Conference Summary

Analgesics in anaesthetic practice

Introduction

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"Analgesics in Anaesthetic Practice" was the title of the second annual conference organized by the Department of Anaesthesia, University of Calgary, which was held in Calgary, Alberta on November 20, 1982.

The meeting began with a review of basic mechanisms of analgesia, by Dr. Sheldon H. Roth (Calgary). He described the now-classical pathways and mechanisms of pain production and relief and the new concept of populations of opiate receptors and their respective properties.

Dr. Donald R. Stanski (Palo Alto) discussed the pharmacokinetics of narcotic analgesics, showing how differences in lipid solubility, volume of distribution, and half-life clearly define the clinical behaviour of these drugs.

The topic "How to give an anaesthetic using intravenous analgesics" introduced geographical differences in anaesthesia practice. Dr. Ian M. Corall (London, England), spoke on "A British Method" and Dr. Allan L. Ross (San Francisco), described "An alternative from California." Although Dr. Ross emphasized a more invasive approach to monitoring, in contrast to Dr. Corall's more traditional "finger on the pulse" method, it was of interest that their dosing regimes of fentanyl and anaesthetic techniques were very

similar. Both authors stressed the use of an oral non-opiate pre-medicant (diazepam) when contemplating a predominantly narcotic analgesic technique.

Dr. Ian M.C. Clarke (Manchester, England), discussed the place of analgesics in chronic pain relief, emphasizing the efficacy and importance of such preparations as slow-release morphine. He also presented a short film, describing the long-term use of analgesics, as practiced in the North West Regional Pain Relief Centre, England.

Lastly, in a session entitled "Is there analgesia after fentanyl?", three speakers contributed. Dr. Jon Phipps (Calgary) described the techniques of radioimmunoassay and gas chromatography used to measure plasma fentanyl and alfentanil concentrations. Dr. Jonathan G. Williams (Calgary) reviewed the interactions between histamine-2 (H₂) receptor antagonists and narcotics. Dr. Ted Stanley (Salt Lake City) described the history of the use of high dose fentanyl and future developments in the use of fentanyl analogues, in particular sufentanil and alfentanil.

Acknowledgements

Our thanks to Mrs. Janet Beyer for expert secretarial help in the preparation of this conference summary. Jocelyn Lockyer and her staff at Continuing Medical Education, Faculty of Medicine, University of Calgary, for organizational help. Janssen Pharmaceutica, Inc., for a generous grant in aid of Continuing Medical Education.

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Cellular activity and mechanisms of analgesia

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Pain is an unpleasant sensory and emotional experience. It is also a protective mechanism often associated with potential or actual tissue damage. Drugs which predominantly relieve the suffering from pain are termed *analgesics* and are generally classified as *narcotic* or *non-narcotic* analgesics.

Stimulation of specialized receptors (nociceptors), which are present in almost every organ system, or their afferent neurons, can result in the transmission of a pain impulse. Certain chemical substances, such as bradykinin, histamine, serotonin and prostaglandins, termed *algesics*, may excite or sensitize nociceptors to various stimuli. Pathophysiological changes in the microenvironment of these receptors may also influence the response. The generated impulses are transmitted via ascending synaptic connections in the spinal cord to various regions in the brain which are involved in the perception and behaviour related to pain. Substance P, serotonin and norepinephrine have been postulated to act as neurotransmitters in these pathways. Endogenous opiate-like substances (enkephalins and endorphins) may modulate the transmission of the pain impulses.

Inhibition of the generation, transmission or perception of the pain impulse can be produced by analgesics. In general, the narcotic analgesics exert their dominant effects at the level of the spinal cord and central (brain) centres; non-narcotics suppress generation of the pain impulse.

The narcotic analgesics include the opiate alkaloids and related synthetic compounds. It has been well established that specific opiate receptors exist in the brain, primarily in the limbic system, spinoreticular tracts (such as periaqueductal grey, medial thalamic nuclei, hypothalamus, and substantia gelatinosa), spinal trigeminal nucleus, nu-

TABLE Actions of opioids on receptor subtypes

Agent	Receptor Types			
	μ	κ	σ	δ
morphine	Ag	Ag	Ag	—
naloxone	Ant	Ant	Ant	Ant
met-enkephalin	—	—	—	—
ketocyclazocine	Ag/Ant	Ag	—	—
dynorphin	—	Ag	—	Ag
nalorphine	Ag/Ant	Ag/Ant	—	—
pentazocine	Ag/Ant	Ag/Ant	Ag	—

Ag = agonist; Ant = antagonist; Ag/Ant = mixed agonist/antagonist; μ = receptor associated with supraspinal analgesia, respiratory depression, euphoria, physical dependence; κ = receptor associated with spinal analgesia, miosis, sedation; σ = receptor associated with dysphoria, hallucinations, respiratory and vasomotor stimulation, mydriasis; δ = receptor associated with inhibition of electrically stimulated contractions of smooth muscle.

cleus tractus solitarius, and vagus nerve. Opiate receptors have been subdivided into four populations: the mu (μ) receptor is associated with supraspinal analgesia, respiratory depression, euphoria and physical dependence; the kappa (κ) receptor is associated with spinal analgesia, miosis and sedation; the sigma (σ) receptor is associated with dysphoria, hallucinations, and respiratory and vasomotor stimulation; the delta (δ) receptor is associated with inhibition of electrically stimulated contractions of smooth muscle. Opiates and related synthetic compounds bind to these receptors with variable affinities and efficacies, exhibiting agonist, partial agonist, and antagonist properties. The summation of agonist/antagonist actions yields the net pharmacological profile on the different receptor populations (see Table).

In addition to the interaction of exogenous substances with opiate receptors, it has recently been suggested that opiate and non-opiate analgesic systems may be selectively activated by different environmental factors (stimuli) which may modulate the perception of pain.

Non-narcotic analgesics, such as acetylsalicylic acid (ASA), acetaminophen, and the newer non-steroidal anti-inflammatory analgesics (NSAIDs) are proposed to act at peripheral sites associated with the nociceptor and the generation of the pain impulse. It has been well documented that the steroid anti-inflammatory drugs inhibit phospho-

lipase A which is involved in the conversion of phospholipids to arachidonic acid. This is the primary stage of prostaglandin synthesis. NSAIDs and the salicylate-like analgesics inhibit the enzyme cyclooxygenase which converts arachidonic acid to prostaglandins and thromboxanes. The prostaglandin PGE_2 has been implicated in pain, inflammation and edema. Although the newer NSAIDs possess some advantages compared to the salicylates (e.g., less gastric irritation and bleeding), there does not appear to be an increase in efficacy, and patients' responses to these agents vary considerably.

Although there is considerable choice for analgesic therapy, there is not an ideal drug. A greater understanding of the pain mechanisms and specific receptor interactions will provide the basis for the development of more effective therapy.

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Narcotic pharmacokinetics

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Morphine ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) and meperidine ($1 \text{ mg} \cdot \text{kg}^{-1}$) have a long duration of narcotic effect (2–4 hours), relative to fentanyl ($10 \mu\text{g} \cdot \text{kg}^{-1}$) which lasts one-half to one hour. Alfentanil ($50 \mu\text{g} \cdot \text{kg}^{-1}$), a new fentanyl derivative, has an even shorter duration of narcotic effect ($\frac{1}{4}$ – $\frac{1}{2}$ hour). Pharmacokinetic principles can readily explain the differences between these four narcotics. Morphine, meperidine, and fentanyl share similar pharmacokinetic properties (Table). They have a large volume of distribution, high hepatic clearance and a relatively long terminal elimination half-life. Slow elimination from the body may explain morphine and meperidine's long duration of effect, but not the short duration of fentanyl's effect. Fentanyl differs from these two narcotics in having very high lipid solubility. This facilitates rapid entry and exit from the brain; thus fentanyl can rapidly redistribute from brain to muscle and fat tissues. Hence, fentanyl's short duration of effect is analogous in mechanism to that of thiopental. As the fentanyl dose is increased, either as a single large dose or multiple repeated bolus administrations, the duration of fentanyl's narcotic effect will progressively increase and begin to resemble that of morphine or meperidine.

Alfentanil has a different pharmacokinetic profile (Table). It has a lower clearance and volume of

TABLE

	Elimination half-life (hr)	Clearance ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Volume of distribution at steady state ($\text{l} \cdot \text{kg}^{-1}$)
Morphine	2.9	14.7	3.2
Meperidine	3.7	12.0	3.7
Fentanyl	4.2	13.3	3.7
Alfentanil	1.5	5.0	0.6

distribution, and thus a shorter terminal elimination half-life. Its shorter duration of narcotic effect is due to two factors. First, there is more rapid redistribution of alfentanil to subtherapeutic concentration relative to an equipotent dose of fentanyl. Second, there is more rapid elimination of alfentanil from the body due to the short terminal elimination half-life. Thus, bolus injections of alfentanil should have significant utility in clinical anaesthesia for short surgical procedures, or as a continuous infusion for longer procedures.

Recommended Reading

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How to give an anaesthetic using intravenous analgesics: a British method

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The Liverpool technique of IPPV/relaxant in combination with N₂O and O₂ had an enormous influence on anaesthetic techniques in the United Kingdom. Although this method of anaesthesia had deficiencies, such as a 2.2 per cent incidence of awareness and a lack of reflex suppression, re-

covery was fast and the technique itself easy to use. The original technique was altered to include volatile or intravenous supplements, but other problems arose, namely intraoperative myocardial depression and postoperative respiratory depression. Subsequently, the latter has emerged as an important factor, both in the choice of intraoperative narcotic and its dosage.^{1,2} Factors such as duration of surgery, lack of good recovery facilities, and variable postoperative supervision are also important.

In patients who are breathing spontaneously, narcotics can be given, either as a bolus with incremental doses or by infusion. A typical anaesthetic sequence for an in-patient requiring short stimulating surgery lasting about 15 minutes, would be (1) a non-opiate premedication, (2) an intravenous bolus dose of fentanyl (approximately 100 µg·70 kg⁻¹), (3) followed after about a minute by an intravenous induction agent such as Althesin, etomidate or methohexitone. Anaesthesia would be maintained with N₂O/O₂ and incremental doses of 25 µg of fentanyl. A similar technique, without premedication, has been used for day case surgery, but it would appear that administration of an anti-emetic drug is advisable when day case patients receive a general anaesthetic.³

For major non-cardiac surgery, doses of fentanyl of 10-50 µg·kg⁻¹ have been used. But although the higher doses were originally shown to obtund the hormonal stress response,⁴ in patients undergoing fallopian tube reconstruction, later work² has failed to show this benefit in other major abdominal surgery; in addition, the higher doses of fentanyl have caused postoperative ventilatory problems. For operations lasting 45-75 minutes, a non-opiate premedication followed by fentanyl 10-15 µg·kg⁻¹, a small dose of induction agent in combination with N₂O/O₂, and IPPV will normally permit the return of spontaneous ventilation after about 60 minutes. Incremental doses of fentanyl can be given, but these must be commensurate with the duration of surgery. Excessive hyperventilation should be avoided as this markedly reduces the patient's respiratory response to a rising PaCO₂ in the postoperative period. Naloxone will reverse the respiratory depressant effects of fentanyl but must be titrated at about 1 µg·kg⁻¹, if disorientation and hypertension, especially in patients taking alpha₂ adrenergic agonists, are to be avoided. If naloxone

is used, the duration of action of a single bolus will usually be much shorter than that of fentanyl. Also, postoperative analgesics should be withheld until required.

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How to give an anaesthetic using intravenous analgesics: an alternative from California

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By definition, a general anaesthetic agent produces profound analgesia, unconsciousness, muscle relaxation and obtundation of somatic and autonomic reflexes. The *ideal* anaesthetic agent provides these four aspects superimposed on a framework of haemodynamic and respiratory stability over the spectrum of age, physiological, and pathological

variability. To date, no single available agent is capable of satisfying these requirements.

The inhalational agents are "complete" anaesthetics but are associated with several disadvantages such as negative inotropic effects, alteration of vascular tone, sensitization of the myocardium to catecholamines, and lack of postoperative analgesia. The potent narcotic analgesics offer several advantages as anaesthetic agents: minimal depression of cardiac contractility, modulation of the autonomic nervous system, lack of myocardial sensitization to catecholamines, and no hepatic or renal toxicity. Postoperative analgesia is often profound and is clearly an advantage. However, doses high enough to produce unconsciousness can be associated with hypotension due to histamine release, bradycardia, variable prevention of autonomic sympathetic and haemodynamic responses, intraoperative awareness and postoperative respiratory depression.

The narcotics and inhalational anaesthetic agents have therefore been employed in a "supplemental" manner which provides a specific advantage: a reduction in the amount of agent required to produce a given benefit, resulting in attenuation of the drug's side effects. Narcotic supplementation of the potent inhalational agents has been demonstrated to decrease MAC.¹ Theoretically, by lowering MAC, less inhalational agent is administered, accordingly decreasing some of the disadvantageous properties, such as myocardial depression. Inhalational supplementation of narcotics augments amnesia, effectively controls blood pressure and systemic vascular resistance and thus decreases intraoperative narcotic requirements, which in turn lessens narcotic related postoperative respiratory depression.

In our opinion, given the available narcotic analgesics in the United States, fentanyl is the drug of choice for supplemental anaesthesia. This drug is approximately 70-200 times more potent than morphine and is associated with far fewer side effects. There is no associated histamine release as is frequently seen with morphine.² The high lipid solubility of fentanyl results in rapid blood brain barrier passage and opiate receptor site binding. Fentanyl has a short "clinical" half life allowing the anaesthetist to titrate the agent to effect. Disadvantages include bradycardia, truncal rigidity and respiratory depression.

As a supplement to other anaesthetic agents, fentanyl produces profound analgesia. Loss of visual awareness in 50 per cent of patients has been reported at a dose of $6-7 \mu\text{g}\cdot\text{kg}^{-1}$.³ Loss of consciousness and amnesia has been noted in the $11-24 \mu\text{g}\cdot\text{kg}^{-1}$ range.⁴

Before the patient arrives in the operating room, a non-opiate premedication is given to increase amnesia and decrease anxiety. Thus, for the average 70 kg patient, diazepam 10 mg is given by mouth 90 minutes preoperatively.

The anaesthetic dosage techniques for fentanyl used as a supplement encompass three methods: (1) primary loading dose, (2) incremental dosing, and (3) continuous infusion.

The primary loading dose is determined by the projected length of surgery in minutes. This value is divided by ten and fifteen. The resulting two numbers are interpreted in $\mu\text{g}\cdot\text{kg}^{-1}$ and represent a range for fentanyl that can be given as the primary loading dose. For example, for a projected 150-minute procedure, this calculation produces a dose of $10-15 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl. This range represents the total amount of drug administered prior to skin incision. No additional amount of fentanyl is given during the procedure. Dosing in this manner results in maximal blood concentration for skin incision while redistribution results in low enough blood levels to allow spontaneous ventilation at the end of the case.⁵ Supplementation with the inhalational agents (enflurane, halothane, or isoflurane), at an inspired concentration of 0.2-0.5 per cent range, are employed to control blood pressure.

The incremental dosing technique starts with induction with $3.5-7.0 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl and less than $2 \text{ mg}\cdot\text{kg}^{-1}$ of thiopental. During the procedure, fentanyl $50 \mu\text{g}$ is given every thirty minutes, up to about one hour before the end of the case, when no additional agent is given. This method decreases the total amount of narcotic administered and allows for "titration." As previously noted, inhalational agents are used to supplement anaesthesia and control blood pressure.

The last method of fentanyl administration is the continuous infusion. The induction technique using $3.5-7.0 \mu\text{g}\cdot\text{kg}^{-1}$ remains the same. However, immediately after induction, an infusion of fentanyl $0.5-1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ is initiated and continued until 15 minutes before the end of the case, at which

time it is discontinued. Supplemental inhalational agents are given as previously described.

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The place of analgesics in chronic pain relief

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The rational use of analgesics in chronic pain requires a re-orientation in prescribing attitudes.

Firstly, and most important, is the use of drugs on a regular basis to anticipate pain and prevent its onset, rather than on a PRN basis as in acute pain states. Regular administration results in lower total daily dosage, fewer adverse effects, lower dependence liability and better pain control as anticipatory fear and anxiety subside.

Secondly, a correct diagnosis of the cause of pain must be made so that appropriate drugs may be selected. It is incorrect to regard all analgesics as uniform in their effects but of differing potencies, since narcotics have a different mode of action from nonsteroidal anti-inflammatory agents (NSAIDs)

and neither are effective in pain due to deafferentation.

Pain due to peripheral tissue damage or bony metastases is provoked by release of nociceptive sensitizing agents such as prostaglandins and prostacyclins and is relieved by non-steroidal anti-inflammatory drugs. Visceral pain, typically that of cancer, is best relieved by narcotics. Causalgic pain, characterised by burning, shooting, paraesthesiae and hyperaesthesia, is probably due to partial nerve damage and regeneration (e.g., by Herpes zoster, surgical trauma, or ischaemia), producing unstable nerve membranes with lowered depolarisation thresholds. Anticonvulsant drugs are effective for this kind of pain. Methylated tricyclic drugs, which increase tissue concentration of 5 hydroxytryptamine and block cholinergic pathways, also have analgesic activity independent of their antidepressant properties.

Other types and causes of pain may require a variety of agents such as beta blockers, muscle relaxants and hormones.

To improve patient compliance and thus efficacy of drugs, the route of administration must be selected for simplicity and convenience: oral or sublingual routes are thus preferred.

Drugs should be selected for freedom from side effects and long duration of action (so long as cumulation does not occur). Recent advances in drug formulations (e.g., slow-release morphine) allow twice daily administration of some oral drugs to provide continuous analgesia throughout 24 hours. This produces a dramatic improvement in quality of life.

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Principles of measurement of plasma concentration of fentanyl and its analogues

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Fentanyl is a commonly used analgesic in clinical anaesthesia and, as a result, measurement of plasma concentration of this drug (and more recently its analogues) is in demand. Such measurement may be made by means of radioimmunoassay¹ or gas liquid chromatography.^{2,3}

Radioimmunoassay (RIA) is the determination of a drug concentration by means of a radioactive-labelled compound that reacts (antigen/antibody) with the substance to be measured. RIA kits are now available commercially for the measurement of fentanyl.

Gas liquid chromatography (GLC) differs from radioimmunoassay in that it is a method of chemical analysis allowing separation of substances, the concentration of one of which is known (the standard). The serum sample is first put through a chemical extraction process to separate out the drug or drugs of interest. Two types of GLC detectors have been used - flame ionisation (FID)² and the nitrogen/phosphorus (NPD)³. Alternatively, a mass-spectrometer may be used as the detector to measure the metabolites of fentanyl and its analogues³ but is not required for the parent compounds.

A recent study⁴ compared these methods and concluded that RIA is a specific, accurate but expensive method of measuring plasma fentanyl. RIA will also measure analogues of fentanyl but separate kits are required. GLC, using an FID, is not sensitive enough for low concentrations of plasma fentanyl. However, GLC using an NPD, is as sensitive as RIA, and has the added advantage

that other analogues of fentanyl may be measured by the same system. Furthermore GLC is slightly cheaper than RIA on a per sample basis.

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Interactions of H₂ receptor antagonists with narcotics

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H₂ receptor antagonists are widely used in the treatment of peptic ulceration and related conditions. There is also increasing interest in the use of these drugs as premedication to reduce the risk of the acid aspiration syndrome associated with anaesthesia. Two H₂ receptor antagonists are currently used clinically: cimetidine, an imidazole derivative, and ranitidine, a substituted amino-alkyl furan derivative.

One possible interaction with narcotics is related to the fact that cimetidine inhibits hepatic oxidative drug metabolism, and is known to prolong the actions of several drugs, including diazepam, barbiturates and propranolol. This effect may also prolong the action of narcotic analgesics. Ranitidine, not possessing an imidazole ring, is free from this side effect.

A second possible interaction relates to the fact that certain narcotic analgesics (e.g. fentanyl, meperidine and methadone) are known to be excreted in gastric secretions, and can be reabsorbed later from the small intestine.¹ As this may amount to up to 20 per cent of a single dose, gastric secretion may be responsible for secondary rise in plasma concentration and for the late respiratory depression which has been reported with fentanyl.² In the case of meperidine, this phenomenon has been shown to be dependant on gastric pH, probably due to the "ion trapping" effect, whereby meperidine, a weak base with a pK of 8.7, is mostly un-ionised at neutral pH and readily crosses lipid membranes. Once exposed to the acid pH in gastric juice, however, it becomes almost fully ionised, and is unable to return to the bloodstream.³ Fentanyl, with a pK of 7.7, is likely to be affected similarly. Modification of gastric pH with oral antacid mixtures virtually prevents gastric secretion of meperidine.³

In summary, the anaesthetist should add to the specific enquiries concerning current drug therapy-H₂ receptor antagonists. In patients receiving cimetidine, it seems that caution should be exercised when administering analgesics, barbiturates and diazepam.

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The new intravenous analgesics (and some of the old)

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The opiates have been used for many hundreds of years to help dispel the pain and anxiety of the surgical experience. In the fourteenth century, sponges filled with the juices of opium, hyoscyamus, and mandragora were employed, although variation in dose often led to asphyxia and death. This provoked a general abandoning of the technique until the mid-eighteenth century, when oral administration of the powdered form of opium became the most common technique of pain relief. However, in the nineteenth century, the isolation of morphine as the active principle of opium, and the invention of the syringe and the hollow needle allowed the accurate use of morphine both as a supplement and as a complete anaesthetic (in combination with scopolamine).¹

The twentieth century has seen this use of morphine as a complete anaesthetic (primarily for cardiac surgery) rejected, re-discovered by Lowenstein and workers,² and (in some centres) rejected again, as newer analgesics, with more advantages and fewer disadvantages are produced.

Fentanyl was first investigated as a complete anaesthetic in patients undergoing mitral valve surgery and then coronary artery bypass surgery.^{3,4} Doses of 50–100 $\mu\text{g}\cdot\text{kg}^{-1}$ produced stable cardiovascular parameters, unless N_2O or intravenous diazepam was added, which resulted in marked cardiovascular depression.

Experience has shown that some of the limitations of fentanyl (such as inability to control cardiovascular responses and prolonged postoperative respiratory depression), may relate to an inability to predict the initial dose required and the changing patient population subjected to cardiac surgery. Therefore, derivatives of fentanyl, which may be more effective than the parent compound,

are now undergoing clinical investigation; these are sufentanil and alfentanil. Sufentanil is 4,521 times as potent as morphine, but is also very safe, with an $\text{LD}_{50}/\text{ED}_{50}$ of 25,111 in rats (morphine = 69; fentanyl = 277). In man, sufentanil is five to ten times as potent as fentanyl, and at doses of up to 15 $\mu\text{g}\cdot\text{kg}^{-1}$ there is little change in cardiovascular dynamics.⁵ Alfentanil is less potent and shorter acting than fentanyl, but is also very safe, with an $\text{LD}_{50}/\text{ED}_{50}$ of 1080 (in rats). Cardiovascular stability is maintained at doses up to 5 $\text{mg}\cdot\text{kg}^{-1}$.

Another fentanyl derivative, carfentanyl, still an experimental drug, has some extremely interesting properties. One crystal of carfentanyl, applied to the mucous membrane of a dog or monkey will produce unconsciousness within seconds. If the animal is allowed to inhale carfentanyl in vapour form for 60 seconds, surgical anaesthesia is produced. This may indicate the way forward for the single drug "anaesthetic" – a non-toxic analgesic, producing unconsciousness and muscle relaxation.

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