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Local anaesthetic agent systemic toxicity

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The introduction of cocaine in 1884 as a local anaesthetic agent started an entire new era in medicine. Since then, the use of local anaesthetic agents has increased as an important part of medicine. Local anaesthesia is widely and regularly used by general practitioners and specialists, but a recent survey in a UK hospital showed that among non-anaesthetists there is a poor understanding of local anaesthesia toxicity and treatment. Local anaesthetic agent systemic toxicity occurs in about 1 in every 1 000 peripheral nerve blocks and, although it is an infrequent complication, it is potentially fatal.

The mechanism of local anaesthetic agents is by blockade of Na^+, K^+ and Ca^{2+} channels, thereby blocking transmission of pain sensation along nerve fibres and providing local anaesthesia and analgesia.

The **amide** group of local anaesthetic agents include: bupivacaine, L-bupivacaine, lidocaine, ropivacaine, prilocaine, dibucaine, etidocaine and mepivacaine. This group is primarily metabolised in the liver and the metabolites are excreted in the urine. Any decrease in hepatic function or hepatic blood flow, e.g. heart failure, will reduce the metabolism of these drugs and predispose the patient to local anaesthetic agent systemic toxicity.

The **ester** group of local anaesthetic agents include: cocaine, chloroprocaine, procaine and tetracaine. These agents are predominantly metabolised by plasma cholinesterase. Metabolism may be slower in patients with genetically abnormal pseudocholinesterase. The exception here is cocaine, which is partially metabolised in the liver and partially excreted by the kidneys (unchanged).

After systemic absorption these ion channel blocking effects of local anaesthetics are extended to the organ systems and toxicity may follow. The presentation of local anaesthetic agent toxicity symptoms is as follows: central nervous system – 45%, cardiovascular system – 11%, or both – 44%.

Examples of commonly used local anaesthetic agents are shown in Table 1.

Symptoms of toxicity

Early symptoms of neurological toxicity include tinnitus, blurred vision, circumoral numbness, metalic taste, tongue paraesthesia and dizziness. Agitation, restlessness, nervousness or seizures (excitatory signs) may precede drowsiness, slurred speech and loss of consciousness (from central nervous system depression).

In the cardiovascular system an early sign is usually peaked T waves on the ECG. Myocardial automaticity is depressed and the duration of the refractory period is reduced. Depression of myocardial contractility and conduction velocity follow. Smooth muscle relaxation gives rise to vasodilation. Hypotension, bradycardia, heart block/dysrhythmias and cardiac arrest may ensue. During general anaesthesia, the only signs of local anaesthetic overdose might be in the cardiovascular system.

The respiratory system may also be affected. Apnoea may result as a central (direct medullary centre depression) or peripheral (intercostal or phrenic nerve paralysis) effect.

Although not a direct toxic effect, one must note that ester derivatives and the methylparaben preservative of the amide derivatives may cause allergic reactions, even though this is quite rare.

Peak plasma levels of injected local anaesthetics depend on the site of injection (intravascular>tracheal>intercostal>caudal>paracervical>epidural>brachial plexus >sciatic nerve>femoral nerve), presence of vasoconstrictors (e.g. adrenaline) and type of local anaesthetic agent used (highly tissue-bound agents are absorbed slower). With regard to toxic effects, the peak plasma level is more important than the dose. A peak plasma level resulting in toxic effects may be well below the maximum recommended dosage for a specific local anaesthetic agent. In some cases a dose well above the toxic dose might not lead to systemic toxicity, e.g. as used in liposuction procedures. Here toxicity is prevented by injecting the local anaesthetic agent during the procedure and almost immediately removing it by suction,

Table 1. Commonly used local anaesthetic agents

Agent	Maximum dose without adrenaline (mg/kg)	Maximum dose with adrenaline (mg/kg)	Maximum total dose without adrenaline (70 kg patient) (mg)	Maximum total dose with adrenaline (70 kg patient) (mg)
Lignocaine	3	7	300	500
Bupivacaine	2	2	150	150
L-bupivacaine	2	2	150	150
Ropivacaine	3	3	200	200
Cocaine	3	3	150	150

thereby giving very little time for systemic absorption.

Prevention of local anaesthetic agent toxicity

Before administering local anaesthetic agents:

- Resuscitation equipment must be present and functioning.
- Check presence of lipid emulsion (20%), i.e. Intralipid™.
- Ensure intravenous access for all procedures other than subcutanous infiltration of small wounds.
- If concerned that the dose and site of injection of local anaesthetic agent are such that systemic toxicity may occur, then monitor the ECG, pulse oximetry and blood pressure.
- Calculate the correct dose.

During injection:

- Stabilise the needle carefully.
- Inject slowly.
- Aspirate frequently for blood.
- With any signs/symptoms of systemic toxicity, stop administering immediately.
- Evaluate patient and vital signs at least every 5 minutes.

After injection:

- Monitor the patient for at least 30 minutes and preferably 60 minutes.
- Maintain frequent verbal contact with the patient to assess neurological status.

Treatment of local anaesthetic agent toxicity

Supportive treatment is the mainstay of local anaesthetic agent systemic toxicity.
Call for help.

Airway:

- Provide supplemental oxygen to maintain saturation >95%.
- If this is insufficient, then ventilate with 100% oxygen using bag and mask prior to intubation.
- Muscle relaxants may be used to facilitate intubation; they will terminate the muscle contractions of seizures, but brain seizure activity may still continue.

Breathing:

- Institute positive pressure ventilation to maintain oxygenation and normocarbia.

Circulation:

- Provide basic and advanced cardiac life support – prolonged efforts might be necessary.
- Rapidly infuse Ringer's lactate bolus to support blood pressure – be cautious in heart failure patients.
- Use conventional therapies to treat hypotension, bradycardia and tachy-arrhythmia.
- Lignocaine should not be used as anti-arrhythmic therapy.
- Propofol should not be used as a substitute for Intralipid™.

Intralipid™ therapy:

- Bolus of 1.5 ml/kg over 1 minute.
- Infuse 0.25 mg/kg/minute.
- Repeat bolus once or twice as necessary.
- Double infusion rate if blood pressure remains low.
- Continue infusion for 10 minutes after cardiovascular stability has been reached.
- Upper limit of 10 ml/kg recommended in the first 30 minutes.

NB: Cardiovascular depression can return after treatment.

Disability:

- Use benzodiazepines to treat seizures.
- Monitor blood glucose levels.

Evaluate:

- For injuries sustained as result of seizures.
- Cardiopulmonary bypass may be considered for resuscitation.
- After any signs of local anaesthetic agent systemic toxicity, monitor the patient for at least 12 hours as cardiovascular depression can recur after treatment.

Conclusion

Local anaesthetic agents are widely used and have a good safety profile if used with caution. Adherence to basic safety principles are of the utmost importance to avoid complications. Early recognition and proper management of local anaesthetic agent systemic toxicity improve morbidity and mortality. Human trials have not been performed to prove the use of Intralipid™ to treat local anaesthetic agent systemic toxicity (especially bupivacaine toxicity), but several anecdotal reports indicate a favourable outcome and its use is recommended.

Suggested reading available at www.cmej.org.za