Local anaesthetic toxicity – is the threat still out there?

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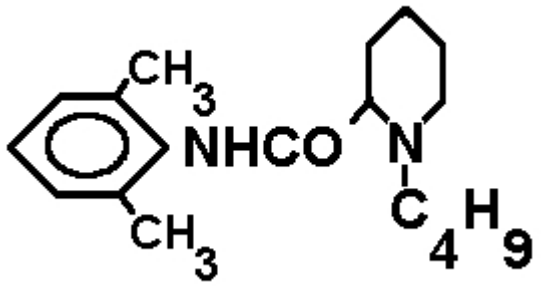
Case report

A new treatment option

Animal studies

Clinical experience: 2 case reports

Practical issues



Bupivacaine

The case

- 65 year old female
- urgent laparotomy (CA)
- Anaesthetic consultant and SHO (after teaching session)
- hypertension, no further cardiac disease known
- frequent unifocal VES on ECG and monitor in theatres
- epidural, GA, CVP, arterial line

The case

- mixture of syringes on machine
- patient covered (warm air blanket)
- CVP and epidural on right side
- CVP line in need of flushing

→ use of ≈ 5 ml 0.5% Bupivacaine instead of NaCl 0.9%

?

What would we have done in case of a cardiac arrest?

Classic treatment of Bupivacaine iv

- CPR according to ALS guidelines
- for a very long time
- Bretylium (not available anymore in the UK)
- Amiodarone

Lessons learnt

! Prevention !

- LA syringes ≥ 2labels
- leave plastic ampoule attached to syringe
- LA kept in separate tray on top of anaesthetic machine
- CVP and epidural secured on different sides of the neck
- and more...

New treatment of LA toxicity

initiated by a chance observation made during experiments testing whether a lipid infusion would increase arrhythmias during bupivacaine toxicity

Rat study

Part 1

- 6 animals/group
- determination of lethal dose (mg/kg), [Bupiv.] (µg/ml)

  - NaCl 0.9%: 17.8 [93.3]
  - Intralipid 10%: 27.6 [115]
  - Intralipid 20%: 49.8 [177]
  - Intralipid 30%: 82.0 [212]

  (3 ml/kg/min for 5 min)

- determination of lipid:aqueous ratio of [Bupivacaine]

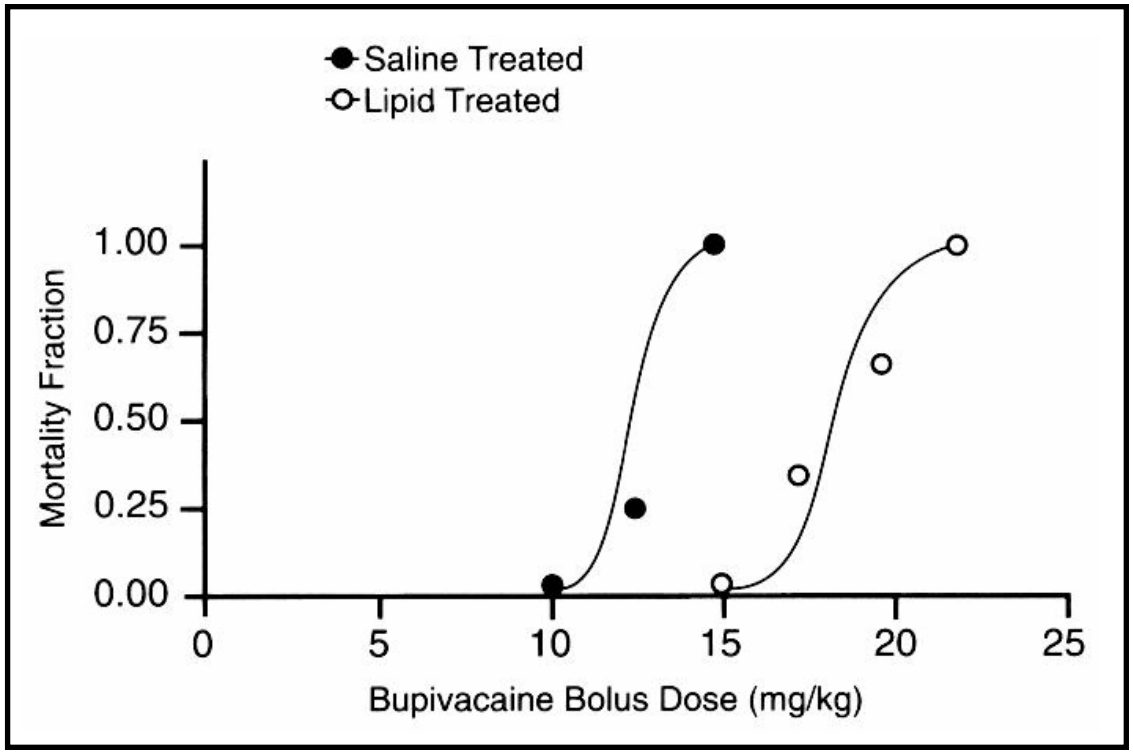
12 : 1

Weinberg GL 1998

Rat study

Part 2

Mortality fraction in groups of six animals after bolus dose of LA. LD_{50} values are 12.5 mg/kg (NaCl 0.9%) and 18.5 mg/kg (lipid).



dose of Intralipid 30%:

7.5 ml/kg bolus, then 3 ml/kg/min for 2 min

Weinberg GL 1998

Dog study

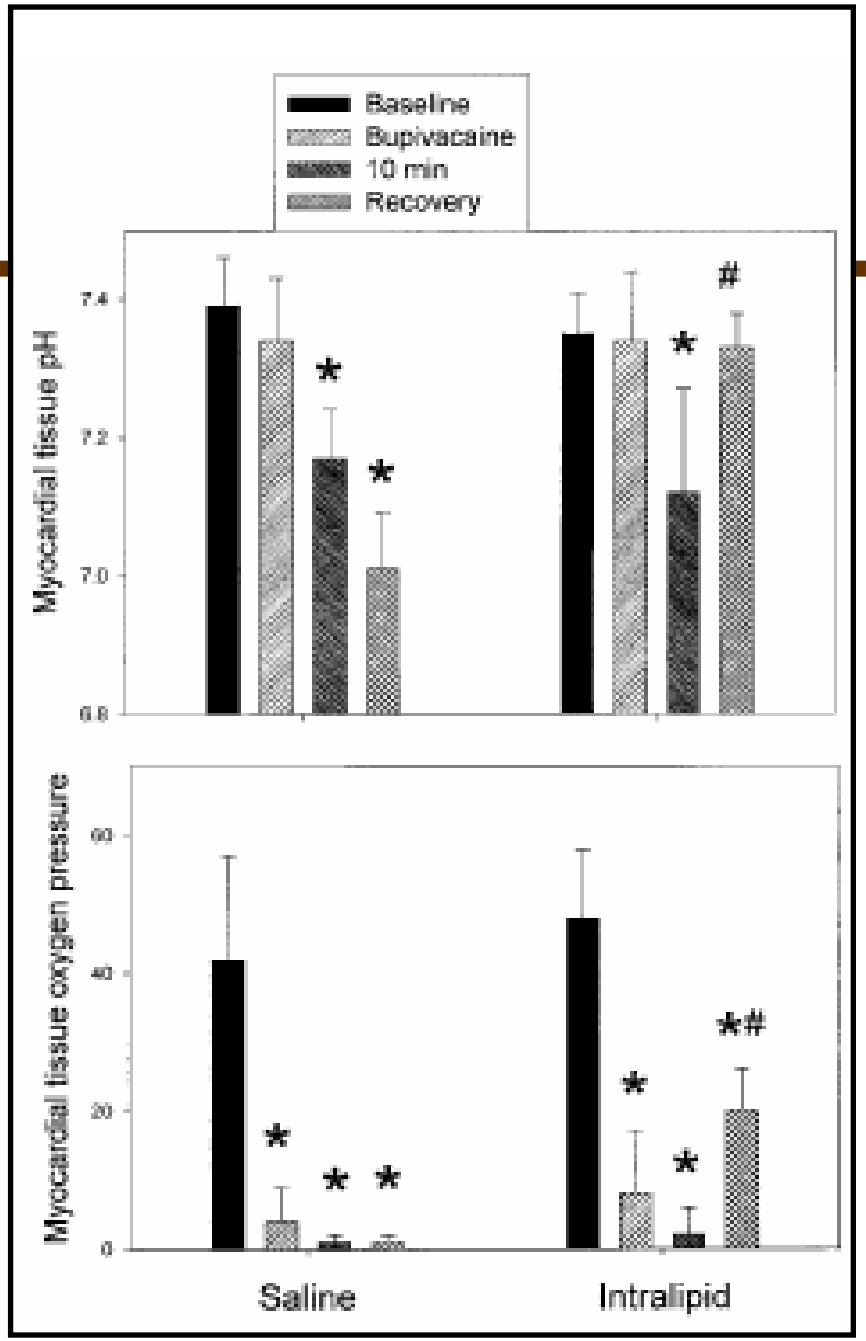
- better model as closer in size/weight to man
- 6 dogs each NaCl 0.9% vs. Intralipid 20% (4 ml/kg bolus, then 0.5 ml/kg/min for 10 min)
- 10 mg/kg bolus of Bupivacaine
- 10 min of CPR prior to treatment

Result:

! All NaCl dogs died, all Intralipid dogs survived with ROSC !

Weinberg GL 2003

Dog study



Time course of myocardial tissue pH and myocardial pO2

Weinberg GL 2003

Limitations

- no blinding
- rats (and dogs) are much more likely to be successfully resuscitated than humans
- excessive Bupivacaine doses → reduction may have increased survival in saline-treated dogs
- varying doses for Intralipid tested
- physiologic and histologic effects of lipid infusion not well described, but:
- contraindications: 'allergic to soybean protein, egg yolk + egg whites'
- complications of Intralipid?

How does it work?

'Meyer-Overton Hypothesis':

• emulsion acts as circulating lipid sink, drawing LA out of the plasma

'Receptor theory':

• LA competitively inhibits carnitine-acylcarnitine translocase (transfers Acetyl-CoA into mitochondria)

• emulsion overwhelms inhibition of translocase by mass action

• energy supply of myocardium restored

Case report 1

58-yr-old, 82-kg, 170-cm male

- arthroscopic repair of a right torn rotator cuff
- previous CABG 43 years old, good exercise tolerance
- Lisinopril, Atenolol, ISMN (Clopidogrel, Aspirin stopped for 7/7)
- ECG: RBBB, LAH, old anterior MI

Interscalene block with nerve stimulator: no blood aspirated

- 20 ml bupivacaine, 0.5% (100mg; 61%[1])
- 20 ml mepivacaine, 1.5% (300mg; 52%[2])
- given over 2 $\frac{1}{2}$ minutes

(% of maximum doses [1]bupivicaine 2mg/kg and [2]mepivacaine 7mg/kg)

30s after removal of block needle

→incoherent → tonic– clonic seizure

Rx O_2, 50mg propofol;

→ seizure; stopped, spontaneous respirations resumed

Rosenblatt MA 2006

Case report 1

90 s later, 2nd seizure
100 mg intravenous propofol was administered
ECG: asystole; no pulse/ blood pressure detectable
ACLS started
Next 20 mins of CPR:

- 3 mg adrenaline, (divided doses)
- 2 mg atropine
- 300mg amiodarone
- 40 U arginine vasopressin

Rhythms included

- ventricular tachycardia + pulse
- pulseless ventricular tachycardia → momentarily VF
- asystole

Rosenblatt MA 2006

Case report 1

@20 mins
- 100 ml of Intralipid 20% given through the peripheral iv
- CPR continued + 360 J shock was given

Within seconds
- a single sinus beat on the ECG
- 1 mg atropine and 1 mg adrenaline

+15 s later
- CPR continued
- the cardiac rhythm returned to sinus at 90 beats/min
- blood pressure / pulse became detectable

Lipid emulsion infusion was started
- 0.5 ml/kg/min over the following 2 h and then discontinued

Rosenblatt MA 2006

Case report 1

- patient remained in sinus rhythm
  - weaned + extubated~ 2 ½ h
  - awake and responsive

- right upper extremity weakness consistent with a brachial plexus block

- no other neurologic sequelae
- monitored overnight

- no evidence of complications 2° to the administration of Intralipid 20%
  → *i.e.* no pancreatitis during the following 2 weeks

Rosenblatt MA 2006

Case report 2

84-year-old, ASA III, 50-kg woman
- –surgery on Dupuytren's contracture
- –LBBB, grade II Mr + TR
- –Premed: oral Midazolam 7.5mg

Axillary brachial plexus block using peripheral nerve stimulation + needle
- –40 ml of 1% (instead of 0.5%) Ropivacaine accidentally injected

15 minutes later
- –dizziness and drowsiness → loss of consciousness → tonic-clonic seizure, Rx Thiopentone 150 mg
- –HR 120, stable BP

2 minutes later
- –ventricular extrasystoles → bradycardia → asystole
- –CPR + 3 x 1mg Adrenaline
- –arterial + CVP lines inserted
- –still asystolic

Case report 2

- after 10 mins of cardiac arrest
  - 100ml 20% intralipid given as bolus (2mg/kg)
  - 10ml/min (0.2 ml/kg/min) given for 10 more minutes

- 10 minutes later
  - tachycardia on ECG
  - blood pressure / pulse became detectable

- patient extubated @ 3 hours + discharged 4 days later

Case report 2

- after 10 mins of cardiac arrest
  - –100ml 20% intralipid given as bolus (2mg/kg)
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Intralipid: Practical issues

Intralipid 20%

•lipid emulsion of soya oil, glycerol and egg phospholipids
•isotonic, virtually identical to solvent in Propofol (10% intralipid)

•particle size / properties similar to those of natural chylomicrons

•500ml=£12.87
•500ml 20%=1100kCal

•stored at room temperature; long shelf life ~1 year
•Bolus of 20% lipid emulsion 1.5 ml/kg over 1 min
whilst continuing chest compressions
•initial dose could be repeated x 2
•then infusion of Intralipid 20%, at 0.25 ml /kg/ min,
continued until haemodynamic recovery
•peripheral i/v feasible; CVP better

Picard J 2006

Intralipid: Practical issues

- Intralipid 20%: side effects little studied

- increase pulmonary artery pressure
- increase in pulmonary events in neutropenic patients
  - Amphotericin in 5% Glucose vs Intralipid
  - 250ml over 1-4 hours
  - significant increase in
  - severe or life threatening dyspnoea
  - 'other pulmonary events'
  - pain, pleuritis, fibrosis, ARDS, need for ventilati

Schoffski P 1998

Toxicity: Prevention

Full monitoring as GA with assistant, resuscitation equipment + IV access
Slow injection, frequent aspiration
5ml injection over 10s then wait 40s + repeat
? Adrenaline in solution (HR rise> 10)
? Benzodiazapines: (fewer fits and death in animals)
Continue full monitoring: delayed absorption + toxicity (30 minutes)

- Early recognition:
  - –auditory changes, visual disturbance (eg difficulty focusing)
  - –lightheadedness, apprehension, perioral numbness, drowsiness
- Later
  - –restlessness, agitation, myoclonus, nystagmus, and slurred speech
  - –unconsciousness, convulsions
  - –tachycardia or bradycardia, hypotension, VF/asystole

Toxicity: Treatment

- stop injection, get help
- 100% O_2, ABC
- Neuro: stop fits with Thiopentone / Propofol / Lorazepam
- CVS: ACLS protocols
  - –other vasopressors may be useful but unfamiliar/unavailable
    - e.g. Vasopressin: 40 U intravenous once
  - –other inotropes may be useful, e.g. Milrinone but unfamiliar/unavailable
  - –Avoid Phenytoin (animal mortality increased)
  - –consider CPBypass, previously successful !
  - –bloods for drug levels (Guy's Poisons Unit), useful in retrospect only
- Intralipid 20% 1-1.5ml/kg (recovery drug cupboard)
  - –repeat x 2
  - –infusion of 0.25 ml/kg/min (~ 15-20ml per minute), i.e. the rest over next ~ 10-15 mins
- aftercare: HDU / ICU

Summary

- local anaesthetic toxicity can have serious effects
- important to take preventive measures
- if neurotoxicity supected –
  - 02, ABC, stop fits
  - get Intralipid 20% out (recovery drug cupboard)
- if CVS toxicity occurs
  - –timing debated, but give Intralipid 20% 1.5ml/kg
- information campaign in theatres

LipidRescue™

TREATMENT FOR LOCAL ANAESTHETIC-INDUCED CARDIAC ARREST

PLEASE KEEP THIS PROTOCOL ATTACHED TO THE INTRALIPID BAG

In the event of local anaesthetic-induced cardiac arrest that is unresponsive to standard therapy, in addition to standard cardio-pulmonary resuscitation, Intralipid 20% should be given i.v. in the following dose regime:

– Intralipid 20% 1.5 mL/kg over 1 minute

– Follow immediately with an infusion at a rate of 0.25 mL/kg/min,

– Continue chest compressions (lipid must circulate)

– Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation is restored

– Continue infusion until haemodynamic stability is restored. Increase the rate to 0.5 mL/kg/min if BP declines

– A maximum total dose of 8 mL/kg is recommended

In practice, in resuscitating an adult weighing 70kg:

– Take a 500ml bag of Intralipid 20% and a 50ml syringe.

– Draw up 50ml and give stat i.v X 2

– Then attach the Intralipid bag to a giving set and run it .i.v over the next 15 minutes
– Repeat the initial bolus up to twice more – if spontaneous circulation has not returned.

If you use Intralipid to treat a case of local anaesthetic toxicity,

please report the case at www.lipidrescue.org, and ensure that a new bag of Intralipid replaces what's been used.

References

- http://www.lipidrescue.org/
- **Litz RJ**, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 2006;61:800-1.
- **Picard J**, Meek T. Lipid emulsion to treat overdose of local anaesthetic: the gift of the glob. *Anaesthesia* 2006;61:107-9.
- **Rosenblatt MA**, Abel M, Fischer GW et al. Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest. *Anesthesiology* 2006;105:217-8.
- **Schoffski P,** Freund M, Wunder R, Petersen D, Kohne CH, Hecker H, Schubert U, Ganser A. Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ* 1998 Aug 8;317:379-84.
- **Weinberg GL**, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998;88:1071-5.
- **Weinberg GL**, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg Anesth Pain Med* 2003;28:198-202.