Balanced anaesthesia 2005: Avoiding the Transition from Acute to Chronic Pain

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ABSTRACT

When general anaesthesia consisted of the administration of a volatile anaesthetic agent according to clinical parameters usually preceded by premedication, was chronic post-operative pain a significant problem? Have we, by working hard to deliver balanced anaesthesia and rapid recovery lost sight of the fundamental importance of abolishing noxious reflexes at the spinal level?

We need to identify, ameliorate and manage specific features and risk factors, including the severity of the acute pain experience, for individuals at risk for the development of a chronic pain syndrome. Anaesthetists' actions and the drugs they use have multiple and profound effects to be taken into account, appropriately modified and controlled, combined with excellent postoperative analgesia, particularly for those patients or procedures at high risk to minimise the transition of acute to chronic pain following surgery.

Acute nociceptive pain is the risk for the transition to chronic neuropathic pain.

When general anaesthesia comprised the administration of a volatile anaesthetic agent at a concentration determined by clinical parameters to ensure adequate depth and was often preceded by a significant premedication, was chronic post-operative pain as significant a problem as it is today?

We can, of course, never know, but the move to light 'balanced' general anaesthesia to avoid single drug toxicity (first proposed by Lundy) as now practiced may have facilitated the development of central sensitisation and led to our present problems.[1]

Have we, by working hard to deliver this balanced anaesthesia, designed today to facilitate the much sought after 'rapid recovery', lost sight of the fundamental importance of abolishing noxious reflexes at the spinal level? Is it wrong to make this conceptual leap? Light balanced general anaesthesia, often without premedication, is now the order of the day. Analgesia and the abolition of autonomic reflexes, amnesia, sleep and muscle relaxation are provided by different agents in small doses and this has enabled surgery to be carried out on the unfit and the elderly but have the rest, the 'fit' population who could (and did in the past) receive many multiples of Minimum Alveolar Concentration (MAC) been thereby denied protection against chronic pain? Research has tended to concentrate on a reduction of the easily measurable early adverse outcomes, side ef-

fects and consequences of anaesthesia; postoperative nausea and vomiting (PONV) is a good example. But have we, by concentrating on the 'big little' problem(s), lost sight of the big picture?

Patients then were not only generally younger and fitter but they were also more grateful, more accepting and did not come with the adverse psychosocial baggage that so many do today. We need to identify and manage specific aspects about individuals with acute pain who may develop a chronic pain syndrome. Is it the pain or is it the individual? Patient characteristics such as, distress, identified by psychosocial questioning to allow treatment preoperatively, and physical deconditioning are risk factors to be included with the severity of acute pain and the degree of physical insult, both of which must be minimised.

Catastrophizing (an exaggerated negative mental state brought to bear during actual or anticipated painful experience), known to be associated with a reduced ability to manage pain, has been demonstrated to be relevant in respect of a greater postoperative pain experience which may predispose a transition to chronicity.[2] We need to be able to plan ahead and deliver the best interventions to those most at risk, moving the emphasis from treatment to prevention.[3] Acute nociceptive pain is the risk for a transition to chronic neuropathic pain although the exact process remains uncertain.

I plan to look at specific elements of our practice of anaesthesia including postoperative pain management and hypothesize that we may be making matters worse than they need to be. Are we sowing the seeds of chronic pain? Goto opines: '(it) becomes increasingly clear that not all general anesthetic agents

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are capable of preventing central neural changes that contribute to the development of long-lasting pain'.[4]

BACKGROUND

The original proposition by Wall is now more generally accepted with agreement that the mechanism of general anaesthesia is not through a single effect or action but by complex and inter-connected effects on a multitude of spinal neuronal systems which are affected by general anaesthetics in a variable way.[5] Indeed, anaesthesia is now considered more of a spinal cord than brain phenomenon.

Peripheral injury, occurring in association with surgery is a repeated noxious stimulation due to acute tissue damage and the development of inflammation. Intense nociceptor activation, both directly and indirectly, through C-fibre evoked responses in the dorsal horn of the spinal cord results in the creation of a facilitated state and an exaggerated response to subsequent noxious stimuli, with central sensitisation, through removal of the magnesium block on the N-methyl-D-aspartate (NMDA) glutamate receptor ion channel. The resultant characteristic excitation of spinal cord dorsal horn cells, wind-up, is the magnification and prolongation of response to subsequent sensory stimuli in the wide dynamic range (WDR) neurones. Following both new injury and peripheral inflammation, associated with surgery this central sensitisation can also be induced by a modified A-fibre response. Wind-up is mediated through the NMDA receptor in post-synaptic location which is the key regulator involved in multisynaptic nociceptive transmission and associated with synaptic plasticity. [6]

Activation or enabling by a stimulus of sufficient intensity amplifies, enhances and prolongs an ongoing nociceptive afferent barrage which is associated with the facilitation of spinal nociceptive reflexes (hyperalgesia) and produces a variety of pathological pain states that persist long after the injured tissue has healed and creates a pain memory.[7]

Nociception at the start of peripheral inflammation evokes expression by the sensitised neurone of the proto-oncogene c-fos in the spinal dorsal horn and its protein product fos is involved in the regulation of neurotransmitter and nerve growth factor synthesis with the c-fos-transcription factor driving nociceptor and dorsal horn plasticity. Fos-like immunoreactivity (Fos-LI) predominantly in laminae I, II and V is a function of the intensity and duration of the noxious stimulus with continuing nociceptive activity shifting the dorsal horn from basal to suppressed and then to sensitised modes further exaggerating the effect of nociceptive input.[8]

A depression of the activities of lamina IV and V neurones can be expected to have a beneficial effect as can any suppression of c-Fos expression for example by NMDA antagonists. In addition, substance P, which modulates nociceptive transmission, may mediate central sensitisation and potentiate NMDA action and effects. Acute pain, which can rapidly evolve into chronic pain even with the neuronal expression of new genes, should be considered as the initiation phase of an extensive, persistent, nociceptive and behavioural cascade triggered by tissue injury which may need prolonged inhibition.[9] Several sites on the NMDA receptor complex, activated by the excitatory amino acid (EAA) glutamate, are analgesic targets and pre-treatment with NMDA antagonist analgesic or anaesthetic agents as neuroprotectants may avoid this post-injury hyperalgesia which suggests that we should be interested in pre-emptive analgesia

produced by opioids, anaesthetics and NMDA antagonists with differential effects on wind-up related to their site of action.[10,11] All general anaesthetics can depress the activities of interneurones in these laminae with Rexed's lamina V cells of particular importance as these are activated by stimulation of C fibres and by thin myelinated fibres coming from skin, muscles and viscera.

The formalin test reflects, as any acute injury, a surprisingly complex series of events which allows a measurement of the effect of central sensitisation.[12,13,14]

Subcutaneous injection of formalin into the hindpaw of the rat, results in a biphasic nocifensive behaviour, recorded as flinches per minute, due to the creation of a hyperalgesic state. Phase 1 reflects an acute noxious response (C-fibre mediated up to10 minutes) and Phase 2 reflects the injury-induced spinal responses, due to central sensitisation, from 10 to 90 minutes, and mediated by excitatory amino acids on NMDA receptors which correlates with the expression of Fos-LI.[4]

ANAESTHESIA ELEMENTS
Intravenous induction agents
In the formalin test thiopentone offers no useful benefit over control whereas propofol reduces the Phase 2 response to 59%; the lack of effect by thiopentone upon phase 2 may represent antanalgesia or an absence of the beneficial effects on spinal sensitisation of gamma-amino-butyric-acid (GABA) action.[15] Gilron and Coderre were unable to demonstrate any pre-emptive effect with either pentobarbitone or propofol but considered that a dose-dependent benefit seen with alphaxalone at 15 minutes might be through a selective action on GABA receptors inhibiting a persistent nociceptive state.[16] In common with barbiturates and ketamine, alphaxalone-alphadalone (Althesin) also depresses lamina V neurones which may, in part, explain this analgesic effect.[17]

The effectiveness of NMDA antagonism favours thamylal with 87% recovery after 6 minutes versus ketamine 82%, thiopentone 78%, propofol 18% and etomidate 13%.[18] Propofol depresses NMDA-mediated excitatory neurotransmission, possibly through allosteric modulation of channel gating by 10-20% at anaesthetic concentrations in vitro.[19] Lipid emulsions themselves, however, such as 20% intralipid 1:80 may activate NMDA receptors.[20] The effect is unlikely to be relevant following a typical induction dose of propofol because of rapid dilution by redistribution, but may be relevant if an infusion is used.

Inhalational anaesthetic agents
Inhalational anaesthetics affect spinal cord processing and may modulate the response to noxious stimuli by suppressing transmission of nociception through modification of the activity of NMDA receptors; GABA agonist action may explain the inhibitory effects of inhalational (and intravenous) anaesthetic agents on spinal sensitisation.[15]

All 3 glutamate ionotropic receptor subtypes (sensitive to NMDA, kainate [kainic acid] and α-amino-d-hydroxy-5-methyl-4-isoxazole-propionate [AMPA] respectively) are susceptible to suppression by inhalational anaesthetics with each compound having its own pattern of action not quite identical to the others.

In Xenopus oocytes Hollman showed that isoflurane, desflurane and sevoflurane all inhibit NMDA receptor action and glutamate signalling potentiated by magnesium and ketamine while Minami found that all inhalational anaesthetics

also inhibit substance P receptors at clinically relevant concentrations.[21,22] The volatile anaesthetics protect against the excitotoxicity of NMDA; halothane > isoflurane > sevoflurane at MAC equivalent concentrations; lipid solubility may be an issue.[23]

Enflurane at clinically relevant concentrations produces a 20-40% inhibition of glutamate receptor-gated currents and isoflurane has an action on the NMDA subtype.[24,25,26] In the rat formalin test inhalational anaesthetics reduce Phase 2 flinching at MAC equivalent levels desflurane>isoflurane>halothane>nitrous oxide>enflurane but a nitrous oxide/halothane combination is the worst and one may oppose the action of the other within the CNS, perhaps through opioid receptor action.[13,15] Isoflurane at clinically relevant concentration shows a weak depressant action to prevent wind-up.[27] Presynaptic isoflurane-induced inhibition of the excitatory postsynaptic potential may contribute to inhibition of glutamate release and influence spinal sensitisation.[28] Sevoflurane suppresses formalin-induced persistent flinching behaviour and c-Fos expression in the dorsal horn, reducing, in part, the effect of nociceptive stimuli possibly through activation of endogenous opioid systems; NMDA-receptor mediated responses are more sensitive than AMPA consistent with a potent action on nociceptive transmission.[29,30]

The level of anaesthesia required to prevent the post-injury state of facilitated processing or wind up (MAC-FAC) may not be achievable with inhalational agents alone but, in the rat formalin test, can be achieved with the addition of preoperative intrathecal opiate at a cost of little physiologic compromise, and this may well avoid the development of chronic pain.[31]

Opioids

There is no dispute that peripheral, spinal and supraspinal opioid receptors mediate the analgesic effects of opioids by a predominantly pre-synaptic action. However, the relative contribution of each site to a given analgesic effect is not clear.

In addition to their direct effects upon opioid receptors, certain compounds also act indirectly as NMDA antagonists and may therefore have superadditive benefits when used perioperatively.[32] Methadone, which has the additional advantage of a long duration of action is the best example of this.[33]

Morphine, with a pre-synaptic action on the μ opioid receptor (MOR) will synergise with any post-synaptic NMDA antagonist action; inhibition of primary afferent transmitter release by morphine and reduced post-synaptic depolarisation via glycine site antagonism results in decreased nociceptive input and hence wind-up to produce a profound inhibitory action, suggesting the clinical possibilities of combining morphine with ketamine which has been demonstrated to be of value following major surgery.[34,35] Intrathecal opioid in combination with an inhalational anaesthetic shows significant benefit.[14] In addition non-opioids may exert their effects in part by activating endogenous opioid systems.[29]

Non-steroidal anti-inflammatory drugs

Inflammation promotes the release of neuropeptides from sensory nerve terminals in the spinal cord which may contribute to enhanced nociception and the development of hyperalgesia through increased excitability of sensory neurones. The central actions of non-steroidal anti-inflammatory drugs (NSAIDs), particularly with respect to hyperalgesia may account in part for their potency in reducing postoperative pain. Cyclooxygenase products play an important part in the regulation of spinal nociceptive processing, with inhibitors playing a significant role and demonstrating significant synergy with morphine.[36] NSAIDs inhibit the nuclear transcription factor κB that is critical for cytokine gene expression during inflammation with possible central effects.

Cyclooxygenase-1 (COX 1) levels in the spinal cord are increased after incisional surgery and may contribute to the development of long-term hypersensitivity which can be inhibited or attenuated by COX 1 inhibitors such as intrathecal ketorolac acting on the spinal cord.[37,38,39]

In vitro ketorolac prevents or reduces the excitation induced by NMDA on spinal WDR neurones suggesting a central effect.[40] In the rat formalin test intrathecal NSAIDs produced minimal effects on Phase 1 but a significant dose-dependent suppression of Phase 2 (indomethacin >= flurbiprofen > ketorolac >= zomepirac > ibuprofen > acetylsalicylic acid >> paracetamol) suggesting a powerful effect on spinal nociceptive processing at doses that are 100-800 times lower than those required after systemic administration.[41]

That the rapid onset of analgesia following cyclooxygenase-2 (COX 2) inhibitors is via a central effect. This has now been confirmed in humans with the demonstration that NSAID-mediated antihyperalgesia follows the intravenous administration of 40 mg parecoxib; paracetamol shows equivalent benefit.[42,43] Ketoprofen has both central actions reducing wind up and peripheral effects. How may this, for example, best be exploited?[44]

Gabapentin

Gabapentin, structurally resembling the GABA molecule, with a major role in pain management has been described as a broad-spectrum analgesic not only acting centrally to modulate GABA synaptic transmission (agonist) but also on sodium and calcium channels, affecting the actions of EAAs and substance P.[45,46] Beneficial effects on acute postoperative pain have been reported and these may serve to reduce the likelihood of chronic pain developing.[47,48,49,50]

Postoperative pain

Surgery with subsequent acute post-operative pain is the risk for the development of chronic pain.[51] The required benefits of meticulous and aggressive perioperative analgesia ensuring a pain-free emergence from anaesthesia to ensure that the patient is not psychologically assaulted by uncontrolled pain may extend beyond the acute phase but the beneficial effects of NMDA-receptor antagonists are reduced after the event once wind-up has occurred.

Pre-emptive analgesia has been applied widely to the reduction of acute pain, including the use of NMDA antagonists but neither has been reliably shown to have a beneficial effect nor studied as it might affect the development of chronic pain.[52] The pre-emptive efficacy of ketamine, when epidurally administered, has, however, recently been reported for post-thoracotomy pain.[53]

CONCLUSION

The introduction of the concept of balanced anaesthesia may have inadvertently created this problem and now we must move on to ensure balance not only with respect to sleep, analgesia and relaxation but also including the suppression of spinal sensitisation.

The sought after rapid recovery through low fat solubility

means that the inhalational agent does not get to where it is needed in sufficient concentration to avoid spinal sensitisation. To ensure MAC-FAC may require a combination of inhalational anaesthetic with other agents such as an opioid, particularly intrathecally administered. The role of opioids in terms of not only their mechanisms and sites of action but also delivery must receive consideration.

In respect of the NSAID's, there is insufficient information about levels in the cerebrospinal fluid after different routes of administration to allow conclusions about efficacy, and the intrathecal option in humans is not currently available. The intravenous bolus use of drugs such as diclofenac, ketorolac and parecoxib may indeed be appropriate, and paracetamol should probably be included for all cases. Psychological assessment and preparation could be beneficially introduced into the preoperative clinic to identify patients at particular risk.

Can we, as anaesthetists, do better for patients at risk?

Numerous signposts to the right direction already exist. Thiopentone should, perhaps, be avoided and nitrous oxide may offset some of the benefits of inhalational agents.[54] Administration of the inhalational agent at a higher concentration than is usual practice has already been shown to reduce postoperative pain in patients receiving isoflurane undergoing bariatric surgery.[55] Opioid must be provided to the right location in sufficient amount and agents with NMDA antagonist action are favoured. Lipid infusions for maintenance of anaesthesia may need to be avoided.

The optimum may be inhalational agent to maximum tolerance, plus intrathecal opioid together with adjuvants. This avoids the 'light' general anaesthetic combined with the epidural administration of both opioid and local anaesthetic in low concentration always being careful to balance benefits with any potential harm for the individual patient. Other drugs such as sodium or calcium channel blockers, adrenergic alpha 2 agonists, GABA agonists and substance P antagonists might all be used together for preemption.

Avoiding the transition from acute postoperative to chronic persistent pain must become the anaesthetist's goal.[56]

FUTURE DIRECTION
Research to study patients before the onset of chronic pain is impractical, except of course with respect to postoperative pain and, although any result would be a long time coming, it is still very worthwhile to undertake. We must develop, evaluate and introduce strategies of prevention to reduce the number of patients with chronic pain following surgery and I contend that this must include the components and conduct of the anaesthetic itself.[57]

A uniform, well-defined method to assess the many chronic pain variables for this must be agreed upon and associated with optimal multimodal acute pain treatment.[58] Because the results of treating chronic pain syndromes are often disappointing, attention must be focused on prevention to identify the following:
1. Which patients are at risk and can they be identified beforehand, perhaps with the involvement of the family practitioner.
2. Whether the pathophysiological pathway leading to chronic pain can be successfully interrupted.
3. Do worthwhile beneficial effects of NMDA-receptor antagonists occur after the event once wind-up has occurred.
4. Can effective levels of NSAID's in the cerebrospinal fluid be achieved by oral or parenteral administration.

Perhaps then we can quantify the benefits of prevention, how clinically and cost effective they are when applied day to day and, together with the improved management of acute postoperative pain put together and promote the right package for Balanced Anaesthesia in 2005.

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