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## Why we use intravenous anaesthesia?

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**Gavin NC Kenny, BSc (Hons), MB ChB, MD, FRCA, FANZCA,**
Glasgow University, Section of Anaesthesia, Pain & Critical Care Medicine, Glasgow, UK

## Better Anaesthesia with Intravenous Drugs?

Intravenous anaesthesia has more to offer than inhalational anaesthesia. We really can get better anaesthesia with IV drugs, emphasised Gavin NC Kenny, Glasgow University Section of Anaesthesia, Glasgow, UK. This advantage is driven by favourable pharmacokinetic and pharmacodynamic effects of propofol and by the target controlled infusion technique (TCI) allowing calibration of an individual patient's requirements.

Modern anaesthesia has complex aims including safe, stress-free induction, simple and predictable control of anaesthetic levels, preventing intraoperative awareness, rapid, smooth extubation and recovery, no more than mild post operative pain as well as no postoperative nausea and vomiting. Gavin Kenny explained why these objectives can be better achieved with IV drugs.

### Adverse effects of volatiles

Inhalational agents have many adverse effects ranging from the pollution of the operating environment, a relatively high incidence of postoperative nausea and vomiting (PONV), emergence agitation with sevoflurane up to increased production of fluoride ions after the administration of sevoflurane and after prolonged use of isoflurane. Concern about the genetic damage caused by routine exposure to inhalational agents has been expressed and exposure to even trace concentrations of waste anaesthetic agents may cause genetic damage comparable with smoking 11 – 20 cigarettes per day. Toxic effects on alveolar surfactant production have also been reported with inhalational agents but not with IV agents.

Even induction with sevoflurane considered often as an advantage of inhalational anaesthesia is not appreciated by many patients: Up to one fourth of patients would refuse a repeat induction with this volatile anaesthetic. Continuous propofol administration has been shown to be superior compared to isoflurane in relieving suxamethonium-induced postoperative myalgia scores.[1] Additionally, creatine kinase serum levels did not increase significantly during anaesthesia in patients receiving propofol whereas in isoflurane patients, creatine kinase serum levels showed a marked, statistically significant increase ($p = 0.0016$).

### Emergence agitation after sevoflurane anaesthesia

Emergence agitation in paediatric patients is another problem associated with sevoflurane anaesthesia. In a clinical study, no child developed emergence agitation when propofol was delivered for maintenance compared to 38% of patients who received sevoflurane for maintenance.[2]

PONV is the adverse effect of anaesthesia most worrying the patients – more than pain. Patients would even tolerate some pain to avoid PONV. IV anaesthesia with propofol is associated with a very low incidence of PONV compared to inhalational agents such as sevoflurane. Vomiting is not only induced by the volatile but also by the very irritant drug mixture used for inhalational anaesthesia, underlined Gavin Kenny.

### Simple and predictable control of anaesthetic depth

A major benefit of intravenous anaesthesia using a target-controlled infusion (TCI) is the ability to calibrate the individual patient's requirements for anaesthesia allowing a simple and predictable control of anaesthetic depth (figure 1). Most analyses showed a variation of only 25 – 35% between the measured and predicted blood propofol blood concentrations for the Diprifusor TCI system.[3]

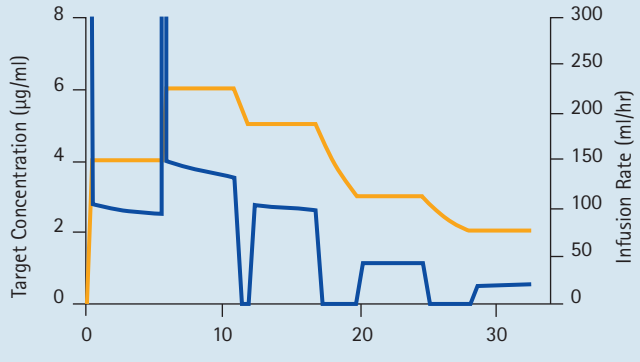


*Figure 1: Propofol concentration and infusion rates during TCI*

# Why we use intravenous anaesthesia?

For inhalational anaesthesia, it is usually stated end-tidal vapour concentrations are equivalent to blood concentrations, the Minimum Alveolar Concentration (MAC) is reliable and drug delivery is performed by sophisticated vaporisers. "Is this really true?" asked Gavin Kenny. Published data contradict this "inhalational fog". A considerable variability between blood and end-tidal partial pressures especially during changes in the inspired vapour concentration has been demonstrated with isoflurane and halothane.[4] Furthermore, MACs for individual subjects vary by more than 80% and change over time. Vapour accuracy is also much poorer than usually believed: limits of ± 15% for the output concentration are already officially accepted, but many vaporizers have outputs outside these limits. There is another important difference: TCI predicts propofol concentrations, end-tidal measures volatile concentrations.

Interpatient pharmacodynamic variability does not differ considerably between propofol and desflurane. The percentage of patients asleep varies with both agents in a similar way depending on blood concentration (propofol) respective end-tidal concentration (desflurane).[5] Propofol variability during induction is also manageable: With propofol target concentrations between 3 µg/ml and 6 µg/ml, 40 – 100% of patients are falling asleep. Premedication of 4 mg midazolam increases the rate of successful inductions in patients receiving 3 µg/ml propofol from 40% to 95%

## Intraoperative awareness

TCI can decrease awareness during general anaesthesia. In a study, loss of consciousness was obtained by progressive stepwise increases of TCI propofol using a Diprifusor in 40 patients.[6] A tape of 20 words was played to 20 control patients before the start of anaesthesia as well as to 20 patients at a constant propofol concentrations associated with loss of consciousness. Three memory tests performed postoperatively demonstrated explicit and implicit memory in the control group but not in the anaesthetised group. The similarity of individual effect-site concentrations of propofol at loss of consciousness and awaking demonstrated in Japanese volunteers also suggests avoiding of intraoperative awareness.[7]

Pharmacokinetic models are used to calculate effect-site concentrations. A recently published study compared the effect site concentrations during propofol TCI sedation (target: 2 µg/ml) predicted by the Schnider model and by the Marsh model using surrogate markers such as Observer Assessment of Alertness/Sedation score and Bispectral index.[8] 20 patients received TCI propofol driven by the Schnider model in effect site control, 20 were sedated with TCI propofol driven by the Marsh model. The observed changes in the sedation score and Bispectral index correlated better with the Marsh than with the Schnider effect site prediction. The Marsh model is more related to reality than the Schnider model, Gavin Kenny pointed out.

**Gavin Kenny concluded that TCI is the only technique which allows calibration of an individual patient's anaesthetic requirement. The effect site concentration of propofol required to induce anaesthesia is close to the effect site concentration of propofol at recovery from anaesthesia when the Marsh model is used. This means altogether: we can deliver better anaesthesia with intravenous drugs.**



**Stefan Schraag MD PhD, Professor of Anaesthesia,**
Department of Anaesthesia and Perioperative Medicine,
Golden Jubilee National Hospital, Clydebank, UK

# Non-anaesthetic benefits of intravenous anaesthesia

The introduction of intravenous anaesthetics resulted in many significant clinical and scientific improvements. Early forms of neuroleptanalgesia provided stable haemodynamics and the safe option for high risk patients and for cardiac surgery. Modern short-acting intravenous drugs like propofol and remifentanil have facilitated better titration of drug effect and enhanced recovery. Additional, non-anaesthetic benefits of propofol such as short-acting antiemesis, organ-protective effects, stabilisation of the immune function and improved patient experience and satisfaction have considerably contributed to the success of modern anaesthesia, explained Stefan Schraag, Golden Jubilee National Hospital, Clydebank, UK.

## Postoperative nausea and vomiting

From the patient's view, postoperative nausea and vomiting (PONV) is one of the most worrying side-effects of anaesthesia. PONV is induced by a wide range of triggers stimulating the chemotherapy trigger zone. The stimuli are conducted to the area postrema being responsible for the induction vomiting. In the literature, it is suggested that reduced levels of serotonin in the area postrema and the cerebro spinal fluid may explain the antiemetic property of propofol.[9] The direct antiemetic properties of propofol were also demonstrated by a clinical study treating PONV patients with subhypnotic propofol doses or placebo.[10]

Stefan Schraag presented a large meta-analysis of randomized controlled studies which reported PONV incidence after propofol anaesthesia. The analysis calculated a number-needed to treat of more than 9 patients for the prevention of one PONV episode when propofol was used for induction and at best 6 when used for maintenance.[11] Within the range of 20 - 60% control event rates, best results were obtained for propofol maintenance with a number needed to treat to prevent early nausea of 4.7 and 4.9 for any emetic event. These very important results should be taken into consideration in clinical practice, demanded Stefan Schraag. How much benefit propofol has to offer demonstrated a study investigating single agent ambulatory anaesthesia:[12] this study observed nausea rates of 3% and vomiting rates of 0% in patients induced and maintained with propofol compared with 30% respective 17% if sevoflurane was used for induction and maintenance (figure 2).

## Organ protection

There is increasing evidence for organ protection by intravenous anaesthetics especially by propofol. Propofol down-regulates oxidative stress by scavenging leading to reduced levels of hydoxyl radicals formed by brain injury (e.g. stroke).[13] In addition to the well known decrease in the cerebral consumption of oxygen following propofol administration, a significantly less cerebral infarct size was demonstrated experimentally when propofol was infused either immediately or at one hour after cerebral infarct was induced.[14] Another animal model suggests renal protection during aortic X-clamping with propofol compared to sevoflurane demonstrated by significantly lower NFkappa in propofol treated animals.[15]

The cardioprotective effects of total intravenous anaesthesia (TIVA) and volatiles (desflurane and sevoflurane) were compared by a randomised study including 414 patients undergoing coronary artery surgery with cardiopulmonary bypass.[16] The primary outcome parameter, the postoperative troponin T release did not differ between the three groups. However, there was a trend towards higher one-year mortality in patients treated with TIVA.

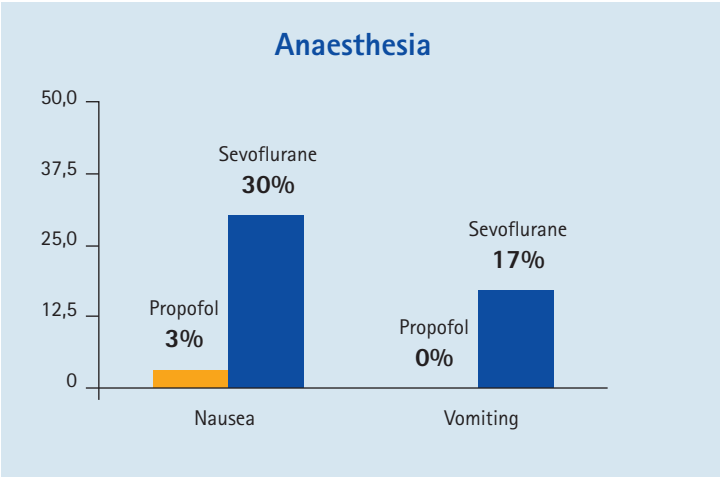


*Figure 2. Incidence of PONV in patients undergoing single agent ambulatory anaesthesia. All patients were induced and maintained with propofol or sevoflurane.[12]*

# Why we use intravenous anaesthesia?

## Physiologic effects of propofol

Important propofol effects on microcirculation have been described by an open-labelled trial including 15 patients anaesthetized by propofol for transvaginal oocyte retrieval.[17] During propofol anaesthesia, microvascular density measured in the sublingual microcirculatory network decreased by 9.1% ($p < 0.05$). Venular vascular density remained unchanged but the density of perfused capillaries was also significantly reduced by 16.7% ($p < 0.05$).

Whereas inhalational anaesthetics have an adverse effect on the hypoxic pulmonary vasoconstriction and also affect the production of pulmonary surfactant, propofol, at clinically relevant concentrations demonstrated protective effects against irritant-induced bronchoconstriction.[18] Additionally, high doses of propofol attenuated endotoxin induced acute lung injury in rabbits.[19] This effect was demonstrated by less leukosequestration, less severe pulmonary oedema and reduced pulmonary hyperpermeability.

## Immune system

Propofol modulates various aspects of the host's inflammatory response such as enhancing immune response by inhibition of prostanoid production, altering macrophage response via $GABA_A$ receptor, decreasing the secretion of pro-inflammatory cytokines, working as a potent antioxidant, and showing radical-scavenging activity. A randomized study including 27 patients with impaired left ventricular function undergoing coronary artery bypass grafting demonstrated the reduction of the inflammatory response by propofol in humans.[20] Propofol attenuated free-radical-mediated lipid peroxidation and systemic inflammation in this group of patients with impaired myocardial function.

## Patient satisfaction

Patient satisfaction after anaesthesia was investigated by a survey including more than 11.000 patients.[21] Most important factors preventing patient satisfaction were nausea and vomiting, pain, awareness, and surgical complications. Propofol anaesthesia influences many of these factors including postoperative pain measured by a numerical analogue scale and demonstrated by less morphine consumption.[22] The reduced postoperative pain can be added to the previously described improvement in nausea and vomiting as a potential benefit of propofol anaesthesia, Stefan Schraag pointed out. A randomized Swiss study including 305 patients undergoing minor elective gynaecologic or orthopaedic interventions confirmed the improved patient well-being and the reduction of PONV incidence by TIVA compared with sevoflurane.[23] Active Mood Scale and State-Trait-Anxiety Inventory scored significantly better in TIVA patients.

**Stefan Schraag concluded that there are several non-anaesthetic benefits of intravenous anaesthesia including prophylactic and therapeutic short-acting antiemesis, organ-protective effects, beneficial physiologic effects to many organ systems, stabilisation of immune function in the perioperative stress response and improved patients experience and satisfaction.**



**Michael G Irwin, Professor of University of Hong Kong,**
Department of Anaesthesiology, President of HK College of Anaesthesiologists, Head of Department, Queen Mary Hospital, Hong Kong

# The magic of using opioids (cardioprotection and more)

Opioids are useful for perioperative cardioprotection and possibly for other organ protection as well. Reduction of infarct size was demonstrated with remifentanil together with the abolishment of the cardioprotective effect by opioid receptor antagonists. Probably, the remifentanil pharmacokinetic may be especially advantageous for organ protection, declared Michael G Irwin, University of Hong Kong.

Ischaemic preconditioning being defined as previous exposure to transient cardiac ischaemia, provides protection from subsequent myocardial infarction and arrhythmia.[24] The phenomenon occurs in two phases: an early phase that starts within a few minutes after the initial ischaemic stimulus and lasts for 2 – 3 hours, and a late phase, which begins 12 – 24 h later and can lasts for up to 3 – 4 days (figure 3).

Certain pharmacological agents can induce the same effects as ischaemic preconditioning and a number of these drugs are used in anaesthesia. This may represent a safer and more practical way of eliciting cardioprotection, particularly in the diseased myocardium and in the perioperative setting where anaesthesia mediated or facilitated cardiac preconditioning around the stressful time of surgery would be particularly beneficial in patients at high-risk for cardiac morbidity.

## Cardioprotection by opioids

Opioids are widely used for the treatment of pain and have been shown to confer both the acute and delayed phase of cardioprotection via opioid receptors, effects similar to ischaemic preconditioning. The cardiac δ-opioid (DOP) receptor (especially δ1) and the κ-opioid (KOP) receptor as well as extracardiac μ-opioid (MOP) receptor are involved in opioid-induced cardioprotection.[25] Activation of DOP and KOP leads to protein kinase C (PKC) activation. Activated PKC acts as an amplifier of the preconditioning stimulus and stabilizes, by phosphorylation, the open state of the mitochondrial KATP channel (the main end-effector in anaesthetic preconditioning) and the sarcolemmal KATP channel. The opening of KATP channels ultimately elicits cytoprotection by decreasing cytosolic and mitochondrial Ca2+ overload.

## Anaesthetics and preconditioning

Volatile anaesthetics can also elicit acute pharmacological preconditioning; however, they do not consistently produce a second window of protection 24 h after administration in animal studies, and may have other undesirable effects. Michael Irwin and co-workers have shown in an animal model that intrathecal morphine doses as low as 1 μg/kg produce comparable cardioprotection to myocardial ischaemic preconditioning and IV morphine.[25] Myocardial preconditioning from intrathecal morphine still occurs in the presence of a peripheral opioid antagonist, and mechanistic studies indicate that intrathecal morphine can remotely protect the myocardium through a neural pathway and may involve multiple types of non opioid receptor activation.[26] Spinal adenosine may be involved in the signalling process within the intrathecal space.

Preconditioning can also occur distal to the site of organ protection and there is evidence that opioids may have a role here also. A recent study showed that in vivo transient limb ischemia releases a low molecular weight (< 15kDa), hydrophobic, circulating factor(s) which induce(s) a potent protection against myocardial ischemia/reperfusion injury in Langendorff perfused hearts and isolated cardiomyocytes in the same species.[27] This cardioprotection is transferable across species, independent of local neurogenic activity, and requires opioid receptor activation.

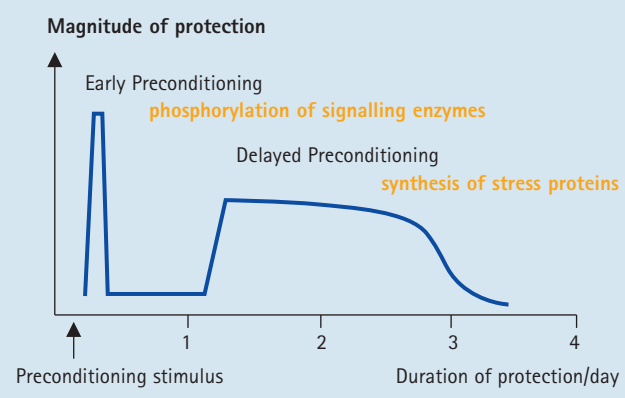


*Figure 3: Course of early and delayed preconditioning*

# Why we use intravenous anaesthesia?

## Experimental evidence with remifentanil

Remifentanil is a potent, ultra-short-acting phenylpiperidine opioid with a rapid onset, which is often used in high doses during anaesthesia and is a suitable replacement for nitrous oxide. It has no direct myocardial depressant effects yet facilitates rapid recovery which makes it attractive as a practical preconditioning agent. Ligand binding affinity studies show that remifentanil has a high affinity for the MOP receptor (EC50 = 2.6 nm) with a relatively lower affinity for the DOP receptor (EC50 = 66 nm) and KOP receptor (EC50 = 6.1 µm).

Michael Irwin's group demonstrated that remifentanil preconditioning confers acute cardioprotection in the intact rat heart and reduced dose-dependently the infarct size.[28] This effect is mediated via cardiac KOP and DOP and extracardiac MOP receptors – remote preconditioning.[29] They also observed delayed cardioprotection in a dose dependent manner in anesthetized rats 12 to 36 hours after remifentanil administration.[30] Remifentanil post-conditioning resulted, in a rat model, in a similar protection of the heart from ischaemia-reperfusion as ischaemic post-conditioning involving KOP and DOP but not MOP activation.[31] Pretreatment with remifentanil also attenuated liver injury in a rat model of ischaemic reperfusion. Inducible nitric oxide synthase might partly mediate this effect by exhausting reactive oxygen species and attenuating the inflammatory response.

Although these modulatory effects on KATP channels have been investigated almost exclusively in laboratory investigations, they may have potential implications in clinical medicine. Important questions regarding the clinical utility and applicability of perioperative cardiac preconditioning remain unresolved and need more experimental work and randomized controlled clinical trials. It is well recognized that coronary artery bypass surgery requiring cardiopulmonary bypass results in myocardial injury as detected by markers of myocyte damage. The mechanism of the injury is multifactorial, but includes ischaemia during cardioplegia induced cardiac arrest and the systemic inflammatory response associated with cardiopulmonary bypass.

## Organ protection with remifentanil – clinical studies

Michael Irwin and co-workers conducted a randomized trial and recruited forty first time elective bypass surgery patients to receive standardized fentanyl (25 µg/kg in total) and propofol anaesthesia.[32] Patients randomized to the remifentanil group (n = 20) received a 1 µg/kg bolus followed by 0.5 µg/kg/min infusion for 30 minutes after induction but before sternotomy, whilst the control group (n = 20) received normal saline. Serial samples for measurement of creatinine kinase (CKMB), cardiac troponin I (cTnI), ischaemia modified albumin (IMA) and heart type fatty acid binding protein (hFABP) were taken to assess the degree of myocardial damage. Patients in the remifentanil group had lower levels of CKMB from T = 2 h to 24 h, cTNI from T = 10 min to T = 12 h, IMA from T = 10 min to T = 2 h and h-FABP from T = 10 min to T = 12 h ($p < 0.05$). The time to extubation was shorter in patients in the remifentanil group. The addition of remifentanil to the anaesthesia regimen reduced the degree of myocardial damage. This incremental benefit may be attributable to either to remifentanil itself or to an overall increased opioid dose, the latter may be necessary to trigger the cardiac protective effect.

A further randomized study comparing TIVA (propofol plus remifentanil) with inhalational anaesthesia (isoflurane) in 40 ASA I – II patients undergoing open cholecystectomy observed a greater suppression of the inflammatory response caused be surgery in the TIVA group compared to isoflurane.[33]

**Michael Irwin concluded that opioids are useful for perioperative cardiac protection and possibly other organ protection. Due to its pharmacokinetics, remifentanil may be especially advantageous.**

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*Every effort has been made to ensure that the published dosages and instructions are correct. However the physician will remain responsible for procedures and dosing in the individual patient. It must be emphasized that actual drug concentrations in individual patients might differ from the predicted values.*


For further information please contact:

**Mrs Janette McBride**
EuroSIVA Scientific Secretariat
Tel: + 44 (0)141 211 4625
Fax: + 44 (0)141 211 1191
e-mail: j.mcbride@clinmed.gla.ac.uk
http://www.eurosiva.org/c/o University Section of Anaesthesia, Pain & Critical Care Medicine
Level 2, QEB, Glasgow Royal Infirmary
10 Alexandra Parade
Glasgow G31 2ER