duration from bolus to infusion (15min-6 hrs)
- Our recommendation

Dosage (Each bottle contains Intralipid 20% 250ml)

Initial dose

Intralipid 20% 1.5ml/kg bolus IV injection over 1 minute through large bore IV catheter, followed by an IV infusion at 15ml/kg/hr for 30-45 minutes*.

HKPIC Antidotes Information Sheet: Intralipid rescue therapy

Intravenous lipid emulsion as antidote: experience in Hong Kong

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Table 2. Patient characteristics in the series

Case	Gender/ age	Indication	Drug exposure (dose from history)	IIE regime (Intralipid®)	Survival	Confirmation by urine toxicology	Adverse events
1	M/45	Cardiac arrest	Dothiepin Propranolol	20% 100 ml bolus	Yes	Yes	Hypoxic brain injury
2	F/46	Shock QRS widening	Amitriptyline (30 tabs)	20% 100 ml bolus + infusion at 0.25 ml/kg/min for 30 minutes	Yes	Yes Blood TCA level: 6327 ng/mL (peak)	Mild liver function derangement Hyperlipidaemia
3	F/45	QRS widening	Amitriptyline (100 tabs)	20% 1.5 ml/kg bolus + infusion at 0.25 ml/kg/min for 2 hours	Yes	Yes	–
4	F/17	Shock	Amlodipine (100 tabs) Propranolol	Bolus (20% 100 ml) x 2 + infusion at 10 ml/min for 30 minutes	No	Yes	Acute renal failure Elevated serum amylase (379 U/L) on day 12
5	F/52	Shock	Nifedipine (Adalat retard 70 tabs) Metformin (50 tabs) Lisinopril (15 tabs)	20% 100 ml bolus + infusion at 0.5 ml/kg/hr for 12 hour	No	No	–
6	F/52	Shock	Amitriptyline Propranolol	Bolus x 3 (20% 10 ml + 10 ml + 100 ml)	No	Yes	–
7	F/37	Cardiac arrest	Hydroxychloroquine (6 g) Chloroquine (6.25 g)	Bolus (20% 100 ml) x 2 + infusion	No	Yes	–
8	F/62	Cardiac arrest	Paracetamol/ dextropropoxyphene (Dologesic) Quetiapine Thyroxine Chlorpromazine	Bolus (20% 100 ml) x 2	No	No	–
9	F/83	Shock	Aconitine (60 g of processed Fuzi)	Bolus (20% 100 ml) x 2 + 300 ml infused over 30 minutes	No	Qualitative test done on blood sample	–
10	F/29	Shock	Hydroxychloroquine (20 g)	10% 100 ml bolus + 400 ml infused over 30 minutes	No	No	–

Safety

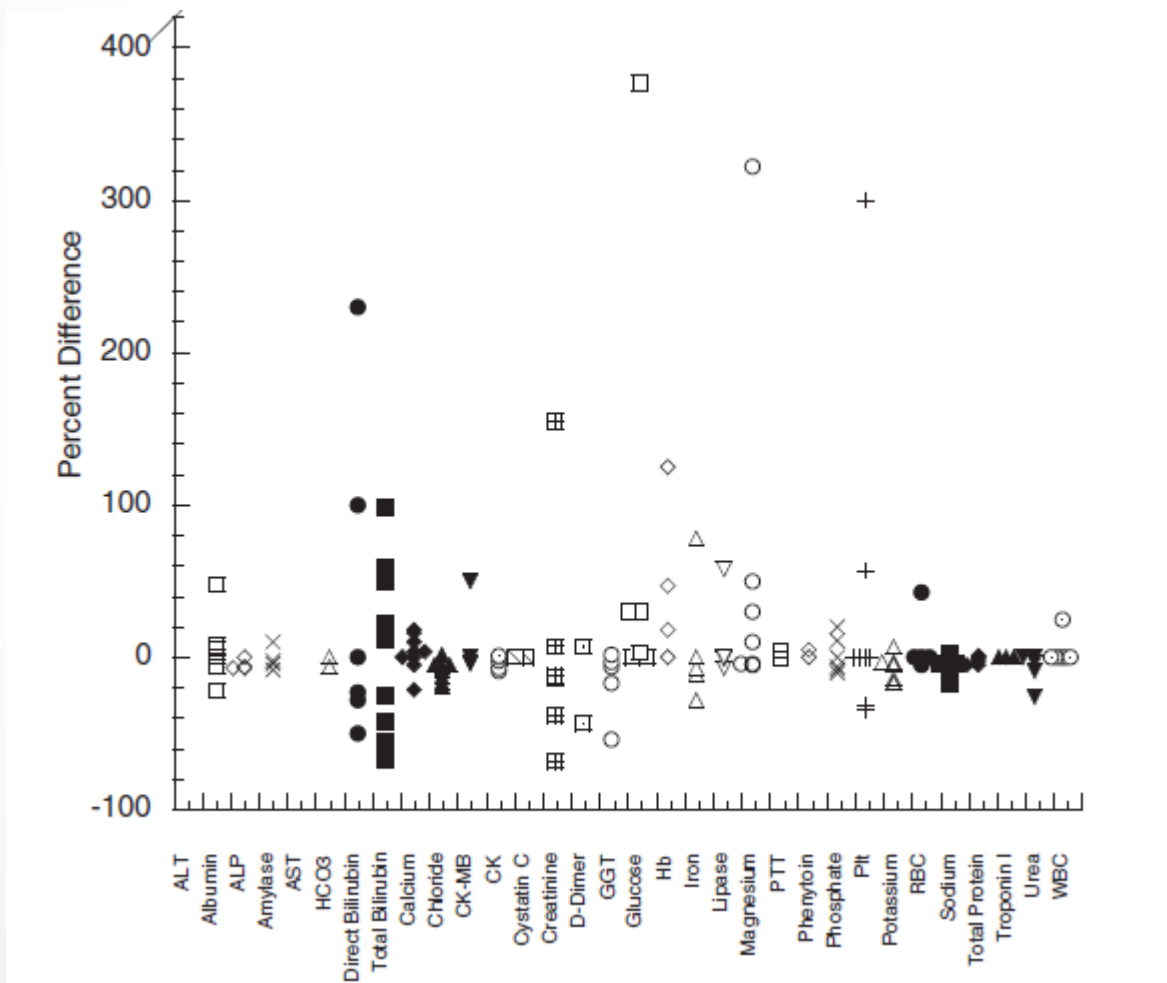
- Generally well tolerated
- Fever, transient deranged liver function, respiratory distress, coagulopathy
- Concern in the HD/HP/HF
- Blood tests



Fig. 1. The filter and circuit used for CRRT were clogged with a thick white lipid, which was thought to be the intravenous fat emulsion.

Review of the effect of intravenous lipid emulsion on laboratory analyses

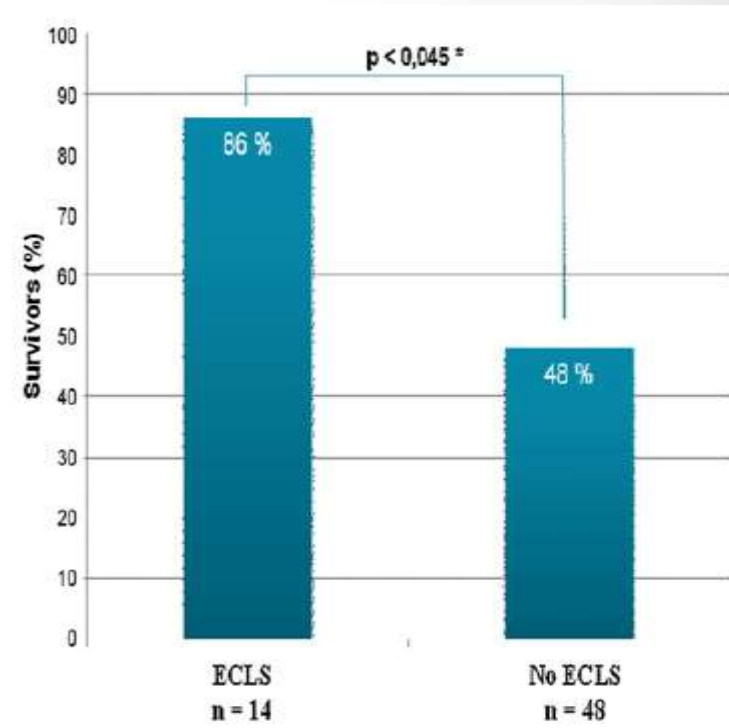
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Summary plot of lipemic interferences reported in the 36 reviewed studies.

ECLS in CCB/BB Poisoning

- 62 patients of cardiac arrest and severe shock recruited
 - 16 cases of CCB / 2 cases of BB
- Overall 35/62 (56%) Survived
- In multivariate analysis, BB, ECLS support remained associated with lower mortality
- Complications – not mentioned



Masson 2012

Resuscitation 83 (2012) 1413–1417

ECLS in CCB/BB Poisoning

- 17 patients of cardiac arrest and severe shock
 - 4 cases of CCB / 5 cases of BB
- All underwent ECLS (2-11 days)
- Overall 13/17 (76%) Survived
 - 4 deaths including 2 CCB/BB
- Complications
 - 6 limb ischemia , 1 femoral thrombus, 1 cava inferior thrombus, and 2 severe bleeding

ECLS in CCB/BB Poisoning

- 12 patients of cardiac arrest from poisoning
 - 2 cases of CCB / 3 cases of BB
- 10/12 ECLS (5 – 108 hours)
- Overall 3/12 (25%) Survived
 - All CCB died
 - All BB survived
- Complications
 - 1 severe bleeding

ECLS in CCB/BB Poisoning

- Other nine case reports of CCB poisoning underwent ECLS
 - 7 survivals. 2 deaths
 - Complications: 1 bleeding, 1 leg amputation
- Overall, based on low level evidence, ECLS was associated with improved survival in patients with severe shock or cardiac arrest at the cost of limb ischemia, thrombosis, and bleeding

Extracorporeal removal in CCB/BB poisoning

- Vd of common CCB / BB

CCB	BB
Amlodipine (21 L/kg)	Atenolol (1 L/kg)
Diltiazem (5.3 L/kg)	Labetalol (9 L/kg)
Nifedipine (0.8 L/kg)	Metoprolol (4 L/kg)
Verapamil (5.5 L/kg)	Propranolol (4 L/kg)

- In general, not recommended

Extracorporeal removal in CCB/BB poisoning

Author/Year	Poisons	Methods
Pfaender 2008	Atenolol, Nifedipine	CVVHDF
Ezidiegwu 2008	Amlodipine	Plasma Exchange
Pichon 2012 (Case series)	2 Diltiazem 1 Verapamil	MARS
Stycula 2013	ACEI, BB, CCB	CVVHF
Koschny 2014	Carvedilol, Amlodipine, Amitriptyline	Plasmapheresis
Garg 2014	Amlodipine	CVVHF + Charcoal HP
Nasa 2014	Amlodipine Lercanidipine	CVVHF + Charcoal HP
Gerard 2015	Amlodipine Valsartan	MARS

CVVHDF - Continuous Venovenous Hemo-Dia-Filtration

MARS - Molecular adsorbent recirculating system

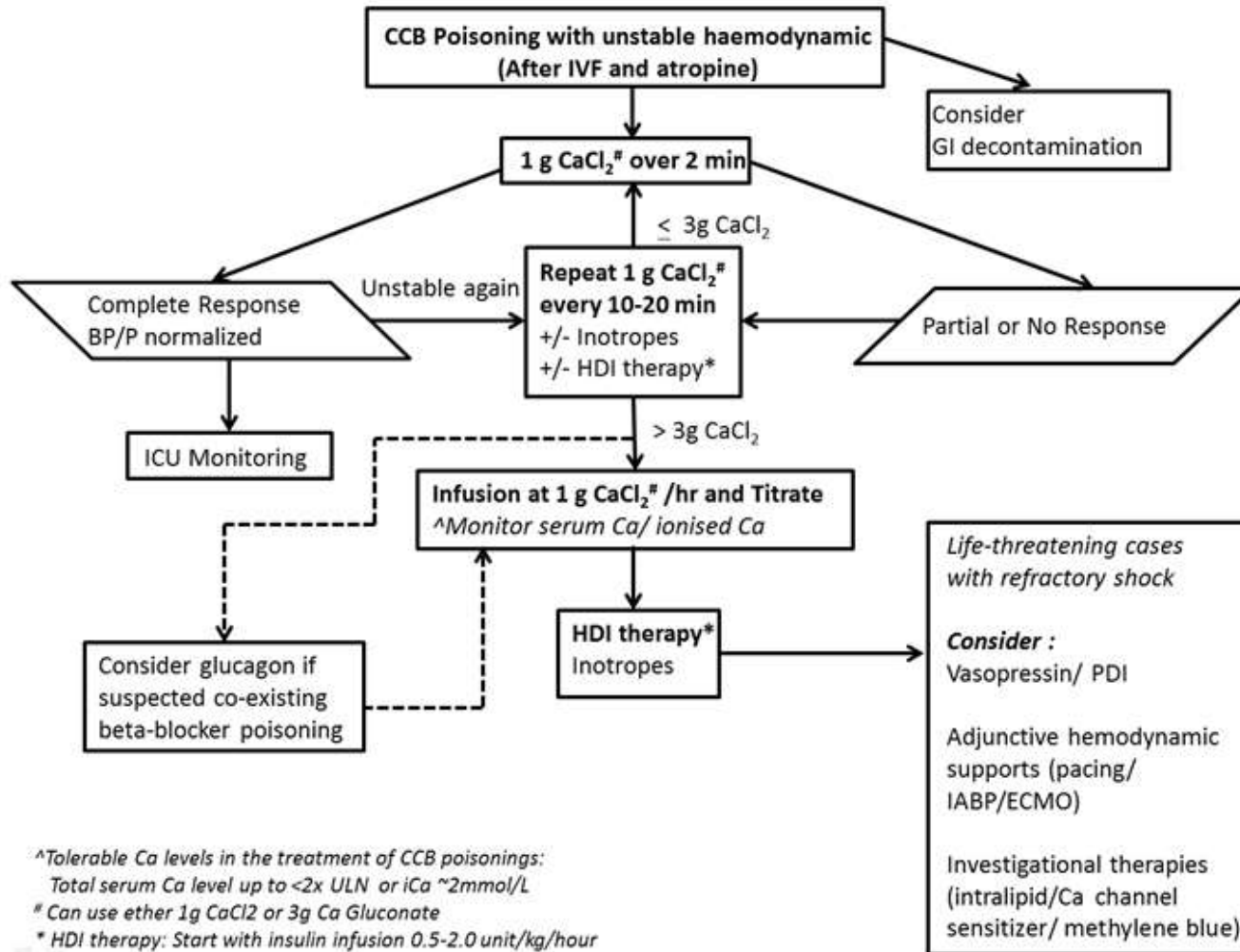
CVVHF - Continuous venovenous haemodiafiltration

HP – Haemoperfusion

Investigational Treatment

- Levosimendan
 - Case Report (Verapamil) [*Varpula 2009*]
 - Case Report (Verapamil) [*Osthoff 2010*]
- Methylene blue
 - Case Report (Amlodipine) (*Jang 2011*)
 - Case Report (Amlodipine + Atenolol) (*Aggarwal 2013*)
- L-Carnitine
 - Case Report (Amlodipine + Metformin) (*St-Onge 2013*)
- Fructose 1,6,diphosphate
 - Animal Study
- Liposomes
 - Animal Study

Flowchart



[^]Tolerable Ca levels in the treatment of CCB poisonings:

Total serum Ca level up to <2x ULN or iCa ~2mmol/L

[#] Can use either 1g CaCl₂ or 3g Ca Gluconate

^{*} HDI therapy: Start with insulin infusion 0.5-2.0 unit/kg/hour

Thank You

