Pain induced by propofol - clinical studies on drug composition and adminstration

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Pain induced by propofol - Clinical studies on drug composition and administration

Abstract

Propofol (2,6-di-isopropylphenol), one of our most common intravenous (iv) anaesthetics, is associated with pleasent sleep, rapid recovery and little postoperative nausea. When used for anaesthetic induction propofol causes severe or even intolerable pain or discomfort on injection in up to 90 % of patients. Pain on injection of propofol is even ranked by anaesthesiologists as the seventh most important clinical problem in modern anaesthesia. The concentration of free propofol within the aqueous phase of the drug formula is thought to be particularly associated with injection pain. The general aim of these studies was to investigate if we could reduce the local propofol-induced pain by various clinical measures.

In study I the influence of iv carrier fluid on propofol-induced pain was evaluated. Simultaneous iv infusion of carrier fluid was found not to influence pain intensity but to decrease the duration of pain at the site of propofol injection.

In study II we investigated the effect of the iv bolus infusion rate of propofol on pain at the site of injection. There were no difference, intensity or duration of pain between the faster and slower bolus infusion rates of propofol compared.

In study III we compared the influence of two different formulas of propofol on local pain at the site of injection. Propofol emulsions based on MCT/LCT were associated with lower pain intensity than those based on LCT only.

Study IV was designed to examine if local venous occlusion applied during and immediately after injection of propofol reduces the intensity of pain at the site of injection. Venous occlusion was found to increase the intensity but not the duration of pain at the site of propofol injection, indicating that the pain response to propofol fades during prolonged intravascular exposure,

Study V was carried out to examine if pain on injection of propofol can be reduced by previous low-dose administration of propofol by the same iv route. A lower incidence of moderate or severe local pain was induced by propofol after the low dose of propofol had been administered. Our most important results has shown that formulas based on MCT/LCT propofol are associated with less pain at the site of injection than traditional LCT formulas. Furthermore the incidence of moderate to severe propofol-induced pain can be reduced by previous low-dos injection of propofol by the same iv route two minutes before.

Key words: anesthesia; emulsion; injection; intravenous; pain; propofol; venous occlusion; visual analogue scale

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Clinical studies on drug composition and administration

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The unexamined life
is not worth living
(Socrates 470-399 BC)

To my family

CONTENTS

PUBLICATIONS

This thesis is based on the following articles, referred to in the text by their Roman numbers. All articles are reprinted with permission from the copyright owners.

I. Liljeroth E, Grauers A, Åkeson J. Pain on injection of propofol with or without infusion of carrier fluid. *Acta Anaesthesiol Scand* 2001; 45: 839-841.

II. Grauers A, Liljeroth E, Åkeson J. Propofol infusion rate does not affect local pain on injection. *Acta Anaesthesiol Scand* 2002; 46: 361-363.

III. Liljeroth E, Åkeson J. Less local pain on intravenous infusion of a new propofol emulsion. *Acta Anaesthesiol Scand* 2005; 49: 248-251.

IV. Liljeroth E, Karlsson A, Lagerkranser M, Åkeson J. Sustained intravascular exposure to propofol does not prolong pain at the site of injection. *Acta Anaesthesiol Scand.* In press.

V. Liljeroth E, Karlsson A, Lagerkranser M, Åkeson J. Low-dose propofol reduces the incidence of moderate to severe local pain induced by the main dose. *Acta Anaesthesiol Scand.* In press.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
CBF	Cerebral Blood Flow
$CMRO_2$	Cerebral Metabolic Rate for Oxygen
CNS	Cerebral Nervous System
CVR	Cerebral Vascular Resistance
GABA	Gamma Amino-Butyric Acid
G	Gauge
EMLA	Eutectic Mixture of Local Anaesthetics
iv	Intravenous
LCT	Long-Chain Triglycerides
MCT	Medium-Chain Triglycerides
NMDA	N-Methyl-D-Aspartate
NSAID	Non-Steriodal Anti-Inflammatory Drug
SD	Standard Deviation
VAS	Visual Analogue Scale

INTRODUCTION

Principles of anaesthesia

History

Clinical anaesthesiology was born in the middle of the 19th century. The isolation of morphine from opium by Sertürner is considered as one of the greatest discoveries of medical history. Back in the early 19th century Davy had reported that nitrous oxide was capable of relieving physical pain and could be used during surgery. The first public demonstration of etherisation was given in 1846 at the Massachusetts General Hospital in Boston. Cocaine began to receive attention as a local anaesthetic in Europe and America in the mid-19th century. Bier gave the first spinal anaesthesia in 1898. An essential concept was proposed towards the development of balanced anaesthesia by Fischer's and von Mering's introduction in 1903 of the first sedative barbiturate. After a gestational period of approximately 100 years modern anaesthesia began around 1940.

Definition

Anaesthesia can be defined as the provision of insensibility to pain with adequate management of vital functions during various therapeutic and diagnostic procedures.

Mechanisms

There are different theories about the mechanisms of action of anaesthetic drugs. Their potency has been proposed to correlate with the lipid solubility as well as with more specific influence on protein receptors.

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Intravenous anaesthetic induction drugs

Thiopental

The barbiturate thiopental, one of our oldest iv anaesthetic drugs, is still used for induction of anaesthesia. It acts on $GABA_A$-receptors and possibly by other mechanisms as well. The effect is fast ($t_{½}ke_0$ 1.2 min) with rapid penetration into the CNS due to a rather small central volume of distribution.

Propofol

Propofol, 2,6-di-isopropylphenol, introduced in clinical praxis in the beginning of 1980s, is today's most popular iv anaesthetic drug for induction and sedation. It is associated with pleasant sleep, rapid recovery and little postoperative nausea. However, pain at he site of injection remains an important problem since the first clinical trial in 1977 *(Kay 1977)*.

Propofol (2,6-di-isopropylphenol)

Physical and biochemical properties

Propofol, $C_{12}H_{18}O$, is a sterically hindered phenol associated with higher chemical stability and lower biotoxicity than most other phenols. However, like most phenols, it irritates the skin and mucous membranes. Propofol is not soluble in water, which is the reason why it is commercially available in a non-buffered isotonic lipid emulsion with a pH range of 6.0-9.0 *(Tan 1998)*.

Formulas

Propofol at concentrations of 10.0 or 20.0 mg/ml has traditionally been formulated in lipid emulsions containing 10 % of LCT soybean oil, but

since 1995 propofol is also commercially available in MCT/LCT emulsions. The concentration of free propofol in MCT/LCT formulas is 26 to 40 % lower than in LCT formulas, corresponding to 0.20 and 0.14 %, respectively, of the total concentration *(Babl 1995, Yamakage 2005),* as also shown in Table 1. Modifying the lipid composition of the emulsion does not have an impact on the pharmacokinetics or efficacy of propofol *(Doenicke 1997)*. Although plasma triglyceride concentrations during sedation did not differ between LCT and MCT/LCT emulsions of propofol, there was a tendency towards more rapid triglyceride elimination after administration of MCT/LCT than LCT *(Theilen 2002)*.

Formula containing	**Formula concentration of**	
10.0 mg/ml of propofol	**total propofol**	**free propofol**
dissolved in	(mg/ml)	(µg/ml)
LCT emulsion		
Diprivan	9.8	19.8
Propofol Abbott	10.0	20.2
Propofol Fresenius Kabi	10.0	19.4
Recofol	9.5	18.8
MCT/LCT emulsion		
Propofol-Lipuro	10.0	14.0

Table 1. Distribution of free and total propofol in some formulas currently available on the Swedish market.

Preparation

Propofol should be prepared in an aseptic manner for immediate use, since the emulsion may promote rapid microbial proliferation after bacterial contamination *(McHugh 1995).* Antimicrobial activity of local anaesthetics *(Schmidt 1979, Fazly 1983)* added to the propofol emulsion before administration to prevent or reduce pain on injection has only been found to limit but not prevent bacterial growth by depolarisation of microbial cell membranes *(Ohsuka 1991, Ozer 2002).*

Pharmacokinetics

The blood concentration of propofol rises rapidly after an iv bolus dose, while the rise in cerebral concentration of propofol is slower ($t_{½}ke_0$ 2.9 min). The time to unconsciousness is mainly determined by the total dose administered.

Pharmacodynamics

Like barbiturates, propofol binds to $GABA_A$-receptors but could also have other mechanisms of action involving various protein receptors. Its cerebral effects are hypnotic and possibly also analgesic *(Canavero 2004, Zacny 1996)*.

In patients with no intracranial pathology, propofol like most other anaesthetic induction agents, decreases CBF, increases CVR and reduces $CMRO_2$ *(Vandesteene 1988, Stephan 1987)*. Most studies show that propofol is a profound respiratory depressant reducing respiratory rate as well as tidal volumes *(Goodman 1987, Grounds 1987)*. Propofol can be administered in patients with coronary artery diseases under careful haemodynamic supervision. Normal induction doses reduce systolic blood pressure *(Coates 1985, Monk 1987, Coates 1987, Clayes 1988)* with variable effects on heart rate and may also reduce cardiac output *(Coates 1987, Monk 1987)*. Propofol has been reported to reset the baroreceptor reflex to allow slower heart rate despite reduced arterial pressure *(Cullen 1987)* and to have minimal adverse effects on hepatic and renal function *(Robinson 1985, Stark 1985)*.

Local pain induced by propofol

Clinical signs and importance

Intravenous injection of propofol causes pain at the site of injection, the incidence varying from less than 10 % in the antecubital fossa to 90 % on the back of the hand *(Scott 1988, Stark 1985, Johnson 1990, McCulloch 1985, Nightingale 1985).*

Pain is often reported as severe or even intolerable. The high incidence of pain on injection is a clinically relevant disadvantage particularly associated with traditional LCT formulas and has been ranked by anaesthesiologists as the seventh most important clinical problem of modern anaesthesia *(Marcario 1999)*.

The incidence of thrombosis or phlebitis after iv cannulation is considered to be less than 1 % *(Stark 1985, Nightingale 1985).*

Mechanisms

The troublesome issue of pain on injection still remains and has never been constistently eradicated. The exact mechanisms of the injection pain are not known.

The immediate vascular pain on propofol injection is attributed to a direct irritant effect of the drug *(Tan 1998)* by stimulation of venous nociceptive receptors or free nerve endings with central transmission of nerve impulse by thin, myelinated A-delta fibres *(Eriksson 1997).* This effect is probably associated mainly with the free concentration of propofol *(Doenicke1996, Doenicke 1997, Scott 1988)*. The free drug within the 10 % lipid *(Doenicke 1997, Scott 1988)* and 90% aqueous phases of available propofol emulsions (Table 1) is considered to be associated with most of the pain at the site of iv injection *(Doenicke 1996).*

The delayed pain of propofol injection has an onset latency of 10-20 s *(Tan 1998)* and is probably mediated by other mechanisms. By indirect action on the endothelium, propofol is believed to release bradykinin by

activation of the kallikrein-kinin system, which induces venous dilation and hyperpermeability, thereby probably promoting contact between free propofol and free nerve endings within the vascular wall, resulting in pain *(Nishiyama 2005)*. Significantly higher concentrations of bradykinin were found in blood mixed with LCT and MCT/LCT propofol than in blood mixed with saline *(Ohmizo 2005)*, further indicating that bradykinin is involved in the induction of pain at the site of propofol injection. Prostanoids, particularly prostaglandin E_2, were recently found to be released in plasma after iv administration of propofol in rats *(Ando 2005)* and could also be involved in this process, particularly when also considering that pretreatment with prostaglandin inhibitors administered with venous occlusion has been reported to reduce pain on injection of propofol *(Nishiyama 2005)*.

Factors other than the free concentration of propofol have also been proposed to affect the incidence and intensity of pain at the site of propofol injection. Such factors include age of patient, site of injection including size of vein, temperature and pH of formula, interaction of formula with lubricant inside plastic syringes, mixing of formula with blood, filtration of formula, speed of injection and infusion of carrier fluid.

Clinically useful techniques proposed to reduce propofol-induced pain mainly refer to modification of the drug composition (Table 1) and of the technique of administration in addition to concomitant use of other drugs as discussed further below. However, reducing the pH or increasing the temperature of the formula – in contrast to mixing with lidocaine or cooling – has been reported to reduce the concentration of free propofol in the formula *(Yamakage 2005)*.

Adjuvant drugs proposed to reduce propofol-induced pain

Several strategies have been suggested to prevent or reduce pain at the site of propofol administration. Most previous and recent work in this area has

been done on adjuvant use of hypnotic, analgesic, anti-inflammatory or local anaesthetic drugs.

Thiopental

The reason why thiopental reduces pain on injection of propofol is unknown but could involve several mechanisms. First, physical properties of thiopental such as its alkalinity or lipid solubility may change the concentration of free propofol at the site of injection *(Klement 1991).* Second, co-administration of subanaesthetic doses of thiopental may inhibit the perception of pain *(Anker-Möller 1991).* Finally, thiopental may also block the release of bradykinin, which causes venous dilation and hyperpermeability and thus promotes exposure of endovascular free nerve endings to free propofol, resulting in pain on propofol injection *(Scott 1988)*. A recent study *(Agarwal 2004)* has reported that pretreatment with thiopental 0.25 mg/kg was as effective as lidocaine in attenuating pain induced by propofol. The effect of adjuvant thiopental on the recovery after propofol anaesthesia has not been evaluated. Pain on injection of propofol was reported by 14 % of paediatric patients also given thiopental 3.0 mg/kg and by 34 % of those also given lidocaine 1.0 mg/kg *(Pollard 2002).*

Ketamine

Racemic ketamine has both hypnotic and analgesic effects. The incidence of pain after propofol administration can be reduced to less than one third by pre-treatment with 5-10 mg of ketamine *(Tan 1998, Koo 2006),* i.e. with a subanaesthetic dose affecting afferent pain pathways rather than the brain. As a non-competitive NMDA receptor antagonist, ketamine blocks NMDA receptors within and outside the CNS, which is another possible explanation for those findings. Furthermore, pharmacodynamic interaction of ketamine with the release of noradrenaline could also play a role, considering that sympathomimetics have also been reported to reduce pain induced by propofol *(Cheong 2002).* It is possible that combinations of

ketamine and propofol may have additive hypnotic and central analgesic effects *(Hui 1995).*

Opioids

Opioids are central receptor-mediated analgesics. Confirmation of opioid receptors within the peripheral nervous system *(Field 1980, Young 1980)* has prompted investigations of opioids for regional analgesia. Pethidine 40 mg and lidocaine 60 mg retained in a tourniquet-occluded vein for one minute have been reported to be equally effective in reducing pain on propofol injection *(Pang 1998)*. However, there were more side effects (skin reactions) with pethidine, whereas peripheral pain-reducing effects of morphine and fentanyl did not reach statistical significance. Accordingly, alfentanil did not relieve pain on injection of propofol by action on peripheral opioid receptors *(Wrench 1996).* Recently slow administration of remifentanil was found to be as effective as lidocaine in reducing propofol-induced pain *(Roehm 2003)*, whereas neither fentanyl nor remifentanil pre-treatment had significant effects *(Basaranoglu 2002).*
Tramadol is a centrally acting weak μ-receptor agonist inhibiting noradrenaline re-uptake as well as promoting serotonin release *(Hennies 1982).* It has been reported to have a peripheral site of action and to be as effective as lidocaine in reducing the incidence of pain on propofol injection, probably by vascular action on free nerve endings *(Wong 2001).*

Non-steroidal anti-inflammatory drugs

The effects of NSAIDs on pain from propofol injection are controversial, partially because NSAIDs themselves induce pain on injection. Although the underlying mechanism of pain induced by propofol is not clear, kinins might be involved *(Scott 1988).* Therefore, NSAIDs might reduce propofol-induced pain by inhibiting prostaglandin synthesis and/or the kinin cascade *(Vio 1983).* An NSAID prodrug, flurbiprofen, given iv just before propofol injection completely abolishes propofol injection pain, but is less effective when administered one minut in advance *(Nishiyama*

2005). Two studies have shown that iv administration of another NSAID, ketorolac, with or without venous occlusion also reduces pain on propofol injection *(Yull 2000, Huang 2002).*

Steroidal anti-inflammatory drugs

In a recent study it was shown that an antiemetic dose of dexamethasone administered one minute in advance reduces the incidence of propofol-induced pain *(Singh 2005)*. Although, the administration of dexamethasone was associated with itching and local pain in some patients, it was recommended by the authors for alleviation of propofol-induced pain in those patients where dexamethasone was to be used for other medical reasons.

Kallikrein inhibitors

Nafamostat mesilate, a kallikrein inhibitor, has been shown to prevent pain on injection of propofol *(Iwama 1998)*, possibly by inhibiting the plasma kallikrein-kinin system and the production of bradykinin *(Nakane 1998).*

Local anaesthetics

Local anaesthetics penetrate nerve cell membranes in uncharged form and interact with intracellular receptors in ionized form. Lidocaine is the local anaesthetic drug most widely used to reduce the pain associated with injection of propofol *(Scott 1988, Tan 1998, Johnson 1990, Eriksson 1997, King 1992, Picard 2000, McCulloch 1985)*. It can be administered either separately or mixed with propofol.

Clinical studies have shown less pain on injection of propofol mixed with than preceded by lidocaine *(Scott 1988, Nicole 1991, Lee 2004).* One explanation could be that lidocaine as a weak base releases hydrogen ions on exposure to lipids while being mixed with propofol. By reducing the pH of the formula lidocaine is believed to reduce the free concentration of propofol and pain at the site of injection *(Brooker 1985, Klement 1991)*. In contrast, a recent study has reported that the concentration of free propofol

in the formula is reduced by acidification but not by the addition of lidocaine *(Yamakage 2005).* Acidification does not affect the anaesthetic potency of propofol, whereas lidocaine may reduce its anaesthetic potency by destabilizing the emulsion *(Eriksson 1999).*

The most effective technique for pain reduction is proposed to be lidocaine administered with local venous occlusion for 30-120 s before the injection of propofol, which has been reported to decrease the incidence of pain to approximately 30 % *(Picard 2000, Mangar 1992),* possibly by a direct effect on vascular smooth muscle *(Arndt 1991).* However, this method is time-consuming and may be unpleasant, especially for children.

An effective way of reducing pain induced by propofol, particularly in young children, seems to be adding enough lidocaine to the formula just before the propofol injection *(Cameron 1992).* Complete abolition of pain has been reported to be achived with a freshly prepared 3 to 1 mixture of propofol and lidocaine *(Morton 1988).* A major clinical concern with such a mixture in paediatric anaesthesia is that since young children require higher doses of propofol (4-5 mg/kg) for induction of anaesthesia, there is also a higher risk of lidocaine-induced neuro- and cardiotoxicity considering that the doses of lidocaine might exceed 1.5 mg/kg. In children the minimum effective dose of lidocaine to prevent pain at the site of propofol injection was 0.2 mg/kg *(Cameron 1992),* whereas in adults half of this dose (0.1 mg/kg) significantly reduced the incidence of pain with no further improvement by higher doses *(Gehan 1991).*

Other local anaesthetics, e.g. prilocaine *(Eriksson 1995)*, have also been mixed with the formula to reduce – but not delay – propofol-induced pain.

Topical anaesthesia with EMLA cream (containing 5 % of lidocaine and prilocaine in equal proportions) applied for 60 min did not significantly reduce propofol-induced pain *(McCluskey 2003),* whereas pretreatment with topical 60 % lidocaine tape did *(Yokota 1997).*

True allergic reactions to local anaesthetics are extremely rare. Four case reports emphasize the importance of sensitivity testing *(Kennedy 1986, Ball 1999)* and of choosing an appropriate local anaesthetic *(Ismail 1997, Chiu 2004)* in patients with a history of probable allergy to lidocaine.

Sympathomimetics

Low doses (30-70 μg/kg) of ephedrine given before propofol injection have been reported to reduce the incidence and intensity of propofol-induced pain as effectively as lidocaine with no adverse haemodynamic effects during induction *(Cheong 2002)*. Bradykinin has been reported to inhibit ephedrine-induced release of noradrenaline from sympathetic nerve terminals innervating canine mesenteric and pulmonary arteries *(Greenberg 1991)*.

Beta-adrenergic inhibitors

Pretreatment with iv metoprolol, a selective β-adrenergic inhibitor, has been reported to be as effective as lidocaine in reducing propofol-induced pain *(Asik 2003)*. The authors propose that their findings resulted from local venous vasodilation induced by drug-induced inhibition of β2-receptors, but this mechanism is unlikely considering that β2-receptors themselves promote vasodilation. It therefore seems that other mechanisms are involved.

Cholinergics

Neostigmine followed by local venous occlusion has been reported to reduce pain on propofol injection *(Pang 2002)*. However, since cardiac adverse effects were found in 17 % of the patients, this technique should not be used to reduce propofol-induced pain in clinical practice.

Antiemetics

Metoclopramide, an antiemetic drug, applied with venous occlusion has been reported to be as effective as lidocaine in reducing propofol-induced pain *(Liaw 1999)*. Its chemical structure is similar to those of procaine, a local anaesthetic, and procainamide, an antiarrythmic, but its anaesthetic and antiarrythmic effects are both weak. Recently a combination of

metoclopramide and lidocaine was found to be more effective than lidocaine alone in reducing pain on iv injection of propofol *(Fujii 2005)*.

Magnesium

One clinical study has reported that magnesium sulphate effectively prevents pain induced by propofol *(Memis 2002)*. The mechanism is not clear, but interference with calcium channels and NMDA receptors may be involved.

Nitrous oxide

Inhalation of nitrous oxide (N_2O) has been reported to reduce propofol-induced pain in children *(Beh 2002),* probably mainly by its analgesic action. In a recent study a combination of lidocaine and N_2O was reported to be more effective than either treatment alone in decreasing pain on propofol injection *(Niazi 2005)*.

Other techniques proposed to reduce propofol-induced pain

Other techniques suggested to reduce pain at the site of propofol administration include modification of the drug composition, cooling, warming, dilution, separation or filtration of the formula, and modification of the site of injection and of the infusion rate of formula or carrier fluid.

Modification of drug composition

In addition to modifying the lipid composition of propofol emulsion, other propofol formulas have also been evaluated in various clinical aspects including pain at the site of iv injection.

A lower-lipid emulsion, Ampofol (Amphastar Pharmaceuticals Inc., Rancho Cucamongo, CA, USA), containing 50 % less soybean oil has been

found to be equipotent for intraoperative sedation but to induce more pain on iv injection than traditional LCT formulas *(Song 2004)*.

Clinical use of a clear solution of propofol, Cleofol (Themis Medicare, Mumbai, India), recently introduced on the Indian market, has been proposed to be associated with lower lipid load and less risk of bacterial contamination than the emulsions *(Sosis 1993, Ozer 2002)*. A recent study *(Dubey 2005)* has, however, shown a more than twice as high overall incidence of pain compared with LCT propofol.

A new water-soluble prodrug, GPI 15715 (AQUAVAN injection, Guilford Pharmaceuticals, Baltimore), hydrolysed to release propofol, has been examined for safety, tolerability, pharmacokinetics and clinical pharmacodynamics and reported to induce less pain on injection *(Fechner 2003)*. However, two subjects of nine had transient unpleasant sensations of burning or tingling on iv administration.

A new smaller-particle-size lipid emulsion of propofol, Anepol (Abbot, Chicago), has been reported to induce pain on injection in fewer patients compared with traditional LCT propofol *(Krobbuaban),* although there was no significant difference in the incidence of severe pain.

Cooling of formula

Even though the incidence and intensity of pain both decreased significantly when propofol was administered at a temperature of 4^{o}C *(McCrirrick 2005)*, the free drug concentration did not change in MCT/LCT propofol but increased slightly in LCT propofol. One explanation for this effect of cooling could be local inhibition of the kallikrein-kinin system and pain transmission from free nerve endings. Cooling of the formula did not influence the concentration of free propofol in a recent study *(Yamakage 2005)*.

Warming of formula

Warming the drug formula to body temperature before administration significantly decreased the concentration of free propofol in both

MCT/LCT and LCT propofol *(Yamakage 2005)*. However, a warm environment promotes bacterial contamination by local growth of pathogenic microorganisms, particularly in MCT/LCT propofol, which does not contain disodium edetate as a bacteriostatic *(Sosis 1993, Sosis 1995)*. In one meta-analysis however, neither cooling nor warming were found to have any effect on pain on injection *(Picard 2000)*.

Acidification of formula

Acidification of propofol formulas was recently reported to be associated with lower concentration of free propofol with less pain at the site of iv injection and maintained anaesthetic potency *(Yamakage 2005)*.

Dilution of formula

Dilution of LCT propofol with either an aqueous 5 % solution of glucose or a lipid 10 % LCT emulsion reduces the formula concentration of propofol and has been reported to be associated with reduced pain at the site of injection. However, less pain was reported after dilution with the emulsion, possibly due to a lower concentration of free propofol *(Klement 1991)*.

Infusion of carrier fluid has been reported to be associated with a higher incidence and severity of pain at the site of propofol injection compared with no infusion *(Huang 1995)*. Possibly the blood concentration of free propofol was increased by dilution of propofol with an aqueous solvent, but the carrier fluid infused simultaneously could also have influenced pain at the site of injection by flow-related effects on drug exposure to the endothelium as well as on drug clearance from the site of injection.

Accordingly, pain at the site of propofol injection has been reported to be reduced by using a double lumen iv set to separate the drug formula from the carrier fluid at the site of injection and possibly reduce local endothelial exposure to the drug by promoting more laminar flow *(Angst 1997)*.

Mixing of formula with blood

The addition of blood or lidocaine to propofol emulsion has been claimed to be equally effective in reducing pain on injection *(McDonald 1996)*. A possible explanation is that the lipid solubility of blood reduces the free propofol concentration or buffers the pH of the drug formula.

Filtration of formula

Intravenous administration of propofol through 0.2 μm microfilters has been reported to reduce both the incidence and intensity of pain at the site of injection *(Davies 2002)*, whereas using larger (5 μm) microfilters has not *(Hellier 2003)*. The underlying mechanisms remain unknown, but possibly smaller-pore microfiltration reduces contamination of silicone lubricant released by the propofol from the surface of disposable plastic syringes *(Finkelstein 1990, Lomax 1994)*.

Site of injection

The incidence of pain on iv injection of propofol ranges from 25 to 90 % on the back of the hand *(Scott 1988, Stark 1985, Johnson 1990, McCulloch 1985)* and from 3 to 36 % more proximally in the upper extremity *(Scott 1988, Stark 1985, McCulloch 1985)*. Injecting the propofol into large veins is a simple, reliable and safe way of reducing the intravascular local concentration of free propofol considered to induce much of the pain at the site of injection. Although the exact mechanisms are not known, this dilutional effect could result from less local endothelial exposure to the propofol, which is being distributed mainly in the mid-stream due to the higher blood flow. Pain at the site of injection is often completely avoided by administration via central venous catheters *(Seki 1999)*. This may be clinically applicable under certain conditions, such as in children requiring several procedures of anaesthesia during a limited period of time.

Infusion rate of formula

Slow iv administration on induction of anaesthesia has been reported to be associated with more pain at the site of injection of propofol *(Scott 1988)*, and accordingly rapid injection of propofol has been reported to induce less pain *(Shimizu 2005)*. However, the most important explanation for these findings is that the iv infusion rate of propofol determines the time to induction of anaesthesia. Consequently, slow iv infusion of propofol by delaying the loss of consciousness is more likely to induce pain at the site of injection while the patient is still being awake. In contrast, rapid injection of propofol would probably decrease the risk of moderate or severe pain before unconsciousness.

AIMS

The present thesis was designed to evaluate clinically useful techniques for reducing pain at the site of iv injection of propofol by

- developing and refining a clinical study design enabling reliable intra-individual comparison of control and study regimens [**I-V**]
- evaluating the influence of simultaneous infusion of carrier fluid [**I**]
- comparing higher and lower bolus infusion rates of propofol [**II**]
- comparing LCT and MCT/LCT emulsions of propofol [**III**]
- evaluating the influence of simultaneous local venous occlusion [**IV**]
- evaluating the influence of previous administration of low-dose propofol by the same iv route [**V**]

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PATIENTS

Study groups (I-V)

Patient characteristics (I-V)

Written informed consents were obtained from 18 to 70 year-old ASA I-II patients scheduled for general, ear-nose-throat or plastic surgery at Malmö University Hospital [**I-III**], Malmö, or the Karolinska University Hospital [**IV-V**], Solna, Sweden. The groups did not differ significantly in sex or age distributions.

Ethics (I-V)

All study protocols were approved by the Ethical Committees of Human Research at Lund University, Lund [**I-III**], and the Karolinska Institute, Stockholm [**IV-V**], Sweden.

Study design (I-V)

No premedication was given in these prospective randomised cross-over studies [**I-V**]. All drug formulas contained 10.0 mg/ml of propofol. Study designs are shown in Figure 1.

In **study I** the patients received two 2.0 ml iv bolus injections of propofol over 2.0 s at 2.0 min interval. In group I (n=15) the first bolus injection was given with no iv carrier fluid and the second one given together with 10 ml of iv carrier fluid (buffered glucose, 25 mg/ml) infused over 10 s. Correspondingly, the patients in group II (n=15) had their first injection with and their second one without the carrier fluid.

In **study II** the patients were given two 2.0 ml injections of propofol at different infusion rates (0.2 or 1.0 ml/s) at 2.0 min interval immediately before induction of general anaesthesia. Half of the patients (n=15)

received the first bolus dose over 2.0 s and the second one over 10 s, and the other half (n=15) had their injections in reversed order.
In **study III** each patient was given two 3.0 ml iv bolus injections of two different propofol emulsions containing LCT or MCT/LCT over 3.0 s in separate catheters at 5.0 min interval. The study drugs were LCT propofol followed by MCT/LCT propofol (n=34) or MCT/LCT propofol followed by LCT propofol (n=39) administered in two different catheters.

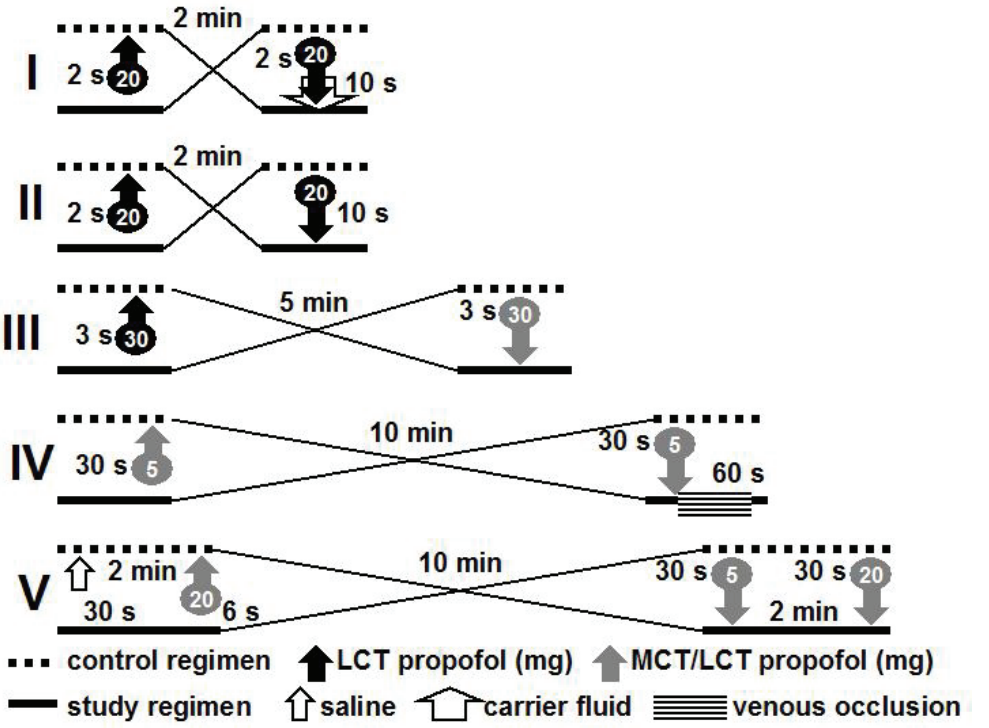

Figure 1. Schematic illustration of study designs of the project.

In **study IV** bilateral 0.5 ml injections of MCT/LCT propofol were given over 30 s at 2.0 min interval in 75 adult patients. The patients were given one injection with 60-second local occlusion of the cannulated vein followed 10 min later by another injection without occlusion (n=41), or

these two injections in reversed order (n=34), according to a randomisation cross-over schedule.

In **study V** 77 patients were given 0.5 ml of aqueous sodium chloride 9.0 mg/ml over 30 s followed 2.0 min later by 2.0 ml of MCT/LCT propofol, over 6 s, and 10 min later 0.5 ml of MCT/LCT propofol followed by 2.0 ml of MCT/LCT propofol (n=41), or given these two pairs of injections in reversed order (n=36) in two different catheters according to a randomisation cross-over schedule.

All patients were asked to score maximal pain intensity on a VAS [**I-V**]. General anaesthesia was induced with more propofol after the last pain assessment [**I-V**].

Elisabeth Liljeroth

METHODS

Control and study drugs (I-V)

Composition and concentration (I-V)

A buffered solution containing 25 mg/ml of glucose was used as carrier fluid [**I**], and sodium chloride 9.0 mg/ml dissolved in sterile water was used as control drug [**V**].
LCT propofol [**I-III**] or MCT/LCT propofol [**III-V**] 10 mg/ml were used as study drugs. The study drugs were stored and administered at room temperature [**I-V**].

Preparation (I-V)

Randomization was made consecutively in the anaesthetic room [**I-II**], or in advance, in blocks of four, by the Hospital Pharmacy at Malmö University Hospital [**III**] and, in blocks of two, by the Competence Centre for Clinical Research of Region Skåne (RSKC) [**IV-V**].

Dosing (I-V)

The doses of the study drugs are given in Table 3.

	Study drug	Concentration	Dose (mg)
Study I	**LCT propofol (Diprivan®)**	**10**	**20**
Study II	**LCT propofol (Diprivan®)**	**10**	**20**
Study III	**LCT propofol (Diprivan®)**	**10**	**30**
	MCT/LCT propofol (Propofol-Lipuro®)	**10**	**30**
Study IV	**MCT/LCT propofol (Propofol-Lipuro®)**	**10**	**5**
Study V	**MCT/LCT propofol (Propofol-Lipuro®)**	**10**	**20**

Table 2. Study drugs and doses.

Venous cannulation (I-V)

Catheters (I-V)

Teflon 20 G catheters with 1.0 mm [**I-II**] or 1.1 mm [**III-V**] internal diameters were used for iv administration of control and study drugs.

Site of cannulation (I-V)

Veins on the back of the hand were cannulated. The patients had unilateral [**I-II**] or bilateral [**III-V**] catheters inserted.

Venous occlusion (IV)

Equipment (IV)

The propofol was administered over 30 s with or without simultaneous occlusion for 60 s of the cannulated vein by inflation of two opposite cuffs (approximate size 30x20 mm) fitted inside an infant tourniquet wrapped around the wrist 6 to 8 cm proximal to the site of venous cannulation.

Pressure levels (IV)

Venous occlusion was achieved at 160 mmHg pressure with the cuffs in dorsoventral positions always covering the proximal course of the cannulated vein, whereas placebo occlusion (pressure without venous occlusion) was attained at 100 mmHg with the cuffs in radio-ulnar positions never covering the proximal course of the cannulated vein.

Pain assessment (I-V)

Dynamic course (I-V)

The patients were asked by blinded investigators to report when possible pain first appeared, was maximal and had disappeared completely in each study or control situation [**I-V**].

Localization (I-V)

The patients were also asked by blinded investigators to report the localization of pain in each study or control situation [**I-V**].

Characteristics (I-V)

The characteristics of pain were reported in each study or control situation [**I-V**].

Intensity (I-V)

At inclusion each patient had been informed in detail on how to use a VAS. All patients were then asked by blinded investigators to score pain on a horizontal 10-point VAS in each study or control situation [**I-V**].

RESULTS

Influence of carrier fluid (I)

There were no statistically significant differences in time to first appearance or maximum intensity of pain between bolus injections given with or without the carrier fluid (Table 3). However, pain was found to disappear sooner ($P< 0.05$) with simultaneous infusion of the carrier fluid.

Influence of propofol infusion rate (II)

There were no statistically significant differences in the incidence (both 86 %), intensity or duration of pain between the higher and lower bolus infusion rates of propofol studied (Table 3).

Influence of drug composition (III)

As shown in Table 2 the maximal intensity of propofol-induced pain was significantly lower after MCT/LCT propofol than after LCT propofol – median 1(1^{st} percentile 0; 3^{rd} percentile 2) range 0-6 versus 3 (0; 5) 0-9 VAS units ($p<0.0001$).

Influence of local venous occlusion (IV)

When injected with local venous occlusion, propofol was found to induce maximal pain of significantly higher intensity at the site of injection than

without occlusion [0.5 (0; 3.5) 0-8 versus 0.5 (0; 1.4) 0-6 VAS units; *P*=0.042)] as shown in Table 3.

Influence of divided doses (V)

Although the reduction of maximal pain intensity did not reach statistical significance (*P*=0.070) significantly fewer patients (*P*=0.045) reported pain intensity of 3 VAS units or more after the main dose of propofol had been preceded by a priming dose of propofol than by the same volume of aqueous sodium chloride (Table 3).

Study number	**Regimen**	**Propofol formula containing**		**Dose of propofol** (mg)	**Intravenous infusion rate of propofol 10 mg/ml** (ml/s)	**Maximal median level of pain intensity** (VAS units)
		LCT emulsion	**MCT/LCT emulsion**			
I	Control	**X**		20	1.0	3.3
	Study	**X**		20	1.0*	3.0
II	Control	**X**		20	0.2	3.3
	Study	**X**		20	1.0	3.1
III	Control	**X**		30	1.0	3
	Study		**X**	30	1.0	1
IV	Control		**X**	5	0.017	0.5
	Study		**X**	5	0.017**	0.5
V	Control		**X**	20	0.33	1.3
	Study		**X**	20	0.33***	0.5

***with carrier fluid**

****with venous occlusion**

*****after priming dose of propofol**

Table 3. Influence of various control and study regimens on local pain intensity.

DISCUSSION

Study design (I-V)

Cross-over design (I-V)

An advantage of the cross-over design [**I-V**] is that all patients were enabled to assess pain induced by various control and study drugs, which excludes interindividual variation in pain perception.

Site of injection (I-V)

The higher incidence of local pain found here could in part have resulted from dorsal hand veins consistently being chosen for propofol injection, particularly when considering that smaller veins have been found to be associated with more local pain on propofol administration *(Doenicke 1996, Doenicke 1997).* In contrast, no patients reported pain at the site of injection after the injection of propofol into large antecubital veins *(Scott 1988)*. The lower incidence of propofol-induced pain found after iv administration into large veins might have resulted from drug being delivered into the midstream of blood at the site of injection, thereby reducing direct and immediate local contact of the drug with the endothelium. Furthermore, the administration of the study drugs by separate iv routes [**III-V**] prevents remaining possible local effects of the first bolus dose from influencing the intensity of local pain resulting from injection of the second one.

Dosage (I-V)

The subanaesthetic doses of propofol used to evaluate local pain on injection [**I-V**] do not seem to have been too low considering the 71 % total incidence of pain after administration of LCT propofol [**III**]. The incidence of local pain associated with the administration of propofol seems to be influenced by whether pain is assessed prospectively or

retrospectively. During the administration of an anaesthetic dose of propofol, maximal pain intensity is even unlikely to be readily assessable before the loss of consciousness, since local pain did not first appear until after 20 seconds. In addition, retrospective assessments of propofol-induced pain intensity could easily be influenced by nausea or surgical pain together with remaining sedation or even amnesia in the early postoperative period. A drawback of this design is that some sedation resulting from infusion of one drug could still render evaluation of the other one more difficult, but consistent influence on outcome is avoided by the cross-over design.

Venous occlusion (IV)

A tourniquet may isolate the distal venous system from the rest of of the circulation. This is a useful model for studying peripheral drug action [**IV**]. By designing a tourniquet containing two small cuffs it was possible to use it in two ways – for venous occlusion or for placeco occlusion. When venous occlusion was used, we placed the cuffs in dorsoventral positions around the wrist 6 to 8 cm proximal to the site of venous cannulation. For placebo occlusion the cuffs were placed in radio-ulnar positions at the same wrist level, never covering the proximal course of the cannulated vein.

Pain assessment (I-V)

Despite its user friendliness some individuals find it difficult to understand how to use the VAS. This difficulty is usually overcome by repeated verbal instructions and individual practice. VAS is a useful clinical tool reflecting human response, experience, and perception. In this clinical project the VAS was used horizontally.

Influence of carrier fluid (I)

It seems, that simultaneous iv infusion of carrier fluid has no considerable effect on local pain following iv administration of propofol, at least not with the infusion rate studied here [**I**]. In contrast, a previous investigation has reported more pain on iv propofol during infusion of carrier fluid *(Huang 1995)*. Although aqueous dilution at the site of injection was proposed to be associated with more pain, the underlying mechanisms are unclear, particularly when taking into consideration that, in contrast, aqueous dilution of a formula – by reducing the concentration of propofol – has been reported to be associated with less pain on iv injection (*Klement 1991*). Since a carrier fluid infusion rate of 800 ml/h *(Huang 1995)* corresponds to less than one fourth of that studied by us and found not to influence pain [**I**], it seems that their higher pain intensity on simultaneous infusion of carrier fluid did at least not result from increasing turbulence of venous blood flow promoting endothelial drug exposure at the site of injection.

Influence of propofol infusion rate (II)

Adjusting iv injection speed does not seem to be a clinically useful tool for reducing the intensity or duration of propofol-induced pain at the site of administration within the infusion rate interval studied [**II**]. In contrast, slow iv induction of anaesthesia has been reported to be associated with more pain at the site of injection of propofol *(Scott 1988),* and accordingly rapid injection of propofol has been reported to induce less pain *(Shimizu 2005).* Certainly, the speed of propofol injection might influence local pain by affecting drug contact time with the endothelium as well as drug clearance from the site of injection. However, the most important explanation for those findings is that since the iv infusion rate of propofol also determines the time to induction of anaesthesia, then slow iv infusion of propofol by delaying loss of consciousness would be more likely to

induce pain at the site of injection while the patient is still being awake. In contrast, rapid injection of propofol would, accordingly, decrease the risk of severe local pain before consciousness is lost.

Influence of drug composition (III)

The considerably lower intensity of local pain found to be associated with iv administration of emulsions of propofol based on MCT/LCT [**III**] has also been demonstrated by others *(Doenicke 1996, Müller 2000, Larsen 2001, Suzuki 2006, Allford 2006, Sun 2005).* One study reported no differences in local injection pain between LCT propofol MCT/LCT propofol in paediatric patients aged between 1 month and 8 years *(Gutmann 2006).* Their patients were given premedication and anaesthetic induction doses of propofol and were then evaluated from observed movements and, for obvious reasons, not by being asked to assess maximal pain intensity on a VAS. The difference in study findings thus probably depends on different study designs.

High concentrations of free propofol within the aqueous phase of an emulsion *(Doenicke1996, Doenicke 1997, Scott, 1988)* have been shown to be associated with pain on injection. It is still not known what biochemical mechanisms are involved in this process, although activation of the kinin cascade has been suggested *(Scott 1988).* MCT/LCT propofol contains less free propofol than does LCT propofol *(Doenicke 1996, Babl 1995),* although both emulsions have the same total concentration of propofol. It has been found that the exchange of LCT for MCT/LCT in a propofol formula reduces the concentration of free propofol in the aqueous phase by up to 50 % and decreases pain on injection *(Doenicke 1996, Babl 1995, Yamakage 2005, Müller 2000).* Recent studies have found that lidocaine mixed with LCT propofol reduces propofol-induced pain more than does MCT/LCT propofol alone *(Yew 2005, Kunitz 20005, Adam 2004, Kam 2004, Nyman 2005).* The addition of lidocaine to MCT/LCT propofol has

also been reported to significantly reduce the incidence of pain on injection *(Yeb 2005, Kunitz 2005).*

In conclusion, the considerably lower intensity of local pain found to be associated with iv administration of propofol dissolved in an MCT/LCT emulsion indicates that MCT/LCT propofol should be preferred to traditional LCT propofol for induction of anaesthesia.

Influence of local venous occlusion (IV)

Our results show that local venous occlusion augments the intensity of pain at the site of propofol injection without affecting pain development over time. These findings imply that propofol-induced pain is associated more with the blood concentration than with the duration of intravascular exposure.

It has recently been found in rats that propofol-evoked vascular pain is mainly initiated by prostanoids, particularly prostaglandin E_2 *(Ando 2005).* By applying prolonged venous occlusion during and after propofol administration we might have augmented, but not prolonged, such a response despite gradual intravascular drug accumulation. Pain has been reported to be induced by propofol in a concentration-dependent manner *(Klement 1991),* where higher concentrations of propofol were associated with higher pain intensity, particularly in formulas containing aqueos instead of lipid diluents.

Influence of divided doses (V)

The reduced incidence of moderate or severe propofol-induced pain after injection of a low priming dose of the same propofol emulsion by the same iv route two minutes in advance, indicates that initial endovascular exposure to a low dose of propofol reduces the pain induced by further injection of propofol [**V**] in agreement with results obtained in a recent

study *(Sun 2005)* and also with our previous findings [**IV**]. Intravenous infusion of propofol after separation of the drug emulsion from the carrier fluid in a double lumen iv set has been reported to reduce propofol-induced pain, possibly by limiting the endovascular surface exposed to the drug *(Angst 1997)*. The findings in our study are in conformity with recent findings indicating that prostaglandin patways are involved *(Vio 1983, Nyman 2005)*.

Our results were probably not considerably influenced by central analgesic effects of the priming or main doses. Low-dose infusion of propofol has been reported to have no significant central analgesic effect and even to be associated with higher ratings of pain intensity *(Zacny 1996, Frölich 2005)*. Our lack of carry-over effects further indicates that the pain-reducing effect of divided doses mainly results from peripheral local action of propofol. Although the pain-reducing effect of divided administration is smaller than of adjuvant lidocaine or opioids, the potential advantage of the proposed clinical technique for reducing pain induced by the main dose of propofol is that no adjuvant drug is required and that any anaesthetist would be able to apply the technique in virtually any situation not calling for rapid induction of anaesthesia.

CONCLUSIONS

Regarding pain at the site of propofol injection

- control and study regimens can be reliably compared in the same individual, considering that the study design was associated with no carry-over effect and similar pain level for comparable clinical regimens in different studies [**I-V**].

- simultaneous infusion of carrier fluid reduces the duration but does not influence the intensity, as indicated by the lack of difference in pain intensity between propofol administered alone or with rapid iv infusion of carrier fluid [**I**].

- the bolus infusion rate neither influences the intensity nor the duration, considering that higher and lower iv bolus infusion rates of subanaesthetic doses of propofol were found to be associated with local pain of similar duration and intensity [**II**].

- MCT/LCT emulsions of propofol should be preferred to traditional LCT emulsions for induction of anaesthesia, since pain of significantly lower intensity was found to be associated with iv bolus infusion of MCT/LCT propofol than of LCT propofol [**III**].

- simultaneous local venous occlusion applied during injection of propofol augments doses not prolong pain, implying that the pain is determined more by the blood concentration than by the duration of intravascular exposure [**IV**].

- initial low-dose administration of propofol by the same iv route can be used to decrease pain induced by further iv bolus infusion of propofol, since the incidence of moderate to severe pain was found to be reduced

by previous administration of a low dose of propofol by the same iv route two minutes before [**V**].

- modification of drug administration [**I, V**] as well as composition [**III**] are clinically useful tools readily applicable together with previously proposed techniques involving the site of cannulation, temperature of drug formula or use of adjuvant drugs.

SUMMARY

Over the last 25 years a number of new anaesthetic drugs have been introduced on the market to allow for better patient satisfaction and faster recovery after anaesthesia and sedation. Propofol (2,6-di-isopropylphenol), one of our most common iv anaesthetics, is associated with pleasant sleep and rapid recovery with little postoperative nausea. When used for anaesthetic induction propofol causes severe or even intolerable pain or discomfort on injection in up to 90 % of patients. Pain on injection of propofol is even ranked by anaesthesiologists as the seventh most important clinical problem in modern anaesthesia.

The concentration of free propofol within the aqueous phase of the drug formula is believed to be particularly associated with injection pain. The general aim of these studies was to investigate if we could reduce the local pain induced by iv propofol by various clinical measures. Traditional long-chain triglyceride (LCT) emulsions of propofol were used in studies I-III, while a new medium- and long-chain triglyceride (MCT/LCT) formula was used in studies III-V. Both formulas were used and compared in study III.

In study I the influence of a carrier fluid was evaluated. Simultaneous iv infusion of carrier fluid was found not to influence pain intensity but to decrease the duration of pain at the site of propofol injection.

In study II we investigated the effect of various bolus rates of propofol on pain at site of injection. There were no differences in the incidence, intensity or duration of pain between the faster and slower rates compared.

In study III we compared the influence of two different formulas of propofol on local pain at the site of administration. Propofol emulsions based on MCT/LCT were associated with lower pain intensity than those based on LCT only.

Study IV was designed to examine if local venous occlusion applied during and immediately after injection of propofol reduces the intensity of pain at the site of injection. Venous occlusion was found to increase the intensity but not the duration of pain at the site of propofol injection, indicating that the pain response to propofol fades during prolonged intravascular exposure.

Study V was carried out to examine if pain on injection of propofol can be

reduced by previous low-dose administration of propofol by the same iv route. A lower incidence of moderate or severe local pain was induced by propofol after the low dose of propofol had been administered.

Our most important results show that formulas of propofol based on MCT/LCT are associated with less pain at the site of iv injection than are traditional LCT formulas. Furthermore the incidence of moderate to severe propofol-induced pain can be reduced by previous injection of a low dose of propofol by the same iv route.

These measures can easily be taken by any anaesthetist in virtually any clinical situation not calling for rapid induction of anaesthesia.

SAMMANFATTNING

De senaste 25 åren har flera nya narkosläkemedel registrerats och fått stort genomslag i vårt land. Den främsta orsaken är att dessa läkemedel medger ett snabbare uppvaknande och bättre postoperativt välbefinnande, vilket gör att många patienter snabbare kan återvända hem efter sina operationer. Propofol (2,6-di-isopropylfenol) som är ett av våra mest använda intravenösa narkosläkemedel, ger behaglig sömn, snabbt uppvaknande och obetydligt postoperativt illamående.

I samband med nedsövningen kan dock propofol orsaka smärta vid injektionsstället hos upp till 90 % av patienterna. Eftersom problemet är så vanligt, har smärta vid injektion av propofol av narkosläkare bedömts vara det idag sjunde viktigaste kliniska problemet inom modern anestesi. Koncentrationen av fritt propofol i den vattenlösliga fasen av injektionslösningen har betydelse för uppkomsten av denna smärta.

Det allmänna syftet med de fem undersökningarna som ligger till grund för denna avhandling var att på patienter som ska sövas inför kirurgiska ingrepp utvärdera och jämföra olika sätt att minska den smärta som kan uppkomma när man sprutar in propofol i ett ytligt blodkärl för att söva patienten. I de första tre undersökningarna [**I-III**] använde vi en äldre beredning av propofol löst i en blandning av vatten och fett innehållande enbart långa fettkedjor (LCT), medan vi i de tre avslutande undersökningarna [**III-V**] använde en nyare propofolberedning med både medellånga (MCT) och långa fettkedjor.

I den första undersökningen [**I**] studerade vi vad som händer om man samtidigt ger dropp till patienterna. Vi upptäckte att smärtan inte påverkas av om man samtidigt ger ett dropp via samma plastnål i kärlet, men att smärtan försvinner något snabbare.

I den andra undersökningen [**II**] utvärderade vi effekten av två olika injektionshastigheter av propofol. Vi upptäckte inget samband mellan hur snabbt man sprutar in propofolet i blodkärlet och hur ofta smärta uppkommer eller hur länge den varar.

I den tredje undersökningen [**III**] jämfördes smärtan av MCT/LCT-propofol med smärtan av LCT propofol. Vi upptäckte att MCT/LCT-propofol gav upphov till mindre smärta än LCT-propofol.
Den fjärde undersökningen [**IV**] gjordes för att utvärdera effekten av avstängt blodflöde från det kärl där propofolet sprutas in. Vi upptäckte att avstängning av kärlet ökar smärtan vid injektionsstället men inte påverkar hur länge den varar. Detta talar för att den lokala smärtan som framkallas av propofol försvinner medan läkemedlet fortfarande finns kvar i blodkärlet, vilket gav oss idén till den avslutande undersökningen.
I den femte undersökningen [**V**] utvärderade vi om man kan påverka injektionssmärtan genom att först ge en liten dos propofol. Vi fann att måttlig till svår injektionssmärta kan minskas genom att på detta sätt dela upp propofoldosen.
Våra studier visar att MCT/LCT-propofol ger mindre smärta vid injektionsstället än LCT-propofol, och att måttlig och svår smärta minskar om huvuddosen föregås av en liten dos propofol via samma plastnål i blodkärlet. Båda dessa tekniker kan till vardags användas i samband med praktiskt taget alla nedsövningar. Är det bråttom att söva ned patienten bör man dock undvika att dela upp doserna och istället injicera propofolet vid ett och samma tillfälle.

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