Review Article

Neuroleptanesthesia: current status

Bruno Bissonnette MD FRCPC,
Hilton Swan MBBS FANZCA,
Patrick Ravussin MD,*
Victor Un MD FRCPC

Purpose: To review the current status and possible future of neuroleptanalgesia/anesthesia, techniques that may be nearly extinct.

Source: Articles from 1966 to present were obtained from the Current Science and Medline databases. Search terms include neurolepananalgesia/anesthesia, conscious sedation, droperidol, benzodiazepines, propofol, ketamine, and opioids. Information and abstracts obtained from meetings on this topic helped complete the collection of information.

Principal findings: Droperidol/fentanyl may still be clinically indicated in the management of surgical seizure therapy for electrocorticography. However, the high incidence of post-operative sedation and restlessness discourage its use for other surgical or diagnostic procedures. Many surgical interventions, once thought ideally suited for neuroleptic agents, now meet better success with newer medications. The use of midazolam and/or propofol, in association with newer opioids, provides ideal anesthetic combinations.

Conclusion: The advantages of newer anesthetic agents have redefined the clinical indications for neuroleptanesthesia. In routine modern anesthesia, anxiolysis, sedation, and/or analgesia is better provided, with quicker recovery, by the new pharmacokinetic and pharmacodynamic characteristics of recent medications than by the neuroleptic component of neuroleptanesthesia.

Objectif : Faire une revue de l'état actuel et de l'évolution possible de la neuroleptanalgésie qui semble maintenant presque abandonnée.

Sources : Des articles de 1966 à aujourd'hui ont été obtenus à partir d'une consultation de Current Science et de Medline. Les mots-clés comprenaient : neuroleptanalgésie, sédation du patient éveillé, dropéridol, benzodiazépines, propofol, kétamine et opiacés. Les informations et les résumés provenant de séminaires sur le sujet ont permis de compléter la cueillette de données.

Constatations principales : La combinaison de dropéridol et d'alfentanil peut être indiquée pour l'électrocorticographie utilisée dans le traitement chirurgical de l'épilepsie. Cependant, l'importante incidence de sédation et d'agitation postopératoires décourage son utilisation pour d'autres interventions chirurgicales ou diagnostiques. Nombre d'interventions chirurgicales où on a cru que les neuroleptiques étaient les agents idéaux sont maintenant mieux réussies avec de nouveaux médicaments. L'emploi de midazolam et/ou de propofol, associés aux nouveaux opiacés, fournit les meilleures combinaisons.

Conclusion : Les avantages des nouveaux anesthésiques ont amené à redéfinir les indications cliniques de la neuroleptanalgésie. Dans la pratique de l'anesthésie moderne, les médicaments récents assurent mieux la réduction de l'anxiété, la sédation et/ou l'analgésie et permettent une récupération plus rapide que les composés utilisés en neuroleptanalgésie, grâce à leurs nouvelles caractéristiques pharmacocinétiques et pharmacodynamiques.

From the Department of Anaesthesia, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada and the Service d'Anesthesiologie,* Hôpital Régional de Sion Herens Conthey, Switzerland.

Address correspondence to: Dr. Bruno Bissonnette, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8 Canada. Phone: 416-813-7445; Fax: 416-813-7543; E-mail: bruno@anes.sickkids.on.ca

Accepted for publication November 14, 1998

Contents

Abbreviations

CBF: Cerebral blood flow
$CMRO_2$: Cerebral metabolic rate for oxygen
CNS: Central nervous system
CPP: Cerebral perfusion pressure
CSF: Cerebrospinal fluid
EEG: Electroencephalography
ICP: Intracranial pressure
MAP: Mean arterial pressure
$PaCO_2$: Partial pressure of carbon dioxide
PaO_2: Partial pressure of oxygen

THE paucity of recent literature on neuroleptanesthesia, once a topic of considerable interest in anesthesia, attests to its current uncertain clinical status. Has this technique, which defined a new anesthetic frontier 40 yr ago, gone the way of ether and cyclopropane, to become a subject only of historical interest? Re-evaluation of its virtues and reassessment of its relevance to current practice is needed. This article, which discusses the virtues and future of neuroleptanesthesia, is intended to help clinicians understand and reassess indications for a technique that may be nearly extinct.

History

The first reference to a neuroleptic anesthetic technique was presented in 1954 by Campan and Lazothes[1] in France. This new anesthetic technique was designed to modify the effects of conventional general anesthesia in eliminating the perception of nociceptive stimuli at the level of the cerebral cortex without affecting cognitive function. Its specific characteristics included modulation of certain endocrine, metabolic, and autonomic responses to nociceptive stimulation. They compared the anesthetic state to that of certain selected animal species during hibernation. This new anesthetic technique, called gangliolegia or neuroplegia, used a lytic cocktail of three components: meperidine, promethazine, and chlorpromazine.[2] It remains in use today in some pediatric centres, referred to as DPT (for their brand names, Demerol, Phenergan, and Thorazine).

The work of Campan and Lazothes[1] was expanded further by de Castro and Mundaleer[3] in Belgium. Using haloperidol (butyropherone) as a major neuroleptic and phenoperidine (an opioid), they produced a state of indifference and immobilization (often referred to by psychiatrists as mineralization) that they called neuroleptanalgesia. It was restricted to patients who, under the combined influence of a neuroleptic and an opioid, become analgesic, sedated, mineralized, and amnestic, maintaining autonomic, neurological, and cardiovascular stability while able to comprehend and obey simple commands during surgery.[2] When the patient was rendered unconscious with the addition of N_2O or a hypnotic drug, the term neuroleptanesthesia was used.

When droperidol and fentanyl citrate, both introduced by Petr Janssen,[4,5] became available, they replaced haloperidol and phenoperidine as the most widely used compounds for inducing and maintaining neuroleptanalgesia. Anesthesia was induced with Innovar, each millilitre of which contained 2.5 mg of droperidol and 50 μg of fentanyl citrate, and supplemented with N_2O and O_2 to attain neuroleptanesthesia. The drug combination was titrated into a fast-running intravenous (*iv*) infusion until the patient was sedated and demonstrated some difficulty in phonation from respiratory depression. Intubation under direct laryngoscopy after topical anesthesia was then possible, with or without muscle relaxants. However, this technique was not without problems, which included unconsciousness to the unrousable level, ventilatory difficulties from muscular rigidity, and postoperative extrapyramidal excitation.

These problems were caused by a lack of investigation and understanding of the pharmacological effects of the individual components.[6] The fixed-ratio mixture of Innovar, with the slow onset–slow offset droperidol and fast onset–fast offset fentanyl, was the obvious reason for overdose and complications. The relatively slow onset time for droperidol (6–8 min) meant more fentanyl was initially required for achieving sedation, resulting in a relative overdose with development of muscle rigidity and/or apnea. If not, as droperidol started to act, excessive sedation and respiratory depression became evident; the relative overdose of droperidol

also caused extrapyramidal excitation. These complications could be prevented by separate, judicious administration of each drug.[6,7]

In the past 20 yr, numerous new anesthetic agents have become available, such as short-acting sedatives and hypnotics (midazolam and propofol) and the newer opioids (alfentanil, sufentanil, and remifentanil). To review the current status and list of indications and techniques for neuroleptanalgesia/anesthesia, we will compare the pharmacology of droperidol and fentanyl with that of the newer alternative drugs.

Before proceeding, it seems appropriate to clarify some terms. Neuroleptanalgesia and neuroleptanesthesia refer to the omission or addition, respectively, of N_2O to the combination of a neuroleptic and an opioid. In recent years, the term conscious sedation has appeared. It describes the administration of a sedative or hypnotic drug either alone (as in pediatric sedation for radiological procedures or as an adjunct to local/regional anesthetic techniques) or in conjunction with an analgesic agent for mild to moderately painful procedures. It constitutes a state of minimally depressed level of consciousness without affecting the ability of the patient to maintain airway reflexes and appropriate responses to physical stimulation or verbal command. Despite the unambiguous nature of these phrases, frequently the terms neuroleptanesthesia and neuroleptanalgesia are erroneously used as synonyms to describe conscious sedation.

A THE NEUROLEPTIC COMPONENT

All neuroleptic drugs used in clinical practice are tertiary aromatic amines based on methyl–ethylamine. Various substitutions around this basic structure produce a series of drugs with a wide spectrum of neuroleptic activities. Two of the main categories are the butyrophenones and the phenothiazines. Drugs such as droperidol (dehydrobenzperidol) and haloperidol belong to the butyrophenones, whereas chlorpromazine and prochlorperazine are phenothiazines. These drugs are effective in alleviating the anxiety accompanying psychotic disorders. Butyrophenones act as allosteric inhibitors at post-synaptic receptor sites to decrease the neurotransmitter activity of dopamine.[8] The antipsychotic effects of these agents have been mostly attributed to their antagonism of the post-synaptic dopaminergic receptors of the central nervous system (CNS); however, other neurotransmitter systems could be involved.

DROPERIDOL

Neurological effects: Although droperidol reduces cerebral blood flow (CBF) 40% by vasoconstricting the cerebral vessels, the cerebral metabolic rate for oxygen ($CMRO_2$) remains unchanged. This may lead to a potential discrepancy between the metabolic supply/demand ratio, which could become important in patients with impaired CBF from cerebrovascular atherosclerosis or surgical intervention, or with increased $CMRO_2$ from seizure activity. One of the advantages of droperidol is its lack of EEG effects,[9] allowing reliable intra-operative EEG monitoring. It is not an anticonvulsive agent;[10] in fact, droperidol can lower the seizure threshold[11] and should be used with caution in patients with untreated epilepsy. This intrinsic effect might be an advantage during intra-operative recording of seizure foci for intractable epilepsy; however, this association has yet to be supported.

Respiratory effects: Clinical doses of droperidol (5 mg) have been reported to cause a reduction in tidal volume (13.3%),[12] minute ventilation (8.4%),[12] airway resistance (50%),[13] and functional residual capacity (25%), whereas larger doses (0.3 $mg \cdot kg^{-1}$) in healthy volunteers did not modify the respiratory drive to CO_2.[14] Partial pressures of carbon dioxide ($PaCO_2$) measured before and after administration of droperidol remained the same. Innovar (a proprietary droperidol/fentanyl combination) has been shown to cause a reduction in functional residual capacity (FRC) that was reversible with succinylcholine, suggesting increased expiratory muscle activity;[12] however, the individual effects of droperidol and fentanyl were not compared in the study. It has been suggested[15] that the anti-dopaminergic action of droperidol on the carotid body could reduce the depressant effect of hypoxemia on the respiratory centre.

Cardiovascular effects: Although droperidol does not affect myocardial contractility or heart rate, it does decrease systemic blood pressure—possibly because of its peripheral α-adrenergic blockade and central antidopaminergic activity.[16] The decrease is usually modest; in the presence of hypovolemia, however, severe arterial hypotension could result. In hypovolemic patients, it is therefore prudent to administer droperidol with extreme caution, to avoid changes in cerebral perfusion pressure (CPP) and intracranial pressure (ICP), which could cause cerebral ischemia.

Conversely, droperidol has been shown to cause hypertension in patients with pheochromocytoma,[17] possibly as a result of the efflux of catecholamines from adrenal medullary cells and/or the inhibition of catecholamine reuptake into neuronal chromaffin granules, resulting in increased systemic catecholamine levels.[18]

Droperidol has cardiac antidysrhythmic properties.[19] At a dose of 0.2 $mg \cdot kg^{-1}$, it doubles the arrhyth-

mic threshold to infusions of epinephrine. In animal studies, Bertolo and associates[20] demonstrated that droperidol delayed the onset of ventricular fibrillation induced by coronary occlusion. Without ß-blocking activities, possible explanations for its antidysrhythmic activity include an antagonistic effect on the myocardial α-adrenergic receptors combined with a local anesthetic-like stabilization of myocardial membranes. Droperidol may be contraindicated in patients with pre-existing myocardial conduction defects. In doses ranging from 0.1 to 0.25 $mg \cdot kg^{-1}$, it has been shown to prolong the QT interval in surgical patients.[20]

Antiemesis: Droperidol has potent antiemetic properties; it is commonly used in small doses to prevent perioperative nausea and vomiting in anesthetic practice. The antiemetic effect of droperidol may be due to inhibition of dopaminergic (notably D_2) receptors in the chemoreceptor trigger zone (the area postrema) in the floor of the fourth ventricle. However, vomiting induced by labyrinthine instability (motion sickness) is not prevented or ameliorated by droperidol. The incidence of post-operative nausea and vomiting can be decreased by intra-operative administration of 25–40 $\mu g \cdot kg^{-1}$ droperidol in obstetric cases.[21] Although a larger dose (75 $\mu g \cdot kg^{-1}$) was suggested as effective in children undergoing strabismus surgery, 21% of this surgical population vomited after discharge from the hospital.[22] At this dose, there was a high incidence of sedation and restlessness (63%).[23]

ALTERNATIVE DRUGS

Many surgical procedures once thought to be ideally suited for the administration of a neuroleptic technique have, over the past two decades, been better performed with non-neuroleptic drugs and techniques. Several new classes of anesthetics have all but replaced the neuroleptic drugs for procedures requiring conscious sedation, total intravenous anesthesia (TIVA), or balanced general anesthesia. The ideal drug to produce anxiolysis, sedation, and/or hypnosis should be pharmacologically predictable and easily titratable in the duration and magnitude of its effect. It should be short-acting as well, with a rapid recovery to preoperative levels of consciousness. Further favourable attributes include a limited metabolism to active or toxic metabolites, water solubility, compatibility with commonly used crystalloids, and lack of severe drug interactions. Furthermore, it should not be irritant upon intravenous injection or cause tissue damage if inadvertently administered extravascularly or intra-arterially. Finally, it should have no effect on cardiovascular, respiratory, hepatic, or renal function, and no untoward side-effects such as nausea and vomiting, allergic reactions, or psychomotor disturbances.[24]

Benzodiazepines were introduced in the 1960s and have assumed an increasing role as anxiolytics and sedative hypnotics, replacing barbiturates in many clinical applications. Because of their safety, as demonstrated by a high therapeutic index (50% lethal dose ÷ 50% effective dose) and a relatively benign adverse-effect profile, they have achieved wide acceptance among clinicians. They have been the main class of drugs responsible for the decline in use of neuroleptic agents in anesthesia practice.

In 1977, the discovery of the benzodiazepine receptor improved the understanding of their mechanism of action and led to the development of more versatile drugs, such as the short-acting agonist midazolam and the specific benzodiazepine antagonist, flumazenil. Since then, the molecular pharmacology of the benzodiazepine receptors and γ-aminobutyric acid (GABA) receptors has been further elucidated and characterized.[25] In short, it was proposed that the benzodiazepine receptor (with two subtypes) was different from the GABA receptor (with types A and B subunits), but that these two receptors are one macromolecular complex associated with the chloride membrane channel. Thus, stimulation of the receptor by an agonist would, by linkage through the $GABA_A$ receptor–chloride channel complex, induce an influx of chloride anions into the neurones, causing hyperpolarization and inhibiting nerve transmission. Not all $GABA_A$ receptors, however, are coupled to benzodiazepine receptor sites; it is possible that the heterogeneity of the four subunits (α, ß, π, Δ) have functional differences and may represent a group of different receptors rather than a single entity.[25]

Alone, benzodiazepines lack GABA-mimetic effects; however, they have been shown to enhance the response. This speculation is based on the suggestion that a $GABA_A$ receptor, a benzodiazepine receptor, and the chloride ionophore form one macromolecule complex; benzodiazepines are consequently not GABA-mimetic but can potentiate the effects of binding with $GABA_A$ receptors.[25] This would explain why the binding of benzodiazepines to their receptor complex can be reversed by a simple competitive antagonist (flumazenil) at the conclusion of anesthesia.[26]

Midazolam

The substance that comes closest to fulfilling the criteria mentioned above for an ideal drug is midazolam. Its effects on the cardiovascular and respiratory systems are dose-related, high doses being depressant. With sedative doses (0.075 $mg \cdot kg^{-1}$), no change in ventilatory response to carbon dioxide or in blood

pressure has been reported;[27] however, the protective upper airway reflexes may be reduced. Caution with ventilation is required when an opioid is added, because of their synergistic effects. The central neurological anxiolytic, anticonvulsant, amnestic, sedative, and hypnotic effects are dose-related.[24] Midazolam reduces $CMRO_2$ and CBF in parallel, such that the $CBF/CMRO_2$ ratio remains normal.

The EEG changes after midazolam (10 mg *iv*) are comparable with those after diazepam,[28] with disappearance of α-rhythm and the onset of higher frequency ß-activity, initially at 22 Hz, followed by additional ß-activity at 15 Hz. Subjects in that study[28] were clinically asleep; these records were not typical of the tracings found in light sleep, and persisted for another 40 min, even after consciousness and orientation were regained. Although midazolam may have a variable effect on cerebrospinal fluid (CSF) production and reabsorption,[29] it does not seem to affect ICP if a clinically relevant dose (mean, 0.27 $mg \cdot kg^{-1}$) is given to patients with reduced intracranial compliance.[30]

Like other benzodiazepines, midazolam is able to produce reliable anterograde, but not retrograde, amnesia. A dose of 5 mg midazolam *iv* produced amnesia within two minutes, followed by a rapid recovery over the next 20 min, with 40% of patients still having memory impairment after 1.5 hr.[31] Despite a wide range of doses (0.05–0.27 $mg \cdot kg^{-1}$) required to achieve the endpoint in a cross-over study, midazolam produced better sedation and anterograde amnesia than did diazepam. This desirable property could reduce the incidence of unfavourable recall of intra-operative events. Finally, recent evidence[32] also suggests that midazolam may possess anti-emetic properties.

Flumazenil

A recently synthesized benzodiazepine, flumazenil is a specific competitive antagonist at the benzodiazepine receptor, which can reverse all the central effects of benzodiazepine agonists in a dose-related manner. It is deprived of almost no intrinsic agonist activity except a slight subjective sedative effect. Large antagonistic doses could result in withdrawal symptoms; carefully titrated increments of 0.1 mg, up to 1 mg, in healthy adults should provide a smooth recovery without any major adverse reactions. Combinations of midazolam and flumazenil have been successful during spinal or neurological surgery requiring a "wake up" test to allow intra-operative neurological assessment.[24]

In healthy male volunteers (mean age 36 yr, standard deviation 5 yr),[33] administration of 0.1 $mg \cdot kg^{-1}$ flumazenil antagonized the reduction in CBF or the EEG changes observed after the administration of 0.15 $mg \cdot kg^{-1}$ midazolam. Flumazenil alone has no cerebral effects, suggesting that there is no intrinsic reverse-agonist activity. These intracerebral changes, however, differ in the diseased brain. Studies in animals subjected to incomplete global cerebral ischemia[34] showed an acute increase in CBF and ICP after flumazenil reversal of midazolam. When high doses were studied in healthy dogs, [35] the administration of 1 $mg \cdot kg^{-1}$ flumazenil to reverse midazolam (40 $\mu g \cdot kg^{-1}$) resulted in marked increases in ICP and CBF for 15 min. Studies in humans have produced similar findings. In a group of 18 ASA III patients (American Society of Anesthesia status III) undergoing craniotomy for tumour or aneurysm surgery,[36] the use of flumazenil (bolus 0.5 mg with 0.1 mg increments to a maximum of 1 mg) to reverse the residual effect of midazolam following an induction dose of 0.2–0.3 $mg \cdot kg^{-1}$ and an infusion of 0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ at the conclusion of surgery resulted in a transient increase (>20% from baseline) of mean arterial pressure in seven patients (39%). Measurements of ICP were not reported in this study. In a study of 15 head-injured patients,[37] midazolam reversal by flumazenil resulted in an increase in ICP and mean arterial pressure. Until more clinical experience is available, reversal of benzodiazepines with flumazenil, especially in the head-injured patient, must be done with prudence and preferably with simultaneous ICP monitoring.

Ketamine: dissociative anesthesia

A hypnotic agent structurally related to phencyclidine, ketamine produces a dose-related clinical state of dissociative anesthesia, but also possesses well defined analgesic properties. The analgesic effects of ketamine are thought to be mediated by binding of the drug to N-methyl-D-aspartate (NMDA) receptors, although the drug may also bind to κ-opioid receptors. Advantages include minimal cardiorespiratory depression, active airway reflexes at lower doses, and marked analgesia. The airway and respiration may be depressed at higher doses. Disadvantages include sympathetic and cardiovascular stimulation, and increases in muscular tone and activity, intracranial and intraocular pressures, $CMRO_2$, and oropharyngeal secretions. Patients may recall vivid dreams and/or experience hallucinations post-operatively. Ketamine may be administered by oral, intramuscular, or intravenous routes.

It is useful to distinguish between the analgesic and dissociative anesthetic effects of ketamine. It exhibits a range of subanesthetic concentrations whereby analgesia is obtained without loss of consciousness. Lower

bolus doses (0.2–0.75 mg·kg^{-1} *iv*, 0.4–2 mg·kg^{-1} *im*) produce analgesia lasting 60–90 min. A dose of 1.0–2.0 mg·kg^{-1} *iv* is recommended for the induction of anesthesia, with unconsciousness usually lasting 5–15 min. For this purpose, in children, intramuscular doses are mostly used, in the range of 4–10 mg·kg^{-1}, with onset in 3–5 min and a duration of action of 10–30 min.

Continuous intravenous infusion of ketamine has been recommended for procedures requiring analgesia without unconsciousness. Idvall *et al.*,[38] in establishing a concentration–effect relationship for analgesia and hypnosis, found that the plasma concentration providing an analgesic threshold was 160 ng·ml^{-1}, whereas the hypnotic threshold was 1.5–2.5 μg·ml^{-1} (with N_2O). An intravenous loading dose of 2 mg·kg^{-1} followed by an infusion of 40 μg·kg^{-1}·min^{-1} resulted in a corresponding steady-state ketamine concentration between 1.7 and 2.4 μg·ml^{-1}. Ketamine doses of 5–20 μg·kg^{-1}·min^{-1}, preceded by an intravenous bolus of 0.2–0.75 mg·kg^{-1} (or 0.4–4 mg·kg^{-1} *im*), are sufficient for analgesia without unconsciousness. For hypnosis, in the presence of N_2O the recommended[38] maintenance dose is 15–40 μg·kg^{-1}·min^{-1}. As the sole agent, ketamine infusion rates of 60–80 μg·kg^{-1}·min^{-1} provide clinical anesthesia.

Ketamine has not been widely used for the induction or maintenance of neuroanesthesia because of CNS side-effects such as central excitation, increased CBF and ICP, and the production of post-operative nightmares.

Propofol

First studied clinically in 1977 as an induction agent, propofol (2,6 di-isopropylphenol) subsequently proved useful as an anesthetic agent for maintenance of TIVA or as a sedative/hypnotic agent for diagnostic procedures and minor surgical procedures to supplement local or regional anesthesia. It has also been used for longer periods for the maintenance of sedation or hypnosis in intensive-care patients, and for patient-controlled sedation (PCS).[39]

PROPOFOL FOR THE INDUCTION AND MAINTENANCE OF ANESTHESIA: When used for the induction of anesthesia for shorter procedures, propofol results in a quicker recovery and earlier return of psychomotor function than do other induction agents (thiopental or methohexital), irrespective of the agent used for the maintenance of anesthesia.[40] However, some investigators have found that this difference could be of lesser clinical significance when the agent is restricted to use as an induction agent. Valanne and Korttilla[41] found that it offered little advantage over the induction of anesthesia by methohexital, maintained with a combination of enflurane and N_2O. The current balance of opinion would suggest, however, that the choice of intravenous induction agents does influence recovery when anesthesia is subsequently maintained for relatively short periods with inhalational agents.

Propofol infusions are used for the maintenance of anesthesia when TIVA is indicated or, in part, for intravenous sedation. For procedures lasting less than 60 min, anesthesia maintenance with continuous and variable infusions of propofol combined with N_2O and O_2 resulted in recovery times more favourable than those of barbiturate intravenous infusions,[42] inhalational isoflurane,[40,43,44] or enflurane.[45] For longer or major surgical procedures, however, the speed of recovery and the incidence of post-operative vomiting after propofol maintenance are similar to those of thiopental–isoflurane anesthesia.[40]

PROPOFOL FOR INTRAVENOUS SEDATION: Propofol is a good sedative agent used alone or supplementing regional anesthesia, either by repeated bolus administration or, preferably, by continuous infusion. It allows ease of adjustment and titration to the level of sedation desired. Intravenous infusions of propofol to induce hypnosis for patients undergoing central neural blockade provide a faster recovery than intravenous anesthesia with methohexital.[46] Using lighter levels of sedation, other investigators have confirmed the rapid recovery observed with propofol. Dubois *et al.*[47] administered a mean infusion rate of 4.3 mg·kg^{-1}·hr^{-1} to adults after a slow induction bolus of 1.7 mg·kg^{-1} for sedation during endoscopy. Recovery was rapid, and 99% of the patients had "adequate" sedation. In another series,[47] a mean infusion rate of 4.9 mg·kg^{-1}·hr^{-1} was required for sedation for inguinal hernia repair under local anesthetic field block. Again, recovery was rapid. In these two studies,[46,47] it was hypnosis rather than sedation that was maintained; one would anticipate smaller dose requirements for conscious sedation. Low-dose propofol infusions (25–75 μg·kg^{-1}·min^{-1} = 1.5–4.5 mg·kg^{-1}·hr^{-1}) can be used to produce intra-operative sedation during local and regional anesthesia. Dertwinkel and Nolte[48] maintained anesthesia for patients having surgery under spinal anesthesia with low-dose propofol infusions of 1, 1.5, and 2 mg·kg^{-1}·hr^{-1} following an induction bolus of 1 mg·kg^{-1} and an opioid premedication. All these rates of infusion provided excellent sedation. Generally, at propofol infusion rates > 30 μg·kg^{-1}·min^{-1} (1.8 mg·kg^{-1}·hr^{-1}), patients are amnestic of the procedure.[49]

The effects of propofol sedation on the incidence of intra-operative seizures and the adequacy of electrocorticographic (ECoG) recordings during awake craniotomy for the management of refractory epilepsy

have been reported.[50] When the authors studied 30 patients undergoing temporal or frontal lobectomy for epilepsy under bupivacaine scalp block with a basal infusion of propofol *vs* neuroleptanalgesia with a combination of fentanyl and droperidol, they found a higher incidence of intra-operative seizures among the neurolept patients (0 *vs* 6, $P = 0.008$). However, evidence of low spike activity on ECoG did not correlate with the type of sedation administered. It is also important that higher-frequency background ECoG activity occurred among the patients who received propofol, which is suggested not to interfere with the ECoG interpretation. The use of propofol sedation does not appear to affect the recording of ECoG during epilepsy surgery, as long as its administration is suspended at least 15 min before recording.

In another study on the safety and efficacy of PCS using propofol during awake seizure surgery performed under bupivacaine scalp blocks,[11] 37 patients were randomized to receive either propofol PCS with a basal infusion of propofol or neuroleptanalgesia using an initial bolus dose of fentanyl and droperidol followed by a fentanyl infusion. The authors compared sedation, memory, cognitive function, patient satisfaction, and incidence of complications between the two groups. Levels of intra-operative sedation and patient satisfaction in both groups were similar; memory and cognitive function were well preserved in both. However, transient episodes of ventilatory rate depression (<8 beats·min) were observed more frequently among patients given propofol (5 *vs* 0, $P = 0.04$), especially after supplemental doses of opioid. Although intra-operative seizures were more common among neurolept patients (0 *vs* 7, $P = 0.002$), it was not stated if the increase in EEG seizure activity limited the ability of the neurologist and neurosurgeon to perform the procedure. Furthermore, there was no mention of the effect of propofol's reported respiratory depression on cerebral venous congestion and bleeding during the surgical procedure. However, PCS with propofol was concluded to represent an effective alternative to neuroleptanalgesia during awake seizure surgery, as long as it was performed in a monitored environment.[11]

Comparative studies with midazolam[49] have shown the superiority of propofol for ease of control and rapidity of recovery. Fanard and colleagues[49] compared subanesthetic infusions of 1.75 $mg \cdot kg^{-1} \cdot hr^{-1}$ of propofol after 1.5 $mg \cdot kg^{-1}$ induction with intermittent intravenous boluses of midazolam to produce light sleep during epidural anesthesia. Recovery was much slower after midazolam: 25% of patients had not recovered fully after two hours, whereas 96% of patients after propofol had recovered by 15 min. Amnesia findings were similar between groups. In patients undergoing minor general or urological procedures with local or regional anesthesia, White and Negus[51] compared maintenance infusions of propofol and midazolam for a sedation level of 3 ("sleepy/easily roused") as their endpoint. Patients receiving sedation during local anesthesia required larger maintenance doses than during regional anesthesia (propofol 6.3 *vs* 4.3 $mg \cdot min^{-1}$, midazolam 0.19 *vs* 0.15 $mg \cdot min^{-1}$). Recovery of cognitive function occurred more rapidly with propofol, whereas midazolam was associated with greater intra-operative and post-operative amnesia. Patients, according to follow-up questionnaires, were highly satisfied with both sedative techniques.

In another study, the administration of 2 mg midazolam *iv* prior to a propofol maintenance infusion was found to be highly effective in enhancing sedation, amnesia, and anxiolysis, without prolonging recovery-room stay (compared with propofol alone).[52] Propofol was compared with diazepam in an infusion titrated until speech was slurred (the endpoint) and then adjusted to maintain clinical requirements based on the desired level of sedation. It resulted in equally good sedation in both groups but recovery and amnesia were better in the propofol group. A mean infusion rate of 4.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ of propofol equated to a mean diazepam dose of 0.28 $mg \cdot kg^{-1}$.[53]

PROPOFOL FOR PATIENT-CONTROLLED SEDATION: Propofol has been used successfully in PCS.[39] Propofol and midazolam were compared for intra-operative PCS in patients undergoing dental extractions under local anesthesia. After 0.7 $\mu g \cdot kg^{-1}$ fentanyl *iv*, patients self-administered either 20 mg propofol or 0.5 mg midazolam with a lockout time of one minute in both groups. Propofol had recovery characteristics superior to those of midazolam and was judged by the investigators to be a more suitable agent because of its rapid response to fluctuating intra-operative requirements.[39]

PROPOFOL FOR SEDATION IN INTENSIVE CARE: Propofol has been used for sedation in patients receiving mechanical ventilation in the intensive care unit (ICU).[54] It is easy to titrate to obtain a proper level of sedation and a rapid recovery, irrespective of the duration of the propofol infusion. In a study of agitated/restless ICU patients, propofol was administered intravenously for sedation for four days (mean dose, 2.8 $mg \cdot kg^{-1} \cdot hr^{-1}$). When the infusion was discontinued, adequate recovery with response to verbal commands was obtained in most patients by ten minutes. Recovery times and decreases in blood propofol concentrations were similar after stopping the infusion 24,

48, 72, or 96 hr after initiation. Untoward cumulative effects were not seen. The plasma concentrations required for sedation and awakening were similar at 24 and 96 hr, implying that tolerance did not develop.[54] Propofol can also be administered for analgesia and sedation on the basis of "target-controlled infusion", in which the plasma concentration of propofol is maintained between 0.5 and 2.0 $\mu g \cdot ml^{-1}$ (for sedation) or betweem 3 and 8 $\mu g \cdot ml^{-1}$ (for hypnosis).

Another report[55] implicated propofol in the deaths (due to secondary respiratory infections) of five children treated with propofol infusions in ICU. The likelihood of propofol being responsible has subsequently been challenged. Although propofol is not yet approved for sedation of children, it will continue to be used with success for specific surgical and invasive medical procedures.

B THE OPIOID COMPONENT

FENTANYL

Fentanyl is related to, but not derived from, meperidine. Although often quoted to be 60–200 times as potent as morphine, clinically 0.2 mg fentanyl (200 μg) is equi-analgesic to 10 mg morphine, with a shorter duration of action (15–30 min *vs* 120 min, respectively).[56] Fentanyl is a pure agonist and acts predominantly on μ-receptors. There is greater retention of fentanyl in poorly perfused compartments, leading to subsequent release that could result in respiratory depression, up to 15 hr after injection. Neonates are more sensitive to fentanyl because of their lower brain myelin content, higher CBF, altered protein binding, and immature respiratory control.[57]

Attempts to relate plasma fentanyl concentration to its effect on the function of the target organ have provided a better picture of the distribution of fentanyl in the brain.[58] With a high-dose infusion of fentanyl, there is slowing of EEG progressing to the formation of delta waves (4 Hz, amplitude 50 μV). The steady-state serum concentration of fentanyl that caused one-half of the maximal EEG slowing is 6.9 ± 1.5 $ng \cdot ml^{-1}$. There is a time lag between the peak concentration of fentanyl and the reduction in EEG spectral edge frequency - the frequency below which 95% of the area under the signal power *vs* frequency histogram was contained. The lag may be due to the high lipid solubility of fentanyl (serum–brain ratio of 1:5), resulting in the solution of fentanyl in CNS lipid rather than at receptor sites.

In neurosurgical patients, it was found that the intraoperative maintenance dose of fentanyl was increased in those receiving anticonvulsant therapy,[59] although the initial loading dose did not differ from that in patients who had never taken anticonvulsants. A history of smoking, alcohol, or caffeine consumption also increased the requirement for fentanyl. The theory of induction of microsomal liver enzymes resulting in accelerated fentanyl metabolism is attractive, but changes in the state of opioid receptors induced by chronic anticonvulsant exposure may also be operative.

Neurological properties. Fentanyl has a variety of effects on cerebral dynamics. These "specific" effects attributable solely to fentanyl have been difficult, if not impossible, to single out, because of the complex relationship between CBF, CPP, and ICP. Moreover, changes in PaO_2 from the respiratory depressant effects of fentanyl can exert their own effects.

The effect of opioids on CBF and $CMRO_2$ is not completely known, mainly because of "contamination" from other non-opioid anesthetics. It has been suggested[60] that fentanyl and sufentanil can reduce CBF and/or $CMRO_2$ while maintaining cerebral autoregulation: 15 min after administration, 6 $\mu g \cdot kg^{-1}$ of fentanyl has been able to reduce CBF by as much as 47% and $CMRO_2$ by as much as 18%.[61] In another study in adult patients undergoing cardiac surgery,[62] 100 $\mu g \cdot kg^{-1}$ of fentanyl and 0.4 $mg \cdot kg^{-1}$ of diazepam caused a 25% reduction in CBF, with no changes in $CMRO_2$.

Moss and colleagues,[45] studying patients undergoing craniotomy and receiving controlled ventilation and hypocapnia, found that 200 μg fentanyl alone did not result in changes in ICP. The authors concluded that CPP was the most important determinant of CBF when they observed that CBF was reduced in parallel with MAP. This contradicted an earlier study (using normocapnia)[43] that showed isolated increases in ICP after droperidol or fentanyl, without details of statistical analysis. In a recent double-blind study, Jamali *et al.*[63] demonstrated a reduction in MAP when sufentanil (0.8 $\mu g \cdot kg^{-1}$) or fentanyl (4.5 $\mu g \cdot kg^{-1}$) was given for elective supratentorial craniotomy. When phenylephrine was administered to maintain MAP within 15% of initial values, there were no changes in lumbar CSF pressure.[63] Another unblinded outcome study in patients undergoing elective supratentorial craniotomy with three different anesthetic techniques (propofol/fentanyl *vs* thiopental/isoflurane/N_2O *vs* thiopental/fentanyl /N_2O)[64] also failed to show any important intergroup differences in mean ICP and in short-term outcomes. Although probably of minimal clinical importance, fentanyl has also been shown to reduce the resistance to reabsorption of CSF, while CSF production was unchanged.[44]

When fentanyl combined with droperidol was used, Innovar decreased CBF by 50% and $CMRO_2$ by 23%, and also reduced CBF response to changes in $PaCO_2$.

Unlike volatile agents, which could increase CSF pressure,[65] the combination of 5 mg droperidol and 100 μg fentanyl decreases CSF pressure and CBF (as a result of decreased MAP), leading to a reduction in cerebrovascular volume.[66] In a study by Fitch and coworkers,[66] this combination resulted in decreased CSF pressure in all six patients with normal CSF pathways and in eight of nine patients with intracranial space–occupying lesions during normocapnia. This result, however, was not confirmed in a later study with Innovar (0.1 $ml \cdot kg^{-1}$),[67] which found no effect on CBF and $CMRO_2$ during normocapnia. On the other hand, in the presence of hypocapnia ($PaCO_2$ < 5 kPa), a moderate decrease in both CBF and $CMRO_2$ has been observed.[68] Innovar–induced respiratory depression in patients breathing spontaneously produced an increase in ICP.[69]

The EEG changes caused by opioids mimic those of other general anesthetic agents, but to a lesser extent. With a high infusion dose of fentanyl, EEG alpha activity slows, and beta activity ceases within one to two minutes. Diffuse theta and some delta activity follow rapidly. Within five minutes of induction, high-amplitude delta activity is dominant, and is synchronized in a high percentage of patients. All these changes reverted to normal upon discontinuation of the fentanyl infusion.[48] Small doses of fentanyl (0.5–1.0 $\mu g \cdot kg^{-1}$) and droperidol can induce slow-wave activity that is consistent and does not interfere with EEG monitoring.[70]

Other neurological effects of fentanyl include the induction of nausea and vomiting by stimulation of the chemoreceptor trigger zone in the area postrema of the floor of the fourth ventricle, and muscle rigidity. Opioid-induced nausea and vomiting can occur in up to 40% of patients post-operatively. Unfortunately, this is not entirely preventable with antiemetic prophylaxis. Nausea and vomiting have been reported intra-operatively in patients undergoing neuroleptanesthesia for awake craniotomy,[71] with an incidence as high as 50% with fentanyl,[72] despite prophylaxis with droperidol and dimenhydrinate. Thoracic and abdominal muscle rigidity of a tonic or clonic nature have been reported after fentanyl, sufentanil, alfentanil, and morphine, without any EEG evidence of seizure activities. Its onset can occur within minutes of administration, or even manifest itself for the first time post-operatively. The mechanism might involve opioid receptors in the brainstem and basal ganglia, since treatment with naloxone is rapidly effective in reversing the rigidity. The threshold of fentanyl plasma concentration below which muscular rigidity ceased was 6.9 ± 1.5 $ng \cdot ml^{-1}$ in human volunteers.[73] It is interesting to note that normeperidine-induced seizures cannot be reversed by naloxone, which suggests a non-opioid-related mechanism of action.

Respiratory effects: Like all opioids, fentanyl causes a dose-related respiratory depression (2 $\mu g \cdot kg^{-1}$ can decrease respiratory rate), which is, however, associated with a compensatory increase in tidal volume. With higher doses, tidal volume is decreased, leading to irregular breathing and finally apnea.[74] The central response to carbon dioxide is shifted to the right. Plasma concentrations of fentanyl of about 3 $ng \cdot ml^{-1}$ cause a 50% depression of the CO_2 response curve; however, an apparent plasma concentration of 1 $ng \cdot ml^{-1}$ is needed to cause ventilatory depression in the presence of enflurane.[74] An *iv* fentanyl dose of 10 $\mu g \cdot kg^{-1}$ in dogs raised cisternal CSF concentration within the first two to three minutes, even though respiratory depression was evident within the first minute.[74] The CSF concentration of fentanyl was 46% of that in plasma because of the lower protein concentration in CSF (fentanyl assays were measured for total fentanyl, not for the unbound portion of the drug). It is likely that this threshold is higher clinically in the absence of any other sedative or hypnotic drug.

The respiratory effects of the fentanyl and droperidol combination have been examined. Ventilatory response to carbon dioxide was studied post-operatively after 21 patients received a mean dose of 5 $\mu g \cdot kg^{-1}$ fentanyl and 0.2 $mg \cdot kg^{-1}$ droperidol.[75] An impaired response was found up to 3.5 hr after the induction of anesthesia, which could extend to six hours in those who also received meperidine premedication. Despite animal experiments suggesting that droperidol had potentiating analgesic and respiratory depressant effects on fentanyl,[76] subsequent studies in humans with[77] or without surgery[78] have failed to confirm it. Both studies[77,78] found a four hour respiratory depression, with or without the addition of droperidol to fentanyl. Neuroleptanalgesia, using droperidol (0.1 $mg \cdot kg^{-1}$), fentanyl, and diazepam, could also reduce laryngeal competence.[79]

Delayed respiratory depression post-operatively has been reported after small intravenous doses of fentanyl given intra-operatively.[79] Although an enterohepatic circulation of fentanyl had been proposed as a means to cause a secondary peak in plasma fentanyl concentration,[80] the near-complete pre-systemic metabolism that exists (hepatic extraction ratio = 1) renders this unlikely. A more plausible explanation is the release of fentanyl from body stores, such as muscle, associated with an increase in body movement during the recovery phase.

Cardiovascular effects: Fentanyl is a drug with marked cardiovascular stability, even at high doses (150 $\mu g \cdot kg^{-1}$). Its lack of histamine release and any myocar-

dial depressant effect make it a popular drug for use in cardiac surgery. The main cardiovascular effect is bradycardia, which is readily reversible by atropine in most cases. At doses up to 20 $\mu g \cdot kg^{-1}$ in animals, left-ventricular performance was not affected.[81]

There have been many reports on the clinical use of the fentanyl–droperidol combination in the context of neuroleptanalgesia/anesthesia. In healthy volunteers not undergoing surgery, 5 $\mu g \cdot kg^{-1}$ fentanyl and 0.22 $mg \cdot kg^{-1}$ droperidol, given either alone or in combination, were compared.[82] Changes in cardiovascular parameters were minimal, except for a decrease in systemic vascular resistance. In general, both medications cause minimal myocardial depression, even in poor-risk patients undergoing major surgery, provided good fluid pre-loading is given. In patients with renal failure undergoing major surgery using neuroleptanesthesia, fentanyl (5.5 $\mu g \cdot kg^{-1}$) and droperidol (0.275 $\mu g \cdot kg^{-1}$) with N_2O provided good cardiovascular stability with no delayed wakening[83] but there was a 20% incidence of intra-operative awareness. In another group, undergoing renal transplantation,[84] a similar technique resulted in very labile blood pressure perioperatively; arrhythmias were very uncommon; and there was no mortality.

In 106 children undergoing cardiac catheterization, fentanyl (1.25 $\mu g \cdot kg^{-1}$, maximum dose 50 μg) and droperidol (62.5 $\mu g \cdot kg^{-1}$, maximum dose 2.5 mg) *im* did not cause changes in heart rate, respiratory arrest, or cyanotic spells (no patients had a tetralogy of Fallot).[85] When larger doses of droperidol (0.3 $mg \cdot kg^{-1}$) and fentanyl (10 $\mu g \cdot kg^{-1}$) were used for major surgery in 15 neonates (<10 days old) and 25 infants (<18 months old), remarkably good cardiovascular stability was reported.[86] The decision to administer an intravascular pre-load with 20 $ml \cdot kg^{-1}$ Ringer's lactate and atropine before induction and the subsequent maintenance with N_2O contributed to the success of this technique.

Alternative Drugs

Alfentanil

A more predictable drug, alfentanil has one-quarter the potency of fentanyl.[87] Its protein binding approaches 90% (mainly to α_1-acid glycoprotein), but this figure is reduced at high doses, which could result in non-linear kinetics and some enhancement of the concentration–effect relationship. In children[88] and infants,[89] it has a faster clearance than in adults. With a target plasma alfentanil concentration of 400 $ng \cdot ml^{-1}$ to provide adequate analgesia in the presence of N_2O 67%, a bolus dose of 176 $\mu g \cdot kg^{-1}$ and a maintenance dose of 1.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was necessary.[90] Clinically, it was found that the 95% effective dose (ED_{95}) for superficial and intra-abdominal operations exceeded 300 $ng \cdot ml^{-1}$ and 400 $ng \cdot ml^{-1}$, respectively. The clearance rate of alfentanil can be lower in the presence of liver disease, resulting in the wide variation observed in clinical responses.[91] When the EEG spectral edge frequency was plotted against the alfentanil plasma concentration, no time lag was found, indicating its rapidly targeted association with intracerebral opioid receptors.[58] With 89% of alfentanil being non-ionized at physiological pH (pKa 6.5), more drug is available to diffuse out of solution, resulting in a faster clinical effect than with fentanyl. Indeed, alfentanil and droperidol have been used successfully to provide neuroleptanalgesia for awake craniotomy.[92]

The effect of alfentanil on ICP has also been studied in children requiring insertion of ventriculoperitoneal shunts.[93] Alfentanil in doses up to 40 $\mu g \cdot kg^{-1}$ did not result in an increase in ICP transduced electronically via the shunt. There was, however, a decrease in CPP (although CBF in dogs with acute intracranial hypertension was maintained at doses of 300 $\mu g \cdot kg^{-1}$).[93] Low-dose alfentanil for sedation in the ventilated newborn could cause moderate to severe muscle rigidity.[94]

Sufentanil

Sufentanil is five times more potent than fentanyl, while its pharmacokinetic properties are intermediate between fentanyl and alfentanil. Ninety-two percent is protein-bound (mainly to α_1-acid glycoprotein), with 19.7% non-ionized at physiological pH (pKa = 8.01). The minimal effective blood level is approximately 0.2 $ng \cdot ml^{-1}$.[95] Although it differs from fentanyl in potency and lipid solubility, the pharmacodynamic effects of sufentanil are generally similar to those of fentanyl.[96] In a study of patients undergoing cardiac surgery, sufentanil (10 $\mu g \cdot kg^{-1}$ infused at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) caused a 25% reduction in CBF and a 29% reduction in $CMRO_2$, with a corresponding increase in cerebrovascular resistance due to its primary metabolic depressant effects.[97] Low-dose sufentanil (0.5 $\mu g \cdot kg^{-1}$) given as a single agent to healthy volunteers did not result in any change in CBF,[98] which suggests that neuroleptic doses should not affect CBF. However, in the presence of intracerebral space–occupying lesions, sufentanil (1 $\mu g \cdot kg^{-1}$) resulted in an 87% increase in CSF pressure,[99] which could be due to cerebral vasodilation.

There have been numerous studies comparing the various clinical effects of fentanyl, alfentanil, and sufentanil. On the whole, it is difficult to declare that either of the newer agents is superior to fentanyl, on the basis of clinical effective outcome, side-effects, or cost.

When their use in neurosurgery for tumour excision was compared, fentanyl (10 $\mu g \cdot kg^{-1}$ loading dose, followed by 2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ infusion), sufentanil, and alfentanil (each at doses equipotent to fentanyl) were found to be equally safe and effective.[100] In a separate study,[101] high-dose sufentanil (20 $\mu g \cdot kg^{-1}$) for both intra- and extracranial neurosurgery provided more adequate anesthesia than that of fentanyl (100 $\mu g \cdot kg^{-1}$). In another prospective study of patients undergoing awake craniotomy for epilepsy surgery,[101] fentanyl (bolus 0.75 $\mu g \cdot kg^{-1}$ with infusion of 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was as effective as sufentanil (bolus 0.075 $\mu g \cdot kg^{-1}$, infusion 0.0015 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or alfentanil (bolus 7.5 $\mu g \cdot kg^{-1}$, infusion 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). However, the incidence of nausea and vomiting, despite prophylactic treatment, was 50% with fentanyl, 30% with sufentanil, and 70% with alfentanil. The drug cost of alfentanil was 13 times and sufentanil 30 times that of fentanyl. When their effects in patients with brain tumours were measured, fentanyl was found to have negligible effect on CSF pressure, whereas sufentanil had the greatest CBF increase.[101] In a separate study,[99] the cerebral vasodilatory effect (with a 70% increase in CSF pressure) of alfentanil also became apparent when systemic blood pressure was held constant with phenylephrine. With the evidence to date, fentanyl remains the opioid of choice for use in neuroanesthesia.

When sufentanil and fentanyl were compared with morphine and meperidine in patients undergoing general, orthopedic, or gynecological surgical procedures,[102] these newer synthetic drugs were found to provide much better intra-operative hemodynamic conditions, earlier return of mental function, and a lower incidence of respiratory depression post-operatively. Overall, it seemed that sufentanil provided the most satisfactory conditions. Patients having short surgical procedures recovered faster with alfentanil than with fentanyl. However, when used in sedative doses in infants and children (1–23 mo), fentanyl was found to provide more stable conditions and fewer side-effects than alfentanil.

Remifentanil

Remifentanil (G187084B) is the latest opioid to be introduced into clinical use. Chemically related to fentanyl, its analgesic potency is similar to that of fentanyl, but it is 20–30 times more potent than alfentanil.[103] Remifentanil is a μ-agonist, analgesic, sedative, and respiratory depressant. The ester linkage of the molecule makes it susceptible to hydrolysis by circulating and tissue–non-specific esterases, resulting in a short elimination half-life. Unlike plasma cholinesterase, these non-specific enzymes are not inhibited by neostigmine; theoretically, there should therefore be no prolongation of drug elimination. Although N-dealkylation of remifentanil occurs, its major route of biotransformation is by de-esterification to a carboxylic acid metabolite (G190291) which, in animal models, has only 1/300th to 1/1000th the potency of the parent compound. The mean terminal half-life of G190291 has been measured at 88–137 min,[104] longer than that of remifentanil; it is excreted by the kidneys. Given the fast onset and offset of action with inactive metabolites, no major adjustment dosage appears to be required. However, most studies to date have been performed in healthy young adults, so extrapolation of these results to include the elderly and children might be inappropriate. Furthermore, studies of its effects in neurosurgical and cardiac anesthesia will be needed as part of remifentanil's clinical evaluation.

Possible advantages of remifentanil include (1) rapid titration of effect, (2) reduced post-operative opioid-induced side-effects, (3) lack of cumulative effects, and (4) no requirement for dosage adjustment in cases of hepatic or renal disease. Theoretical disadvantages include (1) the cost of extra equipment and expertise in infusion techniques, and (2) a lack of prolonged opioid effect (e.g., analgesia into the post-operative period) when such effects are desirable. Remifentanil may become the ideal opioid for neuroanesthesia, allowing rapid recovery and facilitating early clinical neurological assessment.

Conclusion

Neuroleptanesthesia was developed to maintain normal cerebral cognitive function while eliminating the perception of nociceptive stimuli at the level of the cerebral cortex. The procedure was designed to modulate neuroendocrines and metabolic and autonomic responses in response to the nociceptive stimulation. The development of an injectable combination of two new drugs, a neuroleptic agent (droperidol) and an opioid (fentanyl), extensively improved the original technique and quickly extended its use to many surgical procedures. The advantages included an excellent cardiovascular stability, rapid post-operative recovery, and the availability of an antidote for the adverse effects of the opioid component.

However, this technique was not without problems. Unconsciousness to the level of being unrousable and post-operative extrapyramidal excitation, restlessness, and confusion were among several side-effects associated with its use. The relatively slow onset of action of droperidol and the fast onset of fentanyl renders them difficult to manage clinically, with associated overdose of fentanyl and consequential

muscle rigidity and/or respiratory depression necessitating airway support.

New pharmacological agents developed over the past two decades have helped simplify this anesthetic technique. Neuroleptanalgesia/anesthesia has evolved into "conscious sedation", in which control of the patient's vital functions with maintenance of normal cognitive function has been made easier. New benzodiazepines such as midazolam and its reversal agent, flumazenil, have revolutionized this anesthetic technique. Propofol, an anesthetic agent capable of inducing and maintaining general anesthesia, can also be used successfully and predictably to provide sedation and hypnosis for diagnostic procedures and minor and even more complex surgical procedures. The recovery characteristics of these drugs have made them suitable for ambulatory anesthesia and short surgical or diagnostic procedures. The introduction of newer opioids have added more flexibility to these techniques compared to fentanyl, especially in the context of conscious sedation, where analgesia must be excellent. Alfentanil, sufentanil, and remifentanil have contributed to improve intra-operative analgesia while offering better control of post-operative recovery, acute pain management, and discharge time. Unfortunately, the cost of many of these new medications can be considerable—one of the few major concerns about their use.

The need to provide high-quality anesthesia associated with faster recovery, better comfort, and reduced cost are all factors in favour of the concept of neuroleptanesthesia. These new medications have now been used extensively in children, adults, and elderly patients to facilitate the expansion of programs such as ambulatory anesthesia, "satellite" anesthesia (radiology, interventional cardiology, oncology, endoscopy, rheumatology, etc.), acute and chronic pain therapy, and programs for many other indications. Finally, intra-operative electrocorticography and seizure foci removal may remain the only indication left for the use of "conventional" neuroleptanalgesia/anesthesia in modern anesthesia practice.

Acknowledgment

This paper was prepared with the assistance of Editorial Services, The Hospital for Sick Children, Toronto, Ontario, Canada.

References

1 *Campan L, Lazothes G.* L'hibernothérapie en chirurgie cérébrale, sa justification clinique et pathologénique. In: Laborit H, Huguenard P (Eds.). Practique de l'Hibernothérapie en Chirurgie et en Médicine. Paris: Masson et Cie, 1954: 137–80.

2 *Bailey PL, Stanley TH.* Intravenous Opioid anesthetics. *In*: Miller RD (Ed.). Anesthesia, 4th ed. New York: Churchill Livingstone Inc., 1994: 291–389.

3 *de Castro G, Mundeleer P.* Anesthésie sans sommeil: "neuroleptanalgésie". Acta Chir Belg 1959; 58: 689–93.

4 *Janssen PAJ, Niemegeers CJE, Schellekens KHL, Verbruggen FJ, Van Neuten JM.* The pharmacology of dehydrobenzperidol, a new potent and short-acting neuroleptic agent chemically related to haloperidol. Arzniemittelforschung 1963; 13: 205–8.

5 *Janssen PAJ.* A review of the chemical features associated with strong morphine-like activity. Br J Anaesth 1962; 34: 260–8.

6 *Foldes FF.* Neuroleptanesthesia for general surgery. Int Anesthesiol Clin 1973; 11: 1–35.

7 *Foldes FF, Kepes ER, Kronfeld PP, Shiffman HP.* A rational approach to neuroleptanesthesia. Anesth Analg 1966; 45: 642–54.

8 *Richter JJ.* Current theories about the mechanisms of benzodiazepines and neuroleptic drugs. Anesthesiology 1981; 54: 66–72.

9 *Marshall BM, Gordon RA.* Electroencephalographic monitoring in anaesthesia with droperidol and fentanyl. Can Anaesth Soc J 1968; 15: 357–61.

10 *Hashem A, Frey HH.* The effect of neuroleptics and neuroleptic/analgesic combinations on the sensitivity to seizures in mice. Anaesthetist 1988; 37: 631–5.

11 *Herrick IA, Craen RA, Gelb AW, et al.* Propofol sedation during awake craniotomy for seizures: patient-controlled administration versus neurolept analgesia. Anesth Analg 1997; 84: 1285–91.

12 *Soroker D, Barzilay E, Konichezky S, Bruderman I.* Respiratory function following premedication with droperidol or diazepam. Anesth Analg 1978; 57: 695–9.

13 *Cottrell JE, Wolfson B, Siker ES.* Changes in airway resistance following droperidol, hydroxyzine, and diazepam in normal volunteers. Anesth Analg 1976; 55: 18–21.

14 *Prokocimer P, Delavault E, Rey F, Lefevre P, Mazze RI, Desmonts JM.* Effects of droperidol on respiratory drive in humans. Anesthesiology 1983; 59: 113–6.

15 *Ward DS.* Stimulation of hypoxic ventilatory drive by droperidol. Anesth Analg 1984; 63: 106–10.

16 *Whitwam JG, Russell WJ.* The acute cardiovascular changes and adrenergic blockade by droperidol in man. Br J Anaesth 1971; 43: 581–91.

17 *Sumikawa K, Amakata Y.* The pressor effect of droperidol on a patient with pheochromocytoma. Anesthesiology 1977; 46: 359–61.

18 *Sumikawa K, Hirano H, Amakata Y, Kashimoto T, Wada A, Izumi F.* Mechanism of the effect of

droperidol to induce catecholamine efflux from the adrenal medulla. Anesthesiology 1985; 62: 17–22.
19 *Long G, Dripps RD, Price HL.* Measurement of antiarrhythmic potency of drugs in man: effects of dehydrobenzperidol. Anesthesiology 1967; 28: 318–23.
20 *Bertoló L, Novakovi L, Penna M.* Antiarrhythmic effects of droperidol. Anesthesiology 1972; 37: 529–35.
21 *Santos A, Datta S.* Prophylactic use of droperidol for control of nausea and vomiting during spinal anesthesia for cesarean section. Anesth Analg 1984; 63: 85–7.
22 *Lerman J, Eustis S, Smith DR.* Effect of droperidol pretreatment on postanesthetic vomiting in children undergoing strabismus surgery. Anesthesiology 1986; 65: 322–5.
23 *Yentis SM, Bissonnette B.* Ineffectiveness of acupuncture and droperidol in preventing vomiting following strabismus repair in children. Can J Anaesth 1992; 39: 151–4.
24 *Thomson D, Geller E, Lauven P, Whitwam J.* Midazolam and flumazenil: the agonist–antagonist concept for sedation and anaesthesia. Acta Anaesthesiol Scand 1990; 92(Suppl): 108–9.
25 *Goodchild CS.* GABA receptors and benzodiazepines. Br J Anaesth 1993; 71: 127–33.
26 *Lauven PM, Kulka PJ.* Anaesthesia techniques for midazolam and flumazenil - an overview. Acta Anaesthesiol Scand 1990; 92(Suppl): 84–9.
27 *Murphy PJ, Erskine R, Langton JA.* The effect of intravenously administered diazepam, midazolam and flumazenil on the sensitivity of upper airway reflexes. Anaesthesia 1994; 49: 105–10.
28 *Brown CR, Sarnquist FH, Canup CA, Pedley TA.* Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate. Anesthesiology 1979; 50: 467–70.
29 *Artru AA.* Dose-related changes in the rate of cerebrospinal fluid formation and resistance to reabsorption of cerebrospinal fluid following administration of thiopental, midazolam, and etomidate in dogs. Anesthesiology 1988; 69: 541–6.
30 *Giffin JP, Cottrell JE, Shwiry B, Hartung J, Epstein J, Lim K.* Intracranial pressure, mean arterial pressure, and heart rate following midazolam or thiopental in humans with brain tumors. Anesthesiology 1984; 60: 491–4.
31 *Dundee JW, Wilson DB.* Amnesic action of midazolam. Anaesthesia 1980; 35: 459–61.
32 *Splinter WM, MacNeill HB, Menard EA, Rhine EJ, Roberts DJ, Gould MH.* Midazolam reduces vomiting after tonsillectomy in children. Can J Anaesth 1995; 42: 201–3.
33 *Forster A, Juge O, Louis M, Nahory A.* Effects of a specific benzodiazepine antagonist (RO 15-1788) on cerebral blood flow. Anesth Analg 1987; 66: 309–13.
34 *Schulte am Esch J, Kochs E.* Midazolam and flumazenil in neuroanaesthesia. Acta Anaesthesiol Scand 1990; 92(Suppl): 96–102.
35 *Fleischer JE, Milde JH, Moyer TP, Michenfelder JD.* Cerebral effects of high-dose midazolam and subsequent reversal with RO 15-1788 in dogs. Anesthesiology 1988; 68: 234–42.
36 *Chiolero RL, Ravussin PA, Freeman J.* Using flumazenil (Ro 15-1788) after prolonged midazolam infusion for anaesthesia for intracranial surgery. Ann Fr Anesth Reanim 1988; 7: 17–21.
37 *Chiolero R-L, Ravussin P, Anderes J-P, Ledermann P, de Tribolet N.* The effects of midazolam reversal by RO 15-1788 on cerebral perfusion pressure in patients with severe head injury. Intensive Care Med 1988; 14: 196–200.
38 *Idvall J, Ahlgren I, Aronsen KR, Stenberg P.* Ketamine infusions: pharmacokinetics and clinical effects. Br J Anaesth 1979; 51: 1167–73.
39 *Rudkin GE, Osborne GA, Finn BP, Jarvis DA, Vickers D.* Intra-operative patient-controlled sedation. Comparison of patient-controlled propofol with patient-controlled midazolam. Anaesthesia 1992; 47: 376–81.
40 *Doze VA, Shafer A, White PF.* Propofol–nitrous oxide versus thiopental–isoflurane–nitrous oxide for general anesthesia. Anesthesiology 1988; 69: 63–71.
41 *Valanne J, Korttila K.* Effect of a small dose of droperidol on nausea, vomiting and recovery after outpatient enflurane anaesthesia. Acta Anaesthesiol Scand 1985; 29: 359–62.
42 *Doze VA, Westphal LM, White PF.* Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 1986; 65: 1189–95.
43 *Misfeldt BB, Jörgensen PB, Spotoft H, Rønde F.* The effects of droperidol and fentanyl on intracranial pressure and cerebral perfusion pressure in neurosurgical patients. Br J Anaesth 1976; 48: 963–8.
44 *Artru AA.* Effects of halothane and fentanyl anesthesia on resistance to reabsorption of CSF. J Neurosurg 1984; 60: 252–6.
45 *Moss E, Powell D, Gibson RM, McDowall DG.* Effects of fentanyl on intracranial pressure and cerebral perfusion pressure during hypocapnia. Br J Anaesth 1978; 50: 779–84.
46 *Jessop E, Grounds RM, Morgan M, Lumley J.* Comparison of infusions of propofol and methohexitone to provide light general anaesthesia during surgery with regional blockade. Br J Anaesth 1985; 57: 1173–7.
47 *Dubois A, Balatoni E, Peeters JP, Baudoux M.* Use of propofol for sedation during gastrointestinal endoscopies. Anaesthesia 1988; 43(Suppl): 75–80.

48 *Dertwinkel R, Nolte H.* Continuous sedation for regional anesthesia with propofol (Disoprivan®) and midazolam (Dormicum®). A comparative study. Reg Anaesth 1988; 11: 84–91.
49 *Fanard L, Van Steenberge A, Demeire X, van der Puyl F.* Comparison between propofol and midazolam as sedative agents for surgery under regional anaesthesia. Anaesthesia 1988; 43(Suppl): 87–9.
50 *Herrick IA, Craen RA, Gelb AW, et al.* Propofol sedation during awake craniotomy for seizures: electrocorticographic and epileptogenic effects. Anesth Analg 1997; 84: 1280–4.
51 *White PF, Negus JB.* Sedative infusions during local and regional anesthesia: a comparison of midazolam and propofol. J Clin Anesth 1991; 3: 32–9.
52 *Taylor E, Ghouri AF, White PF.* Midazolam in combination with propofol for sedation during local anesthesia. J Clin Anesth 1992; 4: 213–6.
53 *Valtonen M, Salonen M, Forssell H, Scheinin M, Viinamäki O.* Propofol infusion for sedation in outpatient oral surgery. A comparison with diazepam. Anaesthesia 1989; 44: 730–4.
54 *Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC.* Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. Br J Anaesth 1988; 61: 583–8.
55 *Parke TJ, Stevens JE, Rice AS, et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ 1992; 305: 613–6.
56 *Morrison JD, Loan WB, Dundee JW.* Controlled comparison of the efficacy of fourteen preparations in the relief of postoperative pain. BMJ 1971; 3: 287–90.
57 *Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ.* Pharmacokinetics of fentanyl in neonates. Anesth Analg 1986; 65: 227–32.
58 *Scott JC, Ponganis KV, Stanski DR.* EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985; 62: 234–41.
59 *Tempelhoff R, Modica PA, Spitznagel EL Jr.* Anticonvulsant therapy increases fentanyl requirements during anaesthesia for craniotomy. Can J Anaesth 1990; 37: 327–32.
60 *Schell RM, Kern FH, Greeley WJ, et al.* Cerebral blood flow and metabolism during cardiopulmonary bypass. Anesth Analg 1993; 76: 849–65.
61 *Michenfelder JD, Theye RA.* Effects of fentanyl, droperidol, and Innovar on canine cerebral metabolism and blood flow. Br J Anaesth 1971; 43: 630–6.
62 *Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G.* Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $PaCO_2$. Anesth Analg 1987; 66: 825–32.
63 *Jamali S, Ravussin P, Archer D, Goutallier D, Parker F, Ecoffey C.* The effects of bolus administration of opioids on cerebrospinal fluid pressure in patients with supratentorial lesions. Anesth Analg 1996; 82: 600–6.
64 *Todd MM, Warner DS, Sokoll MD, et al.* A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology 1993; 78: 1005–20.
65 *Fitch W, Barker J, McDowall DG, Jennett WB.* The effect of methoxyflurane on cerebrospinal fluid pressure in patients with and without intracranial space–occupying lesions. Br J Anaesth 1969; 41: 564–73.
66 *Fitch W, Barker J, Jennett WB, McDowall DG.* The influence of neuroleptanalgesic drugs on cerebrospinal fluid pressure. Br J Anaesth 1969; 41: 800–6.
67 *Sari A, Okuda Y, Takeshita H.* The effects of thalamonal on cerebral circulation and oxygen consumption in man. Br J Anaesth 1972; 44: 330–4.
68 *Cold GE, Christensen KJS, Nordentoft J, Engberg M, Pedersen MB.* Cerebral blood flow, cerebral metabolic rate of oxygen and relative CO_2 reactivity during neurolept anaesthesia in patients subjected to craniotomy for supratentorial cerebral tumours. Acta Anaesthesiol Scand 1988; 32: 310–5.
69 *Miller R, Tausk HC, Stark DCC.* Effect of Innovar, fentanyl and droperidol on the cerebrospinal fluid pressure in neurosurgical patients. Can Anaesth Soc J 1975; 22: 502–8.
70 *Manninen P, Contreras J.* Anesthetic considerations for craniotomy in awake patients. Int Anesthesiol Clin 1986; 24: 157–74.
71 *Archer DP, McKenna JMA, Morin L, Ravussin P.* Conscious-sedation analgesia during craniotomy for intractable epilepsy: a review of 354 consecutive cases. Can J Anaesth 1988; 35: 338–44.
72 *Gignac E, Manninen PH, Gelb AW.* Comparison of fentanyl, sufentanil and alfentanil during awake craniotomy for epilepsy. Can J Anaesth 1993; 40: 421–4.
73 *Bowdle TA, Rooke GA.* Postoperative myoclonus and rigidity after anesthesia with opioids. Anesth Analg 1994; 78: 783–6.
74 *Bovil JG.* Opioids. *In*: Dundee JW, Clarke RSJ, McCaughey W (Eds.). Clinical Anaesthetic Pharmacology. Philadelphia: Churchill Livingstone Inc., 1991: 203–30.
75 *Vejlsted H, Hansen M, Jacobsen E.* Postoperative ventilatory response to carbon dioxide following neurolept anaesthesia. Acta Anaesthesiol Scand 1977; 21: 529–33.
76 *Greene MJ.* Some aspects of the pharmacology of droperidol. Br J Anaesth 1972; 44: 1272–6.

77 *Smedstad KG, Rigg JRA.* Control of breathing after fentanyl and Innovar anaesthesia. Br J Anaesth 1982; 54: 599–604.

78 *Harper MH, Hickey RF, Cromwell TH, Linwood S.* The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. J Pharmacol Exp Ther 1976; 199: 464–8.

79 *Becker LD, Paulson BA, Miller RD, Severinghaus JW, Eger EI II.* Biphasic respiratory depression after fentanyl–droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology 1976; 44: 291–6.

80 *Stoeckel H, Hengstmann JH, Schüttler J.* Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Br J Anaesth 1979; 51: 741–5.

81 *Ostheimer GW, Shanahan EA, Guyton RA, Daggett WM, Lowenstein E.* Effects of fentanyl and droperidol on canine left-ventricular performance. Anesthesiology 1975; 42: 288–91.

82 *Graves CL, Downs NH, Browne AB.* Cardiovascular effects of minimal analgesic quantities of Innovar®, fentanyl, and droperidol in man. Anesth Analg 1975; 54: 15–23.

83 *Trudnowski RJ, Mostert JW, Hobika GH, Rico R.* Neuroleptanalgesia for patients with kidney malfunction. Anesth Analg 1971; 50: 679–84.

84 *Lindahl-Nilsson Ch, Lundh R, Groth C-G.* Neurolept anaesthesia for the renal transplant operation. Acta Anaesthesiol Scand 1980; 24: 451–7.

85 *Graham TP Jr, Atwood GF, Werner B.* Use of droperidol-fentanyl sedation for cardiac catheterization in children. Am Heart J 1974; 87: 287–93.

86 *Kay B.* Neuroleptanesthesia for neonates and infants. Anesth Analg 1973; 52: 970–3.

87 *Stanski DR, Hug CJ.* Alfentanil—a kinetically predictable narcotic analgesic (Editorial). Anesthesiology 1982; 57: 435–8.

88 *Roure P, Jean N, Leclerc A-C, Cabanel N, Levron J-C, Duvaldestin P.* Pharmacokinetics of alfentanil in children undergoing surgery. Br J Anaesth 1987; 59: 1437–40.

89 *Goresky GV, Koren G, Sabourin MA, Sale JP, Strunin L.* The pharmacokinetics of alfentanil in children. Anesthesiology 1987; 67: 654–9.

90 *Fragen RJ, Booij LHDJ, Braak GJJ, Vree TB, Heykants J, Crul JF.* Pharmacokinetics of the infusion of alfentanil in man. Br J Anaesth 1983; 55: 1077–81.

91 *Shafer A, Sung M-L, White PF.* Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. Anesth Analg 1986; 65: 1021–8.

92 *Welling EC, Donegan J.* Neuroleptanalgesia using alfentanil for awake craniotomy. Anesth Analg 1989; 68: 57–60.

93 *Markovitz BP, Duhaime A-C, Sutton L, Schreiner MS, Cohen DE.* Effects of alfentanil on intracranial pressure in children undergoing ventriculoperitoneal shunt revision. Anesthesiology 1992; 76: 71–6.

94 *Pokela M-L, Ryhänen PT, Koivisto ME, Olkkola KT, Saukkonen A-L.* Alfentanil-induced rigidity in newborn infants. Anesth Analg 1992; 75: 252–7.

95 *Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ.* The pharmacokinetics of sufentanil in surgical patients. Anesthesiology 1984; 61: 502–6.

96 *Sanford TJ Jr.* A review of sufentanil. Semin Anesth 1988; VII: 127–36.

97 *Murkin JM, Farrar JK, McNeill B, Gelb AW, Lok P.* Cerebral oxygen consumption during sufentanil anesthesia: measurement by N_2O uptake *vs* ^{133}xenon clearance. Can J Anaesth 1990; 37: S32.

98 *Mayer N, Weinstabl C, Podreka I, Spiss CK.* Sufentanil does not increase cerebral blood flow in healthy human volunteers. Anesthesiology 1990; 73: 240–3.

99 *Jung R, Shah N, Reinsel R, et al.* Cerebrospinal fluid pressure in patients with brain tumors: impact of fentanyl versus alfentanil during nitrous oxide–oxygen anesthesia. Anesth Analg 1990; 71: 419–22.

100 *From RP, Warner DS, Todd MM, Sokoll MD.* Anesthesia for craniotomy: a double-blind comparison of alfentanil, fentanyl, and sufentanil. Anesthesiology 1990; 73: 896–904.

101 *Shupak RC, Harp JR.* Comparison between high-dose sufentanil–oxygen and high-dose fentanyl–oxygen for neuroanaesthesia. Br J Anaesth 1985; 57: 375–81.

102 *Meretoja OA, Rautiainen P.* Alfentanil and fentanyl sedation in infants and small children during cardiac catheterization. Can J Anaesth 1990; 37: 624–8.

103 *Glass PS, Hardman D, Kamiyama Y, et al.* Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). Anesth Analg 1993; 77: 1031–40.

104 *Davis PJ, Lerman J, Suresh S, et al.* A randomized multicenter study of remifentanil compared with alfentanil, isoflurane, or propofol in anesthetized pediatric patients undergoing elective strabismus surgery. Anesth Analg 1997; 84: 982–9.