MEDICAL INTELLIGENCE ARTICLE

Julien F. Biebuyck, M.B., D.Phil., Editor

Anesthesiology
80:642–656, 1994

The Nonhypnotic Therapeutic Applications of Propofol

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CONTENTS

I. History and Mechanisms of Anesthetic Action

PROPOFOL, 2,6-diisopropylphenol (ICI 35868), whose initial formulation as a 1% solution in 16% polyoxyethylated castor oil (Cremophor EL, ICI-Pharma, England) was associated with severe pain on injection and anaphylactoid reactions,[1–3] has been available since 1982 as a 1% solution in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide, which is largely devoid of allergic problems.

Although propofol has been on the market for almost 10 yr, this drug is still being found to possess new and unexpected properties. First introduced as an induction agent,[4,5] it was rapidly used not only to induce but also to maintain anesthesia.[6–8] A few years later, propofol was shown to be suitable for sedation during regional anesthesia[9,10] and became widely used for the same purpose in intensive care units.[11–13] Recently, antiepileptic properties have been associated with the use of propofol, although this topic still remains controversial. Lastly, at very low doses we found that propofol possesses direct antiemetic properties[14] and is also efficient in the context of pruritus induced by spinal opioids[15] or associated with liver disease.[16,17] This review will deal with

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Received from the Department of Anesthesia and Surgical Intensive Care, University Hospital of Geneva, Switzerland. Accepted for publication October 11, 1993.

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Key words: Anesthetics, intravenous: propofol. Therapeutic applications: nonhypnotic properties.

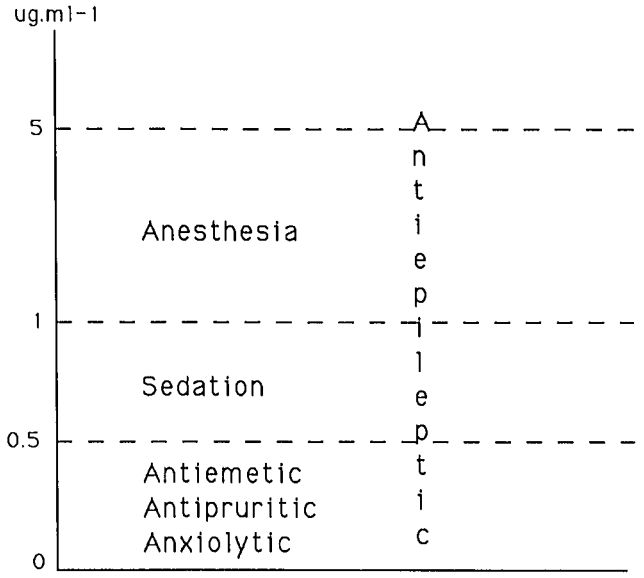

Fig. 1. Nonhypnotic therapeutic applications of propofol to clinical care: the different actions of propofol related to its blood levels concentration.

these new controversies and therapeutic uses of propofol in clinical care (fig. 1).

The mechanisms by which propofol exerts its anesthetic actions are, as for other anesthetics, poorly understood. Propofol inhibits activity at both spinal and supraspinal synapses by interacting with the γ-aminobutyric acid (GABA) receptor complex to potentiate GABA-mediated effects.[18] It seems that propofol exerts its actions at the chloride ion channel without binding directly to the GABA receptors.[19] All central nervous system structures are affected by these actions, which are rapidly reversible. However, it remains unclear whether the potentiation of GABA-ergic actions is the main mechanism by which anesthesia is produced by propofol.

II. Antiemetic Effects of Propofol

The occurrence of nausea, often followed by retching and vomiting, remains one of the most distressing side effects following anesthesia.[20] These problems are observed after general, regional or local anesthesia. Several factors such as age, gender, obesity, anxiety, history of motion sickness or previous postoperative nausea and any conditions associated with gastroparesis have been correlated with a higher incidence of postoperative nausea and vomiting.[21] The incidence of postoperative nausea and vomiting is higher after laparoscopy in gynecology, shock-wave lithotripsy and upper abdominal surgery in adults[22,23]; children who have undergone strabismus and middle ear surgery are also prone to postoperative nausea and vomiting.[24,25]

The reviews of the past 30 yr dealing with this topic do not reveal a significant decrease in the incidence of postoperative nausea and vomiting. However, with the use of propofol for anesthesia, a significant decrease in postoperative nausea and vomiting has been observed.[26]

A. Clinical and Experimental Studies

The incidence of postoperative sickness is either significantly decreased or shows a tendency toward a decrease when propofol is administered irrespective of the anesthetic technique or drug used. In 120 patients scheduled for major and minor general surgery, Doze *et al.*[27] observed a 20% overall incidence of postoperative nausea and vomiting in patients receiving propofol–nitrous oxide *versus* 40% in those receiving thiopental–isoflurane–nitrous oxide. Best *et al.*[28] noted an incidence of nausea and vomiting of 5% *versus* 35% in patients receiving propofol or methohexital respectively for microlaryngeal surgery.

In ambulatory surgery the incidence of postoperative sickness was markedly lower with propofol when compared to enflurane, isoflurane or desflurane.[29–31] Retrospective analysis of data from 200 women who received propofol for minor surgery showed a low incidence of postoperative nausea and vomiting (≤ 3%) in contrast to the usual 10–20% incidence observed with other anesthetics.[32] Raftery *et al.*[33] assessed the incidence of postoperative nausea and vomiting and requirements for antiemetic medication in 80 patients scheduled for assisted conception therapy. They received either total intravenous (iv) anesthesia with propofol or enflurane–nitrous oxide anesthesia; the former was associated with less nausea and vomiting, a lesser requirement for antiemetic medication and a lower probability of unplanned admission to hospital after day-care gynecologic surgery. In children, prospective studies have also demonstrated a lower incidence of postoperative nausea and vomiting.[34,35] Dandoy *et al.*[36] observed an incidence of nausea and vomiting near zero in 100 children aged 4–8 yr undergoing squint surgery under propofol 6 $mg \cdot kg^{-1}$ iv for induction and maintained with a continuous infusion of 11 $mg \cdot kg^{-1} \cdot h^{-1}$. In 120 children aged 6 months to 12 yr Watcha *et al.*[35] found the lowest incidence of nausea and vomiting in the group receiving propofol alone;

interestingly, the addition of nitrous oxide to the propofol anesthetic regimen resulted in an increase in the incidence of emesis.

Several authors have suggested a *specific* antiemetic effect of propofol.[37,38] However, none of these studies directly investigated such an effect. More recently, Borgeat *et al.*,[14] in a prospective, double-blind, placebo-controlled study, examined the efficacy of subhypnotic doses of propofol to treat postoperative nausea and vomiting in the recovery room. Twenty-one of 26 (81%) patients in the propofol group and 9 of 26 (35%) patients in the placebo group were treated successfully ($P < 0.05$). Of these, 6 patients in the propofol group and 2 patients in the placebo group relapsed within the next 30 min (not significant).

In the propofol group, 3 patients (3 of 26 = 12%) needed a second administration of the study drug to achieve a successful outcome. The sedation scale increased by one point in 33% of the patients successfully treated with propofol and in 44% of patients successfully treated with placebo (not significant). The duration of the beneficial effects of propofol was over 30 min in more than 70% of the patients. No change in sedation was noted for failures in both treatment groups. No patient showed a change in postoperative pain score. Failures in the propofol group were all associated with surgery closely linked to vagal stimulation. It has been postulated that hypnotic agents may exert their antiemetic action primarily *via* sedation.[39] In our study we observed no significant sedative effects owing to propofol. Additionally, the duration of antiemetic action in our trial was much longer than the normal duration of hypnotic action (5–7 min) achieved with the 15-fold higher doses of propofol used for anesthetic induction.[40] This is also seen in the prolonged decrease in nausea and vomiting after propofol anesthesia, still evident for a long time after any anesthetic or hypnotic effect of propofol has worn off. Both these factors make hypnosis an unlikely explanation for propofol's antiemetic properties.

Propofol has a profile of central nervous system depression that differs significantly from other anesthetic drugs.[41] In contrast to thiopental, for example, propofol uniformly depresses central nervous system structures,[41] including subcortical centers. Most drugs of known antiemetic efficacy exert their therapeutic effects *via* subcortical structures.[42,43] We therefore suggest that propofol exerts its antiemetic action by the modulation of some subcortical pathways.

Ure *et al.*[44] showed that patient-controlled anxiolysis with subhypnotic doses of propofol is an effective premedication technique for use in patients for day case surgery. Anxiety and emesis are salient side effects of cancer chemotherapy. The efficacy of adjuvant propofol in the prophylaxis of emesis associated with highly emetogenic cytotoxic treatment was investigated in patients previously refractory to selective serotonin antagonist (5-hydroxytryptamine$_3$ [5-HT3]) and dexamethasone during the acute phase (first 24 h) of their first chemotherapy cycle.[45] In the second cycle, an iv infusion of propofol (1 mg · kg^{-1} · h^{-1}) was added starting 4 h prior to induction of chemotherapy and continued up to discharge from hospital. These previously refractory patients presented more than 5 emetic episodes per day, during and after receiving either cyclophosphamide (600 mg/m^2) or epirubicin (120 mg/m^2). The addition of propofol resulted in total emetic control (no emetic episode) during and in the first 24 h after chemotherapy.[45] In a similar group of patients treated by cisplatin (80–100 mg/m^2) antiemetic prophylaxis was successfully obtained in 90% with adjuvant propofol.[46] In addition, the continuous infusion of subhypnotic doses of propofol greatly improved the quality of life during cisplatin and noncisplatin chemotherapy, as assessed by appetite, mood and physical activity.

B. Hypothesis and Possible Mechanisms

The vomiting center is located close to the fourth ventricle and has four principal afferents: first, the chemoreceptor trigger zone, rich in serotonin, dopamine,

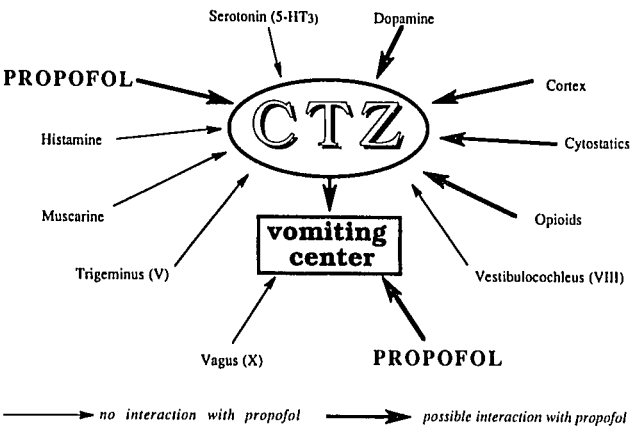

Fig. 2. The chemoreceptor trigger zone (CTZ) and the vomiting center: possible mechanisms of the antiemetic actions of propofol.

histamine, muscarine and opioid receptors; second, the cerebral cortex stimulated by anxiety, smell and physiologic stresses; third, the labyrinthovestibular center; and fourth, the neurovegetative system, sensitive mainly to gastrointestinal irritation, distension or paralysis *via* the vagus nerve.[47] The mechanisms mediating the antiemetic action of propofol are unknown (fig. 2). Propofol is vagotonic.[48,49] The failures observed in the study of Borgeat *et al.*[14] were associated with vagal stimulation, arguing against a vagolytic mode of action. Dam *et al.*[50] using the autoradiographic [^{14}C]2-deoxy-D-glucose method in rats demonstrated that propofol anesthesia induces a widespread depression of local cerebral glucose utilization except in the nuclei related to the auditory and vestibular systems. These observations could explain why propofol may not prevent nausea and vomiting linked to vestibular afferent stimulation. To date, no data are available concerning antiserotoninergic or antidopaminergic properties of propofol. However, propofol does potentiate GABA-mediated effects at both spinal and supraspinal levels, explaining in part the anxiolysis experienced by patients receiving low doses of propofol.[44] Finally, the central nervous system interactions between opioids and propofol remain little investigated.

C. Clinical Indications

Propofol possesses direct antiemetic properties. Subhypnotic doses of propofol (10–15 mg iv) may be used in the recovery room to treat postoperative nausea and vomiting, particularly if it is not of vagal origin. Its advantage lies in a rapid onset of action (within seconds) and the absence of serious side effects. The anxiolysis provided by propofol can also improve the patient's well-being in this setting. However, the benefits, the cost and the efficacy of propofol for this indication as compared to other traditional antiemetic drugs remains to be determined.

The discovery of specific receptors to serotonin (5-HT3) on the chemoreceptor trigger zone led to the development of specific antagonists (5-HT3 antagonists). The introduction of 5-HT3 antagonists led to a great improvement in controlling nausea and vomiting associated with cancer chemotherapy.[51] However, 30% of the patients still have inadequate control of emesis; for these patients, the addition of subhypnotic doses of propofol to 5HT-3 antagonists and dexamethasone seems most promising. Here, propofol not only reduces the incidence of nausea and vomiting but also greatly improves the patient's quality of life. Further studies are needed to assess this new indication of propofol.

III. Antipruritic Effects

Pruritus is an unpleasant sensation that provokes the urge to scratch. Many stimuli are able to induce pruritus. The neural conduction of the itch sensation from the free unmyelinated nerve endings to the central nervous system mainly occurs on unmyelinated C fibers and the anterolateral spinothalamic tract. Pruritus is a common symptom of many dermatologic or systemic diseases, but very little is known about the mechanism of this condition.

A. Spinal Morphine–Induced Pruritus

1. Clinical and Experimental Studies. The use of epidural or intrathecal opioids for the provision of per and postoperative analgesia is constantly increasing.[52–54] However, the administration of spinal opioids, morphine in particular, is associated with a high incidence of pruritus.[55,56] This pruritus is especially frequent after cesarean section.[53] It is difficult to treat, and responds poorly to histamine blockers or other standard therapies.[57] Naloxone is currently the most accepted drug to treat this condition.[58] Unfortunately, this drug has also been associated with a decrease of pain thresholds.[59] We recently investigated the efficacy of propofol (10 mg iv) as compared to placebo (Intralipid®) to treat spinal morphine-induced pruritus in a prospective, randomized, double blind study.[15]

The treatment success rate was significantly greater in the propofol group (84%) than in the placebo group (16%) ($P < 0.05$). The duration of action of propofol was greater than 1 h in 18 patients, 40 min in 2 and 50 min in 1 patient. All successes in the control group lasted more than 1 h. Among the cases of failed treatment in the propofol group, pruritus improved in 2 patients after the open supplementary dose of propofol. The other 2 patients were unresponsive to supplementary open propofol as well as to naloxone. In the placebo group, 90% of patients who did not respond to treatment were subsequently successfully treated by 1 ml propofol (open arm of the study). The other 2 who did not respond to propofol also were resistant to naloxone. The level of postoperative pain remained unchanged after each drug administration and also during the 60 min study observation in both groups.

2. Known and Postulated Mechanisms. It is clear that the syndrome of pruritus consists of two compo-

nents: scratch, a motor disturbance and itch, a change of sensation. However, the mechanisms by which morphine (and other opioids) induces pruritus is still not fully understood. It is evident that the role of opioids in the response to stress and injury goes further than solely producing analgesia. Opioids, morphine in particular, seem to be implicated, either directly or indirectly, in the facilitation of the nocifensive motor reflex (flexion response, scratch) that are an integral part of the physiologic response to injury.[60] On the sensory side, the aversive and excitatory effects (itch hyperpathia) of opioids are well documented.[61–63] It remains unclear if this excitation occurs *via* opioid receptors, *via* modulation of neurotransmitter activity, by a selective depression of certain neurons or by direct excitatory effect on dorsal or ventral spinal cord neurons.[64] Much evidence today suggests that segmental itch and hyperpathia after intrathecal opioids are manifestations of local, segmental excitation by opioids within the spinal cord itself.[65] This hypothesis is attractive because propofol, as opposed to other anesthetics (*e.g.*, barbiturates) in animal studies is associated with a marked depression of *both* the posterior and anterior spinal cord.[41,66] Thus the possibility that propofol exerts its antipruritic action primarily *via* spinal depression, posterior horn for itch and anterior horn for scratch, does not seem unreasonable (fig. 3).

3. Clinical Applications. The administration of subhypnotic doses of propofol to relieve neuraxial opioid-induced pruritus is effective in approximately 80% of patients.[15] The quality of analgesia is not affected by propofol. Propofol may also be given *via* a continuous infusion (0.5–1.0 $mg \cdot kg^{-1} \cdot h^{-1}$) without any serious side effects; this is of benefit for patients with severe pruritus recurring within 1 h after a single bolus dose.

B. Pruritus Associated with Liver Disease

Pruritus is a major, disabling symptom in patients with cholestasis and often interferes with normal daily activities and sleep.[67] This symptom is difficult to treat and is associated with significant morbidity.[68]

Clinical Investigations. Different drugs have been tried with varying degrees of success. Cholestyramine is often efficient but is associated with frequent, unbearable side effects.[69,70] Androgenic steroids have been tried, but they often aggravate the cholestasis.[71] The treatment modalities of phototherapy and plasmapheresis still remain to be defined.[72] Recently rifampicin and ursodeoxycholic acid have been tried with varying

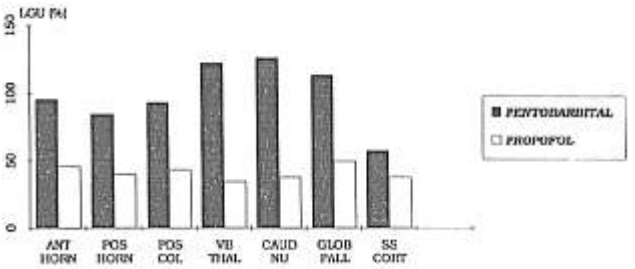

Fig. 3. Local glucose utilization of central nervous system structures after equipotent application of propofol and pentobarbital to rats. This figure shows the differences in glucose utilization induced by propofol or pentobarbital, using the [^{14}C]2-deoxy-D-glucose method. The more uniform and more potent depressant effects of propofol on subcortical centers are emphasized on this diagram. Except for the somatosentory cortex all subcortical areas are more depressed by propofol than by pentobarbital. Control (tissue without anesthetic) = 100%. LGU = local glucose utilization; ant = anterior; pos = posterior; col = column; Vb = ventro-basal; thal = thalamus; caud = caudate; nu = nucleus; gl = globus; pall = pallidum; ss = somato-sensory; cort = cortex. (Adapted from Cavazutti and Crosby.)

success.[73–77] However all of these drugs exhibit a very delayed onset of action and are thus unsuitable for acute symptomatic treatment. The beneficial effect of naloxone in this clinical setting reported by some isolated case reports[78,79] led us to investigate the effects of subhypnotic doses of propofol in this context. Subhypnotic doses of propofol (10 mg iv) were compared to Intralipid in a prospective, randomized, double blind study.[16,17] Each patient received 2 doses of each treatment drug (propofol and placebo). Treatment was successful in 17 of 20 doses of propofol (85%) in the propofol group compared with 2 of 20 doses (10%) in the placebo group ($P < 0.01$). Onset of action was evident within 5–10 min. Among successful treatments the median duration of action was 61 min for propofol *versus* 50 min for the placebo group (not significant). Order of administration of drug treatment had no significant effect. After completion of the study period, 7 patients received a continuous infusion of propofol in an open fashion at a rate of 1–1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for a mean of 3 days before surgery (n = 4), discharge (n = 2), or amelioration associated with antibiotic therapy (n = 1). In all patients but one, symptoms improved with the continuous infusion. Interestingly, it was shown that the administration of barbiturates fails to improve pruritus in this condition.[80]

Known and Postulated Mechanisms. The etiology of cholestatic pruritus remains controversial. Recent studies have demonstrated that it is not related to bile

acid levels.[81] Today, the most likely explanation implicates various pruritogenic agents that may well be opioid or opioidlike compounds.[82] This would place the basic mechanisms of liver disease-associated pruritus close to those suggested for spinal opioids. This hypothesis is supported by a number of observations. Specific opiate antagonists such as naloxone or nalmefene—a specific opioid receptor antagonist devoid of intrinsic activity, and more potent and longer acting than naloxone[83]—are effective in treating both opioid and cholestatic jaundice associated pruritus.[84] Patients with cirrhosis and impaired hepatocellular function exhibit increased central nervous system–mediated sensitivity to the sedative effects of morphine, explained by a downregulation of opioid receptors resulting from chronically increased stimulation by agonist ligands.[85] Finally, such patients experience a severe acute withdrawal-like reaction—similar to the withdrawal reaction of opioid addiction[85,86]—within 1 h of the administration of nalmefene.

These side effects were not observed when nalmefene is given to patients with various other nonhepatic diseases.[87,88] All of these observations are consistent with increased levels of opioid receptor agonists in patients with cirrhosis, an hypothesis further borne out by the finding of elevated plasma levels of methionine enkephalin and leucine enkephalin in patients with chronic liver disease.[87,89,90] At elevated plasma levels, these peptides have been shown to cross the blood-brain barrier.[91] The beneficial effects of subhypnotic doses of propofol in this setting seem to be the consequence, as for neuraxial opioid-induced pruritus, of the strong depressant action of propofol on both the anterior and posterior spinal horns (fig. 3).

Clinical Applications. Subhypnotic doses of propofol have been administered as a bolus (10 mg iv) or a continuous infusion (0.5–1 $mg \cdot kg^{-1} \cdot h^{-1}$) to relieve pruritus in patients with liver disease. The continuous infusion is recommended for patients with extremely severe pruritus that reappears within 1 or 2 h after a single bolus. Its rapid onset of action and the possibility of using it as a continuous infusion make this drug suitable for the acute symptomatic management of pruritus. This treatment is devoid of any major side effects and may be given for several days without any evidence of tolerance or accumulation.

IV. Epilepsy

Numerous anesthetic (methohexital, ketamine, enflurane) and analgesic drugs (high-dose opioids, local anesthetics) have been reported to cause seizures clinically.[92] The role of propofol in epilepsy is still controversial. Although systematic investigations in both animals and humans strongly suggest that propofol possesses anticonvulsant properties,[93–96] several case reports of postpropofol "seizures" or opisthotonus have implicated propofol as a proconvulsant.[97–104]

A. Proconvulsant Properties

The significance of the case reports dealing with propofol as a proconvulsant agent are limited for the following reasons. First, the majority of the reported excitatory movements appeared either in patients with known epilepsy[97,98] or in patients receiving drugs with a known epileptogenic potential.[102,103] Secondly, in none of the reported cases of excitatory movements were simultaneous electroencephalogram (EEG) recordings performed to confirm true cortical epileptic activity. One peculiar case report describes the occurrence of a seizure five days after propofol anesthesia for no apparent reason.[105] In such circumstances it is clearly difficult to implicate propofol as the main factor. Only one case clearly involved propofol as a proconvulsant agent.[106] Here the clinical setting was particular in that the patient was scheduled for a temporal lobectomy for intractable temporal epilepsy; infusion of propofol 2 $mg \cdot kg^{-1}$ iv was associated with discharges of spikes, polyspikes, and spike and slow-wave complexes appearing 20–30 s after propofol and lasting for as long as 7 min.

Seizurelike behavior, characterized by clonus of all four limbs, facial grimacing and tongue clonus were observed in mice receiving 75 $mg \cdot kg^{-1}$ or more of propofol *via* the intraperitoneal route during induction and recovery from anesthesia.[107] EEG recordings showed a generalized decrease in activity and the absence of any cortical epileptic activity. The timing and the nature of the excitatory movements are similar to those found in children (aged 6–12) during induction of anesthesia with 3 $mg \cdot kg^{-1}$ iv of propofol.[108]

Dolin *et al.*[109] hypothesized that glycine antagonism may underlie the excitatory effects of propofol, because strychnine, a glycine antagonist, but not bicuculline, an antagonist to the $GABA_A$ receptor, potentiated both excitatory behavior and EEG paroxysmal discharges when given with propofol. This is the only animal study that would clearly associate propofol and excitatory–epileptic behavior; their hypothesis remains debatable, however, because they were not able to simultaneously

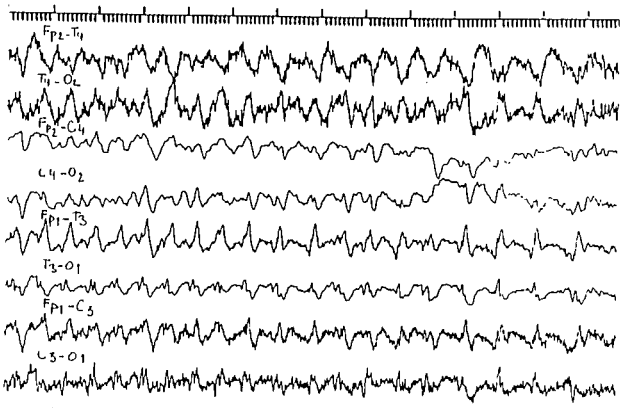

Fig. 4. Electroencephalogram on admission to the intensive care unit. The trace shows slow spike wave discharges in the left temporoparietal area, which were accompanied by right facial clonus.

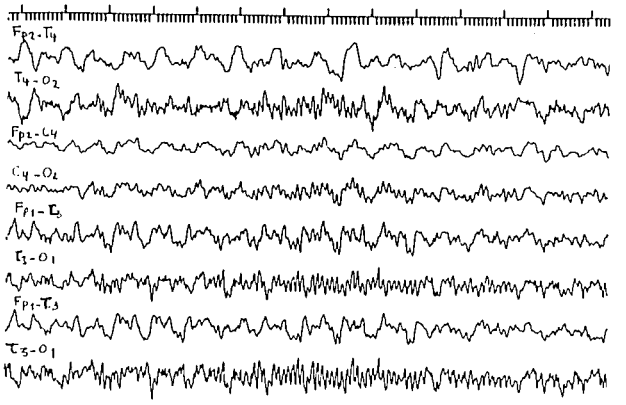

Fig. 5. Electroencephalogram after clonazepam (4 mg), phenytoin (500 mg) and thiopental (150 mg). Recruitment of acute α activity in the left posterior trace, with persistance of spike-wave discharges. No accompanying clinical epileptic activity.

correlate EEG and behavior because mice were given neuromuscular blocking drug when EEG was recorded.

In summarizing these publications two points emerge: first, propofol has never been proven to cause cortical fits in the absence of severe preexisting epilepsy. Secondly, the excitatory phenomena reported are the results of disinhibition in the context of low dosages of propofol depressing inhibitory—but not excitatory—subcortical centers. The fact that inhibitory central nervous system structures are more sensitive to depression than excitatory ones is well known for all hypnotic agents. Thus, it is possible to avoid proexcitatory effects of propofol by using adequate dosage regimen.[108]

B. Anticonvulsant Properties

On the other hand systematic studies in both humans and animals strongly suggest that propofol possesses antiepileptic properties. During electroconvulsive therapy propofol consistently reduces seizure duration when compared to equipotent doses of methohexital, whatever the measurement techniques used. Using a Cerebral Function Monitor, Dwyer *et al.*[110] compared propofol 1.51 $mg \cdot kg^{-1}$ iv and methohexital 1.19 $mg.kg^{-1}$ iv: the duration of seizures were 25% shorter with propofol. Simpson *et al.*[111] observed that seizure durations were 40% shorter following propofol 1.3 $mg \cdot kg^{-1}$ iv than those following methohexital 1.0 $mg \cdot kg^{-1}$ iv using an isolated forearm technique. The observed clinical seizure duration was 42% shorter with either propofol 2.0 $mg \cdot kg^{-1}$ iv as compared to methohexital 1.4 $mg \cdot kg^{-1}$[112] or propofol 1.60 $mg \cdot kg^{-1}$ iv to methohexital 1.08 $mg \cdot kg^{-1}$ iv.[113] Propofol has been successfully used to control status epilepticus in a patient suffering from an overdose of chlomethiazole and unresponsive to therapeutic doses of phenytoin.[114] In another report, a patient with coxsackie encephalitis developed uncontrolled seizures despite combined treatment with diazepam, phenytoin, phenobarbital, and chlomethiazole. The fits were completely suppressed by a single bolus of propofol 100 mg iv and a continuous infusion of 5.7 $mg \cdot kg^{-1} \cdot h^{-1}$.[96] Borgeat *et al.* successfully used propofol to manage a status epilepticus unresponsive to combined phenytoin, clonazepam and thiopental boli in a patient with a drained posttraumatic subdural hematoma.[115] On admission to the ICU the patient had right facial clonus and the EEG shows slow spike wave discharges in the left tempo-

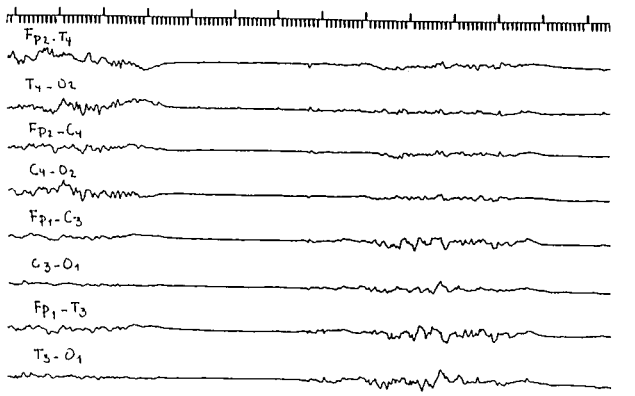

Fig. 6. Electroencephalogram after the addition of propofol ($3 mg \cdot kg^{-1} \cdot h^{-1}$). Burst suppression without epileptic activity.

roparietal area (fig. 4). Despite the administration of clanazepam (4 mg), phenytoin (500 mg) and thiopental (150 mg) within 60 min the EEG disclosed the persistence of spike-wave discharges (fig. 5). Induction of a coma burst with propofol was decided. Figure 6 shows burst suppression without epileptic activity after a bolus of propofol 3 $mg \cdot kg^{-1}$ followed by a continuous infusion of 8–10 $mg \cdot kg^{-1} \cdot h^{-1}$. Mackenzie *et al.*[95] also infused propofol until EEG burst suppression to control fits in two patients resistant to conventional treatment. These results are confirmed by animal studies. In mice, Lowson *et al.*[93] compared intraperitoneal administration of propofol 50 $mg \cdot kg^{-1}$ iv and thiopental 25 $mg \cdot kg^{-1}$ iv against epileptiform seizures induced by electroshock and pentylenetetrazol. Both drugs were equally effective against electroshock seizures, but at the dose mentioned, propofol provided a greater degree of protection against pentylenetetrazol fits than thiopental. In rabbits, De Riu *et al.*[94] demonstrated that a bolus of propofol 12 $mg \cdot kg^{-1}$ iv and an infusion of 50 $mg \cdot kg^{-1} \cdot h^{-1}$ suppressed cortical paroxysmal electric activity in pentylenetetrazol seizures. The infusion prevented the reappearance of electric epileptic patterns in the EEG and tonic–clonic attacks. In the same model, propofol was also effective against cortically applied penicillin G–induced seizures, although it was less potent and its action of shorter duration in this condition.

C. *Postulated Mechanisms of Action*

Although previous original investigations by Glen *et al.*[116] did not associate propofol with either anticonvulsant or proconvulsant properties, recent systematic investigations and well-documented case reports strongly support propofol as an effective anticonvulsant agent.[93,94,113,114]

The efficacy of anticonvulsants is based on their ability to either prevent the spread of epileptic activity in the central nervous system or to increase the threshold of discharge of an epileptic focus.[117] In this context, propofol possesses properties that further support the hypothesis of antiepileptic efficacy.

Propofol, like benzodiazepines and barbiturates, potentiates GABA-mediated pre- and postsynaptic inhibition[1] and interferes with di- or polysynaptic excitation by decreasing the release of excitatory transmitters.[2] Propofol, in common with many other general anesthetic agents, reduces membrane conductance and excitability.‡

Moreover, when compared to barbiturates whose antiepileptic action is mainly *via* their effect on $GABA_A$ receptors, propofol has a more uniform depressant action on the central nervous system including in particular subcortical centers[41,66] (fig. 3). Thus, propofol may exert antiepileptic activity by interacting with multiple mechanisms involved in the genesis of epilepsy: interactions with GABA transmission membrane excitability and *via* NMDA receptor by decreasing the release of L-glutamate and L-aspartate—a property not shared by thiopental—thus explaining its efficacy in patients resistant to conventional treatment[115] (figs. 7 and 8). Another beneficial effect of propofol in this setting is its free radical scavenging properties.[118] *In vitro* studies demonstrate that propofol reacts with free radicals to form a phenoxyl radical with each molecule of propofol scavenging two radical species.[118]

D. *Clinical Indications*

We may surmise that the vast majority of the reported propofol-induced "seizures" during induction or emergence from anesthesia were due to spontaneous excitatory movements of subcortical origin. These movements have been reported in adults as well as in children, with a higher incidence in the latter.[108] Although not fully understood, they are dystonic, may appear during induction or recovery from propofol anesthesia and are not related to cortical epileptic activity.[108] Thus, with the exception of particular cases such as the one with intractable epilepsy scheduled

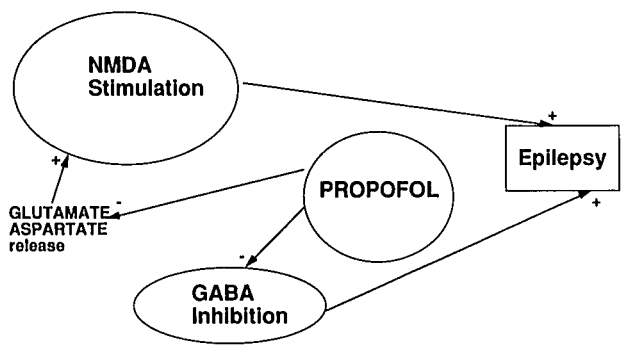

Fig. 7. Possible antiepileptic mechanisms of propofol. Propofol may interact with epilepsy by two main mechanisms: first by increasing the γ-aminobutyric acid-A ($GABA_A$) inhibition and second by decreasing the release of L-glutamate and L-aspartate in the central nervous system. NMDA = n-methyl-D-aspartate.

‡ Frenkel C, Urban BW: A molecular target site for propofol: voltage-clamp studies on human CNS sodium channels in bilayers (abstract). ANESTHESIOLOGY 71:A590, 1989.

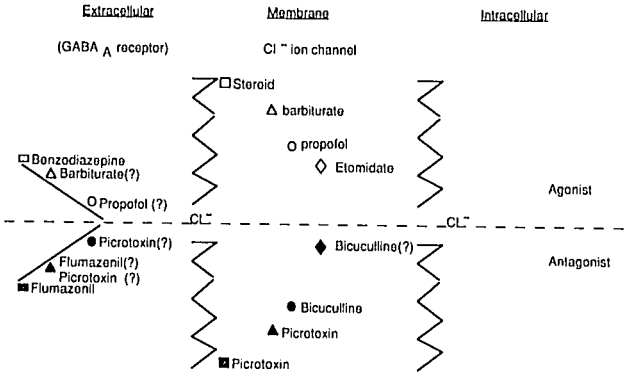

Fig. 8. γ-aminobutyric acid-A ($GABA_A$)–benzodiazepine ionophore receptor complex, and $GABA_A$ receptor–chloride channel complex with hypothetical sites of action for some intravenous anesthetics. GABA-ergic inhibition by propofol and barbiturates may be mediated by two primary actions: an increase in agonist affinity for the $GABA_A$ receptor and a prolongation of the chloride ionophore conductance. Actions on the extracellular receptor site selectively open the chloride channel. Propofol and barbiturates may act on both the receptor site and the chloride channel but at different receptor sites. (*Bottom*) The known or postulated (?) antagonists.

for elective neurosurgery,[106] the use of propofol is neither associated with cortical epileptic activity, nor with the aggravation of seizures. Patients with known and controlled epilepsy may thus receive propofol anesthesia. Moreover, propofol may be used to treat fits unresponsive to conventional treatment. This agent seems particularly useful for the induction of coma therapy for controlling refractory epilepsia; compared to barbiturates, burst suppression is more easily controlled, awakening is more rapid and it is free of hepatic side effects. The dosage of propofol needed to control status epilepticus remains to be determined.

V. Anxiolysis

Anxiety is a common symptom in patients scheduled for surgical procedures carried out either under local, regional or general anesthesia.[119] It is common practice in day case surgery not to administer anxiolytic premedication in order to avoid excessive postoperative sedation and possibly delayed discharge. However, a great number of these patients would prefer to receive anxiolytic therapy.[119]

A. Review of Studies

Few studies to date have investigated the anxiolytic properties of propofol. Ure *et al.*[44] found that patient controlled anxiolysis with subhypnotic doses of propofol (10 mg iv with a 3–5-min lockout period) was, as compared to placebo, an effective premedication for patients presenting for day case surgery. Anxiety was assessed with an anxiety and a sedation linear analogue scale completed by a modified affect adjective checklist. These results were confirmed by Grattidge[120] who found that a fixed dose of propofol, 0.7 $mg \cdot kg^{-1}$ iv, administered during surgery under local or regional anesthesia provided not only sedation but also anxiolysis with a high degree of patient satisfaction. In this study the level of sedation was assessed by the patient himself. The anxiolytic and amnesic properties of propofol (0.95 $mg \cdot kg^{-1}$ iv) were equivalent to these of midazolam (0.08 $mg \cdot kg^{-1}$ iv) in patients undergoing ambulatory endoscopy.[121] In a study conducted by Ferrari *et al.*,[122] low-dose propofol (0.47 $mg \cdot kg^{-1}$ iv) provided anxiolytic and sedative effects comparable to either midazolam or methohexital during retrobulbar and peribulbar ocular block, with the added advantages of reduced postoperative side effects and earlier return-to-home readiness. We also observed a marked decrease of the anxiety level in cancer patients receiving a continuous infusion of propofol 1 $mg \cdot kg^{-1} \cdot h^{-1}$ starting 4 h prior to the induction of chemotherapy.[45]

B. Hypothetical Mechanisms of Action

Recent neurochemical investigations have linked anxiety to dysfunction in central benzodiazepinergic, serotoninergic and noradrenergic systems.[123] α_2-Adrenergic agonists and serotonin antagonists reduce anxiety.[124,125] Benzodiazepines produce their pharmacologic effects by regulating the interaction of GABA with its binding site on the $GABA_A$ receptor complex.[126] The $GABA_A$ receptor complex plays a major role in the pharmacology, neurochemistry and physiopathology of stress and anxiety.[126] Anxiety is modulated by changes in activity of endogenous ligands for the benzodiazepine receptor.[123] The administration of midazolam into the mamillary bodies of the posterior hypothalamus in animals is associated with anxiolysis. This would implicate the mamillary bodies as one of the sites of anxiolytic activity.[127] The anxiolytic effect of benzodiazepines has also been associated with an increase of glycine inhibitory neurotransmitter activity. Moreover, the affinity of the benzodiazepines for glycine receptors in the brain stem correlated with their antianxiety potency.[128] Interactions between propofol and glycine receptors has been suggested to explain some of the excitatory manifestations associated with propofol.[109]

Propofol also potentiates $GABA_A$-mediated effects.[18] The possibility of a mechanism common to propofol and the benzodiazepines, as well as the interactions at the GABA or glycine receptor sites to produce anxiolysis deserves further investigation.

C. Clinical Indications

Preliminary investigations show that subhypnotic doses of propofol possess anxiolytic properties, strengthening the case for its use during sedation and as an adjunct to local or regional anesthesia. It would be interesting to know if these effects persist during the immediate postoperative period following general anesthesia. Subhypnotic doses of propofol have promising antiemetic effects during cancer chemotherapy; in this setting, anxiolysis is one of the factors that greatly improve the patients' well-being.[46] In day case surgery subhypnotic doses of propofol as premedication warrant further investigation because the anxiolysis associated with propofol's relative freedom from side effects, rapid recovery and low level of postoperative amnesia are of significant benefit to the patient.

VI. Muscular Actions

The muscular relaxation associated with propofol administration is another subject of controversy. This question is important in anesthesiology and particularly in medical and surgical intensive care because the use of neuromuscular blocking agents has some limitations.[129] Although the previous formulation of propofol (Cremophor EL solution) modified the activity of neuromuscular blockers,[130,131] the current formulation is devoid of any interactions with vecuronium,[132,133] succinylcholine, or atracurium.[134]

A. Clinical and Experimental Studies

Kumar *et al.*§ investigated the *in vitro* effect of propofol on isolated guinea pig tracheal smooth muscle. They observed that propofol causes a dose-related relaxation of the tracheal smooth muscle, mediated neither by β nor by cholinergic receptors. Human studies have mostly concentrated on the intubating conditions in patients receiving propofol with or without neuromuscular blockers. Previous studies demonstrated that laryngeal reflexes were depressed by propofol, permitting laryngoscopy and intubation at safe induction doses.[134] Dominici *et al.*[135] evaluated the ease of intubating patients following propofol 3 $mg \cdot kg^{-1}$ iv with and without suxamethonium. They did not find any difference concerning the number of successful intubations, although propofol alone was associated with a higher incidence of bucking. The addition of suxamethonium also provided a better opening of the glottis.

They concluded that tracheal intubation can be safely and efficiently performed with propofol without myorelaxation. Saarnivaara and Klemola[136] compared propofol 2.5 $mg \cdot kg^{-1}$ iv added to different doses of alfentanil and found acceptable intubating conditions in 79% of the patients receiving propofol plus alfentanil 30 $\mu g \cdot kg^{-1}$ iv. Mulholland *et al.*[137] compared the quality of tracheal intubation after induction of propofol (2.5 $mg \cdot kg^{-1}$ iv) in patients who received either lidocaine 1.5 mg iv or a placebo. No significant differences were noted between the groups; however, the overall failure rate was 30.6%. The authors do not recommend this technique as it does not seem reliable or predictable enough for routine use. Jacque *et al.*[138] had a 36% rate of intubation success with either propofol 2–2.5 $mg \cdot kg^{-1}$ iv or propofol 1.0 $mg \cdot kg^{-1}$ iv bolus followed by a continuous infusion as compared to 100% success with thiopentone and suxamethonium. They concluded that propofol has no muscle-relaxing properties and did not advise its use as a sole intubating agent.

B. Use in Human Tetanus

Tetanus is characterized by muscle rigidity and reflex spasms that result from the combination of the tetanus toxin and a ganglioside with the synaptic terminals of spinal interneurons. This complex interferes with the release of the inhibitory transmitter substance acting on glycinergic or GABA-ergic cells.[139,140] Thus, disinhibition of α and γ motor neurons occurs, resulting in increased muscular tone, loss of coordination and the spontaneous, simultaneous contractions of both agonist and antagonist muscles that constitute tetanus spasms.[140]

Borgeat *et al.* investigated the effects of propofol in two patients with tetanus.[141,142] In the first patient midazolam up to 16 $mg \cdot h^{-1}$, morphine 5 $mg \cdot h^{-1}$ and vecuronium had been necessary to control painful myoclonus. The introduction of propofol (50 mg iv bolus and continuous infusion 3.5–4.5 $mg \cdot kg^{-1} \cdot h^{-1}$) per-

§ Kumar A, Lee TL, Adaikan PG, Lau LC, Ratnam SS: Effect of propofol on guinea pig tracheal smooth muscle (abstract). ANESTHESIOLOGY 71:A280 1989.

mitted the discontinuation of midazolam and vecuronium and a decrease rate of morphine infusion. In the second patient, masseter and rectus major muscular activity was recorded by means of electromyography. Following a bolus of propofol 50 mg iv, muscular activity decreased from 150 to 10–25 mV within 15 s for a mean duration of 6 min. The mechanisms involved in muscular relaxation by propofol in this setting are not known. A peripheral mechanism is unlikely. From our current knowledge of the pharmacology of propofol a direct spinal action seems likely; it remains to be determined which neurotransmitters (glycine or others) are involved in this process.

C. Other Indications

The various studies dealing with intubating conditions provided by propofol alone are discordant. The evaluation of these data is difficult because the doses of propofol used are not identical, the skills and training of the anesthetists involved are impossible to standardize, and the patient's anatomic particularities may well have played a role. Nevertheless, it seems that propofol provided better intubating conditions as compared to thiopental[143]; thus it may be the anesthetic of choice when neuromuscular blocking agents are not indicated or are even contraindicated. However, its routine use as sole intubating agent is not recommended.

Preliminary results show that propofol may be efficient in patients with tetanus at a dosage of 3.5–7 $mg \cdot kg^{-1} \cdot h^{-1}$ with supplementary boli of 50 mg iv before painful stimulation: muscular relaxation is marked; sedation is easily managed; and complete awakening is rapid even after prolonged infusion—no accumulation.[141]

VII. Abuse Potential and Analgesic Properties

A. Abuse Potential

Intense dreaming activity, amorous behavior or hallucinations are features reported during recovery from propofol anesthesia.[144,145] Mood changes are also distinct characteristics of patients administered subhypnotic doses of propofol: in women scheduled to receive cancer chemotherapy, we observed a change from introvert to extrovert behavior after the continuous infusion of 1 $mg \cdot kg^{-1} \cdot h^{-1}$ of propofol during 4 h.[45,46] In a prospective, randomized, double-blind placebo-controlled and crossover study, Zacny *et al.*[146] observed that healthy volunteers free of any drug abuse or psychiatric disorders underwent changes in mood in a dose-related fashion; five of ten subjects liked high-dosage propofol infusion (2.0 $mg \cdot kg^{-1} \cdot h^{-1}$), three did not. From a psychopharmacologist's point of view, any chemical substance that leads to rapid euphoria and that favors communicative behavior in general facilitates autostimulatory pathways, thus leading easily to toxicomania. Propofol does indeed fit this profile and must therefore be considered to have drug abuse potential. However, its use in this setting is limited to a certain extent by its mode of administration (only iv) and its pharmacokinetic characteristics (very short half-life). To date only one case of propofol addiction has been reported in the literature.[147] It concerns the particular case of an anesthesiologist with a previous history of drug dependence. However, it is always conceivable that some patients at risk may be tempted to abuse a drug such as propofol, and anesthesiology departments should be aware of such a risk.

B. Analgesic Properties

The analgesic properties of propofol remain controversial. In its first formulation (2,6-diisopropylphenol in Cremophor EL) propofol was shown to increase pain threshold using tibial pressure algesimetry. In the same study, thiopentone was demonstrated to possess hyperalgesic properties.[148] In its new formulation, analgesic properties of propofol have not been formally demonstrated. However, some authors have found that the postoperative need for analgesia was decreased following propofol anesthesia, as compared to thiopental–halothane anesthesia.[34] In the intensive care setting, Du Grès *et al.*[149] compared the use of propofol and midazolam for achieving similar levels of sedation following coronary artery bypass grafting. They found that the propofol group needed less morphine than the midazolam group.[149] In the same clinical setting, Mc Murray *et al.*[150] noted that, compared to midazolam, the requirements for morphine and glyceryl trinitrate were less when propofol was given, a finding not confirmed by Kenny and Chandhri.[151]

It is evident that propofol does not possess classic analgesic properties to counter acute pain. However, propofol interacts with di- or polysynaptic excitation by decreasing the release of excitatory transmitters, *e.g.*, L-glutamate and L-aspartate.[19] These amino acids are closely implicated in the stimulation of NMDA receptors in the spine. These receptors are central to the modulation of postoperative hyperalgesia or windup.[152]

By its interactions with the NMDA receptor, propofol may decrease postnociceptive windup and therefore diminish the need for analgesics either in the recovery room or on intensive care units. This fascinating aspect of propofol deserves further studies.

VIII. Conclusions and Therapeutic Implications of Nonanesthetic Properties

Despite the presence of propofol on the European market for almost 10 yr its nonhypnotic therapeutic uses have remained unknown until very recently. Propofol is remarkable in that it possesses, in contrast to other hypnotics, strong depressant subcortical actions that long outlast its corticohypnotic ones.[153] The antiemetic, antipruritic and anxiolytic effects of subhypnotic doses of propofol suggest a preferential involvement of subcortical structures. Because of its favorable pharmacokinetic properties, *i.e.*, short half-life and high clearance rate,[154–156] the use of propofol in such low dosages is safe in clinical practice and devoid of serious side effects. For these indications, it can provide specific therapeutic benefits and improve the general patient's well-being. Propofol seems to interact with various neurotransmitters or specific receptors in the central nervous system in ways still unknown, whose elucidation represent a fascinating challenge for future investigations.

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