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Saturday May 28, 2005

17:00-17:45

Room I

Anaesthesiologists usually prefer drugs with a rapid onset and a short duration of action in their intraoperative work. However, for the management of postoperative and chronic pain drugs with a prolonged action are preferred. Unfortunately, analgesics such as morphine last only a few hours, so repeated doses are required. Many approaches have been used to prolong the action of these drugs by alterations in their formulation. These include sustained-release oral suspensions, transdermal preparations, microparticulate delivery systems using liposomes or microspheres, implanted matrices and drug complexes with cyclodextrins. New formulations continue to be synthesised and tested, and this review lecture will discuss some of the current advances in slow-release technology.

**ORAL-SUSTAINED RELEASE PREPARATIONS**

Oral administration is the preferred delivery route for most drugs. For many drugs, however, standard oral formulations result in short duration therapeutic concentrations. In order to prolong the therapeutic effect, various sustained-release oral formulations have been developed. These are commonly prepared by incorporating the drug into a matrix of a hydrophilic polymer that is water-soluble and swells in an aqueous medium. Although many different polymers have been used, cellulose ethers are the most frequently encountered. Cellulose ether polymers are non-toxic, easy to compress into tablets, and can incorporate a large amount of drug.

Sustained release opioid preparations are widely used in the treatment of chronic pain [1]. MS Contin (called MST continus in some countries), a modified release tablet formulation, was the first to be introduced, in the 1980s. It allowed an 8-12 hour dosage interval, compared to 4-hourly dosing with a standard oral morphine formulation. Today there are a number of modified release formulations of morphine with dosage intervals of either 12 or 24 hours, including tablets (MS Contin, Oramorph SR), capsules (Kapanol, Skenan, MXL), suspension and suppositories. Other opioids available in sustained-release formulations include oxycodone, hydromorphone, codeine and tramadol. A sustained-release paracetamol preparation has also been developed [2].

In the majority of these formulations the opioid is adsorbed onto a hydrophilic cellulose polymer embedded in a hydrophobic matrix such as a wax. The gastric fluid dissolves the tablet surface and the polymer becomes hydrated to form a gel. The rate of drug release depends on the rate of diffusion of the dissolved opioid through the gel layer at the surface of the tablet. This approach is used for MS Contin and Oramorph SR. A liquid formulation with morphine suspended in an ethylcellulose polymer has been developed that provides controlled release of morphine over 24 hours [3]. This may be of great help to patients (especially children and older persons) who have difficulties in swallowing.

An alternative approach is to form a small pellet or granule composed of an inner core surrounded by a defined amount of drug and a polymer. Each granule contains an identical small quantity of drug, and dose is determined by the number of granules packaged in a capsule. In the GI tract water diffuses through the outer polymer coat to dissolve the drug. This approach is used for Kapanol and Skenan morphine capsules.

**DRUG ENCAPSULATION DELIVERY SYSTEMS****LIPOSOMES**

Liposomes are microscopic lipid vesicles formed when phospholipid molecules with a polar head and two hydrophobic hydrocarbon tails are suspended in an aqueous medium. The polar head and the hydrophobic tails spontaneously form into a bilayer, resembling a cell membrane, with the hydrocarbon chains oriented towards one another and the polar heads in contact with the aqueous phase (Figure 1). Liposomes can be manufactured in a variety of configurations, with single (unilamellar vesicles) or multiple bilayers (multilamellar vesicles). Some, known as multivesicular vesicles, are composed of many smaller vesicles within larger ones.

FIGURE 1.

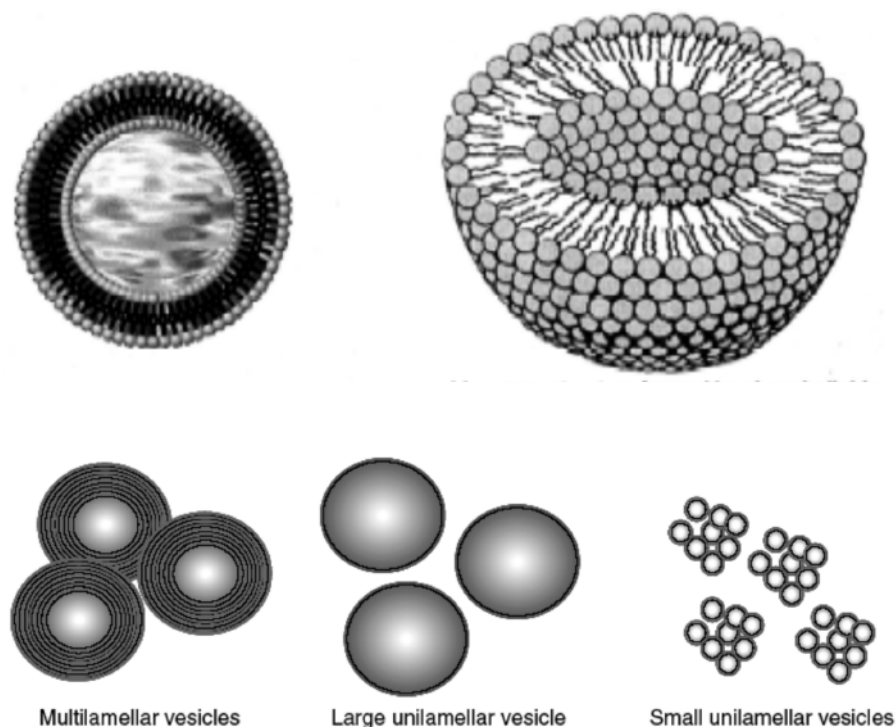


Figure 1. Structure of various types of liposomes.

By enclosing a drug in a liposome, the rate of release and the time it remains within the body can be considerably extended. Liposomes are a versatile drug delivery system, acting as reservoirs for continuous drug delivery, providing slow and sustained release of the encapsulated drug. They are biocompatible and non-immunogenic, and have been used to deliver drugs by using various routes including intravenous, intramuscular, subcutaneous, intrathecal, intratracheal, oral, intranasal and topical. Liposomal formulations of a variety of drugs have already been introduced clinically. Water-soluble drugs can be incorporated into the aqueous phase and lipid-soluble drugs into the lipid phases of liposomes.

Important factors determining drug release characteristics include vesicle size and the drug-to-phospholipid (D/PL) ratio. Higher D/PL ratios are desirable to reduce the lipid load. Liposome size can vary between 20 nm and several  $\mu\text{m}$  in diameter. Those less than 120 nm in diameter readily gain access to the systemic circulation and are rapidly distributed away from the site of injection, whereas those with larger diameters tend to remain at the site of injection. After epidural administration multilamellar liposomes with diameters up to 15  $\mu\text{m}$  form a depot at the injection site for 24 h, whereas small unilamellar liposomes with average size 50 nm enter the systemic circulation within 30 min, and are drained as intact vesicles by the lymphatics [4]. The number of bilayers and the physicochemical properties of the lipids used determine drug release. Incorporation of other constituents such as cholesterol also markedly influences the release characteristics.

Although no liposomal formulations of drugs directly related to anaesthesia are yet available for clinical use, liposomal formulations of other pharmaceuticals, including antifungal and antineoplastic drugs, are already marketed worldwide. Liposome encapsulated local anaesthetics and opioids have been developed and extensively studied in animals and human volunteers. A large diameter (2.4  $\mu\text{m}$ ) liposomal bupivacaine formulation injected intradermally in human volunteers produced analgesia lasting from 19 hours after 0.5% bupivacaine to 48 hours after 2.0% bupivacaine (Figure 2) [5].

FIGURE 2.

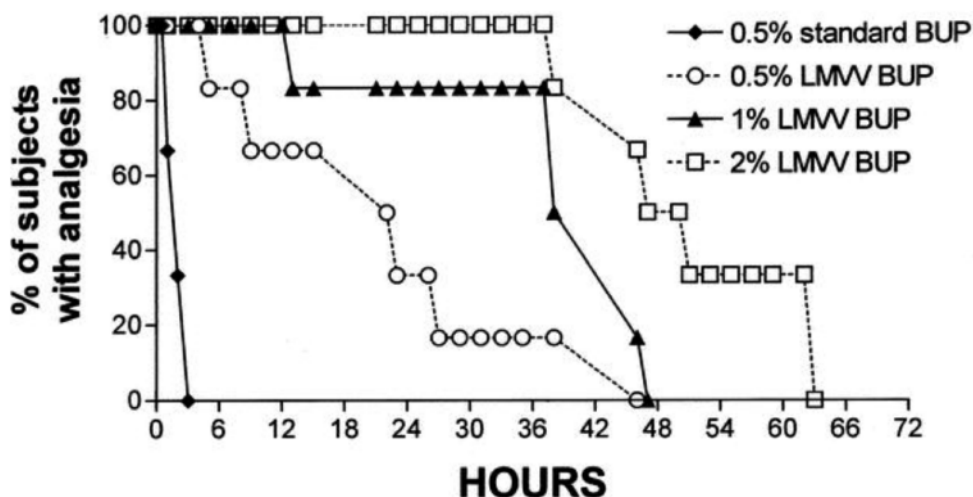


Figure 2. Duration of skin analgesia in human subjects as assessed by pinprick after subcutaneous injection of 0.5% standard bupivacaine (BUP) or 0.5, 1.0, or 2.0% formulations of large multivesicular vesicle (LMVV) liposomal bupivacaine. From Grant et al. [5].

In dogs the duration of lidocaine-induced sensory block was tripled when liposome-encapsulated lidocaine 2% was given epidurally [6]. Epidural liposomal bupivacaine has been investigated for postoperative analgesia [7] and in a patient with cancer pain [8]. In both situations the liposome form increased the duration of analgesia 2-3 fold compared to plain bupivacaine.

Opioids are commonly administered epidurally or intrathecally for management of postoperative and chronic cancer pain. Their limited duration of analgesia, however, often requires continuous administration via an indwelling catheter. Liposome-encapsulated opioids may be an alternative for prolonging their action. Bethune et al [9] investigated the incorporation efficiency and *in vitro* release rates when morphine, alfentanil, fentanyl, and sufentanil were loaded into dipalmitoyl phosphatidylcholine multilamellar liposomes. As one would expect from the very different lipid solubilities, liposome encapsulation efficiency was significantly greater for sufentanil (100%) than for the other opioids (25%–30%). The *in vitro* release rate was slowest for morphine ( $t_{1/2}$  1038 h), intermediate for alfentanil ( $t_{1/2}$  46 h) and fentanyl ( $t_{1/2}$  54 h) and fastest for sufentanil ( $t_{1/2}$  28 h). When injected into either the epidural or intrathecal spaces of pigs, morphine was released more slowly than sufentanil, with all the sufentanil but only half the morphine being released from the liposomes by 6 hours.

In animal models intrathecal administration of liposome-encapsulated alfentanil and morphine increased the duration of antinociception, with lower plasma concentrations and a reduction in systemic side effects [10, 11]. The pharmacokinetics of inhaled liposome-encapsulated fentanyl has been investigated in human volunteers [12]. The data suggest that this offers a simple and non-invasive route of administration of fentanyl, with a rapid increase of plasma concentrations and prolonged analgesia compared to intravenous administration.

#### MICROSPHERES

Polymer-based biodegradable microspheres have been used for the sustained release of a variety of therapeutic agents, including antibiotics, anticancer drugs, local anaesthetics and opioids. The commonest polymers are based on lactic acid (polylactides and their copolymer with diglycolide) because of their good biocompatibility and toxicologically safe by-products that are eliminated by normal metabolic pathways. These polymers have a long history of safe use in humans in the form of surgical sutures. Other materials that have been used include albumin, poly(epsilon-caprolactone) and chitosan, a polysaccharide structurally related to glycosaminoglycans.

By careful choice of polymer composition and microsphere size they provide a means of controlling release rate for the precise delivery of drugs over a prolonged period, up to 14 days. Varying microsphere characteristics such as shell size and thickness allows control of the rate of drug release. Larger spheres generally release the encapsulated drug more slowly. The duration of drug release from such systems usually far outlasts the duration of clinical effect. There is, therefore, a long period where drug release is continuing, but is insufficient to achieve clinically effective concentrations.

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Microspheres can be manufactured with uniform diameters from 3 to 500  $\mu\text{m}$  (by comparison, a human hair has a diameter of about 100  $\mu\text{m}$ ). These can be administered subcutaneously or intramuscularly, but are too large to give intravenously. Recently a technique has been developed that allows preparation of particles in the 200-1000 nm range (nanospheres), suitable for intravenous injection [13].

The pattern of drug release from polymer microspheres is biphasic, a combination of diffusion and biodegradation. Initially drug is released via diffusion through the polymer matrix and through porous voids of the polymer structure. As the polymer matrix absorbs water, the polymer chains become degraded and drug is more slowly released during dissolution of the matrix. There is often an initial burst caused by release of drug embedded in a superficial region of the microsphere.

In the case of bupivacaine, release can be further prolonged by co-encapsulation of dexamethasone. The mechanism by which this occurs is unclear, but is not due to a modification of the pharmacokinetics of the released bupivacaine [14]. Prolongation of the duration of local anaesthesia by bupivacaine-containing microspheres has also been achieved by the incorporation of tetrodotoxin [15]. Tetrodotoxin is a naturally occurring sodium channel blocker with very potent local anaesthetic properties. Although systemic toxicity limits its use as a sole agent, it can provide very long durations of block, with improved safety, when co-injected with bupivacaine. The combination of bupivacaine and tetrodotoxin produced analgesia lasting 35 hours, compared with 6 hours with bupivacaine alone. Adding dexamethasone further prolonged the duration of analgesia to 220 hours. This preparation, however, had a narrow margin of safety and its long-term significance remains to be established.

Fentanyl loaded poly(l-lactide-co-glycolide) microspheres were studied as a possible delivery device for post-operative analgesia and control of chronic cancer pain [16]. Fentanyl was slowly released from the microspheres over 10 days *in vitro*. Microspheres loaded with bupivacaine, nalbuphine and diclofenac have been produced and tested in various animal models. To date, however, there is no human experience with these preparations. Subcutaneous injection of bupivacaine-loaded microspheres (average size  $< 3 \mu\text{m}$ ) in rats resulted in maximum plasma bupivacaine concentrations of  $237 \pm 58 \text{ ng/ml}$  at 105 h, and drug was detected in plasma for 16 days [17]. Bupivacaine-loaded microspheres could be useful in the treatment of severe pain that is not responsive to opioids, e.g. cancer-related pain or intractable herpetic neuralgia.

## DRUG COMPLEXES

One of the most interesting ways of obtaining controlled drug release is the formation of drug complexes with cyclodextrins. Cyclodextrins are cyclic seven-membered glucose pyranose structure that form reversible inclusion complexes with the lipophilic portion of a drug molecule by noncovalent bonding. A bupivacaine-cyclodextrin complex has been investigated in animals [18].

Various opioids have been complexed with cyclodextrins. Hydroxypropyl- $\beta$ -cyclodextrin increased the effectiveness of sufentanil after epidural and intrathecal administration in rats, both in terms of a longer duration of analgesia after a fixed dose of sufentanil, and in a reduction of the  $\text{ED}_{50}$  for analgesia [19]. In rats, intrathecal administration of complexes of morphine, lofentanil, alfentanil and sufentanil with 2-hydroxypropyl-beta-cyclodextrin prolonged the duration of analgesia and reduced side effects [20].

## OSMOTIC PUMPS

Osmotically controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of drugs. These systems are most commonly used orally, and have been used to deliver a wide variety of drugs, including theophylline and salbutamol sulphate for asthma. An osmotically driven implantable pump is currently under development to deliver sufentanil subcutaneously for the treatment of chronic pain [21]. The pump consists of a titanium cylinder (diameter, 4 mm; length, 4.4 cm) plugged at one end with a semipermeable membrane and at the other with an orifice. A piston separates the osmotic engine (which contains a sodium chloride tablet) from the drug reservoir, which contains a concentrated solution of sufentanil (Figure 3).

Figure 3.

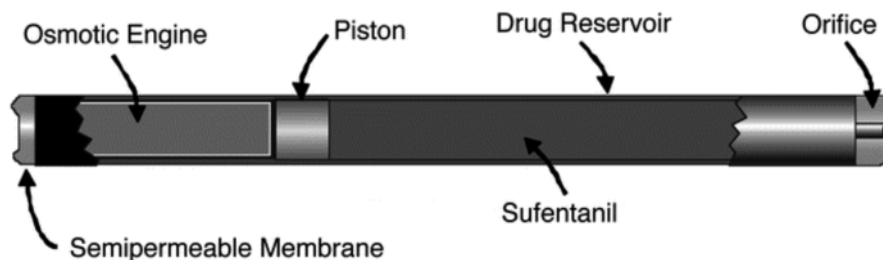


Figure 3. An osmotic pump designed to be implanted subcutaneously and deliver sufentanil at a slow, constant rate. From Fisher et al. [21].

When implanted subcutaneously, the osmotic potential of the salt engine causes tissue water to cross the membrane, increasing the size of the engine, displacing the piston, and forcing sufentanil through the orifice. After the initial start-up period, sufentanil is delivered at a constant rate. Although units in the present study delivered sufentanil for 60 days, future units will deliver the drug for more than 90 days.

## TRANSDERMAL DRUG DELIVERY SYSTEMS

The skin has been utilised for drug delivery for centuries. Whereas drug absorption is often extremely variable with creams and ointments, recently developed transdermal delivery systems can deliver a drug through the skin at a constant controlled rate into the systemic circulation. One of the first such systems was the fentanyl transdermal patch (Duragesic<sup>®</sup>), introduced in 1991. This system allows the constant release of fentanyl for up to 3 days [22]. The patch, with an overall thickness of 0.5 mm, consists of a fentanyl-saturated adhesive behind which is a rate control membrane and the drug reservoir containing fentanyl gelled with hydroxyethyl cellulose. The rate of fentanyl delivery is directly proportional to the area of the patch in contact with the skin, and by choice of the appropriate area patches are produced delivering from 25-100  $\mu\text{g/h}$ . With the first application of a patch a depot of fentanyl forms in the upper skin layers, so that it takes several hours for effective plasma fentanyl concentrations to be reached. Thereafter, plasma concentrations increase steadily for 72 hours while the patch is in situ. Because of the depot formation, plasma concentrations may continue to rise for several hours after patch removal. Steady state concentrations can, however, be maintained by patch renewal.

This system has proven very popular and effective for the treatment of cancer-related pain. However, because of the delayed onset, and more especially the continued increase in plasma fentanyl concentration after patch removal, it is contraindicated for acute and postoperative pain because of the risk of respiratory depression. Indeed, several deaths have been associated with its use in these circumstances [22].

## IONTOPHORESIS

Because transdermal permeation requires adequate lipid solubility, only fentanyl, sufentanil and buprenorphine are suitable for passive transdermal opioid delivery, and lipophobic drugs such as morphine are poor candidates for this technique. One way of overcoming the disadvantages of conventional transdermal systems is iontophoresis, the introduction of ions of soluble salts into the skin or mucosal surfaces by means of an electrical current (Figure 4) [23].

The main advantages of iontophoresis over passive transdermal drug delivery is the ability to rapidly change the dose of drug delivered by adjusting the iontophoresis current and immediate discontinuation of drug delivery with removal of the delivery current (no 'depot' effect). Clinical trials have shown that this delivery system can produce therapeutic plasma concentrations of fentanyl within about 2 hours, compared to 12-24 hours with a passive patch. A related method is electroporation, in which a series of short, high voltage electrical pulses (500-1500V, 1-250 ms duration) are applied to the skin. This increases drug transport by several orders of magnitude, mainly due to electrophoretic movement and diffusion through aqueous pores created by the electrical pulses [24]. Drug delivery systems using both methods are currently being commercially developed for the delivery of fentanyl and sufentanil.

FIGURE 4.

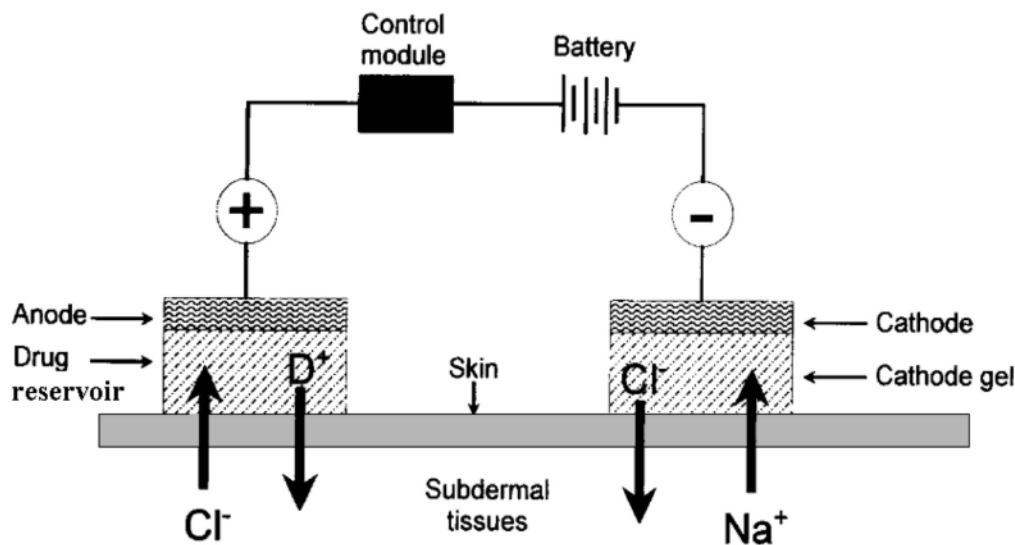


Figure 4. Cartoon illustrating the principle of iontophoretic transdermal drug delivery. Application of an electrical potential causes current to flow through the circuit. The current carries the positively charged drug molecule from the anodal reservoir into the skin and subdermal tissues. To preserve electrical neutrality, chloride ions move from the cathode to the anode.

## CONCLUSIONS

The past decade has seen important technological advances in the preparation of slow-release or sustained-release drug formulations. Several oral sustained-release opioid preparations are available that provide good pain relief with a single daily dose. These are commonly prepared by incorporating the drug into a matrix of a cellulose ether polymer that is water-soluble and swells in an aqueous medium. For parenteral administration local anaesthetics and opioids have been encapsulated into liposomes or microspheres. These allow a slow, controlled release of the drug. Other techniques for extending the duration of drug action include the formation of drug complexes with cyclodextrins, use of osmotic pumps and transdermal technology. Although few of these techniques have as yet been approved for clinical use they are likely to be made available for clinical practice in the near future.

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