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EXPERT REVIEWS

Microelectronic control of drug delivery

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Evaluation of: Farra R, Sheppard NF Jr, McCabe L *et al.* First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci. Transl. Med.* 4(122), 122ra21 (2012).

Microelectronic control of drug delivery devices enables precise management of drug delivery profiles. Iontophoresis patches offer microelectronic control over delivery in a noninvasive manner, but these are limited to the administration of relatively small molecules at small doses. Infusion pumps are widely used for delivery of insulin and other drugs; however, they require an invasive catheter that many patients find inconvenient and can be a site of infection. Implanted pumps avoid these problems, but they require long-term commitment associated with surgical implantation. An alternative is an implanted microchip containing many protected reservoirs filled with drug powder that is selectively released under microelectronic control. This device offers the promise of long-term drug stability in the solid state and precise digital drug dosing. Building on more than 10 years of preclinical studies, this wirelessly controlled microchip technology recently underwent a first-in-human clinical study. The microchip was implanted subcutaneously in the abdomen of eight female patients with osteoporosis. A remote operator was able to establish a wireless link with the microchip to program the schedule of human parathyroid hormone dosing from the device. This study showed that the wireless microchips produced pharmacokinetics similar to those from subcutaneous injections of the drug and produced less variable drug levels in the blood. There were also no toxic or adverse events due to the microchip or drug. This study represents an important step towards more widespread use of microelectronic control of drug delivery to improve pharmaceutical therapies.

Keywords: drug delivery • human clinical study • human parathyroid hormone • microchip • microelectronic control • osteoporosis

Microelectronic-controlled drug delivery devices are particularly desirable when compliance to complicated drug regimens is critical [1,2]. Various microelectronic-controlled drug delivery devices have been developed to improve the performance of conventional dosing approaches in terms of safety, efficacy, pain and convenience, including iontophoresis patches, extracorporeal pumps, implanted pumps and, most recently, implanted microchips. These devices are able to control drug release on demand for extended periods. The idea of a programmable implantable microchip-based drug delivery device was first demonstrated preclinically in 1999 [3] and was recently evaluated in the first human clinical study for delivery of human parathyroid hormone fragment 1–34 (hPTH[1–34]) [4]. This study showed that microchip-based delivery achieved pharmacokinetics similar to multiple injections and produced no significant adverse effects.

Methods & results

An early clinical study of the microchip-based device by Farra *et al.* was conducted to assess the pharmacokinetics, safety, tolerability and bioequivalence of the microchip for delivering hPTH(1–34) [4]. Eight postmenopausal women between 65 and 70 years of age with osteoporosis participated in the study. The titanium microchips used in the study stored 20 individual 40-µg doses of freeze-dried hPTH(1–34), individually sealed in tiny reservoirs measuring 600 nl in size, and contained a wireless transmitter that communicated with a small portable computer. Upon activation, an individual reservoir could be opened by electrochemical dissolution of the reservoir cover, thereby exposing the hPTH(1–34) to bodily fluid for drug dissolution and release.

The microchip device was implanted subcutaneously via a 1-inch incision in an outpatient procedure requiring local anesthesia only.

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The release of hPTH(1–34) was initiated 8 weeks after device implantation to ensure formation of a stable fibrous capsule around the microchip, because one of the central questions of the study concerned possible interference of a capsule on drug release. After device-mediated dosing was complete on day 84, two subcutaneous injections of hPTH(1–34) (Forsteo®, Eli Lilly) at a dose of 20 µg each were administered on days 91 and 96 to compare pharmacokinetics of the microchip with subcutaneous injection. After the microchip was explanted on day 103, two additional pharmacokinetic analyses were carried out on days 131 and 138, during each of which 40 µg of Forsteo was administrated in the form of two sequential injections (2 × 20 µg). In this work, one device failed to release the drug in one patient. All results from this patient were excluded from analysis.

To assess comparative pharmacokinetics, the ratios of average C_{max}, T_{max} and area under the drug–concentration curve (AUC) for hPTH(1–34) release from the microchips to the 2 × 20 µg injections administered in this study were 101, 196 and 157%, respectively. The pharmacokinetics were also compared with those of a 40-µg Forsteo injection from published literature [101]. The ratios of average C_{max}, T_{max} and AUC were 88, 77 and 98%, respectively, which the authors concluded was bioequivalent. However, the coefficients of variance of C_{max}, T_{max} and AUC were much lower for the microchip release than for the subcutaneous injections. In the context of these studies, the authors further concluded that the collagen layer that grew to surround the implants did not block the drugs from reaching the bloodstream.

In addition, daily release of hPTH(1–34) from the microchip device yielded increases in bone formation, according to an evaluation of bone markers. Serum type I collagen propeptide and type I collagenolysis fragment (CTX) levels, resulting from microchip therapy, were measured to be qualitatively and quantitatively similar to those reported in previous studies during daily subcutaneous injections of Forsteo [5]. As for the safety of the microchip, no change in average concentrations of uric acid, creatinine and blood urea nitrogen were observed during the dosing period. The microchip device was also reported not to affect quality of life, according to patient reports.

Expert commentary

Compliance is an important issue in many drug regimens, and it can be difficult to get patients to accept a drug regimen, especially when they have to give themselves frequent painful injections of a drug. To address the unmet medical needs related to dosing, various microelectronic-controlled drug delivery devices have been developed, such as iontophoresis patches, extracorporeal pumps, implanted pumps and, most recently, implanted microchips. The early clinical trial by Farra *et al.* demonstrates the improvement in outcome with a wireless microchip as a potential candidate to replace frequent injections [4]. A comparison of these four types of microelectronic-controlled drug delivery devices is summarized in Table 1.

Iontophoresis patches use an electrical current to drive molecules into the body via the skin. This approach offers the power of real-time control over drug delivery using microelectronics in a noninvasive, nonsurgical approach. Depending on the formulation, iontophoresis patches can stabilize drugs in the solid state during storage, but most systems are liquid based. While the total dose and number of doses in an iontophoresis patch is limited usually to at most a few days' supply, the ease of applying a new patch whenever needed generally overcomes this limitation. The primary limitation, however, of iontophoresis patches is that they can only deliver smaller-molecular-weight hydrophilic drugs (generally under 7 kDa) owing to the barrier properties of the skin [6]. Iontophoresis patches have been used clinically to administer tap water to treat hyperhidrosis [7], pilocarpine to induce sweating as part of a cystic fibrosis diagnostic test [8] and fentanyl to treat acute pain after surgery [9].

Extracorporeal pumps are also used to provide real-time controlled drug delivery. To overcome the skin barrier, these pumps employ indwelling catheters, which are invasive and carry a risk of infection. They can also be bulky in size. Using liquid formulations, these pumps have great flexibility to deliver small drugs and macromolecules alike over a range of doses. As an extracorporeal device, the drug reservoir can easily be refilled as needed. These pumps are used clinically, for example, to administer insulin to diabetic patients [10] and for patient-controlled analgesia, which uses a microprocessor-controlled infusion pump to deliver a preprogrammed dose of drug when the patient pushes a demand button [11].

Microscale pumps can also be incorporated into implantable devices that deliver drugs using schedules that can be preprogrammed or adjusted through the use of a wireless controller. Device implantation requires surgery and, when the drug reservoir runs out, an invasive procedure is needed to refill the device with drug. Implanted pumps can deliver a variety of different drugs and doses using a liquid formulation. Implanted pumps are currently used for intrathecal delivery of baclofen to treat severe spasticity [12] and morphine to treat intractable pain [13].

Table 1. A comparison of microelectronic-controlled drug delivery devices.

Device	Real-time control over delivery	Noninvasive	No surgery	Little risk of infection	Stability of solid-state formulation	Delivery of macromolecules	Drug dose
Iontophoresis patch	+	+	+	+	+/–	–	+/–
Extracorporeal pump	+	–	+	–	–	+	+
Implanted pump	+	–	–	+	–	+	+/–
Implanted microchip	+	–	+/–	+	+	+	–

Finally, implanted microchips are being developed to provide real-time wireless control over drug delivery from a device that requires minor surgery to implant and explant. There is an opportunity to increase drug stability in these devices, because they store drug in the solid state. While macromolecules can be delivered using this approach, the small size of the microchips limits the size and number of doses per device.

When assessing the potential of the microchip system, the most important finding from the first-in-human study reported by Farra *et al.* is that the microchip delivery of hPTH(1–34) had a good safety profile, with similar pharmacokinetics but lower coefficients of variation, and therapeutic bone formation benefits compared with subcutaneous injection of the drug [4]. The reservoirs were filled with lyophilized drug, which is better for the stability of drugs compared with implanted pumps. The microchip device can be both implanted and explanted in a physician's office using a local anesthetic. On the basis of surveys, the implant size was well tolerated, and the patients indicated that they would repeat the implant procedure. Another important advantage of the microchip is that a bidirectional wireless communication link was established with the implant to precisely program the dosing schedule and receive the implant status. However, more doses per device are necessary to provide daily dosing for extended therapy.

Five-year view

Microelectronic control of drug delivery is already established in medicine with a number of widely used technologies. As the non-medical microelectronics industry advances, so will the capabilities of medical applications of microelectronics, including drug delivery. We believe that there are expanding opportunities to use increasingly smaller and more powerful microelectronic systems to control drug delivery through extracorporeal and implanted devices.

Of special interest, implanted microchips for drug delivery have been shown to have good safety, pharmacokinetic and patient acceptability profiles in initial studies. In the near future, efforts have to be made to increase the doses per device so that they can provide daily dosing for more extended therapy that justifies its implantation and explantation. Further studies should also include more patients to assess the safety and therapeutic efficiency of the wireless microchips. The microchip could also be combined with a sensor that can adapt drug treatments in response to the patient's condition. In the future, these wireless-controlled microchips may be especially beneficial for patients suffering from chronic diseases requiring frequent painful injections.

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Key issues

- Drug therapy compliance is an important problem in chronic disease management, especially when the patients have to give themselves frequent painful injections of a drug.
- The first-in-human study shows good safety, pharmacokinetic and patient acceptability profiles with a wireless-controlled drug delivery microchip.
- Study of more patients is necessary to assess the safety and therapeutic efficacy of the wireless microchips (as only eight patients were enrolled in this initial study).
- The reliability and durability of the microchip needs to be further developed, as it failed in one out of eight patients.
- Driven by advances in the non-medical microelectronics industry, there is an excellent future for microelectronic control of drug delivery with increasingly small and powerful devices.

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