

Anesthetic Pharmacology Update 2010
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This talk is meant to review many of the articles featured in the medical literature pertaining to anesthetic clinical pharmacology, but mainly from *Anesthesia & Analgesia* and *Anesthesiology* during the 2009 calendar year. In theory, these articles should represent the current thinking in how pharmacologic principles are brought to bear in order to solve clinical problems in anesthesia practice and perioperative medicine. Undertaking this sort of review each year always leaves me wondering, “What if there was nothing of particular interest to tell?” Being a regular reviewer for *Anesthesia & Analgesia* and having been an Associate Editor for *Anesthesiology* and current frequent reviewer gives me encouragement that this approach is worthwhile, as some remarkably good and relevant science continues to be submitted to both journals. In fact, I think it is getting steadily better and more exciting.

Of course, not every article published in 2009 is contained in this review, meant to last 40 minutes. The criteria I used in selecting articles were pretty straightforward. I simply looked at each title and article from each issue of the journals while asking myself two questions: “Does this have any clinical relevance either now or in the near future?” and “Do I want to talk about this?”

What follows are the selected articles and key phrases lifted from the articles’ texts. This should give you a platform to for additional thoughts that I may express during the talk or that you may note for your own opinions about the matter and questions.

The Articles:

¹ Guay J. **Methemoglobinemia related to local anesthetics: a summary of 242 episodes.** *Anesth Analg* 2009;108:837-45.

Methemoglobin describes the oxidized form of the iron moiety (Fe^{3+}) within the hemoglobin molecule. It is formed in the presence of an oxidizing substrate and is useless for oxygen carrying. An abnormally high level of methemoglobin will occur when the production exceeds the capacity of the methemoglobin reduction processes. This may happen after exposure to various toxic substances and drugs which may be divided into direct and indirect oxidizers, which are capable of inducing methemoglobin formation when added to erythrocytes. Local anesthetics are indirect oxidizers.

Because it is impossible to predict which individuals will be susceptible to develop methemoglobinemia after benzocaine exposure, and also because there is no therapeutic window (between the doses required to produce a therapeutic effect and those producing toxicity) in susceptible individuals, the clinical use of benzocaine should be abandoned.

² Brookes ZL, McGown CC, Reilly CS. **Statins for all: the new premed?** *Br J Anaesth* 2009;103:99-107.

There is evidence that statins have beneficial effects beyond those of lipid lowering, including reducing the perioperative risk of cardiac complications and sepsis. Statins appear to have actions on vascular nitric oxide through the balance of inducible and endothelial nitric oxide synthase.

Statins reduce low-density lipoprotein (LDL) in the body and also plasma triglycerides and apolipoprotein B. There is also some evidence that they may increase high-density lipoprotein (HDL). The UK MRC/BHF Heart Protection Study^[22] enrolled 20 536 patients (aged 40-80 yr) with coronary disease or other occlusive arterial diseases and determined that simvastatin 40 mg daily reduced the rates of myocardial infarction and stroke by about one-quarter. Furthermore, a non-randomized study of 551 patients with systolic heart failure, 45% of whom had CAD and were receiving statin therapy, demonstrated improved survival rates from ischaemic and non-ischemic heart failure in the patients taking statins.

Despite limited prospective clinical data, some studies have been performed in animals with death as the endpoint. In mice, pretreatment with simvastatin for 18 and 3 h before induction of sepsis using the caecal ligation puncture model increased survival rate four-fold. Patients hospitalized with an acute coronary syndrome, ischaemic stroke, or revascularization and prescribed a statin demonstrated a lower incidence of sepsis compared with controls (71.2 vs 88.0 events per 10 000 person-years). A retrospective cohort analysis in 438 patients also determined that statin use before hospital admission, and continued after sepsis, correlated with decreased mortality rates from septicemia.

There is reasonably strong evidence that patients already taking statins should continue on them perioperatively. However, the evidence for the prophylactic use of statins perioperatively is weak and lacks prospective controlled studies.

³ Dreixler JC, Hagevik S, Hemmert JW, Shaikh AR, Rosenbaum DM, Roth S. **Involvement of erythropoietin in retinal ischemic preconditioning.** *Anesthesiology* 2009;110:774-80.

An endogenous protective capacity in the rat retina, produced by ischemic preconditioning (IPC) can induce tolerance to retinal ischemia. A potential signaling pathway in retinal IPC is the hematopoietic cytokine erythropoietin. Intriguingly, erythropoietin, in addition to its hematopoietic effects, protects neurons from ischemic damage, and it may decrease neuronal injury in stroke.

The authors demonstrate role of erythropoietin (EPO) and EPO-receptors in retinal neuroprotective pathways. EPO-receptors but not erythropoietin protein levels are increased with IPC. Soluble EPO-receptors attenuated the protective effects of IPC on retinal function, retinal ganglion cell loss, and apoptosis after ischemia.

Also, activation of extracellular-signal-regulated kinase (ERK) of ERK and heat shock protein 27 (HSP27), potential neuroprotective pathways, occur downstream of upregulation of the EPO-receptors after IPC.

⁴ McKay A, Gottschalk A, Ploppa A, Durieux ME, Groves DS. **Systemic lidocaine decreased the perioperative opioid analgesic requirements but failed to reduce discharge time after ambulatory surgery.** *Anesth Analg* 2009;109:1805-8.

However, whereas decreased hospital stay after inpatient surgery has been demonstrated, the effect of intraoperative and early postoperative lidocaine infusion on duration of stay after ambulatory surgery is not known. Although it seems logical that decreased pain would allow earlier discharge, it is conceivable that, e.g., mild sedating effects of lidocaine could prolong postanesthesia care unit (PACU) admission and interfere with discharge.

A meta-analysis of 8 randomized, controlled, clinical trials in patients undergoing abdominal surgery showed that continuous perioperative IV lidocaine administration reduces the duration of postoperative ileus, pain, nausea, and vomiting and shortens hospital stay.

Found an opioid-sparing effect in the perioperative and early postoperative period. These effects did not affect recovery time by more than half an hour. The opioid-sparing effect of IV lidocaine did not affect the incidence of nausea and vomiting or time to discharge in our study population of ambulatory surgery patients.

⁵ Wu CL, Liu SS. **Intravenous lidocaine for ambulatory anesthesia: good to go or not so fast?** *Anesth Analg* 2009;109:1718-9.

Although rarely used as a component of ambulatory anesthesia, perioperative infusion of IV lidocaine is attractive. Low-dose IV lidocaine is easy to administer, has well-established analgesic, antihyperalgesic, and antiinflammatory effects, and has minimal toxicity in commonly studied doses (typically 1.5–3 mg/kg/1 h). Researchers examining infusion of IV lidocaine for various major abdominal procedures in previous randomized controlled trials reported quite favorable effects that have been summarized in a recent meta-analysis.

Use of lidocaine significantly reduced the incidence of nausea and vomiting (32% vs 52%), marginally reduced pain scores (□5/100 mm visual analog scale), and decreased duration of postoperative ileus (□8.4 h) and hospital stay (□0.84 days). These are impressive results from a simple intervention and compare favorably with the effects from the more technically cumbersome and expensive use of epidural analgesia. Thus, it makes sense to investigate whether such positive outcomes from IV lidocaine can be transported to the field of ambulatory anesthesia. Currently, most surgeries in the United States are performed on an ambulatory basis (60% of all procedures in 2007), and an inexpensive, technically

simple, and time-limited intervention that provides long-lasting benefit would be valuable.

However, the effects of IV lidocaine in this study were much less gratifying than previously reported for major abdominal surgery. The reason may lie with lidocaine's antiinflammatory effects, which may play a bigger role following major abdominal surgery.

⁶ Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. **The effect of perioperative intravenous lidocaine on postoperative pain and immune function.** *Anesth Analg* 2009;109:1464-9.

It has been shown that IV lidocaine provides effective postoperative analgesia, reduces opiate consumption, accelerates the recovery of bowel function, and facilitates rehabilitation after surgery. Tissue and peripheral nerve injury leads to a local inflammatory reaction accompanied by increased levels of proinflammatory cytokines, including interleukin (IL)-1 α and IL-6, which induce peripheral and central nervous system sensitization leading to hyperalgesia. IL-1 induces long-lasting synthesis and release of substance P from peripheral nerve terminals of primary afferent neurons, which may contribute to neurogenic inflammation. Lidocaine has an antiinflammatory property reflected by decreased upregulation of proinflammatory cytokines both *in vitro* and *in vivo*

The group receiving preincisional and intraoperative IV lidocaine experienced better pain relief in the immediate postoperative period, which was associated with an attenuated suppression of a lymphocyte proliferative response and attenuated production of both pro- and antiinflammatory cytokines (IL-6 and IL-1 α , respectively).

⁷ Dietis N, Guerrini R, Calo G, Salvadori S, Rowbotham DJ, Lambert DG. **Simultaneous targeting of multiple opioid receptors: a strategy to improve side-effect profile.** *Br J Anaesth* 2009;103:38-49.

There is now good laboratory evidence to suggest that blocking delta opioid receptors while activating mu opioid receptors produces analgesia (or antinociception) without the development of tolerance. Simultaneous targeting of mu opioid receptors and delta opioid receptors can be accomplished by: (i) co-administering two selective drugs, (ii) administering one non-selective drug, or (iii) designing a single drug that specifically targets both receptors; a bivalent ligand. Bivalent ligands generally contain two active centres or pharmacophores that are variably separated by a chemical spacer and there are several interesting examples in the literature. For example linking the mu opioid receptors agonist oxycodone to the delta opioid receptors antagonist naltrindole produces a MOP/DOP bivalent ligand that should produce analgesia with reduced tolerance. The type of response/selectivity produced depends on the pharmacophore combination (e.g. oxycodone and naltrindole as above) and the space between them. Production

and evaluation of bivalent ligands is an emerging field in drug design and for anaesthesia, analgesics that are designed not to be highly selective morphine-like (MOP) ligands represents a new avenue for the production of useful drugs for chronic (and in particular cancer) pain.

⁸ Nelson AM, Battersby AS, Baghdoyan HA, Lydic R. **Opioid-induced decreases in rat brain adenosine levels are reversed by inhibiting adenosine deaminase.** *Anesthesiology* 2009;111:1327-33.

Opioids provide excellent pain management but cause the unwanted side effect of sleep disruption. Interrupted sleep heightens the perception of pain, which increases opioid requirement. Adenosine increases sleep, and adenosine can contribute to pain management in a manner that can be opioid sparing.

Opioids disrupt sleep even in pain-free human volunteers. Sleep disruption reduces emotional well-being, causes hyperalgesia, and exacerbates pain.

The pontine reticular formation (PRF) and the substantia innominata (SI) region of the basal forebrain contribute to the regulation of sleep and anesthesia. Sleep is disrupted by delivery of opioids to the PRF or to the SI. In contrast, sleep is increased.

For more than 10 yr, adenosine has been investigated as a potential adjunctive tool for pain management. Therefore, reversing the opioid-induced decrease in adenosine within both the PRF and the SI region of the basal forebrain, prevented any opioid induced decreases in adenosine. This encourages continuing efforts to develop adjunctive therapies to counter opioid-induced disruptions of sleep and wakefulness.

⁹ Moore JT, Kelz MB. **Opiates, sleep, and pain: the adenosinergic link.** *Anesthesiology* 2009;111:1175-6.

The work by Nelson et al., suggests a promising strategy to break the insidious cycle of opiate use leading to poor sleep, worsened pain, and back to more opiate use.

Within the basal forebrain and the pontine reticular formation, fluctuating adenosine levels modulate propensity to sleep. The BF provides much of the cortical cholinergic excitatory input necessary for sensory awareness and cognition.

¹⁰ van Dorp EL, Kest B, Kowalczyk WJ, et al. **Morphine-6beta-glucuronide rapidly increases pain sensitivity independently of opioid receptor activity in mice and humans.** *Anesthesiology* 2009;110:1356-63.

Chronic opioid use is associated with several unwanted side effects, including a paradoxical increase in pain sensitivity. This opioid-induced hyperalgesia has been

reported in preclinical studies with rodents and humans and described in the clinical literature. N-methyl-D-aspartate (NMDA) receptor antagonists, such as MK-801, reverse morphine hyperalgesia. Because NMDA antagonists also potentiate opioid analgesia, they might attenuate hyperalgesia indirectly, by increasing the latent opioid analgesia obscured by the concurrent increased nociception. However, this possibility is not supported by the demonstration that MK-801 reverses morphine hyperalgesia in naltrexone-pelleted mice.

One of the metabolites of morphine, morphine-6-glucuronide (M6G), displays affinity at opioid receptors equal to that of morphine and is a potent opioid analgesic in humans and mice. However, data from some studies suggest that acute M6G doses can cause hyperalgesia. Furthermore, morphine conjugation also yields morphine-3-glucuronide (M3G), a pronociceptive metabolite thought to underlie morphine hyperalgesia.

Despite whatever advantages M6G may afford for the treatment of pain, the current results suggest that the absence of hyperalgesia is not one of them.

¹¹ Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F.

Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. *Anesthesiology* 2010;112:34-40.

¹² Lien CA. **Neostigmine: how much is necessary for patients who receive a nondepolarizing neuromuscular blocking agent?** *Anesthesiology* 2010;112:16-8.

Incomplete neuromuscular recovery may cause reduction in vital capacity and hypoxic ventilatory response, as well as obstruction of the upper airway and disruption of pharyngeal function. In addition, Murphy et al. recently confirmed that residual paralysis was an important contributing factor to critical postoperative respiratory events. In their case-control study, the mean train-of-four (TOF) ratio when arriving in the postanesthesia care unit was 0.62 in patients experiencing critical respiratory events, whereas it was 0.98 in control patients. Moreover, no control patients had TOF values less than 0.7.

Unfortunately, these low degrees of residual paralysis cannot be detected reliably either by the anesthesiologist alone or by using a simple peripheral nerve stimulator, so reversal (perhaps at a reduced dose) may be indicated. There is now a consensus that these low degrees of residual paralysis are relatively frequent, difficult to detect, and still potentially harmful. However, the appropriate dose of anticholinesterase for this situation has not yet been determined.

According to the results of this study at least 20 mcg/kg of neostigmine should be given to reverse a TOF ratio of 0.4 or 0.6 within 10 min. Indeed, taking a TOF ratio of 0.9 as the endpoint of adequate neuromuscular recovery, the probability of success was 100% after the administration of 20 mcg/kg of neostigmine—whether it was given at a TOF ratio of 0.4 or 0.6.

In the editorial by Lien, she states that on the basis of the results of this study clinicians can be reassured that administration of 50 mcg/kg of neostigmine is not necessary if a patient has four equal responses to TOF stimulation and that a dose of 30 mcg/kg will be sufficient. Routine use of even smaller doses of anticholinesterases when no fade is appreciable in the TOFR requires that quantitative monitors be available to document the depth of block being antagonized as well as the time to complete recovery of neuromuscular function.

¹³ Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. **Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine.** *Anesthesiology* 2009;110:1020-5.

Succinylcholine is associated with a variety of adverse events and contraindications. Unfortunately, decades of efforts to develop a new nondepolarizing NMBA both safer and shorter-acting than succinylcholine have failed. The nondepolarizing NMBA rocuronium is also indicated to facilitate tracheal intubation during routine and rapid-sequence intubation, especially where succinylcholine is contraindicated. No significant differences have been observed between 1 mg/kg succinylcholine 0.9 to 1.2 mg/kg rocuronium. However, higher doses of rocuronium have a long duration of action; this is inappropriate in situations where rapid recovery of neuromuscular function is required.

A plausible new approach to both rapid onset and rapid recovery of neuromuscular block might involve blocking with high-dose rocuronium and reversal using high-dose sugammadex. In this study reversal of profound high-dose rocuronium-induced neuromuscular block (1.2 mg/kg) with sugammadex (16 mg/kg) was significantly faster than spontaneous recovery from succinylcholine (1 mg/kg).

¹⁴ Martin LJ, Oh GH, Orser BA. **Etomidate targets alpha5 gamma-aminobutyric acid subtype A receptors to regulate synaptic plasticity and memory blockade.** *Anesthesiology* 2009;111:1025-35.

¹⁵ Dai S, Perouansky M, Pearce RA. **Amnestic concentrations of etomidate modulate GABA_A slow synaptic inhibition in hippocampus.** *Anesthesiology* 2009;111:766-73.

Located at extrasynaptic sites on pyramidal neurons, receptors containing GABA_A α 5 subunits have been shown to mediate tonic inhibition. The finding that tonic inhibition is enhanced at low anesthetic concentrations, together with the demonstration that mice lacking the α 5 subunit are resistant to the amnestic action of etomidate, thus pointed to tonic inhibition in the hippocampus as the principal mechanism for this behavioral effect.

A molecular process that is thought to be essential to the storage of information involving the hippocampus is the long-term modification of excitatory

glutamatergic transmission, which is known as long-term potentiation (LTP). Etomidate, studied at a concentration that occurs in vivo during memory impairment, abolished LTP induced by high-frequency stimulation in hippocampal slices from wild-type (WT) but not mice lacking the GABA_A α 5 subunit.

In addition, recent findings indicate that receptors containing α 5 subunits are also located at dendritic synapses and that they underlie a slow form of synaptic (phasic, as opposed to tonic) inhibition in hippocampal CA1 pyramidal neurons. The ability of GABA_B antagonists to impair long-term potentiation demonstrates the effectiveness of GABA_{A,slow} in controlling dendritic depolarization and synaptic plasticity.

¹⁶ Perouansky M, Hemmings HC, Jr. **Neurotoxicity of general anesthetics: cause for concern?** *Anesthesiology* 2009;111:1365-71.

¹⁷ Patel P, Sun L. **Update on neonatal anesthetic neurotoxicity: insight into molecular mechanisms and relevance to humans.** *Anesthesiology* 2009;110:703-8.

Recent laboratory data call for a cautious reassessment of the assumption that general anesthesia is a fully reversible process. In the past decade, it has become apparent that anesthetics can affect gene expression, protein synthesis and processing, and cellular function in poorly understood ways that provide plausible biochemical substrates for durable long-term effects in a number of tissues. Although in most patients physiologic homeostasis is restored soon after general anesthesia, anesthetics have potentially profound and long-lasting effects that, in animal models, seem particularly consequential in specific developmental periods and pathophysiologic contexts.

Could a class of drugs used for many decades without evidence of long-term damage have insidious and heretofore unrecognized neurotoxic effects? Because it might take years to accurately define these risks, it is appropriate to comment on the existing laboratory data from the clinical perspective.

When effects on learning and memory were observed, be it improvement in adult or deterioration in aged rodents, they seemed to last for weeks, which is considerably longer than predicted by the pharmacokinetic properties of potent inhalational agents. Although the mechanism of neurodegeneration in Alzheimer's disease is still unclear, the leading theory implicates toxic effects mediated by the accumulation and aggregation of amyloid-peptides into a variety of soluble oligomers. A 2-h isoflurane anesthetic in mice activated biomarkers compatible with a transient neurotoxic effect: an increase in caspase 3 (a marker of apoptosis) 6 h after anesthesia was followed by increased amyloid B peptides 24 h after exposure.

Clinical studies have not identified an effect of general versus regional anesthesia, which suggests that the surgical insult itself might play a critical role in POCD.

Recent experiments provide evidence for a role of inflammation in early cognitive abnormalities, at least in adult animals.

Receptors for the most abundant excitatory (L-glutamate) and/or inhibitory (γ -aminobutyric acid [GABA]) neurotransmitters are affected by all known anesthetic drugs at concentrations achieved during clinical anesthesia, but the contributions of these and other known drug-receptor interactions to their desirable or undesirable effects are far less clear. It is important to note that the signaling systems activated by these two transmitters undergo dramatic changes during the maturation of the CNS. In contrast to the mature brain, transient pharmacologic blockade of N-methyl-D-aspartate (NMDA) receptors in the developing rodent brain causes excessive neuronal apoptosis, whereas neuronal degeneration caused by ethanol is even more widespread, perhaps because of its ability to enhance GABA_A receptors in addition to blocking NMDA receptors.

¹⁸ Sanders RD, Xu J, Shu Y, et al. **Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment in neonatal rats.** *Anesthesiology* 2009;110:1077-85.

Early in life, α 2 adrenoceptors are thought to play a trophic role in central nervous system signaling, with endogenous norepinephrine activating cellular survival mechanisms such as the Ras-Raf-pERK pathway. Activation of this Ras-Raf-pERK pathway has been associated with neuroprotection against the apoptosis induced by NMDA antagonists in the young.

This study shows that dexmedetomidine protects against anesthetic-induced apoptosis in vivo and in vitro, indicating that it does possess antiapoptotic qualities. Importantly, this study again establishes that isoflurane injury provokes a long-term neurocognitive deficit and then demonstrates that this functional deficit can be attenuated by dexmedetomidine.

The use of α 2 adrenoceptor agonists in pediatric practice is expanding as a result of their potent sedative/ hypnotic qualities, analgesic action, potential organ-protective effects, reduction in postoperative nausea and vomiting and delirium, and relative lack of respiratory side effects. Their use in neonatal practice requires evaluation based on these factors. In the future, their organ-protective, including neuroprotective, effects may be of importance to the provision of safe, balanced pediatric anesthesia.

¹⁹ Cotten JF, Husain SS, Forman SA, et al. **Methoxycarbonyl-etomidate: a novel rapidly metabolized and ultra-short-acting etomidate analogue that does not produce prolonged adrenocortical suppression.** *Anesthesiology* 2009;111:240-9.

Etomidate also potently inhibits 11 β -hydroxylase, an enzyme in the biosynthetic pathway leading to adrenocortical steroid synthesis. Etomidate's potency for inhibiting 11 β -hydroxylase is at least 100-fold greater than its hypnotic potency.

Therefore, inhibition of steroid synthesis occurs even with subhypnotic doses of etomidate.

In this report, the authors describe the results of studies characterizing (R)-3-methoxy-3-oxopropyl-(1-phenylethyl)-1H-imidazole-5-carboxylate (MOC-etomidate), the first etomidate analogue designed to undergo ultra-rapid metabolism by esterases. MOC-etomidate is a soft analogue of etomidate. A soft analogue is a derivative of a parent compound that is specifically designed to undergo rapid and predictable metabolism after exerting its therapeutic actions.³⁴ Commonly used soft analogues include the opioid remifentanyl and the β -blocker esmolol.

It has been hypothesized that etomidate inhibits 11β -hydroxylase by competing with steroid precursors at the enzyme's hydrophobic catalytic site. MOC-etomidate was designed to be rapidly metabolized by esterases to a highly hydrophilic carboxylic acid; therefore, MOC-etomidate should not produce prolonged adrenocortical suppression after administration.

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