Drug delivery techniques of the future

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Background

There is a great deal of data to indicate that better knowledge of diseases, better preoperative preparations, better monitoring and better anaesthetics have significantly reduced mortality during general and regional anaesthesia in the past 60 years. Anaesthetic death rates of approximately one in 1000 in the 1940s were reduced to one in 10 000 in the 1970s, and are now estimated to be as low as one in 250 000 to one in 400 000 in 2008. This is about 250 times better that it was just 60 years ago. This paper will focus on the improvements in anaesthetic and analgesic agents and their delivery in the past 20 years and speculate on how these drugs and drug delivery systems will continue to get better in the future.

One way in which anaesthetics and anaesthetic adjuvants have dramatically improved is in speed, namely speed in onset and offset (recovery). The new intravenous and inhalation anaesthetics, analgesics, sedative hypnotics and muscle relaxants all have much faster onsets of action than their predecessors. These agents are also much more titratable than older agents. However, almost all of our drugs still have reasonably low therapeutic indices (which means that their lethal doses are still fairly close to their effective doses). Thus it is reasonable to suggest that most of our anaesthetics and anaesthetic adjuvants should be able to be made safer and better. One way in which this might happen would be to synthesise more potent, receptor-specific anaesthetic agents. Generally, more potent, receptor-specific drugs have higher therapeutic indices than less potent drugs in the same class. An example of this is the opioids. If meperidine has a potency unit of .01, morphine = 1.0, fentanyl = 100 and sufentanil = 1000, their therapeutic indices are 4 to 7, 70 to 90, 270 to 400 and 25 000 respectively.

The technology of anaesthetic and analgesic drug delivery has not progressed as rapidly as the development of new drugs in the past 150 years. The reason for this is difficult to comprehend, but it should be considered that anaesthetics are still delivered via needles and syringes (first discovered in 1854), potent liquid anaesthetics are vaporised (an art that is over 200 years old), and pills or solutions are still swallowed (techniques that are also hundreds of years old).

It is likely that much of this technology may change rapidly in the near future. One important reason for this is that the costs of new drug discovery and development have become dramatically higher. In the late 1980s, a typical new drug cost about $125 million from discovery to Food and Drug Administration (FDA) approval, and this process took about 10 years. By 1991, the time for approval increased to an average of 12 years and the cost to an average of $231 million. By 1995, it still took 12 years to get an average drug through the FDA, but the cost had risen to $285 million. By 2001, the average new drug cost $802 million to bring through the FDA process and today it ranges between $800 million and $1 billion and still takes about 12 years. The principal reasons for these dramatic increases are that the FDA now requires that many more patients be studied and many more complex and expensive clinical studies be undertaken.

One of the more important reasons why ‘new routes and delivery systems’ are likely in the near future is that many of these new systems will use older, well-known drugs, thus requiring fewer patients to be studied and clinical studies to be performed, and hence be much cheaper to get through the FDA. These new routes and delivery systems will provide the incentive for commercial companies to invest in them, because there will be new patents for older drugs, new uses for older drugs, a decreased cost and time for FDA approval, and an ability to maintain or increase their market share. The new routes and delivery systems will provide increased convenience, safety (with reduced side effects), bioavailability, and effectiveness of the drugs and decreased peaks and valleys of drug blood and brain levels, decreased dosage and frequency of administration and less cost for the patients and clinicians using them. The current average cost of developing an older drug in a new delivery system ranges from 10 to 15 million dollars (on the low side) to about 50 to 70 million on the high side (depending on the drug and its indication).

Drug delivery of the future promises to be simple, safer, non-invasive, titratable and inexpensive, and provide the rapid onset and offset of our techniques of today. Some of the new techniques, such as transdermal patches, creams, gels, ointments and pastes, are already familiar to many clinicians. Iontophoresis is a technique that is already being used to deliver local anaesthetics (lidocaine) to the skin of children and needle-phobic adults. A variant of the iontophoretic technique may soon be available for the delivery of fentanyl for postoperative pain in a non-invasive, patient controlled analgesia (PCA)-like approach. EMLA® cream is also familiar to many clinicians. A new, faster-onset local anaesthetic patch (a eutectic mixture of 7% lidocaine and 7% tetracaine) that also employs heat to hasten the onset of action has recently become available. Similarly, new anaesthetic creams employing local anaesthetics and patches with COX-1 non-steroidal anti-inflammatory drugs (NSAIDs) are being studied. Non-invasive pulmonary drug delivery techniques employing older, well-known drugs are also being evaluated by numerous companies.

In the past 15 years, a number of drugs have been developed and approved by the FDA for oral transmucosal drug delivery. The most commercially successful has probably been oral transmucosal fentanyl citrate (Actiq®) for the treatment of...
breakthrough cancer pain. New approaches for oral transmucosal fentanyl delivery include fentanyl lozenges, buccal tablets, buccal patches and wafers. Numerous companies are also evaluating the transnasal mucosal delivery of fentanyl, hydromorphone, ketamine, buprenorphine and other analgesia-producing drugs.

It is possible that anaesthesia and analgesia of the future will be provided without drugs. The author believes that it is possible to stimulate or manipulate the release of neurotransmitters using physical forces (electrical and magnetic energy) to create anaesthetic states and thus avoid chemicals (drugs). Some early concepts will be discussed below.

**Drug delivery through the skin and mucosal surfaces**

When compared with drugs administered orally, drugs administered through the skin (as well as those given intravenously and inhaled) bypass hepatic first-pass metabolism and avoid gastrointestinal degradation. Long-term transdermal and iontophoresis drug delivery systems reduce the variability of serum drug concentration profiles, eliminate peak and trough concentrations, and allow for improved drug safety by reducing high plasma concentrations, which often occur with intramuscular and intravenous drug administration. Steady blood concentrations reduce drug dosing frequency, simplify dosing schedules and improve patient compliance.

**Transdermal drug delivery**

The transdermal application of medications is not new, as mankind has been applying ointments, creams, lotions and gels (primarily for local effects) for centuries. However, the stratum corneum, which is 15 to 20 cells thick and covers 99% of the body surface area, has proved difficult to penetrate, and systemic delivery using this route has increased only gradually over the past 25 to 30 years. Nonetheless, there are more and more transdermal drugs receiving approval and becoming available to clinicians. A few of interest to anaesthesiologists include scopalamine (for nausea and sedation), nitroglycerine (for angina), a number of oestrogen preparations (for oestrogen replacement after menopause), clonidine (for hypertension), testosterone (for male hormone augmentation), lidoderm (transdermal lidocaine for relief of pain associated with postherpetic neuralgia), ketoprofin (for mild to moderate pain) and fentanyl (for moderate to severe chronic pain).

The development, introduction and clinical use of transdermal fentanyl (TTS fentanyl), also called Duragesic®, is a useful example. Transdermal fentanyl was developed by the Alza Corporation (now part of the Johnson & Johnson family of companies) in the 1980s. Early studies demonstrated that the TTS fentanyl patch could deliver fentanyl through the skin at a constant rate of 25, 50, 75 or 100 mg/hour. They also showed that the fentanyl patches provided steady-state plasma concentrations similar to those resulting from constant-rate IV infusions. One problem with transdermal fentanyl was that it took between 15 and 20 hours for the serum concentration of fentanyl to plateau. Another issue was that, once a patch had been removed, the fentanyl blood levels decreased only slowly (due to a depot of fentanyl in the skin). In some patients, the half-life of fentanyl given by the transdermal route was 20 hours or more.

Numerous investigators have reported that transdermal fentanyl reduces the need for morphine or other opioids in the early postoperative period in patients coming for a variety of surgical procedures associated with significant postoperative pain. However, the delay in reaching steady-state blood concentrations necessitates the first application of the fentanyl patch preoperatively or at least during the operation. More important is the fact that, while continual steady delivery of fentanyl is advantageous for sustained analgesia, it can be problematic if drug delivery has to be reduced or discontinued secondary to overdosage or for the treatment of drug-induced side effects. The incidence of significant respiratory depression (in some studies over 10%) and the frequent need for naloxone or other opioid antagonists to antagonise respiratory depression resulted in regulatory agencies like the FDA voting against its use for pain relief in opioid-naïve patients. It was approved for moderate to severe pain in opioid-tolerant patients, for example those with advanced cancer. Transdermal fentanyl (Duragesic®) has proven to be one of the most successful transdermal drug delivery products ever developed. Tens of thousands of patients with severe pain experience impressive analgesia and have been using the product continuously for many years. In 2004, sales of Duragesic® were worth over $2 billion. Its success has stimulated many other pharmaceutical companies to start developing other opioids and non-opioid analgesic drugs in a variety of transdermal patches, creams and gels. Some of these are non-steroidal anti-inflammatory compounds like ketoprofin in patches (now approved in Japan and some European countries), and a number of local anaesthetics.

**Iontophoresis**

Because of difficulties in the passive delivery of drugs through the skin, physical and chemical methods of enhancing transdermal drug delivery are being investigated. Iontophoresis is a method of transdermal administration of ionisable drugs in which the electronically charged components are propelled through the skin by an external electric field. Since this technique was first conceived in 1740, drug delivery from the positive electrode has been limited by the generation of H+ ions, which compete for charge transport and thus decrease the amount of drug which can be delivered. In addition, the generation of H+ ions leads to a decreased pH within the electrode, which can lead to significant skin burns. Finally, the current passing from a metal electrode frequently causes its dissolution, resulting in additional competing ions within the drug delivery compartment. Because of these problems, drug delivery times were at first limited to 15 to 30 minutes, depending upon the current intensity and the specific drug.

Recent research leading to the development of a silver electrode and chloride solutions of different positively charged drugs has made it feasible to deliver drugs iontophoretically for three hours or longer. The utilisation of the silver electrode allows for the iontophoresis of positively charged morphine molecules while generating insoluble AgCl at lower voltages than those required for the electrolysis of water. Iontophoresis of lidocaine for analgesia for superficial surgical procedures has been reported by a number of authors, and an FDA approved device is available in the United States of America (USA). In addition, iontophoresis has been utilised to deliver corticosteroids for the treatment of painful joints. However, documentation of the use of iontophoresis for these purposes is still limited, and iontophoresis has not met with widespread use, in spite of the availability of low-cost iontophoresis units and improved electrode technology. Perhaps this is due in part to the time necessary to achieve analgesia (10 to 15 minutes with lidocaine) and the slight risk of burns with this technology.

Iontophoresis of morphine HCl for the management of moderate to severe postoperative pain has been reported recently. No
studies have been reported to date on the bioavailability of morphine administered via iontophoresis. In addition, no data are currently available evaluating the use of iontophoresis to deliver opioids for periods of time greater than six hours. However, this technology shows promise as a method of delivering systemic doses of potent opioids and possesses the advantage of changing the dose of the drug delivered by adjusting delivery currents. In addition, iontophoresis should allow for discontinuation of drug delivery with discontinuation of the delivery current, avoiding the “depot” effect currently seen with transdermal fentanyl. A new product using a variation of the iontophoretic concept is nearing clinical approval in the USA. This device promises to deliver intermittent, small boluses of fentanyl for postoperative analgesia in a patient-controlled analgesia mode.

**Intranasal transmucosal drug delivery**

Intranasal transmucosal drug delivery is another drug delivery alternative that potentially has the advantages of the non-invasive delivery of drugs that undergo extensive inactivation in the gastrointestinal tract following oral administration. The surface of the nasal cavity in an adult is approximately 180 cm² and has a large blood supply, about 40 ml/min/100 g of tissue, allowing for potentially easy access for the systemic delivery of medications. To date, only a few drug preparations intended for systemic delivery via the intranasal route are available in the USA. These include desmopresin (DDAVP®), lypressin (Diapid®), oxytocin (Syntocinon®) and butorphanol (Stadol®). However, extensive research into the intranasal delivery of a variety of drugs is currently being conducted.

The nasal administration of sufentanil as a pre-anesthetic medication has been studied in children and adults. Henderson and associates evaluated the use of intranasal sufentanil (1.5, 3.0, or 4.5 μg/kg) or saline placebo in 80 children aged six months to seven years scheduled for elective surgery. They found that children given sufentanil were more likely to separate willingly from their parents than children receiving a placebo. In addition, the children moved or coughed less during tracheal intubation, required less halothane, cried less and were given fewer analgesics following surgery. However, 61% of all the children in the study cried during intranasal drug administration and the incidence of vomiting in the recovery room and during the first postoperative day was higher in the intranasal sufentanil group. In adult patients, intranasal sufentanil (10 and 20 μg) was found to provide effective, rapid sedation (onset: 10 minutes) and minimal side effects. Intranasal midazolam and ketamine have also been studied and are not uncommonly used for premedication in children before the induction of general anaesthesia.

Multiple factors have been noted to affect the delivery of intranasally administered drugs, including the surface temperature of the nasal mucosa, airway resistance, atmospheric conditions, drug factors (pH, lipid solubility, molecular weight, pKa), and the technique of drug administration (droplet size, site of deposition, etc.). There is little information on the effects of intranasal delivery of opioids for the principal purpose of providing analgesia (such as pain following surgery), or on the effects of long-term intranasal opioid delivery, and therefore the future role of this drug delivery route for analgesia still remains unclear.

**Oral transmucosal drug delivery**

Potential advantages of oral transmucosal drug delivery include less hepatic first-pass metabolism and improved patient comfort, convenience and compliance. In addition, since the oral cavity is rich in blood vessels and lymphatics, drug absorption is fast and the onset of action is rapid when compared with oral (GI) and transdermal routes. The fast onset action enables titration of the drug dosage to specific endpoints of effect. The mouth has three areas for potential transmucosal delivery: beneath the tongue (sublingual), between the gums of the upper molars and the cheek (buccal), and between the gum of the incisors and the upper lip (gingival). Drug permeability appears to be highest in the sublingual area and lowest at the gingival site.

Buccal administration of morphine has been evaluated, with mixed results. In one study, Bell and associates reported on a prospective, double-blind, placebo-controlled study of buccal and intramuscular (IM) morphine in 40 patients undergoing elective orthopaedic operations. Patients received either an intramuscular injection or a buccal tablet of morphine (15.3 mg). The tablet was placed between the upper lip and the gum above the incisor teeth and allowed to slowly dissolve over six hours. These authors reported that IM and buccal morphine provided similar analgesia following surgery. In addition, plasma morphine concentrations were similar, with peak levels being slightly higher following IM administration, but the bioavailability of buccal morphine was 40 to 50% greater that that of IM morphine. However, several reports have failed to reproduce these findings. Fisher and associates reported a wide variability of systemic morphine delivery and a bioavailability of about 15% after buccal morphine, much lower than that of oral morphine. In another double-blind study comparing IM with buccal morphine as a preoperative medication in orthopaedic patients, IM morphine was more effective and had fewer adverse side effects. Certainly, the relatively low lipid solubility of morphine makes it an unlikely candidate for effective transmucosal absorption. In fact, while sublingual administration of morphine may provide some analgesia and a low incidence of side effects, bioavailability is poor when compared with sublingual administration of other more lipid soluble opioids.

Investigations into the oral transmucosal delivery of fentanyl have been ongoing for the past 20 years. Fentanyl was first incorporated into a sucrose-based lozenge on a stick (Oral Transmucosal Fentanyl Citrate, OTFC, Anesta Corp, Salt Lake City, UT) for transmucosal delivery in the 1980s. OTFC, also called fentanyl orale, has been evaluated as a premedicant and as an analgesic in the emergency department, following surgery, and for breakthrough cancer pain. Fentanyl orale was approved by the FDA for use as a premedicant in children and adults before anaesthesia and painful procedures. Initial studies with fentanyl orale in adult volunteers and children showed that the device produces reliable sedation and anxiolysis when used as a premedication. In children, OTFC leads to rapid sedation and decreased anxiety within 30 minutes of beginning administration. Compared with children receiving nasal sufentanil, 61% of whom cried during drug administration, children readily accepted orale. In addition, patients who receive orale required less potent inhalational anaesthesia during operation and less pain medication in the recovery room. Recovery times were not prolonged, but orale administration did delay discharge from the hospital by 30 to 40 minutes in outpatients when compared with placebo controls in one study. Chief side effects of fentanyl orale when used for premedication are postoperative nausea and vomiting. However, the incidence of these problems appears to be no greater than when fentanyl is given intravenously.

In the emergency department, fentanyl orale provides good analgesia for patients following painful injury or illness, without
an increase in the incidence of opioid-related adverse effects. Fentanyl orale® also provides effective postoperative analgesia for patients undergoing joint replacement surgery. During use as an analgesic for the treatment of breakthrough and incident cancer pain, fentanyl orale® appeared to be well suited for this indication; the route of administration was well accepted, the onset of analgesia was rapid (five to 15 minutes), and patients appeared to be able to titrate the drug to effect.

In the early to mid-1990s, extensive studies were undertaken on the use of oral transmucosal fentanyl citrate for breakthrough cancer pain in opioid-tolerant patients. The ability to titrate the drug, using the handle attached to the lozenge, proved particularly useful for patients with moderate to severe pain. In addition, the speed of pain relief namely five to 10 minutes in most patients, was remarkable and considered extremely important. The new product was called Actiq® and was approved in six dosages, namely 200, 400, 600, 1200 and 1600 μg, which enabled it to be used in many patients. Actiq® grew in popularity between 2000 and 2006 before it lost its patent status in the United States. Indeed, sales of Actiq were worth more than $620 million in 2006.

The popularity of Actiq® encouraged many pharmaceutical companies to develop other oral transmucosal products using fentanyl and other opioids, as well as ketamine. A new product, called Fentora® (a rapidly dissolving fentanyl-containing buccal tablet), has been approved for use in breakthrough pain in opioid-tolerant patients. The product is marketed by Cephalon, but many other companies are evaluating fentanyl for buccal transmucosal delivery using lozenges, wafers and buccal patches.

**Creams, gels, ointments and pastes**

The first transdermal anaesthetic cream introduced into anaesthesiology and pain practice was EMLA®, a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine. It was introduced by Astra first in Europe and then, in the 1990s, in the USA. EMLA® was particularly useful in paediatric anaesthesia for starting intravenous infusions or obtaining a blood sample. It also was effective in needle-phobic adults. Its principal disadvantage was its slow onset of action: 60 to 90 minutes. Two new products, Synera® (in the USA; Rapydan® in Europe) and PliaglisTM have been developed by ZARS, a small company in the USA, and these could be considered second-generation improvements on EMLA®. Synera® and Rapydan® are eutectic mixtures of 7% lidocaine and 7% tetracaine, which are integrated into a patch that also possesses a heating element. The lidocaine and tetracaine mixture itself creates skin anaesthesia faster than EMLA®, but the heating element enables the onset of anaesthesia to be still faster (five to 15 minutes), and twice as deep as that which occurs after EMLA® application at the same time interval. PliaglisTM is a cream that comes in a tube and has the look and consistency of toothpaste. It contains the same eutectic mixture of lidocaine and tetracaine as does Synera® and Rapydan® but, in addition, the cream dries after 30 minutes and becomes a skin that can be peeled off the patient’s skin just as the skin is peeled from an orange. This allows the application of the product to any surface (smooth or irregular) on a patient’s body (for example an elbow or ear), and the rapid (30 minute) onset of anaesthesia, which is often as deep as one centimetre. The development of gels, ointments and pastes that contain solvents that can evaporate both rapidly (to create non-tacky surfaces) and slowly (to enable drug delivery to continue for many hours) will enable the development of a plethora of new products that will provide skin analgesia and anaesthesia, as well as anaesthesia in the tissues below the skin (muscles and joints). These new products will have application in anaesthesia, pain management, dermatology and other medical specialties.

**Future concepts**

New approaches and the increased understanding of central nervous system receptors and of natural and synthetic neurotransmitters (drugs) that act or interact at these sites has enabled numerous researchers to consider ways in which more specific drugs could be developed or drugs could be made more selective. This has introduced the expression ‘drug focusing’. Drug focusing addresses the concept of the limitation of drug action to specific receptor sites within certain organs or specific tissues or cells within these organs. The development of liposomes, microscopic lipid bags in envelopes that encase drugs, now provides a mechanism by which these compounds could be carried in an inactive form after injection into the blood stream. The idea of exploiting liposomes as biodegradable slow-release packaging material for drugs was put forward in early 1969. The advantages of liposomes as useful vehicles for the purpose of delivering drugs include their biodegradability and similarity to natural membranes, and the possibility of modifying them to suit a variety of compounds and situations. Disadvantages have included the fact that liposomes are recognised as foreign and quickly dispatched to the reticulo-endothelial tissues for destruction, and the lack of ability to ensure that these lipid bags will discharge their contents at exactly when and precisely where they are desired. The disadvantages now appear to be solvable using recent developments in wave technology, computer-directed imaging techniques and photomedicine.

**Wave technology, computer-directed imaging, photomedicine and anaesthesiology**

Practical applications of high-tech medicine in the sphere of new wave techniques, computer-directed imaging and photomedicine abound in hospitals throughout the world and in changes occurring in everyday life. In medicine, these developments are still largely diagnostic (nuclear magnetic imaging and transdermal thoracic and transoesophageal echo cardiography), but are beginning to become therapeutic (laser and monoclonal antibodies). The question is how are or will these developments affect or alter the principles and practice of anaesthesiology? The answer is that they will do so by helping the specialty improve drug focusing and perhaps entirely substitute the analgesics, sedatives, hypnotics and anaesthetics we use now.

It is now possible to encapsulate any of our currently available anaesthetics in lipid bags. It is also possible to selectively break these lipid bags by focusing microwave, ultrasonic or other waves on these bags so that the temperature of the membrane of the bag is increased only slightly (perhaps 1.5 to 2.0°C) to a temperature that will rupture the bag (B Hills, personal communication). Only the bags within the focal spectrum of the wave being utilised will break, thus the drugs that are contained therein will be released only in the desired local area. It would seem possible that laser energy could also be used to selectively destroy lipid bags (liposomes) and focus anaesthetic compounds, but to my knowledge this has not been accomplished yet. It would also seem possible that the wave force (energy) utilised to selectively release compounds from their inactive envelopes could be focused on very precise organelles and perhaps receptor sites within the spinal cord or brain, principles utilised that would be similar to those evolving with monoclonal
antibodies. Unfortunately, it does not appear that this is yet possible, but my suspicion is that this situation will change in the not too distant future.

Can the revolutionary developments in imaging technology be utilised to focus drugs or lipid bags containing pharmacologically-active compounds on precise organelles in the central nervous system? The experts (D Allion, personal communication) say it might be possible, in a few years, to identify the receptors or chemical components of the receptors via a technique called high resolution focusing. However, direct steering of the drug to the identified receptor seems extremely difficult. The reason seems to be related to the fact that current computer-directed imaging technologies do not steer but rather orient molecules (nuclei, etc.). Having identified the location where the drug is to act, and having a mechanism to activate the drug, only leaves the problem of focusing the drug on the receptor. One wonders if this final problem might be solved by attempting to design the drug to be attracted to the receptor via an antigen-antibody attraction or similar mechanism, or by systemically flooding an inactive drug that is then activated by an energy source (laser) focused on the receptor.

Drug activity without the drug

Concepts related to affecting and particularly slowing or quieting central nervous system (CNS) activity without the use of pharmacologic compounds are not new. Indeed, it is possible to trace the use of electrical currents for the precise purpose of producing anaesthesia to the turn of the last century and some authors have even traced ideas back to biblical times. More recently, acupuncture and methods of producing analgesia via transcutaneous electrical stimulation have become popular and apparently are effective, at least in some patients. The recognition of transmitter-receptor interactions as a cause of many natural cerebral activities, the evolution of specific CNS-acting drugs that depress the spinal cord and/or brain via interference with or effects on neurotransmitters or receptors or both, and the realisation that drug and neurotransmitter action in the CNS (perhaps profound drug action) without the need for the drug may be a possibility are causing much excitement in some (perhaps profound drug action) without the need for the drug. The trick now is to identify the precise (best) energy source and set of characteristics, and to focus that source precisely on that part of the cell membrane to depolarise, hyperpolarise or whatever to prevent nerve conduction. Either one or both could be the desired effect. The power of current imaging technology and the availability and growing knowledge base of energy and wave sources are critical to future drug focusing. However, it is already quite clear that externally applied electrical fields can induce and/or alter depolarisation in pyramidal and other neural elements. What is not clear is the range of fields that produce reversible neurological effects and the possible magnitude of induced changes. Our laboratory is currently investigating the effects of a variety of photo, magnetic and micro-energy waveforms on nerve conduction. Early progress is extremely encouraging and we now believe that anaesthesia in the 21st century will undoubtedly offer the possibility of analgesia, sedation, hypnotis and complete anaesthesia without a foreign compound via computer-focused physical activation of receptor sites and/or neurotransmitter modulation with non-invasive external wave or energy forms.

Bibliography

1. Duhaie DJR, Rowbotham DJ, Wyld R, et al. Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth 1980;60:614-8.
2. Streissand JB, Stanley TH. Opioids: new techniques in routes of administration. Current Opinion in Anaesthesiology 1989;2:456-2.
3. Courlay GK, Kowalski, SR, Plummer JL, et al. The efficacy of transdermal fentanyl in the treatment of postoperative pain: a double-blind comparison of fentanyl and placebo systems. Pain 1990;40:21-7.
4. Harris PR. Iontophoresis: clinical research in musculoskeletal inflammatory conditions. Journal of Orthopedic and Sports Physical Therapy 1982;4:103-8.
5. Petelenz T, Petelenz AI, Iwinski TJ, et al. Mini set for iontophoresis for topical analgesia before injection. Int J Clin Pharmacol Ther Toxical 1984;22:152-5.
6. Weinberg AL, Freestone DS. The administration of drugs and vaccines by the intranasal route. Br J Clin Pharm 1976;3:821-7.
7. Leigh J, Pandit UA, Rosen D, et al. Intranasal midazolam premedication in preschool children does not cause respiratory depression or delayed recovery: Proceedings of 9th World Congress of Anaesthesiologists (abstracts) II. A0825, 1988.
8. Bell MD, Murray GR, Mishra P, et al. Buccal morphine-a new route for analgesia? Lancet 1985;1:71-3.
9. Pannuti F, Rossi AP, Iafiele G, et al. Control of chronic pain in very advanced cancer patients with morphine hydrochloride administered by oral, rectal, and sublingual route. Clinical report and preliminary results on morphine pharmacokinetics. Pharmacological Research Communications 1982;14:369-80.
10. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. Anaesthesia 1979;34:463-7.
11. Streissand JB, Ashburn MA, LeMaire L, et al. Bioavailability and absorption of oral transmucosal fentanyl citrate. Anesthesiology 1989;71:A240.
12. Stanley TH, Hague B, Mock RL, et al. Oral transmucosal fentanyl citrate (loppip) premedication in human volunteers. Anesth Analg 1989;69:21-7.
13. Ashburn MA, Fine PG, Stanley TH. Oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain. A case report. Anesthesiology 1989;71:615-7.
14. Bangham AD. Liposomes in Nuce. Biol Cell 1983;47:1-10.
15. Cammoun D, Hendee WR, Davis KA. Clinical applications of magnetic resonance imaging – current status. W J Med 1985;143(6):793-803.
16. De Castro J, Van de Water A, Wouters L, Khonneux R, Reneman R, Kay B. Comparative study of cardiovascular neurological and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiologica Belg 1979;30:5-9.
17. Haider HJ, Adhojanian GK, Sreotonin receptors in the brain. Fed Proc 1977;36:2159-64.
18. Hause L, Sances A, Larson S. Polarization changes induced in the pyramidal cell and other neural elements by externally applied fields. In: Wielsdoth NL, Sances A, editors, The nervous system and electrical currents. New York: Plenum Press; 1971. p. 93-5.
19. Krugie KM, Joseph SA, Norton J. Topography of the ACTH-immunoreactive neurons in the basal hypothalamus of the rat brain. Brain Res 1981,216:333-4.
20. Leysen JE, Laduron PM. Receptor binding properties in vitro and in vivo of some long-acting opioids. Arch Int Pharmac Res Ther 1978;252:343-6.
21. Martin W. Multiple opioid receptors. Life Sci 1981;28:1547-54.
22. Myers RD, Oeltgen PR, Spurrer WA. Hibernation ‘trigger’ injected into the brain induces hypothermia and hyperphagia in the monkey. Brain Res Bul 1981;7:691-5.
23. Pasternak GW, Childers SR. Opiate receptors. Nature 1981;31:1511-5.
24. Poznansky MJ, Juliano RL. Biological approaches to the controlled delivery of drugs: a critical review. Pharmacological Reviews 1984;36:277-436.
25. cherzinger AL, Hendee WR. Basic principles of magnetic resonance imaging. An update. W J Med 1985;145:782-92.
26. Synder SH, Goodman RR. Multiple neurotransmitter receptors. J Neurochem 1988;35:513.
27. Stanley TH, Cazalos JA, Limoge A, Louville Y. Transmucosal cranial electrical stimulation increases the potency of N2O in man. Anesthesiology 1982;57:293-7.
28. Versgeagen R, Bossel MT, Bogaert M, Roly G. Maptazind in use in anaesthesiology in the 21st century will undoubtedly offer the possibility of analgesia, sedation, hypnotis and complete anaesthesia without a foreign compound via computer-focused physical activation of receptor sites and/or neurotransmitter modulation with non-invasive external wave or energy forms. SASA

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