Best Practice & Research Clinical Anaesthesiology
Vol. 18, No. 3, pp. 509–527, 2004
doi:10.1016/j.bpa.2004.01.004
available online at http://www.sciencedirect.com

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Regional anaesthesia, local anaesthetics and the surgical stress response

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Epidural anaesthesia has the potential to improve patients' outcome after major surgical procedures by reducing postoperative morbidity and duration of recovery. Possible benefits include the attenuation of cardiac complications, an earlier return of gastrointestinal function associated with an increase in patients' comfort overall, decreased incidence of pulmonary dysfunction, beneficial effects on the coagulation system and a reduction in the inflammatory response. The underlying mechanisms, however, remain unclear. Since local anaesthetics (LAs), reabsorbed from the epidural space, seem to contribute to these effects, it is not easy to differentiate between the systemic effects of LAs and the effects of neuraxial blockade by epidural anaesthesia.

Thus, in patients not able or willing to receive intra- and/or postoperative epidural analgesia, systemic administration of LAs may be considered to be a new therapeutic approach for the prevention of postoperative disorders by modulation of the peri- and postoperative inflammatory.

Key words: drugs; anaesthetics, local; inflammation; infection; lung injury; anesthetics, local, mechanisms; inflammation, mediators.

Major surgery is associated with a stimulation of the immune system, leading to a broad variety of alterations in haemodynamic, endocrine–metabolic and immune responses.

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Vasodilation, increased release of multiple chemical substances, e.g. catecholamines, cytokines, bradykinin, prostaglandins and increased lipolysis or hypercoagulability are only a few characteristics of the various changes that occur peri-operatively.

Although many of these effects can be detrimental, structural and functional repair of injured tissue is crucially dependent on an appropriate immune response and most patients recover uneventfully from surgery.

However, its excessive stimulation may lead, at least in a certain patient population, to a significant increase of postoperative morbidity. Perioperative excessive stimulation of the inflammatory and haemostatic systems was shown to play a major role in the development of postoperative ileus, ischaemia–reperfusion syndromes (e.g. myocardial infarction), hypercoagulation syndromes (e.g. deep venous thrombosis) host auto-injury inflammatory syndromes [e.g. systemic inflammatory responce syndrome (SIRS), acute respiratory distress syndrome (ARDS)] and pain, altogether representing a significant fraction of major postoperative disorders.

Since these responses are initiated during surgery, intraoperative interventions might decrease their frequency and severity. Recent evidence suggests that regional anaesthesia exerts protective effects against the perioperative stress response.

Epidural administration of local anaesthetics (LAs) was primarily designed to provide intraoperative anaesthesia and postoperative analgesia. However, in the past it has become clear that epidurally administered LAs have benefits far beyond anaesthesia and pain relief and, indeed, the technique seems to have a significant impact on the outcome of major surgical procedures. We refer to these as 'alternative' effects.

But since placement of an epidural catheter is not without risks for the patient, a considerable number of patients reject this technique. In addition, epidural anaesthesia (EA) is not suitable for all types of surgical procedures (e.g. neurosurgery or surgery where the catheter needs to be placed above the thoracic level) and/or under all conditions (e.g. in anticoagulated patients). Yet, most of the alternative effects, obtained when EA with LA is used, do also occur when LAs are administered differently, suggesting that these beneficial effects are not dependent on pure blockade of spinal nerves, in contrast to classic epidural anaesthesia and analgesia, but instead on systemic levels of LA.

This review will provide an overview of current knowledge about the effects of regional anaesthesia on the surgical stress responses, with a main focus on the properties of LAs, since LAs themselves may play a significant role in the perioperative modulation of such responses.

REGIONAL ANAESTHESIA

Recent evidence suggests that regional anaesthesia has a protective effect against the perioperative stress response. A recently published meta-analysis concluded that neuraxial anaesthesia using LAs decreased overall mortality by approximately one-third, reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39% and respiratory depression by 59%. Incidences of myocardial infarction and renal failure were also reduced.[1]

In addition, EA using LA has been shown to attenuate the endocrine and metabolic response to upper abdominal surgery.[2] Lattermann et al[3] observed, in a study conducted in patients undergoing elective colorectal surgery, a suppressive effect of EA on whole body lipolysis without affecting plasma glycerol or free fatty acid concentrations. Supporting these findings, Holte and Kehlet showed a reduction of fat metabolism, lactate and ketone, as well as the classic endocrine metabolic response

parameters such as catecholamines, cortisol and glucose concentrations, in patients receiving epidurally administered LA for lower body procedures. Postoperative hyperglycaemia was reduced, whereas insulin concentration remained largely unaltered and glucose tolerance improved.[4] Thoracic EA (TEA), however, was found to be less effective in attenuating catabolism and improving protein economy, because of a decreased afferent blockade with TEA during sub- or supradiaphramatic surgery. Unblocked vagal afferents with TEA as observed in experimental studies might contribute to the difference between lumbar EA and TEA.[5]

One of the main causes of morbidity and prolonged convalescence after major surgery is the development of postoperative ileus, due to increased nociceptive and sympathetic neural activity. In several studies, EA was shown to reduce the incidence of postoperative ileus and shorten the time until first passage of stool[6] and thus increase patients' comfort and shorten length of hospital stay. In patients undergoing radical prostatectomy, gastrointestinal function recovered significantly earlier when general anaesthesia was combined with TEA (33.8 ($\pm$ 13.0) h to first postoperative passage of flatus) versus general in combination with lumbar EA (39.3 ($\pm$ 13.6)) and general anaesthesia alone (50.6 ($\pm$ 11.1)).[7] EA in women undergoing elective hysterectomy, however, was found to be less effective for improving gastrointestinal motility.[8]

As well as gastrointestinal function, EA was shown to shorten the time to extubation and intensive care stay in patients undergoing abdominal aortic operations.[9]

The beneficial effects of the epidural administration of LAs have been attributed to the changes in physiology induced by neuraxial anaesthesia and better pain management.[10] Perioperative pain control using regional anaesthesia techniques may be a powerful tool for reducing perioperative stress.[1,11] Serum markers that may reflect the humoral stress response (i.e. catecholamines, corticotropin, thromboxane A_2 (TXA_2) and antidiuretic hormone) are decreased by epidural blockade[5], but not by general anaesthesia.[12] Most authors have interpreted the better effectiveness of postoperative pain management with epidural anaesthesia as being the underlying reason for the diminished stress response[10], compared with intermittent on-demand opioid analgesia.

In this regard the close link between inflammation and coagulation should be addressed. Leukocytes activate the plasma coagulation cascade[13] by binding tissue and coagulation factors/complexes to their membranes. Being actively and specifically recruited to platelet clots, leukocytes are then covered by platelets and can then adhere to the endothelium, migrate into the tissue and release inflammatory mediators—key events in the inflammatory response.[14] Lower incidences of vascular graft occlusion, re-operation for inadequate tissue perfusion[15] and fewer thromboembolic complications have been demonstrated with EA.[10] This is in agreement with observations of decreased perioperative coagulability, when epidural anaesthesia and analgesia were compared with general anaesthesia, suggesting a direct effect on platelet aggregation.[10]

Cardiac surgery and, in particular, the initiation of cardipulmonary bypass (CPB) is well known for inducing an increase in blood cortisol and catecholamine concentrations resulting in, among other things, beta-adrenergic receptor dysfunction. Thoracic epidural anaesthesia has previously been shown to attenuate the stress response in patients undergoing coronary artery bypass graft (CABG) surgery.[16] Lee et al[17] demonstrated a reduction of beta-adrenergic receptor desensitisation and downregulation, as well as a lower stress hormone response (significantly lower epinephrine-, norepinephrine- and cortisol-concentrations, significantly higher cardiac index after separation from CPB) for CABG cases involving CPB times in excess of 1 hour. Similar results were obtained for patients who underwent beating heart surgery without the aid of CPB. TEA was found to inhibit an increase in cortisol

and catecholamine concentrations and to reduce ischaemia reperfusion injury but not to affect cytokine levels.[18] Significantly improved quality of recovery (fewer major organ complications) from routine CABG surgery was observed in patients with TEA compared to general anaesthesia alone in 420 patients.[19]

In a recent study, the superior effects of TEA on the recovery process after colorectal surgery were shown. The use of epidural anaesthesia had long-lasting effects on exercise capacity and health-related quality of life compared to patients managed with patient-controlled analgesia with intravenous morphine.[20]

There is evidence suggesting an improvement of splanchnic perfusion by TEA[18], but TEA-induced changes in splanchnic perfusion remain a point of discussion. As recently published by Bach et al[21] no significant improvement in the haemodynamics of the hepatosplanchnic region could be observed in cardiac surgery patients treated with continuous epidural infusion of bupivacaine 0.25%. Several other studies, however, have described splanchnic perfusion to be improved with the use of TEA and have thus argued that this anaesthetic technique could play a role in improving patients' outcome after surgical procedures.[18]

In summary, there is increasing evidence that epidural anaesthesia and analgesia improves surgical outcome by affecting the trauma-associated stress response and thereby reducing postoperative morbidity and duration of recovery.[21] The underlying mechanisms still remain to be elucidated and further research on the possible reduction of the inflammatory response by EA needs to be done.

However, as discussed below, there are hints that the pharmacodynamic effects of LAs themselves may contribute to these effects.

ALTERNATIVE EFFECTS OF LA

LAs exert significant alternative effects besides their ability to block Na^+ channels, in particularly with regard to their anti-inflammatory and antithrombotic actions. Interestingly, the concentrations of LAs required to achieve these beneficial effects are much lower than those needed for inhibition of Na^+ channels. For example, the half-maximal inhibitory concentration (IC_{50}) of lidocaine at the neuronal Na^+ channel is approximately 50–100 μM (depending on the specific channel subtype and study preparation)[22], whereas it inhibits signalling through m1 muscarinic receptors (when expressed recombinantly in *Xenopus oocytes*) at an IC_{50} of 20 nM, i.e. a 1000–5000-fold lower concentration.[23] This sensitivity of other targets has two important consequences. Firstly, LAs might, at concentrations resulting in significant Na^+ channel blockade, also affect a number of other cellular systems. Secondly, relatively low LA concentrations (as attained in blood during epidural anaesthesia/analgesia, or during intravenous (iv) LA infusion) that block neuronal Na^+ channels to a limited extent only, could still have significant pharmacological effects. Taken together, these beneficial effects could present a new alternative method for modulating the inflammatory response in a variety of postoperative disorders in the clinical setting. The following sections will, therefore, focus on the effects of LAs on components of the inflammatory cascade and then describe the modulation of different disease states by LA in more detail.

LA and inflammation

Polymorphonuclear granulocytes (PMNs) are a fundamental component of the non-specific immune response. Rapidly recruited to the site of inflammation, they respond

to harmful agents by releasing proteolytic enzymes and toxic oxygen metabolites. Inadequate overstimulation by activating compounds, e.g. cytokines, such as are released during/after surgical procedures, seems to contribute to the enhanced inflammatory responses and major postoperative disorders seen after surgery. With regard to their anti-inflammatory properties, LAs have been shown to directly affect PMN as well as macrophage and monocyte function.

Adhesion of PMNs to the endothelium, when excessive, may induce endothelial injury, which is mediated by several adhesion molecules. One that is important for the firm adhesion of PMNs to endothelial cells and their subsequent transmigration (diapedesis) is CD11b/CD18, a member of the integrin family.[24,25] This receptor is constitutively expressed on the surface of non-activated PMNs, but its expression increases markedly after inflammatory stimulation. Binding of activated PMNs to endothelial cells increases their intracellular peroxide levels and might lead to detrimental effects of the reactive oxygen species.[25] In vitro studies have shown protective effects against endothelial cell injury when monoclonal antibodies against CD11b/CD18 were used.[25] Ropivacaine and lidocaine (100–300 μM) decreased tumour necrosis factor-alpha (TNF-α)-induced up-regulation of CD11b/CD18 surface expression on PMN in vitro.[24] One possible mechanism contributing to the beneficial in vivo effects of rectally administered ropivacaine on ulcerative colitis is described below.

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is known to affect PMN–endothelial interactions by stimulating PMN functions and up-regulation of certain cellular adhesion molecules, such as CD11b/CD18.

These effects were completely abolished (in a concentration dependent manner (4–40 mM), when PMNs, incubated with rhG-CSF, were treated with lidocaine (20 mM), resulting in a decrease of PMN adherence in vitro.[26]

Since PMN activation and up-regulation of CD11b are dependent on intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$), LA (14 mM) effects might be due to the inhibition of increasing $[Ca^{2+}]_i$ in vitro.[27]

As well as certain adhesion molecules, adherence to surfaces requires the flattening of PMNs, which can be prevented by low temperature, colchicine and cyclic adenosine monophosphate (cAMP). However, inhibition of phagocytosis, lysosomal enzyme release, superanion production and postphagocytic oxygen consumption are all associated with marked cell rounding and withdrawal of cell processes.[28] Exposure to LAs in vitro (lidocaine 12 mM or tetracaine 1.5 mM) induces these morphological changes, followed by inhibition of adherence and, thus, impaired PMN delivery to sites of inflammation.[29,30] Perfusion with LA-free medium reverses these effects. Rounding also occurs after Na^+ depletion of, or Mg^{2+} and Ca^{2+} addition to, the medium. Since tetrodotoxin does not affect rounding, the LA effect seems to be unrelated to Na^+ channel inhibition. Rabinovitch and DeStefano[28] reported that macrophages cultured in vitro and incubated with either lidocaine (12 mM) or tetracaine (1.5 mM) underwent reversible cell rounding, associated with cell contraction and the withdrawal of cell processes.

In vitro, lidocaine induces a dose-dependent reduction of granulocyte adherence; significant effects are obtained with concentrations ≥ 100 μM. In vivo, bolus injection of 2.5 $mg^{-1}kg^{-1}$ lidocaine in rabbits caused a transient decrease in adherence (to 40% of control) 5 minutes later.[31] Adherence recovered 15 min after injection. Continuous lidocaine infusion (0.3 mg kg^{-1} $minute^{-1}$) after bolus injection maintained this inhibitory effect for the duration of infusion. Similar results were obtained in humans receiving a 100 mg bolus of iv lidocaine for the treatment of arrhythmia.[31]

Peritonitis is associated with a profound increase in PMN adherence and subsequent delivery into the exsudate. In rabbits, lidocaine (1.5 $mg^{-1}kg^{-1}$ bolus, followed by 0.3 mg $kg^{-1}minute^{-1}$) markedly inhibited both adherence (to 25% of control) and delivery (to 2% of control), when measured 6 h after the induction of peritonitis and the initiation of lidocaine infusion. In that experiment, lidocaine treatment caused a more than 10-fold greater inhibition of inflammation than did methylprednisolone (2–3 kg rabbits were given 15 mg doses of the depot form sub-cutaneously (s.c.) twice at 7-day intervals, and 1–3 days after the second dose sterile peritonitis was induced).[31]

Thus, local anesthetics decrease the ability of PMNs to adhere to surfaces. As a result, one would anticipate a significant effect on PMN migration and accumulation at the site of inflammation.

In fact Hammer et al[32] showed that lidocaine (4–20 mM) inhibits human PMN metabolism and random mobility in a concentration-dependent manner, with complete immobilisation of PMNs occurring in the presence of 20 mM lidocaine in vitro. Destruction of the functional integrity of cytoskeletal structures, interference with Ca^{2+}-dependent cellular processes[33], and/or interaction with membrane lipids, causing changes in stability and fluidity of the membrane, may contribute to the observed effect of the compound.[34]

LA effects on PMN accumulation at a site of injury were investigated by Eriksson et al[35] using an in vivo rat model. Inflammation was induced by implantation of a titanium chamber close to the peritoneum. Pre-treatment of the wound with 10 mg of lidocaine reduced the accumulation of PMNs in the wound area compared with saline-treated rats. Inhibition of PMN accumulation, however, might be explained by inhibition of PMN adherence and therefore inhibition of migration[31], as mentioned above, or by a direct inhibitory effect on motility and migration of PMNs.[31,32] In addition, it is conceivable that LAs inhibit chemoattractant release by impairing cell metabolism.[35,36] In summary, it appears that LAs reduce the ability of PMNs to migrate to the site of inflammation by interfering with the critical steps of adhesion and migration. The result is decreased PMN accumulation.

In addition to inhibiting adherence and migration, LAs were shown to inhibit PMN priming.[37] Priming describes a process whereby the response to an activating stimulus is potentiates as a result of previous exposure to priming agents such as TNF-α, platelet activating factor (PAF), interleukin-8 (IL-8), lipopolysaccharid (LPS) or granulocyte-macrophage colony stimulating factor (GM-CSF). For example the release of oxygen metabolites is markedly enhanced when neutrophils have previously been primed. The priming process is a key regulatory mechanism of PMN function and seems to play a pivotal role in the 'overstimulation' of inflammatory pathways, being a crucial component of neutrophil-mediated tissue injury both in vivo and in vitro. As such, the process is being investigated intensively. NADPH-oxidase activity, Ca^{2+}, protein kinase C (PKC), phospholipase (PLD) and phosphoinositide 3-kinase (PI3K) are likely to be involved but the mechanisms are poorly understood as yet.

Interestingly, the effects of LAs on PMN priming have not been investigated in detail. In other settings, inhibition of NADPH-oxidase activity, Ca^{2+} transients and PKC have been described for several Las[38] so that the compounds might be expected to affect priming.[27] We have shown in vitro that lidocaine blocks priming of PMNs by lysophosphatidic acid in a concentration-dependent manner ($IC_{50} = 1\ \mu M$) but does not affect the process of activation at all.[37] In contrast to other LA actions on these signalling systems (see below), the LA appeared to act at an extracellular site, since the non-permeable lidocaine analogue QX314 had effects similar to those of lidocaine. It is possible that inhibition of priming contributes to the anti-inflammatory actions of LAs and, in particular, suppresses

the deleterious effects of the uncontrolled, overactive response of inflammatory cells to a stimulating agent. This might explain how LAs can decrease tissue damage without significantly inhibiting the PMN functions required for host defence.

LA and inflammatory mediators

Cytokines, including TNF, interleukins (IL) and growth factor, are a heterogenous group of low molecular weight proteins acting on cell surface receptors to stimulate gene transcription resulting in the regulation and modification of cell growth, maturation and especially inflammation. As reviewed by Lin et al[39] surgery stimulates the production and release of a large amount of cytokines by different inflammatory cells. IL-1 e.g. acts on PMN receptors, inducing phagocytosis, respiratory burst, chemotaxis and degranulation. In vitro, amide-LAs, such as lidocaine, were shown to inhibit IL-1 release by LPS-stimulated mononuclear cells concentration-dependently (0.2–20 mM).[36] Lahav et al[40], furthermore, reported a direct inhibition of the secretion of the chemokine IL-8 from cultured epithelial cell lines and freshly isolated colonic epithelial cells stimulated with TNF-α by lidocaine, suggesting that lidocaine's beneficial effects in the treatment of ulcerative colitis are, at least in part, mediated by the attenuation of IL-secretion.

Leukotrienes, particularly leukotriene B_4 (LTB_4), were also shown to play an important role in the inflammatory response. LTB_4 is known for the induction of PMN margination at endothelial cells, degranulation, superoxide anion generation, diapedesis and synergistic activity with prostaglandin E_2 (PGE_2) in order to enhance vascular permeability. In addition, it is a potent leukoattractant (in vivo and in vitro), recruiting PMNs to the site of tissue injury and thereby promoting the inflammatory process. LTB_4 release in vitro was nearly abolished when human PMNs or monocytes were pre-incubated with different concentrations of lidocaine or bupivacaine (2–20 mM and 44–4400 μM, respectively).[36] Since LTB_4 in combination with PGE_2 induces oedema formation, inhibition of LTB_4 release might explain the beneficial effects of LAs on microvascular permeability and oedema formation, as described below.[24,41]

Lidocaine was also shown to inhibit histamine secretion from human peripheral leukocytes, cultured human basophils and mast cells at concentrations in the high μM range in vitro.[42]Taken together LAs are able to inhibit the release of several critical inflammatory mediators and, additionally, to directly influence the functioning of various inflammatory cells. These effects might be one possible explanation for the anti-inflammatory properties of LA.

LA and lung injury

As described above PMNs, macrophages and cytokines play crucial roles in the pathogenesis of inflammatory lung injury. PMNs accumulate in the lung, causing endothelial cell injury and increasing microvascular permeability.

Pre- or early post-treatment with lidocaine (bolus 2 mg kg^{-1} + 2 mg kg^{-1} $hour^{-1}$ continuous infusion, yielding plasma concentrations of 1.2–2.5 μg ml^{-1} (5–10 μM)), was shown to attenuate the late phase of acid installation-induced lung injury in rabbits, resulting in decreased PMN accumulation in the lung and reduced free radical generation.[43] This, inturn, would mean a reduction of endothelial damage and, therefore, decreased pulmonary oedema. Indeed, the HCl-induced increase in pulmonary wet/dry ratio and albumin extravasation was attenuated in lidocaine-treated rabbits and decreased cytokine levels in the bronchoalveolar fluid were found,

although more probably resulting from a reduction in the inflammatory response than from direct suppression of cytokine production. (It is relevant to note that the fluid used for bronchoalveolar lavage routinely contains high (mM) concentrations of LAs in the clinical setting[44] and in animal experiments.[45] These concentrations of LAs have been shown to significantly affect the behaviour of alveolar macrophages.[30]

Lidocaine treatment after tracheal HCl installation improved lung function most probably by the inhibition of PMN sequestration and activation, leading to an increase in P_aO_2 and attenuation of the decrease in compliance and increase in resistance at the same time.[43] Interactions between PMNs and endothelial cells may also be important in the pathogenesis of organ dysfunction induced by endotoxin.

Since LAs interfere with the initial steps of inflammation in vitro, a protective effect might be expected for these drugs in endotoxin-induced lung injury. Schmidt et al[46] reported that, in a rat model of sepsis, pre-treatment with lidocaine (plasma concentration 1.4–2.5 $\mu g\ ml^{-1}$ (6–10 μM)) attenuated endotoxin-induced increases in PMN adherence, PMN activation and migration to the inflammatory site, as well as PMN metabolic function, as assessed by an inhibition of free radical production. The protective action of lidocaine was not due to differences in venular wall shear rate. Instead, inhibition of PMN adherence to endothelial cells, PMN function and suppression of histamine release by lidocaine may explain the observed decrease of microvascular permeability in lidocaine-pretreated rats. Nearly similar results were obtained by Mikawa et al[47], who showed that pre-treatment with lidocaine (single dose of $2\ mg\ kg^{-1}$ iv followed by continuous infusion of $2\ mg\ kg^{-1}\ hour^{-1}$) significantly attenuated endotoxin-induced lung injury in rabbits, by attenuating the accumulation and the O_2^- production of PMNs.

Considering these effects of LAs on inflammatory cells and mediators, one would expect that their anti-inflammatory properties would help to prevent hyperoxic lung injury. Takao et al[48] demonstrated a protective effect of LAs on inflammatory responses and pulmonary function in a rabbit model of hyperoxia-induced lung injury. Lidocaine infusion in systemically relevant plasma concentrations (1.4–2.5 $\mu g\ ml^{-1}$ (6–10 μM)) decreased chemotactic factors (C3a, C5a, TNFa, IL-1B) in bronchoalveolar lavage fluid and resulted in less PMN accumulation in comparison to control animals. PMN release of free radicals was reduced, the treated animals developed less lung oedema (as demonstrated by a decrease in albumin extravasation and improved wet/dry ratio of the lung) and fewer histopathological changes of lung damage were seen. Summarising these results, LAs have been shown to be protective in various animal models of ARDS due to their anti-inflammatory properties. Use of lidocaine for acute lung injury (ALI), however, remains controversial, as its usage might be associated with several risks that still need clarification in further studies. As discussed below, the risk of infection might be increased since PMN function is inhibited by LA, therefore this might be potentially harmful in ALI patients in whom infection is a frequent cause and complication. Furthermore, lidocaine was described as being the underlying cause for ALI in three patients who sustained an a anaphylactoid reaction to the drug.[49]

There is increasing evidence that LAs seem to be potent inhibitors of bronchial hyper-responsiveness. Intravenous administration of LAs in patients with bronchial hyper-reactivity is recommended in standard textbooks and review articles to mitigate bronchoconstriction during tracheal intubation. Groeben et al[50] showed that both intravenous and inhalational administration of lidocaine significantly attenuated histamine-induced bronchial hyper-reactivity; both were equally effective, but inhaled lidocaine produced lower plasma concentrations (0.7 versus 2.2 $\mu g/ml$).

In this regard, Tanaka et al[51] found the T cells of patients with bronchial asthma, which is characterised by persistent inflammation, were immunoregulated by lidocaine. The compound inhibited proliferative responses to specific and non-specific stimulation, as well as inhibiting cytokine production by both T_H1 and T_H2 cells, suggesting a possible alternative that could be studied in relation to the treatment of patients with severe asthma.

LA effects on microvascular permeability

Increased microvascular permeability is a common feature in many inflammatory diseases. Examples relevant to anaesthesiologists include ARDS, sepsis, burns and peritonitis, shown to be attenuated by LAs in various studies. In an in vivo model of ligature-induced obstructive ileus in rats, lidocaine, administered either iv (2 mg kg) or directly sprayed onto the serosa, suppressed the inflammatory reaction, as indicated by a marked inhibition of fluid secretion and albumin extravasation.[41] Although blockade of neurons in the enteric nervous system (especially the myenteric plexus) with subsequent reduction in the release of secretory mediators such as vasoactive intestinal peptide (VIP), may have contributed to the anti-secretory action of lidocaine, this can not easily explain why lidocaine pre-treatment of the serosa of the obstructed jejunum reduced the inflammatory reaction in the bowel wall even 18 h later. Lidocaine's interference with several steps of the inflammation cascade may be a more likely explanation for the protective effect observed in this study.[52] Similar results were obtained by Rimback et al[41] They studied the effects on HCl-induced peritonitis of topical pre- and post-treatment of the peritoneal surface with lidocaine (37 mM) and bupivacaine (17.5 mM). Both LAs significantly inhibited Evans-blue albumin extravasation, a marker of microvascular permeability. Although both drugs were titrated to the same non-ionised fraction (based on pKa), lidocaine showed a more potent inhibitory effect.[41]

Using the hamster cheek pouch model, Martinsson et al[24] observed reversible inhibition by ropivacaine (100 μM) of LTB_4-induced plasma exsudation, indicating that the effect is not specific to lidocaine.

Thermal injury activates the complement system and other inflammatory cascades, resulting in progressive plasma extravasation with subsequent hypoproteinaemia and hypovolaemia. Anti-inflammatory drugs inhibit burn-induced albumin extravasation[53], suggesting a role for inflammatory mediators in the pathogenesis of oedema. Therefore, it was of interest to study whether the anti-inflammatory properties of LAs could protect microvascular integrity, without increasing infection rate. Using skin burns in rats, Cassuto et al[54] reported that topical application or systemic administration of amide-LAs significantly inhibited plasma exsudation, compared with placebo-treated rats. Similar results were obtained by Mattsson et al[55] who investigated the effects of intravenously administered lidocaine in volunteers with partial thickness skin burns. Lidocaine-treated burns showed a significantly faster restitution of residual erythema compared to control sites at 12 hour post-burn.[55] This protective action could be explained by several of the known effects of LAs. Inhibition of PMN delivery to the site of inflammation[31], direct suppression of PMN-endothelial adhesiveness[56], reduced generation of toxic oxygen metabolites[57], impaired prostaglandin and leukotriene production[53], increased local prostacyclin production or reduced PMN stickiness and adherence to injured endothelium, may all contribute to the reduced plasma extravasation. However, these findings were not confirmed by Nishina et al[43], who did not find that LAs affected leukotrienes and prostacyclin. Inhibition of sensory

neurons with a resultant decrease in substance P release, was suggested as being important for oedema development after thermal injury and may be another possible explanation.[58] Cassuto et al[54] reported that the protective effect was lost when the systemically administered concentration of lidocaine was increased from 10 to 30 $\mu g\ kg^{-1}\ minute^{-1}$. A potential explanation for this unusual concentration-dependency is activation or block of additional pathways at the higher lidocaine concentration. A similar, and possibly related, phenomenon is the concentration-dependent action of LAs on vascular smooth muscle in vitro and in vivo[59]: low concentrations (for lidocaine 1 $\mu g\ ml^{-1}$–1 $mg\ ml^{-1}$ corresponding to 4 μM–4 mM) induce vasoconstriction, whereas greater concentrations induce vasodilation. It is conceivable that vasocontriction would decrease oedema formation, whereas vasodilation would enhance it.

Inhibiting the inflammatory response could potentially increase the incidence of infection, but Brofeldt et al[60] reported that 5% lidocaine cream, applied to the skin of patients with partial thickness burns in concentrations of up to 2.25 mg/cm^2, was associated with good pain relief, plasma concentrations below toxic levels, no infections or allergic complications and excellent wound healing. Similar results were found by Pedersen et al[61], yet LAs neither reduced local inflammation nor late hyperalgesia. These studies suggest that benefits may be obtained from topical treatment with LAs, even in cases of extensive burns.

LA effects on inflammatory diseases of the gastrointestinal tract

Inflammatory processes contribute to the development of several bowel diseases. Ulcerative colitis and proctitis are caused by both immunological and inflammatory stimuli. In a rat colitis model, ropivacaine showed protective effects[62] and clinical studies have shown that LAs can be effective against the severe mucosal inflammation of these diseases.[63] Arlander et al[64] reported that patients with ulcerative colitis treated rectally with ropivacaine 200 mg twice daily (mean peak plasma concentrations 1–1.4 $\mu g/ml$ (3.6–5 μM)) demonstrated decreased inflammation and reduced clinical symptoms after only 2 weeks of treatment. However, no effect was found for 200 mg of rectally administered ropivacaine in patients with distal ulcerative colitis, in a study conducted by Hillingso et al[65] An explanation for this discrepancy might be the duration of treatment, since ropivacaine was only administered once in comparison to 2 weeks of treatment in the former study, confirming the idea that LA effects might be time-dependent, as discussed below.

Disturbance of the link between inflammatory and immunocompetent cells, as well as blockade of hyper-reactive autonomic nerves (which may also play a causative role in these diseases) were suggested as possible explanations for the LA effect.[66] Decreased release of pro-inflammatory lipoxygenase products (LTB_4 or 5-hydroxyeicosatetraenoic acid (5-HETE), while leaving other, potentially cytoprotective eicosanoids (15-HETE and prostacyclin) unaffected, may also contribute to this beneficial effect of ropivacaine.[67] However, lidocaine failed to inhibit prostanoid release by human gastric mucosa in vitro at concentrations less than 250 $\mu g/ml$.[68]

Lidocaine (plasma concentration 5–15 μM) accelerated the return of bowel function in patients undergoing radical prostatectomy, resulting in a significant shortening of hospital stay.[69] LA (lidocaine 100 mg bolus iv + 3 $mg\ minute^{-1}$ continuous iv infusion or bupivacaine 2 $mg^{-1}kg^{-1}$ intra-abdominal installation) also shortened the duration of postoperative ileus in patients undergoing major abdominal surgery.[70] Peritoneal surgery is associated with the release of inflammatory mediators

such as histamine, prostaglandins and kinins.[70,71] The activation of abdominal reflexes resulting in a long-lasting inhibition of colonic motility after surgery is likely to be due to inflammatory reactions in the area of surgery. Since LAs affect the release of inflammatory agents, beneficial effects on bowel function may be, at least in part, due to lidocaine's anti-inflammatory effects. This hypothesis is supported by the observation that non-steroidal anti-inflammatory drugs are also effective. The anti-inflammatory effect of LA is prolonged and persists after serum levels have decreased.[72] This might explain lidocaine's effect on bowel function 36 h after infusion was discontinued.[70]

Taken together, these findings show significant promise for the use of LAs in the treatment of inflammatory bowel disease, as well as for the attenuation of postoperative ileus.

LA effects on myocardial infarction and reperfusion injury

Acute myocardial infarction is usually not considered to be an inflammatory disease, but ischaemia and, in particular, the subsequent reperfusion (ischaemia–reperfusion injury), is accompanied by a significant cardiac inflammatory response. PMN–endothelial interactions occurring during myocardial ischaemia and reperfusion are thought to play a crucial role and PMN-derived oxygen metabolites are important in myocardial injury associated with reperfusion of the ischaemic heart.[73] Activated PMNs can induce structural changes in the heart through the action of free radicals and arachidonic acid metabolites.[74] In 1984, Mullane et al[75] reported that drugs that impair PMN function may reduce infarct size. Recent studies have shown that IL-6 and IL-8 are important regulators of the inflammatory response in myocardial infarction[76] and C5a has been suggested as being a key mediator of tissue injury in this setting.[77] Moreover, expression of PMN and monocyte adhesion molecules and their ligands increases in the acute phase of myocardial infarction.[78] Thus, it is not surprising that blockade of adhesion molecules, reducing PMN accumulation in the myocardium, exerts significant protective effects on myocardial ischemia–reperfusion injury in rats.[79] Intravenous administration of antibodies against CD11b/CD18 reduced myocardial reperfusion injury in an animal model.[80]

Experiments in a porcine model of myocardial ischaemia have shown that lidocaine, administered either iv or retrogradely perfused before onset of reperfusion, preserved the ischaemic myocardium and reduced infarct size after reperfusion.[81] Lidocaine infusions in dogs reduced infarct size, possibly by inhibiting the release of toxic oxygen metabolites.[82] Ebel et al[83] found that lidocaine reduced ischaemic but not reperfusion injury in the isolated rat heart. In contrast, De Logeril et al[84] reported that in their dog model, lidocaine (plasma concentration 13 μM) neither reduced infarct size nor myocardial PMN accumulation significantly. These discrepancies might be due to differences between the models, particularly the duration of occlusion.

Lidocaine is often used as an anti-arrhythmic drug after myocardial infarction. It is conceivable that part of the anti-arrhythmic effect in this setting is due to the anti-inflammatory effects of lidocaine in areas of myocardial infarction. Although lidocaine administration failed to be effective in treating reperfusion arrhythmias in several experimental studies in dogs and pigs[84], lidocaine decreased reperfusion arrhythmias caused by free radical-induced enhanced automaticity, without any effect on re-entry arrhythmias.[85]

LAs and the increased risk of infection

Since LAa impair PMN presence and function, concerns have arisen that LAs might increase the susceptibility to infections, since LA-mediated depression of PMN oxidative metabolic response may decrease the host's ability to control bacterial proliferation. This is supported by two studies. The first study showed the death of five out of six lidocaine-treated rats within 48 h of *Straphylococcus aureus* inoculation, compared to just one survivor in the non-treated control group.[71] In a second study, Powell et al[86] reported that the risk of infection after the application of entectic mixture of local anesthetics (EMLA) cream to contaminated wounds was increased.

Although an increased risk of infection might be expected in theory, several investigations have suggested that the remaining PMN function is sufficient to minimise the risk.[57] Nevertheless, LAs should be employed with caution in settings of gross bacterial contamination, when an appropriate inflammatory response is required to eliminate invading micro-organisms. However, their use in sterile inflammation, where the excessive inflammatory response is a major pathogenic factor (e.g. SIRS), appears to be beneficial.

Antibacterial actions by LAs reported in vitro and in vivo are obtained only at millimolar concentrations. Lidocaine (37 mM), for example, inhibits the growth of *Escherischia coli* and *Streptococcus pneunoniae*, but is without any effects on *Staphylococcus aureus* or *Psendomonas aeruginosa*. In contrast, Schmidt and Rosenkranz[87] found that lidocaine produced a reduction in growth of all the above-mentioned bacteria. LAs inhibited all pathogens except *S. aureus* and *P. aeruginosa*. More recent studies though report conflicting results regarding the sensitivity of *S. aureus* to LAs. Using a guinea pig wound-model, Stratford et al[88] demonstrated a lidocaine (74 mM)-induced reduction of bacterial growth to approximately 30% in *S. aureus* contaminated wounds. The mechanisms underlying these antibacterial effects are not clear in detail yet. Recent studies suggest bactericidal rather than bacteriostatic activity. In this regard, Sakuragi et al[89] reported temperature- and concentration-dependent bactericidal effects of bupivacaine (4.4–26 mM, no preservatives) on human skin micro-organisms, with *S. aureus* being more resistant to bupivacaine than *Staphylococcus epidermidis* and *Escherichia coli.* Confirming these temperature- and concentration-dependent inhibitory effects of LAs, a recent study showed ropivacaine to be more potent at 37 °C than at room temperature.[90]

The antibacterial potency of LAs is a topic of debate. Pere et al[91] reported stronger inhibitory effects for bupivacaine than for ropivacaine, since bupivacaine 5.8 mM significantly reduced the growth of *E. coli*, whereas Rosenberg et al[92] did not find any inhibition at all of *E. coli* by bupivacaine (3.9–7.8 mM). Differences in methods of evaluating bacterial growth (direct versus indirect) could explain these contrary findings. Regarding bactericidal potency, starting with the most potent, LAs were ranked as follows: dibucaine–tetracaine–bupivacaine–prilocaine–lidocaine–procaine, whereby inhibitory properties are four times less for bupivacaine in comparison to dibucaine. Feldman et al[93] observed only limited antibacterial activity and no inhibition at all of coagulase negative staphylococci for bupivacaine at low concentrations and, therefore, concluded that a prevention of epidural catheter associated infections by the use of LAs is highly unlikely. Only bupivacaine at concentrations of 3 mM or higher seems to exert antimicrobial effects, whereas one has to admit that LA concentrations reach the mM range in the epidural area. Thus, it might be conceivable for epidurally administered LAs to contribute to the prevention of epidural infections by their antibacterial properties. In that case, elimination of LAs in epidural infusions would

result in an increase in infections. In addition, LAs could decrease the rate of infections after accidental contamination when added to preparations and storage of syringes or infusions. Nevertheless it is rather unlikely that sufficient treatment for infections would be achieved when LAs are used solely. Recent studies have suggested synergistic effects for lidocaine in combination with antibiotics.[94]

Furthermore, LAs exert antiviral activity when applied in high concentrations. Using an in vitro test to study the antiviral properties of LAs against *Herpes simplex I* (HSV I), De Amici et al[95] found a mepivacaine-induced reduction in viral replication to 50%. However, LA concentrations greater than 35 mM (1%) or the additional administration of adrenaline were required to achieve this effect. Bupivacaine showed anitiviral activity as well, but with a profound decrease in action when used without adrenaline. Maximal inhibition was obtained when bupivacaine 1% (31 mM) was used, suggesting that the effect is concentration-dependent. Most probably, the virus itself is targeted by the LA, in contrast to most antiviral drugs which interfere with the mechanisms of cellular replication. Moreover, the antiviral effect seems to be dependent on osmolarity and the presence of adrenaline (possibly pH-related), especially when less concentrated LA solutions are used.

In summary, the anti-inflammatory properties of LAs in systemic concentrations might, theoretically, increase the risk of infections, since antibacterial and antiviral effects are only attained with the use of high LA concentrations. Yet, this seems to be of minor importance in most studies, except for settings of severe bacterial contamination. LAs are known for their inhibition of excessive inflammatory responses without a significant impairment of the host's immune system.

MECHANISMS OF ACTION

The underlying mechanisms for all of these alternative actions have not been clearly worked out in detail yet. As described above, a variety of LA actions on inflammatory cells and mediators has been reported, suggesting a modulatory role for LAs with regard to the inflammatory response in various diseases.

Interestingly, most in vitro studies require LA concentrations above the clinically relevant range, whereas in vivo studies often demonstrate the same or similar effects at clinically relevant concentrations. The underlying reasons for this discrepancy are still unknown. This is particularly remarkable since one would anticipate that larger free LA concentrations would be available in many protein-free in vitro solutions, compared with an in vivo situation. It may well be that the multiple molecular targets of LAs allow potentiating interactions in vivo that can not be attained in a simplified in vitro model. Alternatively, the more prolonged exposure to LA during in vivo investigations may play a role. One possible explanation could be a time-dependent effect. Our group was able to show that the sensitivity of thromboxane A_2 and lysophosphatidic acid signalling to lidocaine and bupivacaine in *Xenopus* oocytes increased more than fivefold when incubation times were extended from 10 minutes to 12 hour.[96] Unfortunately virtually nothing is known about the specific molecular mechanisms that these effects are based upon. LAs are traditionally known for their ability to block Na^+ channels but, in several circumstances, this mechanism of action can be ruled out, since several cells that were studied do not even possess these channels, e.g. PMNs, or the effects were exerted at LA concentrations that were much lower than normally required for Na^+ channel blockade. Several mechanisms have been suggested, but only a few targets have been described in molecular detail.

LA interactions with G protein-coupled receptors might be one of these molecular mechanisms since most of the mediators involved in the inflammatory process signal through receptors of this class. It was recently demonstrated that LAs selectively inhibit Gq protein function.[97]

Since Gq is important for many inflammatory (lysophosphatic acid[98] and thromboxane A_2[99]) and haemostatic signalling pathways, the effects of LAs might be explained, at least in part, by functional inhibition of Gq protein. Offermanns et al[100] demonstrated that platelets from mice deficient in the α-subunit of Gq were unresponsive to a variety of physiological platelet activators, resulting in protection of these mice from collagen and adrenaline-induced thromboembolism. Thus, inhibition of Gq protein function in platelets might explain, in part, the antithrombotic actions of LA.[100]

The signalling pathway further downstream from the G protein was not shown to be involved in the LA effect.[98] Interactions of LAs with PKCsignalling have been described[27], but only a small amount of specific information is available. Controversial results exist for the involvement of protein kinases in this regard. This area clearly deserves further research.

CONCLUSION

Increasing evidence has shown that epidural anaesthesia (EA) has the potential to improve patients' outcome after major surgical procedures by reducing postoperative morbidity and duration of recovery. Probable benefits include the attenuation of cardiac complications, earlier return of gastrointestinal function associated with an increase in overall patients' comfort, decreased incidence of pulmonary dysfunctions, beneficial effects on the coagulation system and, of course, a reduction in the inflammatory response.

The underlying mechanisms, however, remain unclear. Since local anaesthetics (Las) seem, when reabsorbed from the epidural space, to contribute to these effects by exertion of the above-described actions, it is difficult to differentiate between the systemic effects of LAs and the effects of neuraxial blockade by EA.

Anti-inflammatory properties of LAs have been clearly demonstrated in vitro as well as in vivo. However, their molecular mechanisms are poorly delineated, but effects on polymorphonuclear granulocyte (PMN) mediator and free radical release, as well as migration to the site of action, appear to be most important.

The clinical use of LAs for the explicit purpose of modulating the excessive inflammatory response may well be feasible. Treatment of ulcerative colitis with topical ropivacaine is just one example in this regard. Thus, in patients not able or willing to receive intra- and/or postoperative epidural analgesia, systemic administration of LAs may be considered as a new therapeutic approach in order to prevent postoperative disorders by modulation of the peri- and postoperative inflammatory responses.

Further research should, therefore, be directed primarily to two areas. Firstly, we need to gain a detailed understanding of the basic mechanisms of action of LAs on the inflammatory system. Structure–function studies are particularly essential, since they might lead to the development of new selective compounds without the 'side effects' of Na channel blockade. Secondly, better designed clinical studies should be performed, to assess the impact of systemically administered LAs in patients who would benefit from epidural anaesthesia/analgesia but are not candidates for this technique.

Practice point

- epidural anaesthesia has the potential to improve outcome after major surgery by:

  attenuation of cardiac complications
  earlier return of bowel function
  beneficial effects on pulmonary function
  beneficial effects on hypercoagulability

  there is evidence that the systemic effects of local anaesthetics (Las) contribute to the benefits of regional anaesthesia
  alternative effects of LA can not be explained by classical Na^+ blockade

  local anaesthetics exert anti-inflammatory properties

Research agenda

There is a need for better designed clinical studies to differentiate between the neuraxial and systemic effects of local anaesthetics (LAs: e.g. control group with intravenous LA). Further research is warranted to evaluate the molecular mechanisms underlying the alternative effects of LAs

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