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REVIEW ARTICLE

Pain on injection of propofol

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Summary

Pain on injection of propofol is a common problem, the cause of which remains unknown. The chemical properties and preparation of propofol, proposed mechanisms for the cause of the pain and clinical strategies to prevent pain on injection of propofol are reviewed in the hope of shedding some light on the subject.

Keywords *Anaesthetics, intravenous*; propofol. *Complications*; pain.

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Propofol (Diprivan, di-isopropylphenol) is a popular intravenous anaesthetic induction agent, especially for brief cases, day surgery or when a laryngeal mask airway is to be used. Propofol can also be used in a total intravenous anaesthesia (TIVA) technique for the maintenance of anaesthesia and sedation. It has also been used for the prevention of emesis [1], tracheal intubation without neuromuscular blocking drugs [2] and the treatment of pruritus [3, 4].

Pain on injection with propofol is a common problem and can be very distressing to the patient. The incidence of pain varies between 28% and 90% in adults during induction of anaesthesia and may be severe [5, 6]. In children, the incidence of pain varies between 28% and 85% [7, 8]. The younger the child, the higher is the incidence and severity of propofol injection pain [9]. This could be due to the smaller veins in children. There is no gender difference in the incidence of propofol injection pain. Propofol has a high incidence of pain on injection when compared to other intravenous anaesthetic agents. The incidence of pain on induction with thiopentone is about 7% [5], whereas with methohexitone it varies between 12% and 64% [10, 11]. Diazepam in the organic solvent propylene glycol (Valium) has an incidence of pain on injection of 37% but this becomes 0% when diazepam is reformulated in soya bean oil (Diazemuls) [10]. Pain on injection is infrequent with midazolam at 1% [10]. The incidence of pain after etomidate administration varies between 24% and 68% [12, 13].

This article reviews the chemical properties and preparations of propofol, the postulated mechanisms for causing injection pain and methods that have been investigated to minimise the incidence of pain.

Chemical properties and preparation of propofol

Propofol is a hindered phenol that is chemically dissimilar to any other compounds used in anaesthesia. It has a molecular weight of 178 Da and is a colourless liquid at room temperature. The compound absorbs light in the ultraviolet range of the electromagnetic spectrum ($\lambda_{max} = 275$ nm) and fluoresces at 310 nm with an excitation wavelength of 276 nm. Fluorescence detection with high-performance liquid chromatography forms the basis of the blood concentration assay technique.

Propofol was initially formulated as a 2% solution in 16% polyethylated castor oil (Cremophor EL) and 8% ethanol because of its low aqueous solubility and then as a 1% solution in 16% Cremophor EL. However, it was reformulated in a soyabean emulsion because of concerns over the high incidence of injection pain with this preparation and in order to avoid Cremophor-related reactions [14]. The currently available preparation is a 1% w/v aqueous emulsion containing 10% w/v soya bean oil (as a solubilising agent), 1.2% w/v egg phosphatide (as an emulsifying agent) and 2.25% w/v glycerol (to make the preparation isotonic), sealed under nitrogen. The pH is

6–8.5 and the pKa of the drug in water is 11. The preparation is compatible with injection into fast running infusions of 5% dextrose, 4% dextrose/0.18% sodium chloride and 0.9% sodium chloride. It should be stored below 25 °C to prevent degradation.

Mechanisms of pain on injection of propofol

Many factors appear to affect the incidence of pain on propofol injection. These include the site of injection, size of vein, speed of injection, propofol concentration in the aqueous phase and the buffering effect of blood. These factors will be discussed in this section. Other important factors include the speed of intravenous carrier fluid, the temperature of propofol, syringe material and the concomitant use of drugs such as local anaesthetics and opiates. These factors will be discussed later in the review.

Pain on injection of propofol can be immediate or delayed. Immediate pain probably results from a direct irritant effect whereas delayed pain probably results from an indirect effect via the kinin cascade. Delayed pain has a latency of between 10 and 20 s [15]. The cause of pain on propofol injection is obscure and there are several proposed mechanisms. Klement and Arndt [16] postulated that pain on injection of some of the anaesthetic agents is evoked via a direct effect by the unphysiological osmolality or pH of their formulations. They found that pain occurred at 1.0 osmol.kg^{-1} during infusion and 3.0 osmol.kg^{-1} during rapid injection. Acidic and alkaline solutions evoke pain at pH values less than 4 and more than 11, respectively. They also found that the pain latency decreased with increasing osmolality, acidity and alkalinity. Both the osmolar concentration and pH of the solutions brought into contact with the intima of a superficial hand vein were factors determining the production of pain. The degree of pain also depended upon the volume injected and the flow of blood through the vein. They also suggested that the painful sensation from veins probably originates from neural elements within the vein walls, possibly from free afferent nerve endings between the media and intima. The pain-conducting axons probably belong to the myelinated A delta group [17]. Examples of intravenous drugs with a high osmolality include diazepam (7.8 osmol.kg^{-1}) and etomidate (5.0 osmol.kg^{-1}) [18]. Pain on injection of these drugs is therefore likely to be due to the extreme osmolalities of their conventional formulations. Consistent with this view, the incidence of pain on injection was reduced to less than 1% with new formulations of diazepam and etomidate [19–21] that have osmolalities near that of blood. However, propofol is almost isotonic, is nonhyperosmolar and has a pH between 6 and 8.5. This theory cannot therefore account for the pain produced by the injection of propofol.

Scott *et al.* [22] pointed out that certain factors are important in the causation of pain on injection of propofol. Vein size is important as they noted that there was no pain when propofol was injected into a large vein in the antecubital fossa. This is presumably because the drug is injected into the midstream of blood flow in the lumen of the vein and its contact at high concentration with the sensitive wall will therefore be minimal. Moreover, the drug may also be effectively buffered by blood with which it can mix freely. Another factor that is important is the duration of exposure of the vein wall to the propofol injection. They noticed that a slow injection of propofol caused more pain than a rapid bolus. Perhaps a rapid bolus of the drug is quickly cleared from the vein and is replaced with blood. They also observed that there was a species variation in propofol injection pain. They suggested that the pain is likely to be an indirect irritant effect via the release of mediators rather than a direct irritant effect. Furthermore, when the active component of the propofol emulsion comes into contact with vascular endothelium, it causes release of mediators such as kininogen from the kinin cascade and results in the stimulation of pain. This causes a slightly delayed sensation of pain compared to the immediate sensation of pain that results from a direct effect.

Klement and Arndt [23] suggested that the pain is related to the concentration of propofol in the aqueous phase and is not due to the formulation, as propofol has an almost physiological osmolality and pH (0.303 osmol.kg^{-1}; pH 8.0). They showed that pain intensity increased with the increased concentration of propofol and, at a given concentration, was always greater with glucose than with intralipid as the diluent. By reducing the propofol concentration in the aqueous phase with intralipid, pain on injection was reduced. Doenicke *et al.* [24] hypothesised that propofol concentration in the aqueous phase may be an important variable for pain associated with propofol injection. They noticed that results of *in vitro* investigations show that the propofol concentration in the aqueous phase of Diprivan is relatively high (18.57 μg.ml^{-1}), which indicates that the active component is not completely dissolved in the lipid vehicle. In the propofol emulsion preparation, the drug will be distributed differently between the two phases, with an outer aqueous phase and an inner lipid phase. In a bolus injection, only the outer aqueous phase comes into contact with the intima of the vein. The concentration of an irritating agent in the aqueous phase may be the factor causing venous pain on administration. Propofol, like all phenols, irritates the skin and mucous membranes. Thus, bolus injection of propofol preparations can be expected to cause pain. They went on to show that by increasing the lipid content of the propofol and thereby decreasing the concentration of propofol in the

aqueous phase, the incidence of pain associated with propofol injection could be reduced.

Clinical strategies for the prevention of propofol injection pain

Based on the proposed mechanisms and factors associated with propofol injection pain, several methods for the prevention of pain have been tried with varying degrees of success. Published studies have produced differing results, in part because of different methodologies.

The methods which have been investigated so far include: site of injection, use of aspirin and other nonsteroidal anti-inflammatory drugs, premedication, speed of injection, speed of carrier intravenous fluid, the use of local anaesthetics, dilution of propofol, different temperatures, opiates, metoclopramide, glyceryl trinitrate, thiopentone, ketamine, different syringe material and the aspiration of blood.

Site of injection

With the Cremophor EL preparation, there was a marked association between the site of injection and the incidence of pain on injection. Briggs *et al.* [15] reported a 39% incidence when it was injected into the dorsum of the hand compared with a 3% incidence in the forearm or antecubital fossa. While the pain is less with the emulsion preparation, the relationship between pain and the site of injection still applies. Briggs and White [25] reported that pain on injection was rare in the antecubital fossa but was a frequent occurrence (30%) in the dorsum of the hand. McCulloch and Lees [26] produced similar results: the incidence of pain was 37.5% using dorsal hand veins compared to 2.5% when a forearm vein was used. Scott *et al.* [22] pointed out that using a vein in the antecubital fossa for the administration of propofol was the only approach that caused no pain. Hannallah *et al.* [27] also showed a low incidence of propofol injection pain in children when using the antecubital veins. The proposed reason for this observation is that the antecubital veins are larger and contact between drug and endothelium is reduced, as the drug tends to stay in the midstream of the blood flow in a large vein.

Aspirin and other nonsteroidal anti-inflammatory drugs

Studies on the use of nonopioid analgesics to decrease pain on injection have been performed. Bahar *et al.* [28] showed that pretreatment with acetyl salicylic acid 1 g given intravenously 15 min before propofol injection significantly reduced the incidence of severe pain from 70% to 20% but did not reduce the overall incidence of pain. Smith and Power [29] found a similar incidence of pain in a group of patients given an intravenous injection of ketorolac 10 mg immediately before intravenous injection of propofol and in a control group not given ketorolac. They suggested that this was because either ketorolac does not block local vascular endothelial prostaglandin synthesis, because prostaglandins are not important in the pathogenesis of the pain or because a longer time is required for an effect to be produced.

Premedication

Nicol *et al.* [30] reported that the use of oral premedication made no difference to the incidence of propofol injection pain. However, Briggs and White [25], using pethidine and atropine as premedication, found that although the incidence of painful injection with propofol was not reduced, the severity of pain was less. Fragen *et al.* [31] found that premedication with an opiate and a sedative reduced the incidence of injection pain. This may be due to the additive effect of both drugs on increasing the pain threshold.

Speed of injection and speed of infusion of carrier intravenous fluid

At a slow rate of propofol injection, the contact between the endothelium and the active component of propofol is more prolonged. This results in mediator release, while a high rate of injection allows the propofol to be cleared from the vein and replaced with blood. This suggestion was put forward by Scott *et al.* [22], who found that decreasing the speed of propofol injection caused the greatest discomfort.

When the speed of carrier intravenous fluid infusion is slow, fewer kininogen molecules may be produced as a result of the smaller contact area between the propofol and the endothelium of the vein, due to the smaller volume of carrier intravenous fluid given. In addition to this, propofol may be buffered by the dilutional effect of venous blood. However, when the speed of infusion of the carrier intravenous fluid is fast, the dilutional effect of venous blood will be decreased by the large amount of intravenous fluid injected and the propofol is therefore diluted mostly by the aqueous solution. The intensity of pain associated with propofol will therefore be increased, as there is an increase in propofol concentration in the aqueous phase. These findings were reported by Huang *et al.* [32].

Lignocaine

The use of lignocaine to prevent propofol injection pain is the most extensively studied technique and is the commonest method used in clinical practice. Many studies have shown the use of lignocaine to be effective. The manufacturer of propofol now recommends this approach.

Two methods have been studied: pretreatment with lignocaine and mixing it with the propofol.

Lignocaine pretreatment

The use of lignocaine as a pretreatment to decrease propofol injection pain is based on its presumed local anaesthetic effect on the vein. Due to the different methodologies used in the studies, different reductions in the incidence of pain associated with propofol injection have been reported. McCulloch and Lees [26] showed that the administration of lignocaine 10 mg immediately before propofol injection reduces the incidence of pain from 37.5% to 17.5% when using the veins in the back of the hand. This result was not statistically significant. However, Ganta and Fee [33] reported that the incidence of pain using lignocaine 10 mg immediately before propofol injection was significantly reduced from 49.4% to 21.1%. The difference between the two studies could be due to the premedication used and the different speeds of propofol injection. McCulloch and Lees did not use premedication and administered propofol over 20 s, whereas Ganta and Fee used diazepam 10 mg as premedication and administered the propofol over 30–40 s. Lyons *et al.* [34] reported that pretreatment with lignocaine 10 mg 10 s before propofol injection could significantly reduce the incidence of injection pain from 64% to 44%. Nicol *et al.* [30] reported that lignocaine 10 mg 15 s before propofol administration into veins in the back of the hand could significantly reduce the incidence of pain from 51% to 35%. Mangar and Holak [6] found that administering lignocaine 100 mg 1 min before propofol injection reduced the severity but not the incidence of pain, whereas lignocaine 100 mg administered after an arm tourniquet was inflated to 50 mmHg for 1 min (a modified Bier's block) virtually abolished the pain associated with propofol injection. Ewart and Whitwam [35] found that the incidence of pain increased with an increased time interval between the injection of the two drugs. Lignocaine 20 mg was injected into a dorsal hand vein with a tourniquet placed on the proximal part of the forearm in order to produce a 'mini-Bier block'. The tourniquet was released after varying time intervals and propofol was then injected. Pain was significantly reduced in the groups given lignocaine 10 or 30 s before propofol. Their study showed that lignocaine was effective at reducing pain when given before propofol.

Lignocaine mixed with propofol

The rationale behind the use of lignocaine mixed with propofol is based on the premise that lignocaine may act as a stabiliser for the kinin cascade, as proposed by Scott *et al.* [22]. Recently, another mechanism was proposed by Eriksson *et al.* [36]. They showed that lignocaine mixed with propofol decreased its pH, resulting in a lower concentration of propofol in the aqueous phase and therefore less pain. Several studies using different doses of lignocaine have shown that the technique is effective in decreasing the incidence of pain associated with propofol injection. Brooker *et al.* [37] found that lignocaine 7.5 mg mixed with propofol 142.5 mg before injection was associated with a decrease in the incidence of pain from 57% to 7%. However, this was only a pilot study and there was no randomisation, variable premedication and the administration of different opiate drugs before propofol injection. Helbo-Hansen *et al.* [38], in their double-blind randomised trial, found that the addition of lignocaine 10 mg to propofol 190 mg could significantly reduce the incidence of pain from 32.5% to 5%. The severity of pain was also reduced.

Similar results have been found in other double-blind randomised studies. Newcombe [39] reported that mixing lignocaine 10 mg with propofol could significantly reduce the severity and incidence (from 86.9% to 48.9%) of propofol injection pain. Nathanson *et al.* [40] also reported that the incidence of propofol injection pain could be reduced significantly from 67% to 13% using lignocaine 40 mg mixed with propofol before injection. King *et al.* [41], in their study on different doses of lignocaine mixed with propofol, found that lignocaine 20 mg significantly reduced the incidence of injection pain from 73% to 32%. There was an inverse relationship between the amount of lignocaine used and the incidence of pain.

Similar results have been obtained in children. Valtonen *et al.* [8] found that lignocaine 10 mg mixed with propofol 2.0–2.5 mg.kg^{-1} significantly decreased the incidence of pain caused by propofol as compared to a control group (from 85% to 20%). Hiller and Saarnivaara [42] found that mixing lignocaine 10 mg with propofol significantly reduced the incidence (from 40% to 4%) of injection pain in children when compared to pretreatment with alfentanil 10 μg.kg^{-1}.

The efficacy of lignocaine mixed with propofol may be weight-related. Gehan *et al.* [43] showed that the optimum dose for preventing propofol injection pain was 0.1 mg.kg^{-1} in adults and that there was no improvement when the dose was increased above this. Tham and Khoo [44] found that the optimum minimum dose required for the effective reduction of propofol injection pain was a propofol emulsion containing 0.05% lignocaine. Gajraj and Nathanson [45] reported that the optimum lignocaine dose mixed with propofol 160 mg in adult females was 30 mg. However, the optimum dose of lignocaine needed to prevent propofol injection pain appears to be higher in children. Cameron *et al.* [9], in their study on the minimum effective dose of lignocaine to prevent propofol injection pain in children, found that

0.2 mg.kg^{-1} was needed. This is twice the adult value and may be related to the higher volumes of distribution in children compared to adults.

Lignocaine – comparisons between pretreatment and mixing

Studies have been performed to compare the effectiveness of lignocaine pretreatment and lignocaine mixed with propofol. Scott *et al.* [22] found that lignocaine mixed with propofol was more effective than pretreatment with lignocaine in decreasing propofol injection pain. They reported a significant decrease in the incidence of pain from 46.7% to 13.5% by mixing lignocaine 10 mg with propofol as compared to pretreatment with lignocaine 10 mg 30 s before propofol injection (from 46.7% to 40%). However, there was no mention of observer blinding. Scott proposed that lignocaine may act as a stabiliser for the kinin cascade when mixed with propofol whereas lignocaine injected before propofol may be washed away in the blood before the arrival of the propofol bolus, making less lignocaine available. Johnson *et al.* [46] found no significant difference between a group of patients that received lignocaine pretreatment and a group that received propofol mixed with lignocaine. Pain was significantly reduced in all groups in which lignocaine was used and a 40 mg dose was more effective than 20 mg. A factor which may have given rise to this result is that venous occlusion was used before injection in the pretreatment group. This may have enhanced the local anaesthetic effect.

Procaine

Nicol *et al.* [30] found that procaine was comparable to lignocaine in significantly reducing propofol injection pain from 51% to 34% when procaine 10 mg was injected 15 s before propofol.

Prilocaine

Eriksson [47] found that prilocaine mixed with propofol was comparable to lignocaine in significantly reducing the incidence of pain caused by propofol injection.

Eutectic mixture of local anaesthetics (EMLA)

Valtonen *et al.* [7] found that the use of topical EMLA cream in children did not significantly reduce pain on injection with propofol.

Dilution

Dilution of propofol with either glucose or intralipid decreases the concentration of propofol, which results in a decrease in the incidence of pain. This is based on the findings by Stokes *et al.* [48], Klement and Arndt [23] and Doenicke *et al.* [24]. They proposed that pain associated with propofol injection is directly related to propofol concentration in the free aqueous phase. Stokes *et al.* [48] found that dilution of propofol with 5% dextrose was able to reduce significantly the incidence of severe pain from 32% to 10% and all pain from 50% to 24%. Klement and Arndt [23] reported that the dilution of propofol with 10% intralipid was more effective than dilution with 5% glucose in decreasing propofol injection pain, while Doenicke *et al.* [24] showed that propofol injection pain could be reduced further when a higher concentration of fat emulsion was used in the propofol formulation.

Temperature

McCrirrick and Hunter [49] studied the effect of injectate temperature on propofol injection pain. They found that when giving propofol at 4 °C, the incidence of injection pain could be significantly reduced from 46% to 23%. The efficacy of propofol was not affected. They postulated that a temperature of 4 °C might decrease the speed of the kinin cascade. Cold saline was used by Barker *et al.* [50] to decrease the incidence of propofol injection pain. They found that pretreatment with 0.9% saline 10 ml at 4 °C before propofol injection was comparable to cold propofol (4 °C) and room temperature propofol mixed with 0.05% lignocaine in significantly reducing the incidence of propofol injection pain. There was no significant difference between the treatment groups.

Fletcher *et al.* [51] found that warming propofol to 37 °C significantly decreased the incidence of propofol injection pain from 59% to 22%. They suggested two mechanisms: that the temperature may have affected mediator release and that the high temperature may affect the partition coefficient and therefore the concentration of propofol in the aqueous phase. However, extreme care is needed to avoid contamination of the propofol with water from the water bath used to warm the injection. Bennett *et al.* [52] have recently reported an analysis of multiple outbreaks of postoperative infection related to the use of extrinsically contaminated propofol.

Alfentanil and fentanyl

The use of opioids, especially short-acting drugs such as alfentanil and fentanyl, was observed to decrease the incidence of pain on injection of propofol. Several studies have confirmed these observations. Helmers *et al.* [53] found that using alfentanil 0.5 mg as a pretreatment before propofol injection was effective in significantly reducing the incidence of propofol injection pain from 40% to 16%, while studies by Fletcher *et al.* [54] and Nathanson *et al.* [40] showed that pretreatment with alfentanil 1 mg 15 and 30 s before propofol injection in adults could significantly reduce propofol injection pain from 84% to 36% and 67% to 24%, respectively. Hiller and Saarnivaara [42] found that the optimum dosage of alfentanil in children to reduce propofol injection pain was 15 μg.kg^{-1}.

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