Prefilled syringes point to the future

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Injections – what's the point?

The hypodermic syringe for subcutaneous drug administration was introduced in the 1850s. Perhaps it is no coincidence that the artist Georges Seurat, no doubt scarred by a clumsy physician, was driven to invent the *pointilliste* method of painting within a few years. Even today there are some among us who curse the concept of introducing drugs into our tender flesh by means of a sharp needle connected to a reservoir of liquid pharmaceutical preparation. But of course there are good reasons for administering drugs by this route.

For example, the direct administration of drug into the systemic circulation can produce a very rapid effect, which is desirable under particular circumstances (such as acute pain). In addition, there is no requirement for active compliance on the part of the patient, ie the injection route works for unconscious patients. Injections also are suitable for nauseous patients who might not be able to tolerate the oral route of drug administration.

Furthermore, the injection route provides a means of accurate dosage. The healthcare worker can precisely measure the volume to be delivered, and deliver precisely that volume. Not all drug delivery routes offer this certainty, and many are also plagued by variability in drug absorption, particularly the oral route (eg due to interactions with food, effects of gut motility and rate of gastric emptying, and so forth). Injections, by contrast, offer predictable pharmacokinetics, and may allow smaller doses of drug to be delivered - advantageous in cases where the drug has relatively low absorption characteristics. ('Absorption' refers to the process which results in the drug moving from the site of administration to the circulatory system. The amount of drug that is absorbed varies according to factors such as type of drug and site of administration, giving a measure known as 'bioavailability' – the proportion of drug that is available to the circulation. The various barriers that a drug must penetrate in the absorption process, such as lipid membranes of intervening cells, will hinder its absorption and decrease its bioavailability. Intravenous administration by injection bypasses the absorption step, and gives essentially 100% bioavailability.)

There are other advantages to bypassing the digestive system in drug delivery. Non-oral delivery allows us to avoid gastro-intestinal enzymes which can interfere with the drug, and other sources of instability such as low pH. For example, the drug phenytoin is well-known to be poorly soluble at low pH; hence the unpredictable pharmacokinetics of oral phenytoin (due to the effect of the acid pH of the stomach on the phenytoin solution). Furthermore, non-oral routes such as injection allow us to avoid the first-pass effect associated with by-mouth administration. (The 'first-pass effect' refers to the conversion in the body of the drug to a form or forms different from that in which it was administered. Thus, drugs that are taken orally are absorbed from the gastrointestinal tract, whence they pass into the circulation and are taken to the liver by the hepatic portal vein. In the liver, various enzymes work on the drugs, converting them to products known as drug metabolites. This occurs before the drug has had the opportunity

to have any kind of therapeutic effect via the systemic circulation. Some drugs are completely inactivated by this route and therefore are unsuitable for oral administration. Clearly the injection route is an important way of administering some drugs that otherwise would be ineffective).

So, although there are numerous other routes of administration besides injection, these are not suitable for all drugs under all circumstances, and in some cases are inferior to the injection route. It seems then that the needle will be with us for some time to come.

Points for improvement

Nevertheless the parenteral (injection) route of administration does have particular problems. As we all know, it can sting a bit, particularly when applied enthusiastically and intramuscularly. Also, injectable drugs usually must be stored under specific conditions of temperature, often around 4^{o}C. This results in costs associated with the logistics of the 'cold chain', ie keeping drugs at an appropriate temperature through the entire distribution system from the factory to the point at which they are given to a patient. In addition, there are real safety concerns regarding the transmission of blood-borne disease such as HIV via accidental injury from needles that have been used on infected patients. This problem has become significant enough for there to be specific legislation passed in the US (the "Needlestick Safety and Prevention Act") requiring the use of safety injection devices wherever possible. There now is a wide variety of approaches aimed at the reduction of this particular risk, but a discussion of safety needles and needleless injectors is beyond the scope of this article. Problems that are more relevant to the topic of prefilled syringes include the following.

Firstly, drugs for injection usually require a specialist healthcare worker to administer them. The necessity for a healthcare worker is dictated not so much by the actual process of injection, but by the need for careful preparation of the injection, for example accurate reconstitution of freeze-dried medicines using aseptic procedures. Clearly there will be a cost to a healthcare provider of allocating personnel for this function, particularly when the drug is being given at the patient's home on a daily basis and over a long period of time.

In addition, there may be wastage of product due to human error in the process of reconstitution, and this will further add to the cost associated with an injectable drug. Also, reconstitution inevitably is associated with a time delay that may be disadvantageous in emergency settings, where the emphasis is on speed of treatment.

Furthermore, the reconstitution step generates an additional cost in that manufacturers routinely overfill injectable product packages by as much as 25% in order to ensure that there is a sufficient volume to allow accurate reconstitution and withdrawal. This clearly will affect the cost of the product and decrease the supply of drugs, which in some cases may be scarce and difficult to produce.

The production of drugs formulated and packaged as ready-to-inject, prefilled syringes will address the above problems by:

- Dispensing with the need for a specialist to reconstitute the drug
- Eliminating the time delay due to the reconstitution step, allowing more rapid treatment of emergency patients
- Eliminating the possibility of reconstitution errors

- Decreasing or eliminating the need to overfill, thereby avoiding an additional cost and decreasing wastage of possibly scarce drug.

One of the knock-on effects of such formulation will be that patients will be able to more easily self-administer the drug at home, clearly advantageous for chronic ailments requiring frequent drug administration.

Prefilled syringes – the turning point

The prefilled syringe is not a new phenomenon, but to some extent it has crept up on us in terms of the importance that it currently appears to enjoy as a delivery concept. The market for prefilled syringes has seen healthy growth in recent years, and some expect it to continue growing at a similar rate for the foreseeable future. Part of the reason for this expectation may be the clear cost advantages of prefills - price may be an important product-differentiating factor in an environment that currently is emphasising cost-containment in healthcare systems. Another part of the reason may be the apparent improvements in terms of speed and ease of use for both healthcare professionals and self-administering patients. It may also be that the expectation of strong market growth for prefills is related to the perception that 'biotech drugs' – by which people usually mean novel proteins for injection – will become increasingly important in healthcare.

This perception may be both a result of the development efforts of biotechs (some reports estimate that there are about 900 biotech products currently in development) and a consequence of the massive increase in knowledge about the diversity and identity of human proteins – both disease-associated and therapeutic – that is likely to stem from the completion of the Human Genome Project. The market for 'speciality injectables,' such as novel protein drugs, has other features to recommend it, not least the prices that it will bear. Speciality injectables commonly cost over $1000/month; egregious examples include Amgen's Enbrel, which is reported to cost over $17,000 per year; and two drugs approved by the FDA in March of this year, Genentech's Avastin and ImClone's Erbitux, which are suggested to cost about $48,000 and $120,000 per annum respectively. A proportion of such speciality injectables will be candidates to formulate as prefills.

The turning point for prefills in this market, if it comes, may be advances in formulation technology to allow protein drugs routinely to be stable as prefilled packages. The point of no return, in terms of a step-change in demand for prefill capabilities and associated technologies, may well be increasing competition (more products addressing the same disease), which might provide an impetus for companies to find a means of adding value or cutting costs to differentiate their (substituted) product from the competition. Prefilled syringes could both add value in terms of speed and convenience, and also cut costs in terms of avoiding prefills and reducing dependence on specialist personnel for administration. Perhaps, therefore, some of the companies and technologies pertinent to the prefilled syringe market would merit close attention in the coming years.

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