ADVERSE EFFECTS OF LOCAL ANAESTHETICS

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Local anaesthetics have direct effects at high concentration upon tissues near the site of injection: local effects; they have remote effects resulting from nerve conduction blockade: regional effects; they produce an odd collection of localized effects resulting from transport of relatively high concentrations by strange routes such as the arterial supply to parts of the brain: these I have termed focal effects; and they produce effects at low concentration following absorption into the general circulation: systemic effects. Adverse reactions to local anaesthetics may be manifestations of any of these types of effect, a fact which is frequently overlooked.

LOCAL EFFECTS

Local anaesthetics are drugs which reversibly block nerve conduction when applied locally in appropriate concentrations, therefore by definition they do not produce irreversible neurological damage. However, the concentration of a local anaesthetic at the site of injection is likely to be 10,000 times the systemic concentration, and when from time to time neurological complications do follow regional blockade, the drug itself may be blamed, particularly if it is a relatively new one. Thus every local anaesthetic has been the subject of reports of neurological sequelae following extradural and spinal blockade, including lignocaine (Harrison, 1975), bupivacaine (Cuerdon, Buley and Downing, 1977), etidocaine (Ramanathan et al., 1978) and more recently chloroprocaine (Covino et al., 1980; Ravindran et al., 1980; Reisner, Hochman and Plumer, 1980; Moore et al., 1982).

In the reports such as those cited for bupivacaine and etidocaine above, neural blockade persisted only for a few days, in which case it is plausible to suggest that the drug itself was contributory. Some cases of unexpectedly prolonged neural blockade following delayed extradural spread can be attributed to subdural extra-arachnoid placement (Conklin and van der Wal, 1980; Brindle Smith, Barton and Watt, 1984; Pearson, 1984). There are occasional reports of longer lasting neurological sequelae from apparently correctly conducted spinal anaesthesia (Meeuvis, Soetens and van Zundert, 1980). Where sequelae are permanent, however, and particularly following extradural blockade there are many other, more likely causes such as cord ischaemia. The causative importance of hypotension in this respect is emphasized by the occurrence of paralysis following hypotensive general anaesthesia (Costello and Fisher 1983; Schreiner et al., 1983).

Injecting the wrong solution to the extradural space, or an inappropriate formulation to the subarachnoid space, are other clearly avoidable non-local anaesthetic causes of disaster. The possible neurotoxicity of local anaesthetic drugs themselves is the continuing subject of laboratory research, sparked off most recently by problems following the use of chloroprocaine in the United States. The work of Gentili and colleagues (1980) suggested that there was some difference between local anaesthetics in their neurotoxicity following intrafascicular injection in rats, but differences in formulation could have influenced the outcome. Ravindran, Turner and Muller (1982) showed that, following subarachnoid administration in dogs, persistent paralysis followed chloroprocaine, but not bupivacaine or acidified saline. More recently, Li and colleagues (1985) showed that bupivacaine, lignocaine and chloroprocaine all produced equivalent paralysis following subarachnoid infusion in rats, with no significant histological changes, while the findings of Rosen and colleagues (1983) for large volume subarachnoid injections in monkeys and sheep were similar. On the other hand, Seravalli, Lear and Cottrell

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ADVERSE EFFECTS OF LOCAL ANAESTHETICS

Fig. 1. Causation of neurological complications following regional (principally spinal and extradural) block. (Data from: Urquhart-Hay, 1969; Usubiaga, 1975; Chaudhri, Kop and Dhruva, 1978; Covino et al., 1980; Gentili et al., 1980; Meeuwis, Soetens and van Zundert, 1980; Reisner, Hochman and Plumer, 1980; Moore et al., 1982; Newrick and Read, 1982; Schimek and Fink, 1982; Newman, 1983; Wang et al., 1984; Rendell-Baker, 1985; Shanker, Palkar and Nishkala, 1985).

(1984), using tissue cultures, showed that chloroprocaine produced cell membrane fusion, while lignocaine, procaine and metabisulphite did not. Numerous workers have demonstrated other extraneous causes of tissue toxicity, and these are outlined in figure 1. A fuller discussion of the issues may be found elsewhere (Reynolds 1984a, b).

REGIONAL EFFECTS

Regional adverse effects result from the normal action of local anaesthetics in producing nerve conduction blockade, when administered extradurally or intrathecally. The principal effects are hypotension, hypoventilation, Horner's syndrome and hypoglycaemia. All may wrongly be attributed to an idiosyncratic, allergic or toxic effect of the local anaesthetic itself, and the importance of regional blockade be overlooked. Thus motor nerve block is an important contributory cause of hypoventilation, as is preganglionic sympathetic blockade of hypotension. The occurrence of the second two complications is also dependent upon the intrinsic susceptibility of the B (preganglionic, motor) fibres to blockade by local anaesthetics.

*Horner's syndrome* results from blockade of B fibres in the nerve roots T1–4 (Evans, Gauci and Watkins, 1975). The patient is usually aware of nasal congestion, while ptosis, miosis and dry facial skin are readily observed if unilateral (Clayton, 1983), but some degree of ptosis and miosis may occur very frequently (Carrie and Mohan, 1976), and if bilateral they commonly go unnoticed. Despite the surprising extent of spread implicated in Horner's syndrome, extensive block of other modalities, or even hypotension is not inevitable.
Hypoglycaemia. The suppression by high extradural blockade of the hyperglycaemic response to surgery is well recognized, and depends in part on interruption of afferent stimuli, and in part on blockade of preganglionic sympathetic fibres to the adrenal. Consequently, there is a danger of hypoglycaemia as a result of an exaggerated response to insulin in a diabetic patient given a high extradural block (Romano and Gullo, 1980).

Other regional effects. Urinary retention is an obvious complication of sacral block, but if it outlasts the normal reversible nerve conduction blockade, the cause is unlikely to be regional (implying neurotoxicity), but rather that the bladder has been allowed to become overdistended during the block, or because of urethral trauma in surgery or obstetrics.

Sundry unexpected regional effects are reported following dental (Laskin, 1984) and other regional anaesthesia to the head and neck, but these generally result from transport of local anaesthetic solution to an unintended site, and are therefore considered focal effects.

FOCAL EFFECTS

Occasionally, signs of central nervous system toxicity follow abruptly on injection of small doses of local anaesthetic in the head and neck. For example, in stellate ganglion blockade convulsions have been reported following bupivacaine 7.5 mg (Korevaar, Burney and Moore, 1979), aphasia, facial weakness and blindness for 5 min following 2.5 mg (Szeinfeld, Laurencio and Pollares, 1981), and apnoea and coma followed by aphasia and hemiparesis after lignocaine 50 mg (Scott, Ghia and Teeple, 1983). Such localized, profound but brief changes can be accounted for by direct carotid or vertebral artery injection. As the blood flow in any one of these four arteries is about one-quarter of 15% of the cardiac output, Korevaar and his colleagues point out that intra-arterial toxicity would occur when 3.75% of the i.v. toxic dose had been given. Indeed, such a prediction fits the known facts. It therefore follows that a test dose for stellate block should be less than 3.75% of the i.v. maximum safe dose.

Profound lethargy (Barclay, 1981) and even death (Bromage, 1975) have been reported following only 10–32 mg of lignocaine for dental blocks. Subperineural (Bromage, 1975) and retrograde intra-arterial (Aldrete et al., 1977; Aldrete et al., 1978) spread have been evoked to explain these phenomena. Diplopia (Kronman and Kabani, 1984) and temporary blindness (Laskin, 1984) are also reported following maxillary blocks. It has been postulated that injection under pressure may cause local anaesthetic to diffuse through the inferior orbital fissure to the optic nerve, the external ocular muscles or their nerve supply, or again to pass by retrograde arterial spread into the skull.

Interscalene block has been associated with a Jacksonian fit and Todd’s paralysis following a bupivacaine test dose to an epileptic patient (Collier and Engelking, 1984) and with respiratory arrest following a massive dose (Lauckner, 1982). A focal element is likely, certainly in the former case.

There have been several reports of respiratory arrest associated with retrobulbar block using lignocaine and bupivacaine in ophthalmic surgery (Hathaway, 1983), on occasion following doses as small as 2 ml of 0.75% bupivacaine (Smith, 1982). The patients were readily resuscitated provided anaesthetic expertise was available. Such phenomena may be explained by subarachnoid spread via the optic nerve or by retrograde spread to the brain via a venous sinus. The respiratory centre is particularly accessible from the ventricles and the frequent citing of bupivacaine probably reflects its popularity and potency rather than any specific danger in its use.

SYSTEMIC EFFECTS

Local anaesthetics entering the systemic circulation produce adverse effects primarily on the central nervous system, but may also produce circulatory effects, methaemoglobinaemia and allergic reactions. Local anaesthetics cannot reach a sufficient systemic concentration to block nerve, ganglionic or neuromuscular transmission.

Central nervous system toxicity

The first sign of systemic toxicity of gradual onset in an unpremedicated patient is drowsiness or inebriation akin to alcoholic intoxication (Reynolds, 1971). People receiving local anaesthesia do not often stand up, but if they do, balance is disturbed (Kjaeregard et al., 1984) as it is by alcohol. Later, circumoral pins and needles, numb tongue, roaring in the ears, visual disturbances, restlessness and twitching may occur, with severe intoxication progressing to convulsions, coma,
ADVERSE EFFECTS OF LOCAL ANAESTHETICS

respiratory and circulatory depression. In toxicity of rapid onset, convulsions may occur immediately, closely followed by circulatory depression, but after a modest i.v. bolus and correct management, these should be short-lived. Major overdose may depress all systems simultaneously, but this does not mean all systems are equally susceptible to the local anaesthetic.

Only cocaine is a true stimulant. Synthetic local anaesthetics do not cause initial CNS stimulation followed by depression, as is reflected in that both lignocaine and procaine infusions have been used for sedation in anaesthesia. Psychotic reactions have, however, been reported during infusions of lignocaine to control arrhythmias (Buckman et al., 1980; Turner, 1982). Shivering during extradural analgesia in obstetrics is sometimes regarded as a systemic effect of bupivacaine, but it may often be observed during labour before extradural insertion, and may be attributable to infusion and extradural injection of cold fluids (Mehta et al., 1984).

CNS toxicity of local anaesthetics depends largely upon their membrane stabilizing effect, thus the i.v. LD$_{50}$ bears a direct relationship to potency in nerve conduction block (fig. 2), a fact which has also been demonstrated in monkeys (Munson et al., 1975). A clear exception to this rule is cocaine, the toxicity of which stems, not from membrane stabilization, but from inhibition of noradrenaline re-uptake. Thus provided equipotent concentrations are used, the danger from accidental i.v injection is similar for all other agents and, of course, much greater for high concentrations of any agent. The differences between them arise if they are given extravascularly for regional blockade, when they are absorbed into the circulation and eliminated from it at rates which are partly independent of potency. These can be predicted to some extent by examining the subcutaneous toxicity measured in animals (table I). Clear differences emerge between equipotent agents such as bupivacaine and amethocaine because the latter, a vasodilator (Willatts and Reynolds, 1985), is more rapidly absorbed than the former, while prilocaine is cleared more rapidly from the circulation than the equipotent lignocaine and mepivacaine.

**Circulatory toxicity**

Cardiovascular effects of local anaesthetics arise not only from systemic absorption, but also, and much more importantly, as a regional effect of spinal and extradural blockade. The possibility of an allergic response, although unlike with amides, should also not be overlooked.

Systemically, the CVS is considerably more resistant than the CNS to local anaesthetic toxicity, as has been demonstrated in various experimental animals. Clinically, however, CNS toxicity may be masked by generous premedication with anticonvulsant sedatives such as barbiturates or benzodiazepines, or toxicity may be so overwhelming as to affect both systems simultaneously.

It is well recognized clinically that, in modest doses, lignocaine has therapeutic effects upon the heart, and a useful margin of safety between antiarrhythmic and myocardial depressant doses.

**Table I. Animal toxicity data.** (From Reynolds (1970) distilled from various sources)

<table>
<thead>
<tr>
<th></th>
<th>i.v.</th>
<th>s.c.</th>
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</thead>
<tbody>
<tr>
<td>Amethocaine</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8</td>
<td>82</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>30</td>
<td>400</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>35</td>
<td>900</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>40</td>
<td>270</td>
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</table>

**Fig. 2.** The relationship between i.v. toxicity and potency. The correlation is good except in the case of cocaine, which has a separate mechanism for producing toxicity.
In conscious dogs, cardiac contractility is increased, possibly because of a reflex increase in sympathetic tone (Edouard et al., 1986). Moreover, in low doses, a number of local anaesthetics may increase cardiac output in ventilated dogs (Liu et al., 1982), although procainamide is an exception. In man not only lignocaine but also bupivacaine may increase arterial pressure (Wiklund, 1984), even when three times the maximum safe dose is administered i.v. over 3 h (Hasselstrom et al., 1984).

**Adverse cardiac effects** are recognized, however, in a number of circumstances. Bradycardia in the fetus, heart block and ventricular tachycardia in the newborn are reported following lignocaine and other agents (Chase and Bray, 1977; van Dorsten and Muller, 1981; Garner, Stirt and Finholt, 1985). Lignocaine infusions in the management of arrhythmia have been associated with bradycardia (Demczuk, 1984), asystole (Antonelli and Block, 1982) and ventricular tachycardia (Burket, Fraker and Temesy-Armos, 1985), while heart block is reported particularly in association with concomitant therapy *(vide infra: Drug interactions)*. Ventricular tachycardia (Mallampati, Liu and Knapp, 1984) and fibrillation (Prentiss, 1979) may also follow quickly after convulsions with etidocaine and bupivacaine. Circulatory arrest has, of course, followed gross overdose of lignocaine (Deacock and Simpson, 1964; Buckman et al., 1980), amethocaine (Adriani and Campbell, 1956) and mepivacaine (Sunshine and Fike, 1964) as it has more recently etidocaine and bupivacaine (Albright, 1979; Moore, Crawford and Scurlock, 1980; Moore and Scurlock, 1983). Occasionally, associated factors such as β-blockade (Baraka, Srouji and Haroun, 1983), widespread sympathetic block from spinal, extradural or intercostal administration, or supine hypotension in pregnancy (Marx, 1981; Conklin and Ziadlou-Rad, 1983) combine to precipitate profound hypotension. A fatal outcome has been attributed to "irreversible" cardiac depression from modern long acting local anaesthetics, but it must be stressed that there is nothing new in this phenomenon; it was observed with lignocaine before we learnt caution with the older agent. Bupivacaine is known to be three to four times as potent and toxic as lignocaine, yet not infrequently the upper safe dose limit is taken to be similar (table II).

In nearly every patient convulsions preceded or, when onset was rapid, accompanied circulatory problems, and poor initial resuscitation contributed to the fatality, both in the American patients after extradural and other blocks (Moore, Thompson and Crawford, 1982), and in the British patients after IVRA (Heath, 1982). It must be acknowledged, however, that ventricular fibrillation would appear to be a more frequent feature of bupivacaine than of lignocaine toxicity, although it is undoubtedly precipitated by hypoxia and acidosis resulting from inappropriate or delayed resuscitation. Successful resuscitation has followed some quite massive overdoses of bupivacaine, the records probably being 64 mg kg⁻¹ in a dog (Kasten and Martin, 1985) and 11.4 mg kg⁻¹ in a man (Davis and de Jong, 1982).

**Experimental evidence** has been sought to establish the existence of selective cardiotoxicity among local anaesthetics. Much of it is bedevilled with methodological errors, such as the administration of predetermined doses, and of so-called "equivalent" doses of bupivacaine and lignocaine which are nothing of the kind. Moreover, even when a plausible ratio of cardiovascular:CNS toxic doses (CVS:CNS ratio) is demonstrated, this overlooks the actual therapeutic ratio of the agent. Animal work confirms consistently that the CVS is considerably more resistant than the CNS to toxicity from all agents in all species tested (Liu, Feldman and Covino, 1981; Morishima and Covino, 1981; Chadwick, 1982; Liu et al., 1982; Liu et al., 1983), while the ratio would appear to be higher (i.e. safer) for bupivacaine (4:5) than for

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bupivacaine</th>
<th>Lignocaine</th>
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</thead>
<tbody>
<tr>
<td>LD₉₀ i.v. mice</td>
<td>7.8</td>
<td>30</td>
</tr>
<tr>
<td>Maximum safe dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.6-2</td>
<td>2</td>
</tr>
<tr>
<td>Other {+ adrenaline}</td>
<td>2⁻³.5</td>
<td>3⁻⁴.5</td>
</tr>
<tr>
<td>Toxic plasma concentration</td>
<td>4-6</td>
<td>7</td>
</tr>
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</table>

**TABLE II. Toxicity data (mg kg⁻¹ or mg litre⁻¹).** *The U.K. Data Sheets state that the maximum safe dose of bupivacaine is 2 mg kg⁻¹ in any 4-h period. † The maximum safe dose of lignocaine is sometimes said to be 200 mg (Deacock and Simpson, 1964), without any regard to patient weight. (Data from: Reynolds, 1970, 1971; Grimes and Cates, 1976; Zinman, 1976; Moore, Mather and Bridenbaugh, 1977; Yamashiro, 1977; Moore et al., 1978; Moore, Balfour and Fitzgibbons, 1979; Buckman et al., 1980; Moore and Balfour, 1981; Morerell and Bean, 1981; Davison, Parker and Atkinson, 1982)*
lignocaine (2:4). However, bupivacaine cardiotoxicity is said to be enhanced more than that of lignocaine by hypoxia and acidosis (Rosen et al., 1985) and by hyperkalaemia (Avery et al., 1981, 1984), although the relevance of the latter factor to clinical practice is disputed (Moore and Bridenbaugh, 1983, 1985).

Although both lignocaine and bupivacaine have been shown to increase the arrhythmogenic threshold to adrenaline in dogs (Chapin et al., 1980), bupivacaine is itself more likely to induce arrhythmias (de Jong, Ronfield and DeRosa, 1982; Marx, 1984; Tanz et al., 1984). The relative effects of local anaesthetics in isolated hearts (Sage et al., 1984; Tanz et al., 1984) are hard to interpret, because predetermined in vitro doses are not necessarily comparable to free concentrations present in vivo. However, Block and Covino (1981), using the rabbit heart, showed that the depression of conduction and contractility produced by six local anaesthetics was roughly proportional to their potency as local anaesthetics.

It has been suggested that highly lipid soluble agents such as bupivacaine become "fixed" in the heart, a term more relevant to formalin or photography than to pharmacokinetics. As I trust has been explained, irreversible cardiac depression is not unique to bupivacaine or etidocaine.

**Adverse vascular effects and hypotension.** Concentrations of local anaesthetics that may arise systemically are insufficient to affect blood vessels directly, while the lowest effective concentrations of modern local anaesthetics are constrictor rather than dilator (Aps and Reynolds, 1976; Reynolds, Bryson and Nicholas, 1976). Vasodilatation follows regional blockade of sympathetic nerves or vasomotor centre depression consequent upon severe CNS toxicity. The possible causes of hypotension during local anaesthesia are summarized in table III.

<table>
<thead>
<tr>
<th>TABLE III. Causes of hypotension and circulatory collapse during local anaesthesia</th>
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<tbody>
<tr>
<td>1. Sympathetic blockade from spinal, extradural or intercostal administration.</td>
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<tr>
<td>2. Depression of vasomotor and cardiac centres in the medulla.</td>
</tr>
<tr>
<td>3. Hypoxia and acidosis following neglected CNS toxicity.</td>
</tr>
<tr>
<td>4. Administration of sedatives/anticonvulsants instead of oxygen.</td>
</tr>
<tr>
<td>5. Concomitant treatment with β-blockers etc.</td>
</tr>
<tr>
<td>6. Allergic reaction, histamine release.</td>
</tr>
<tr>
<td>7. Aortocaval occlusion.</td>
</tr>
<tr>
<td>8. Cardiac depression.</td>
</tr>
</tbody>
</table>

**Respiratory depression** may be associated with systemic toxicity resulting in medullary depression, but is more likely to result from oversedation before regional blockade, or from treating convulsions with diazepam or thiopentone (Moore, Crawford and Scurlock, 1980). It may also be caused by motor block following high spinal or extradural blocks; it may occur as a focal effect following retrobulbar block in ophthalmic surgery (Smith, 1982; Hathaway, 1983) or from possible subarachnoid spread following an excessive dose by interscalene brachial plexus block (Lauckner, 1982). Delayed respiratory arrest has been reported 3 h after uneventful extradural administration, as a quasi side effect of bupivacaine (Holmboe and Kongsrud, 1982), but as the patient was fully conscious but totally paralysed, subdural extra-arachnoid spread, which commonly produces a delayed but extensive effect, is a more likely explanation. An increase in extradural pressure may cause transient respiratory depression (Gissen and Leith, 1985). Respiratory distress (ARDS) occasionally occurs as an allergic response to local anaesthetics (see later).

**Causes of Systemic Toxicity**

Systemic toxicity affecting principally the CNS and secondarily the CVS, arises because of acute or cumulative overdose. Acute toxicity may be precipitated by rapid entry to the circulation from accidental or deliberate i.v. injection, rapid absorption from a vascular site or transplacental passage. Cumulative toxicity may be aggravated by slow elimination, drug interactions, etc.

The plasma concentrations of local anaesthetics that have been measured in association with mild toxicity and convulsions may vary widely (Table II), partly because they may well be changing rapidly following a bolus entry to the circulation. For example, seizures following a dose of bupivacaine 4.8 mg kg⁻¹ have been associated with a measured plasma bupivacaine concentration of only 1.1 μg ml⁻¹ (Hasselstrom and Mogensen, 1984), while no fits have occurred in association with concentrations as high as 6 μg ml⁻¹ (Neill and Watson, 1984), albeit in deeply anaesthetised patients! However, following reasonably steady administration, bupivacaine concentrations of approximately 1.6 μg ml⁻¹ (Reynolds, 1971) and lignocaine concentrations of approximately 3 μg ml⁻¹ (Aps et al., 1976) are associated with mild toxic symptoms.
Acute toxicity

Acute overdose. Some may believe manufacturers' stated minimum safe doses to be over-cautious, others may be ignorant of them, or simple errors may be made. Hardly surprisingly, reactions do occur from time to time, particularly when the maximum safe dose is exceeded (Davis and de Jong, 1982; Lauckner, 1982; Coates, Sanders and Edmonds-Seal, 1983; Goodson and Moore, 1983; Gould and Aldrete, 1983; Moore and Scurlock, 1983).

A fact which is frequently overlooked is that the dose requirement to produce successful block is not directly related to the safe dose. Thus the former dose may depend on frame size, and in the case of peripheral blocks on operator skill, while the toxic dose depends upon body weight.

How often does the tyro weigh his patient, and calculate the maximum safe volume of local anaesthetic, before embarking on some hit-or-miss infiltration procedure?

Those who consider manufacturers' recommendations to be overcautious should appreciate that the maximum safe dose has to be less than the minimum toxic dose, and while an operator may "get away with it" nine times out of 10, there is no assurance he will be lucky in the 10th, if he is sailing near the wind. Such may even apply with a drug which purports to have a high therapeutic index (fig. 3).

Because the LD\textsubscript{50} i.v. is proportional to potency (fig. 2), the danger of accidental i.v. injection should be the same for all agents, provided equipotent concentrations are used. The risk for extravascular injection however, will also depend upon speed of absorption, and to some extent elimination, of the individual agent. A long acting drug such as bupivacaine is, by definition, more slowly absorbed from the site of action. Thus reference to the data in table II reveals that the margin of safety with bupivacaine if correctly sited should be greater than that of lignocaine; the maximum safe doses sometimes quoted are similar, yet bupivacaine is three to four times as potent. The therapeutic ratio for lignocaine even in single dose by the extradural route would, indeed, appear to be less than that of bupivacaine. Kileff and her associates (1984) found that, even by giving approximately 9 or 10 mg kg\textsuperscript{-1} of lignocaine for Caesarean section, analgesia was inadequate in six of 23 mothers while, not surprisingly, "several" mothers reported symptoms of CNS toxicity. By contrast bupivacaine 1.9 mg kg\textsuperscript{-1} gave a successful block in all patients and no adverse reactions. However, where major overdose or accidental i.v. injection are concerned,

![Figure 3: Theoretical quantal dose-effect curves, used to derive the therapeutic index or ratio ($TD_{50}:ED_{50}$). In practice the actual safety margin (interval between maximum effective dose and minimum toxic dose) does not necessarily bear a direct relationship to the theoretical therapeutic ratio.](https://academic.oup.com/bja/article-abstract/59/1/78/263017)
ADVERSE EFFECTS OF LOCAL ANAESTHETICS

the dose of bupivacaine can much more readily approach its lethal dose. Thus bupivacaine as used in recent years may be more like drug A in figure 3: it has a wide therapeutic margin for all normal use, but excessive doses are naturally dangerous. Bupivacaine has become so popular recently among non-anaesthetists partly because, being so potent, it is possible to produce profound effects by overgenerosity with it.

Rapid entry to the circulation. Toxicity may follow small doses injected intravascularly (see also Focal Effects). Accidental i.v. injection should be avoided by keeping the needle moving in peripheral blocks, or by careful aspiration where more appropriate. Slow injection is also a vital safeguard. Beeby and Jenkins (1984), in questioning why deaths have occurred from inadvertent i.v. injection during extradurals in the U.S.A. but not in the U.K., suggest that the bacterial filter, used routinely in the U.K., may usefully prevent over-rapid injection. Brief convulsions may occur from “safe” doses of bupivacaine (Morrell and Bean, 1981), while respiratory and cardiac arrest are reported following lignocaine 100 mg injected to a central vein (Grenadier et al., 1981)—a dose that had been found safe in 1100 other patients when injected peripherally.

Local anaesthetics are absorbed very rapidly from mucous membranes, a route by which they are frequently given with scant regard for the maximum safe dose. Toxicity and even death following urethral application of lignocaine, for example, is not new (Deacock and Simpson, 1964) yet, more recently, toxicity has been reported following the administration of 20 mg kg⁻¹ by this route (Panacek, Beninger and Albertson, 1984) and of sundry doses of lignocaine and amethocaine via burnt skin and oral mucosa (Barnard, 1984; Wehner and Hamilton, 1984; Parish, Moore and Gotz, 1985).

Intravenous regional anaesthesia (IVRA). Convulsions and circulatory collapse associated with IVRA have been attributed to cuff failure and to drug, yet errors of technique and dosage are probably more crucial, while errors in resuscitation may contribute to a fatal outcome (Reynolds, 1984c). A technique which depends upon perfect occlusion is inherently unsafe because solution may leak past a correctly inflated tourniquet (Rosenberg et al., 1983; Davies, Wilkey and Hall, 1984), convulsions may occur following intended cuff release (Henderson, 1980) and peak concentrations of local anaesthetic may be higher after prolonged than after brief tourniquet time over a range of 10–56 min (fig. 4). Both venous pressure (Lawes et al., 1984) and arterial pressure (Davies et al., 1984) may increase during the procedure to exceed cuff pressure, particularly if prior exsanguination has been omitted. The value of occluding the brachial artery when other methods are impracticable should not be overlooked.

IVRA is contraindicated for leg surgery because an overdose of local anaesthetic is necessary (Hanton and Punchihewa, 1982), while venous occlusion is impossible in the calf, where two bones are present (Davies and Walford, 1986).

Adverse reactions have occurred using lignocaine, prilocaine and bupivacaine (Goold, 1985; Henderson and Sujitkumar, 1986) although fatalities have been reported in the U.K. only with bupivacaine (Heath, 1982). Part of the reason for this is that relatively larger doses of bupivacaine than of lignocaine or prilocaine have been used (Reynolds, 1984c). Although 0.125% and 0.2% bupivacaine have been found to give similar but more prolonged analgesia compared with 0.5% and 0.8% prilocaine (McKeown, Meiklejohn and Scott, 1984), a bupivacaine concentration of 0.2% or even greater has often been deemed necessary, and even found to be safe in experienced hands.

![Fig. 4. I.v. regional anaesthesia: relationship between maximum plasma bupivacaine concentration and injection to tourniquet release time. There is a significant positive correlation (P < 0.05) indicating the longer the tourniquet time the higher the plasma bupivacaine concentration increases. (Reproduced from Davies, Wilkey and Hall (1984) by kind permission of the authors and publishers.)](https://academic.oup.com/bja/article-abstract/59/1/78/263017/5917/8263017?target=)
necessitate at the end of a long labour raises the
finding that maximum bupivacaine concentration
given beyond the time to plasma plateau. The
Caesarean section, the large dose this might
would normally allow bupivacaine top-ups to be
of mild intoxication with a dose of 320 mg. This
using plain bupivacaine, there was a 5% chance
was dependent upon total dose, and not at all upon
plasma during continuous extradural analgesia
to which bupivacaine increased in maternal
concentration will depend upon the dose rate, and
indefinitely during labour (Duthie, Wyman and
Lewis, 1968).

With intermittent or continuous administration
of a drug, its plasma concentration can be expected
to increase for four to seven half-lives. Thus with
a terminal half-life of about 3.5 h (Tucker and
Mather, 1975), the concentration of bupivacaine
can be expected to increase for 14-24 h, within the
timespan of most extradural blocks in labour,
while toxicity does not build up further when
extradural analgesia is continued for days or weeks
(personal observation). The ultimate steady state
concentration will depend upon the dose rate, and
on the distribution volume of bupivacaine in the
given individual. Indeed, Reynolds, Hargrove
and Wyman (1973) found that the concentration
to which bupivacaine increased in maternal
plasma during continuous extradural analgesia
was dependent upon total dose, and not at all upon
dose rate. From their data they predicted that,
using plain bupivacaine, there was a 5% chance
of mild intoxication with a dose of 320 mg. This
would normally allow bupivacaine top-ups to be
given beyond the time to plasma plateau. The
finding that maximum bupivacaine concentration
is dependent on total dose and not on dose rate has
since been confirmed (Laishley, Morgan and
Reynolds, in preparation) and is in keeping with
pharmacokinetic principles.

With the growing popularity of extradural
Caesarean section, the large dose this might
necessitate at the end of a long labour raises the
possibility of acute-on-chronic toxicity. Thorburn
and Moir (1984) reported two such patients. In
each case, following difficulty with extending the
block and a total dose of 356 and 357 mg
respectively, the patient convulsed and went blue,
but recovered rapidly on resuscitation. Thompson
and her colleagues (1985) confirmed that doses
exceeding 2 mg kg
-1
were associated with some
plasma concentrations exceeding that reputed to
be toxic (Reynolds, 1971), and that acute-on-
chronic extradural blockades produced the highest
concentrations, although no signs or symptoms of
intoxication were noted.

The U.K. data sheet gives the maximum safe
dose of bupivacaine as 2 mg kg
-1
in any 4-h period.
Clearly, in both practical and theoretical terms
this limitation is overcautious during the initial
period, but should certainly be strictly applied
after some hours of topping-up.

Although both etidocaine and prilocaine are
cleared more rapidly from the circulation than is
bupivacaine, neither is suitable for continuous
extradural analgesia because the former gives
intense motor blockade at analgesic doses, and the
latter increases methaemoglobin concentration.

Continuous extradural analgesia. When ligno-
caine, and in the U.S.A. mepivacaine, were used
for this purpose, they had to be given at such a
frequency that systemic toxicity was almost
inevitable (Reynolds, 1970; Reynolds and Taylor
1970). With the advent of bupivacaine, it became
possible to maintain analgesia apparently safely,
indefininitely during labour (Duthie, Wyman and
Lewis, 1968).

Lignocaine infusion. Lignocaine, with a terminal
half-life of 2.4 h, can be expected to accumulate in
the circulation for 12–18 h if given at a steady
infusion rate. If given at 2 mg min
-1
or more for
a prolonged period, toxicity will probably occur
sooner or later in most individuals, whereas even
following a bolus, 1 mg min
-1
will be ineffective
in many cases during the vital early post-infarct
period. Using an infusion regimen of bolus
followed by 4 mg min
-1
for 30 min, 2 mg min
-1
for 2 h, and 1 mg min
-1
thereafter (the 4–2–1
regime), which was established as a result of i.v.
bolus studies in volunteers (Reynolds, 1970), Aps
and colleagues (1976) showed that suitable steady
state lignocaine concentrations were obtained by
30 min and were maintained. Such a regimen,
however, was excessive in the presence of a
reduced cardiac output.

Lignocaine is cleared rapidly from the circula-
tion by the liver with a first pass effect of > 0.7,
to produce the primary metabolite monoethyl-
glycine xylidine (MEGX) which may contribute
to the toxicity. Both agents have been found to
accumulate to higher concentrations in the
presence of congestive cardiac failure (Halkin et
al., 1975; Davison, Parker and Atkinson, 1982),
although as lignocaine clearance is flow dependent
ADVERSE EFFECTS OF LOCAL ANAESTHETICS

and liver blood flow is determined principally by cardiac output, it is this latter factor which yields a closer correlation and is associated with an increase in terminal half-life (Aps et al., 1976).

**Drug interactions**

Drug interactions may also potentiate the toxicity of lignocaine in intensive care, and of bupivacaine.

Hepatic blood flow and therefore lignocaine clearance may be reduced by cimetidine and propranolol (Gilman and Ego, 1983; Ochs, Carstens and Greenblatt, 1980; Feely et al., 1982), while the former may also depress microsomal enzyme activity. Thus lignocaine toxicity during an antiarrhythmic infusion is enhanced by co-administration of these drugs. Ranitidin produces only a small reduction in lignocaine clearance (Robson et al., 1985), and both H₂-antagonists would appear to have a negligible effect on the more slowly cleared bupivacaine.

Interactions may, however, be dynamic as well as kinetic. Cardiovascular collapse is reported following regionally administered bupivacaine in patients treated with verapamil (Collier, 1985) and the B-adrenoreceptor blocker timolol (Baraka, Srouji and Haroun, 1983), although both these drugs were more likely to have been potentiating the effects of regional blockade of sympathetic fibres rather than any systemic effects of bupivacaine.

Prenylamine, the catecholamine-depleting agent used in prophylaxis of angina, contra-indicates the use of lignocaine for arrhythmias as this combination may precipitate A-V block (Grenadier et al., 1982) and ventricular tachycardia.

The effect of brain amine concentration on the convulsant threshold to local anaesthetics has been studied in rats. While Ciarlone (1981) found that dopamine and 5-hydroxytryptamine depletion both reduced the convulsant threshold to lignocaine, Niederlehner and colleagues (1982) found that 5-hydroxytryptamine increased the convulsant threshold, but that other monoamines had no significant effect.

Pethidine, which can itself inhibit brain monoamine inactivation, increases the incidence of lignocaine-induced convulsions in mice (Gangarosa, Ciarlone and Hung, 1978), possibly also because norpethidine, its primary metabolite, is actually convulsant. Baraka and Haroun (1985) also found that lignocaine reduced the seizure threshold to fentanyl in man. There is every reason to suppose that narcotics are proconvulsant in man as in animals.

Goodson and Moore (1983) pointed out that the opioid-antiemetic combinations used for sedation in children by many American dentists could reduce the convulsant threshold to local anaesthetics and certainly increased the CNS depressant effects. They report 10 deaths following local anaesthesia for dentistry in children given a combination amounting to more than three times the maximum recommended dose of local anaesthetic—usually lignocaine, and opioid analgesic (fig. 5). The problems of resuscitation posed by such gross overdoses in any circumstances are, of course, familiar.

Finally, the place of adrenaline in regional block repays examination. The addition of adrenaline to local anaesthetic solution can reduce peak plasma concentration, particularly following injection in vascular areas, and hence reduces the likelihood of acute toxicity if correctly sited, as witness the low incidence of toxicity following large doses in the Seattle series (Moore et al., 1978). It has been claimed, moreover, that adrenaline might prevent myocardial depression following bupivacaine overdose (Moore and Scurlock, 1983), but the

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**Fig. 5.** Relationship between local anaesthetic and narcotic analgesic producing toxic effects. MRD = maximum recommended dose. Squares represent fully reversible reactions. Death or brain damage (circles) occurred when %MRD₉₅ + %MRDₙ > 300. Patient 7 was given lignocaine also for “resuscitation” indicated by the arrow. Reproduced from Goodson and Moore (1983) by kind permission of the authors and publishers.
patients reported who suffered this complication received considerably more bupivacaine than the ones who did not.

Adrenaline greatly increases the danger should the solution be accidentally injected intravascularly. In some patients reported to be suffering from bupivacaine toxicity, ventricular tachycardia and fibrillation may be attributed to adrenaline (Mallampati, Liu and Knapp, 1984), although these complications are by no means the usual accompaniment of CNS toxicity following regional block (Moore, Thompson and Crawford, 1982). However, another possible explanation for the apparent increase in cardiotoxicity of accidental i.v. bupivacaine in the U.S. may be a greater use of adrenaline-containing solutions, rarely used in the U.K.

Metabolic and other factors

In animals, hypoxia and acidosis have been shown to enhance both the CNS and the CVS toxicity of lignocaine (Englesson and Matousek, 1975; Morishima and Covino, 1981) and the cardiotoxicity of bupivacaine (Rosen et al., 1985). In clinical practice such changes commonly accompany convulsions (Moore, Crawford and Scurlock, 1980) and can be expected to exacerbate cardiac sequelae.

Pregnancy may also increase the circulatory toxicity of bupivacaine in ewes (Morishima et al., 1985), quite irrespective of the contribution by aortocaval occlusion in clinical practice. Crawford (1985), however, reported a series of 27000 bupivacaine extradurals and some 100000 top-ups by midwives, in which there were no deaths or permanent sequelae.

Hyperkalaemia has also been shown experimentally to enhance bupivacaine cardiotoxicity and has been implicated in ventricular tachycardia following suxamethonium (Conklin and Ziadlou-Rad, 1983) and hypotension in a patient with renal failure (Gould and Aldrete, 1983), although in the latter the thiopentone used to treat agitation may have contributed, while hyperkalaemia does not normally occur following suxamethonium given to treat convulsions (Moore and Bridenbaugh, 1985).

Perinatal factors

Local anaesthetics are not noted for producing congenital malformations, although Lee and Nagele (1985) managed to induce neural tube defects in chick embryos following massive doses of lignocaine, procaine and amethocaine.

Decelerations in the fetal heart rate may occur during extradural analgesia using chloroprocaine, lignocaine or bupivacaine (Abboud et al., 1984); these may result from placental drug transfer, or they may be secondary to maternal circulatory changes.

Neonates may break down bupivacaine, mepivacaine and etidocaine more slowly than adults (Reynolds, 1984d) and in experimental circumstances exhibit toxicity at lower total plasma concentrations because of reduced protein binding. Symptoms occur in the same order as in the adult, namely: convulsions, hypotension, respiratory arrest, circulatory collapse (Morishima et al., 1983). In clinical practice neonatal effects have latterly been found to be slight for all agents (Abboud et al., 1982; Kuhnert et al., 1984) and largely limited to hypotonia (Wiener, Hogg and Rosen, 1979), although neonatal depression has in the past been associated with the more cumulative agents lignocaine and mepivacaine (Morishima et al., 1966; Shnider and Way, 1968) rather than with the longer-acting bupivacaine. The maternal and fetal concentrations of the latter increase slowly because it has to be administered less frequently to maintain analgesia (Reynolds and Taylor, 1970). It is sometimes maintained that the low fetal:maternal ratio of bupivacaine, attributable to its reduced fetal binding (Tucker et al., 1970) is of no importance as free concentrations are equal in mother and baby. It is clear, however, that the slow placental transfer of bupivacaine consequent on this reduced binding does retard its accumulation in the fetus (Hamshaw Thomas and Reynolds, 1985), and its extensive use in obstetric extradurals attests to its safety for the baby.

The baby does suffer however, and indeed may die, if he receives excessive doses of any local anaesthetic either following paracervical block (Goodlin, Crocker and Haesslein, 1976), a phenomenon which is not new and probably results from direct entry of drug to the placental circulation (Beazley, Taylor and Reynolds, 1972), or because solution is injected to the head in mistake for the caudal canal (Finster and Popper, 1965) or the paracervical region (Hillman, Hillman and Dodson, 1979).

Prevention and Management of Systemic Toxicity

Toxicity from normal slow absorption of correctly placed local anaesthetic in a dose not exceeding the manufacturer's recommended maximum is
ADVERSE EFFECTS OF LOCAL ANAESTHETICS

not a problem. The danger from accidental i.v. injection is minimized by:

(1) Keeping the needle tip moving in peripheral blocks.

(2) When this is unsuitable, gentle aspiration before injection. This will be reliable down an epidural catheter only if the tip has multiple holes.

(3) Slow injection of local anaesthetic, which can be halted at the first sign of trouble.

(4) Treating convulsions immediately with oxygen. Provided (3) above is complied with, convulsions will cease before any anticonvulsant could take effect.

(5) Avoiding heavy premedication, which will mask early signs of CNS toxicity, while an anticonvulsant may even suppress seizure activity until circulatory collapse supervenes.

With a more massive overdose than is to be anticipated by obeying the above rules, an anticonvulsant may be required, but should never take precedence over oxygen administration (Moore, Crawford and Scurlock, 1980). Although animal work has suggested diazepam might be better than barbiturates in the treatment of local anaesthetic-induced convulsions, thiopentone is quicker to act and produces less hangover (Scott, 1981). However, both agents, but particularly thiopentone, will seriously exacerbate circulatory and respiratory depression.

Persistent convulsions may also be managed using suxamethonium, although it has been argued this might cause hyperkalaemia and so exacerbate cardiotoxicity (Conklin and Ziadlou-Rad, 1983) while not suppressing seizure activity in the brain. Moore and Bonica (1985), however, pointed out that seizures rapidly cause hypoxia, hypercapnia and lactic acidosis, and suxamethonium is to be preferred to thiopentone and diazepam because it stops the muscle activity and hence the lactate overproduction; it permits intubation and artificial ventilation which is essential to treat the acidosis; it does not depress the heart; its half-life is short; it will not cause neonatal depression; and it does not normally increase the plasma potassium concentration.

Early prevention of hypoxia and acidosis should minimize the risk of serious arrhythmias and cardiac arrest but, should they occur following bupivacaine overdose, it must be admitted that patients have survived (in spite of?... because of?) treatment with diazepam, lignocaine (Davis and de Jong, 1982), procainamide, phenytin (Prentiss, 1979), thiopentone and ketamine (Gould and Aldrete, 1983).

OTHER EFFECTS

Methaemoglobinaemia

Methaemoglobinaemia is repeatedly reported following surface application and ingestion of benzocaine (Douglas and Fairbanks, 1977; O’Donohue, Moss and Angelillo, 1980; McGuigan, 1981; Klein et al., 1983; Seibert and Seibert, 1984; Spielman, Anderson and Terry, 1984), although neither drug nor problem are exactly new. An increased methaemoglobin concentration is also a recognized reaction to prilocaine, the hydrolysis product of which, o-toluidine, is the causative agent. A methaemoglobin concentration of approximately 30% is associated with obvious cyanosis and serious signs of cerebral hypoxia, although less than this may cause problems in the presence of cardiorespiratory impairment. A dose of approximately 8 mg kg⁻¹ of prilocaine is generally necessary to produce symptoms (Kreutz and Kinni, 1983), but the very young are considerably more susceptible (Ludwig, 1981; Duncan and Kobrinsky, 1983). The onset of trouble is generally some hours after dosage. Haemoglobinopathies, glucose 6-phosphate dehydrogenase deficiency and oxidizing drugs (sulphonamides, antimalarials) may all predispose to methaemoglobinaemia. Treatment involves the slow i.v. administration of methylene blue 2 mg kg⁻¹.

Allergic reactions

Less than 1% of all adverse reactions to local anaesthetics are allergic in origin (Johnson and de Stigter, 1983), yet how often patients tell us they are allergic to lignocaine when they have suffered a faint or an adrenaline reaction in the dental chair. Do they tell dentists the same story when we have given them an overdose or a hypotensive extradural block? Only a small minority of those tested for local anaesthetic allergy show positive responses (Babajews and Ivanyi, 1982; Fisher and Graham, 1984).

Ester local anaesthetics are more allergenic than amides and, moreover, they may show cross-reactivity with p-aminobenzoate (a sunscreen as well as a metabolite of procaine), p-hydroxybenzoate and its derivative the preservative Methylparaben, which are commonly included in local
anaesthetic formulations in multidose vials—rarely used by British anaesthetists. Evidence regarding their contribution to the incidence of apparent local anaesthetic sensitivity is conflicting, however (de Shazo and Nelson, 1979; Babajews and Ivanyi, 1982; Fisher and Graham, 1984), although their allergenic capability is undoubted (Schatz, 1984). Proven allergy to amide local anaesthetics is occasionally encountered, involving prilocaine, mepivacaine, lignocaine and bupivacaine (Brown, Beamish and Wildsmith, 1981; Fisher and Pennington, 1982; Yeoman, 1982), while cross-reactivity within the group is by no means universal (de Shazo and Nelson, 1979; Fisher and Pennington, 1982). The majority of cases involve dental blocks, although lignocaine given by many routes has been implicated in respiratory distress syndrome (Howard, Moshenifar and Simon, 1982; Promisloff and DuPont, 1983; Woelke and Tucker, 1983; Rooke and Milne, 1984). I have found no record of a verified allergic reaction to extradural bupivacaine.

True hypersensitivity to local anaesthetics may be manifested as general oedema and urticaria, lymphadenopathy, bronchospasm and respiratory distress syndrome. A type I reaction is probably the most usual, although type III may also occur, while contact dermatitis (type IV) is also reported in response to local anaesthetics (Johnson and de Stigter, 1983; Fernandes de Corres and Leanizbarrutia, 1985). Immediate diagnosis can at times be very confusing. Wheezing has been reported during extradural blockade with bupivacaine in labour, leading to the denial of further top-ups, but it also coincided with the advent of a midwife who possessed a dog, the patient having a known allergy to dogs, while bupivacaine sensitivity tests were negative (Mehta and Luxton, 1986). Psychogenic reaction can masquerade very convincingly as allergy. Milam, Giovannitti and Bright (1983) tell of a patient who repeatedly produced psychogenic urticaria following dental blocks. Following a putative allergic reaction, diagnosis is best made by intradermal testing, which carries little danger provided something approaching a 1 in 10000 dilution of the dosage form is used initially, and a 1-mm bleb only is raised.

Management of acute allergic reactions. Adrenaline is frequently stated to be the first line of treatment in anaphylaxis, the logic of treatment being that the increase in cyclic AMP concentra-

BRITISH JOURNAL OF ANAESTHESIA

Complications of local anaesthesia in general have been considered in so far as they may be confused with adverse effects of local anaesthetic drugs. Local anaesthetics may give rise to adverse reactions by a number of mechanisms. They affect nerve conduction and vasculature at the site of injection: a local effect; but is it unlikely that they ever produce an irreversible noxious effect on nerve fibres. They produce regional effects resulting from nerve conduction blockade; hypotension and respiratory depression by this mechanism are frequently mistaken for pharmacological effects of the agent concerned. They produce focal effects, usually when carried in high concentration via the arterial supply to the brain. They produce systemic effects following absorption or intravenous administration, which are manifested principally in the central nervous system. Ignorance or carelessness are frequently causative factors in serious reactions. Adequate oxygenation is vital in prophylaxis and immediate treatment of systemic toxicity, while resuscitative skill and equipment must always be to hand. Idiosyncrasy or allergy can only rarely be an excuse for adverse reactions to local anaesthesia.

REFERENCES


ADVERSE EFFECTS OF LOCAL ANAESTHETICS


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