Local anaesthetics and their orally administered congeners are sometimes useful as third- or fourth-line drugs in the treatment of neuropathic pain. An analgesic effect has been reported when such drugs have been administered systemically:  

- **lidocaine** TD, CSCI, IVI 
- **flecainide** PO (see p.000) 
- **mexiletine** PO (see p.000) 
- **tocainide** PO. 

The mechanism by which they provide relief is not fully understood, but probably includes blockade of sodium channels. This stabilizes the nerve membrane and thus suppresses injury-induced hyperexcitability in the peripheral and central nervous systems. Antidepressants and anti-epileptics which benefit neuropathic pain also have membrane stabilizing properties, e.g. **carbamazepine**, **amitriptyline**. 

A systematic review of 32 RCTs, mostly of IV **lidocaine** and PO **mexiletine**, for neuropathic pain of various causes concluded that systemic local anaesthetics are better than placebo and as effective as **amantadine**, **carbamazepine**, **gabapentin**, **morphine** (Box A). Even so, despite the occasional impressive anecdotal account, RCT evidence of benefit is not overwhelming. Thus, the overall degree of improvement is small, and some studies suggest that not all components of neuropathic pain are relieved, e.g. constant pain and allodynia to touch improve but cold-induced allodynia does not. Benefit is inconsistent in some types of pain, e.g. diabetic neuropathy, and absent in others, e.g. cancer-related neuropathic pain. Further, in elderly patients (mean age 77 years), lidocaine 5mg/kg IVI over 2h provides no greater analgesic benefit than 1mg/kg, despite producing higher serum levels which were potentially toxic in some patients. 

<table>
<thead>
<tr>
<th>Box A</th>
<th>Systemic local anaesthetics and neuropathic pain</th>
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<tbody>
<tr>
<td>Of overall benefit in:</td>
<td></td>
</tr>
<tr>
<td>• trigeminal neuralgia</td>
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<tr>
<td>• post-herpetic neuralgia</td>
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<tr>
<td>• diabetic neuropathy</td>
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<td>• lumbosacral radiculopathy</td>
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<tr>
<td>• post-stroke pain</td>
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<td>• chronic post-surgery pain</td>
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<tr>
<td>• chronic post-trauma pain</td>
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<tr>
<td>• spinal cord injury pain</td>
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<tr>
<td>• complex regional pain syndrome</td>
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<tr>
<td>Not of benefit in:</td>
<td></td>
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<tr>
<td>• cancer-related neuropathy (but see main text)</td>
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<tr>
<td>• HIV-related neuropathy.</td>
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<tr>
<td>Lidocaine dose used ranged from 1mg/kg IV over 2–3min to 1–5mg/kg IVI over 30min–2h</td>
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<tr>
<td>Mexiletine median dose 600mg/day (range 300–1200mg/day)</td>
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<td>Improvement equivalent to a reduction of 10mm on a 100mm VAS, but about 50% of patients achieve an improvement of ≥30%</td>
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</tbody>
</table>
Although improvement lasting 8–20 weeks following a single dose of IV lidocaine has been reported in patients with central pain syndrome, generally benefit is limited to a few hours.\textsuperscript{10} Thus, the need for ongoing relief will necessitate CIVI or CSCI lidocaine or the use of an oral analogue, e.g. mexiletine. However, the response to IV lidocaine does not reliably predict subsequent benefit from mexiletine and undesirable effects can limit its chronic use.\textsuperscript{5,11}

There are case reports of patients with cancer-related neuropathic pain benefiting from lidocaine:

- IV, e.g. 1–2mg/kg over 15–20min\textsuperscript{12}
- CIVI, e.g. 0.5–1mg/kg/h\textsuperscript{12,13}
- CSCI, e.g. 4 or 10% lidocaine hydrochloride solution, generally 10–80mg/h; 100–160mg/h reported in younger patients (age ~ 60years).\textsuperscript{13,14}

Continuous infusions have been given for up to 6 months.\textsuperscript{14} As a minimum, some suggest monitoring serum levels 24–72h after commencement or dose escalation and when toxicity is suspected.\textsuperscript{13}

Analgesia is generally seen with serum levels of 1.5–5microgram/ml and severe neurotoxicity with levels ≥10microgram/ml.\textsuperscript{3,15} However, there is large interindividual variation and the beneficial/toxic effect relates more to the amount of free local anaesthetic (unbound to protein), rather than the total serum level (bound plus unbound).\textsuperscript{16}

With a continuous infusion, cummulation of lidocaine and its active metabolites, e.g. monoethylglycinexylidide and glycinexylidide can occur and lead to toxicity. Particular caution is required in the elderly in whom clearance is already reduced.\textsuperscript{16-18} For example, two elderly patients (≥70 years) despite normal renal/hepatic function and receiving a relatively small dose of lidocaine (200–300mg/day), developed severe somnolence after 10 days.\textsuperscript{19}

Generally, developing toxicity should be clinically obvious because as serum levels rise, there is a progressive worsening of neurotoxicity:

- lightheadedness, dizziness
- circumoral numbness
- tinnitus
- visual changes
- dysarthria
- muscle spasm
- convulsions
- coma
- respiratory arrest.

However, the monitoring of serum levels is the most effective way of maintaining a consistent and safe lidocaine dose.\textsuperscript{3,17,19}

Prolonged toxicity has also been reported when 10ml of 2% viscous lidocaine was used hourly for a painful mouth ulcer, and was probably partly caused by cumulation of metabolites.\textsuperscript{18}

More recently the TD route has been used to treat localized non-cancer peripheral neuropathic pain. Modest benefit, i.e. a reduction of 10–20mm on a 100mm VAS, is seen with 1–4 lidocaine 5% patches covering the maximally painful area.\textsuperscript{2}

In conclusion, certainly in cancer-related neuropathic pains, systemic local anaesthetics should be considered for use only when the combination of a strong opioid + NSAID + tricyclic antidepressant + anti-epileptic are ineffective or poorly tolerated. Even then, ketamine (see p.000) may be preferable because:
• the serum level does not need to be monitored
• it can be given PO
• it is more effective than lidocaine in spinal injury pain.

1 Challapalli V et al. (2005) Systemic administration of local anesthetic agents to relieve neuropathic pain. The Cochrane Database of Systematic Reviews. CD003345.
