Physicians' Corner

The Pen Is Mightier Than the Sword

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Over a century ago, Edward Bulwer-Lytton declared in his play, *Richelieu*, that the pen is mightier than the sword.[1] This truth has been universally accepted for hundreds of years. It's a shame that insulin wasn't known back then so he could shed similar light on insulin pens versus syringe delivery, since swords have little clinical utility in diabetes therapy. Because we now have a choice between pen and syringe when delivering every basal and rapid-acting insulin analogue, every premixed insulin product, and the amylin analogue pramlintide, the question of pen versus syringe seems quite pertinent.

Bulwer-Lytton made his declaration about the pen without the benefit of randomized, prospective studies. He just recorded his analysis of retrospective events. I realized recently that my perspective of insulin pens versus syringes also is largely based on experience. I recently prescribed pramlintide for a patient with type 1 diabetes mellitus (DM) and discovered that her insurance carrier would not cover the pen delivery system. She was facing a $100/month copay for the pen, the same as she was paying for each of her pens for basal and rapid-acting insulin analogues. I was amazed when she insisted on increasing her total copay to $300/month instead of using a syringe. This event sent me searching for data to provide evidence-based insight into the utility of pen devices, particularly whether the added cost is associated with additional benefits.

My prejudiced notion was that pen use is more expensive, but would lead to lower glycosylated hemoglobin (A1C) levels, fewer complications, and greater overall cost savings—all because pens are easier to use. I was quite confident that my conclusion was an obvious statement of fact. When I did a PubMed search of published articles on insulin pens, I was quite surprised! I even went to the purveyors of the various pen devices and asked them for help in confirming my opinions. Once again, my notions were challenged. Bulwer-Lytton probably saved himself a lot of work by just declaring his opinion based on personal prejudice and not on evidence-based inquiry.

A ROSE BY ANY OTHER NAME?

Pen-style insulin injectors have been around for >2 decades, and they were enthusiastically greeted from the outset. Various pen styles and features are offered by the manufacturers of insulin, the glucagon-like peptide-1 agonist, and pramlintide. The American Diabetes Association (ADA) Web site offers excellent information about the properties of the various pen devices.[2] Some manufacturers offer systems that use prefilled cartridges loaded into a permanent pen device, whereas others offer fully disposable pens that are prefilled and simply discarded after the final use. As the ADA Web site indicates, some devices are especially suitable for children. Patients in my practice, 90% of whom have type 2 DM, seem to prefer the disposable pen devices because they are usually smaller and lighter, and they eliminate the recurring need to load new insulin cartridges. The features of the disposable pens that are preloaded with basal or rapid-acting insulin analogues or premixed human derivatives are listed in the **table**.[3–8] Unlike Shakespeare's rose, pens do have different qualities.

Because pens containing diabetes therapies do not require refrigeration after opening, the issue of nonrefrigerated in-use storage is seemingly important. The **table** shows a nonrefrigerated in-use shelf life of 10 days to 6 weeks. However, this seeming chasm is somewhat overshadowed by the number of units of insulin used by the typical patient with type 2 DM. In the Treat-to-Target Trial,[9] a major study of basal insulin (detemir) added to oral agents, patients used an average of 47 units of glargine daily. That trial reported slightly higher daily doses for basal coverage. Because pens containing basal insulin analogues hold ~300 units each, the contents of a pen will typically be used in 7 to 10 days, making longer shelf life a moot point in most cases.[10] Even pens containing rapid-acting insulin analogues are likely to be used up before their nonrefrigerated in-use shelf life expires. Most experts estimate the amount of rapid-acting insulin that is distributed over 3 meals daily will be roughly the same as (or slightly less than) the daily basal dose,[11] so the same use/shelf-life dynamics should hold for basal and rapid-acting insulin analogues in pens used by patients with type 2 DM. Of course, any pen should be discarded when the nonrefrigerated in-use or not-in-use (unopened) shelf life has expired.

Another interesting fact is that the pens listed in the **table** differ considerably in the force that needs to be applied to the plunger to inject the insulin. Although this should not be a major issue for most patients, it may be a factor for the infirm and those with arthritis or other conditions that affect the strength or dexterity of the hands. Similar concerns

Table. Characteristics of preloaded pens.[3–8]

Feature	LANTUS® and Apidra® SoloSTAR® Pen	Novo FlexPen®	Lilly Pen
Maximum capacity, IU[3]	80	60	60
Injection force, N[3]	11.3	16.4	24.4
Dial extension at 60 U, mm[3]	25.5	33	11.2
Needles[4,5]*	Push on or screw on	Screw on only	Screw on only
Storage (nonrefrigerated, while in use [opened])[4,5–8]*	28 Days	42 Days – Levemir® 28 Days – NovoLog® 14 Days – NovoLog® Mix 70/30	14 Days – Humulin N 10 Days – HumaLog® Mix 75/25 and Humulin 70/30

*Data on file (sanofi-aventis U.S. LLC, Bridgewater, New Jersey). Personal communication (Deborah Epps, May 2009).

could be entertained about the distance the plunger must travel, because a longer distance might result in greater difficulty with injection for some patients. It is important to note that differences in injection force and plunger travel distance have not been studied comparatively; hence, the clinical impact of these differences is unknown.

SATISFACTION PREVAILS

As mentioned, patients liked pens from the beginning. In an early study on pen delivery of insulin,[12] patient satisfaction ratings were 78% for effect on lifestyle and 81% for increased flexibility. Interestingly, no significant difference in A1C levels was observed between the pen users and the syringe users.[12] Over the next 2 decades, studies continued to report high patient satisfaction with insulin pens. Recent studies reported almost uniform satisfaction with pens over syringes.[13]

MONEY MATTERS

Although it is clear that patients like pens, the question remains whether use of pens results in better outcomes. In fact, studies have reported that pen use resulted in overall cost savings in a variety of settings.[14–16] A study conducted in a long-term care setting concluded that pen delivery of insulin was an attractive, cost-effective alternative to syringe delivery in nursing facilities.[14] The authors cited benefits related to dosing accuracy, improved administration process, and freed-up nursing time (vs the syringe method). Clearly, this is encouraging news as we encounter unprecedented numbers of aging patients and concerns about rising health care costs.

But what about settings other than long-term care? A fascinating study of the North Carolina Medicaid program[15] reported that, over a 5-year period, the study group assigned to pen use had significantly lower total annualized health care costs than did those assigned to a syringe. Although the per-patient cost was higher for the pen users than for the syringe users ($840.33 vs $535.70; $P < 0.05$), the annualized health care cost was lower for the pen users than for the syringe users ($14,857.42 vs $31,764.78; $P < 0.05$).[15] Savings were seen in the areas of hospital costs, diabetes-related costs, and outpatient costs.[15] A review of third-party managed care data by Lee et al[16] also reported cost savings. Clearly, overall cost savings from a variety of benefits related to pen use can be achieved.

A1C IMPROVEMENT?

Now the final question—one I was sure I knew the answer to: does pen use improve glycemic control? I was sure that benefits such as better compliance, easier use, and more confident dose delivery would lead to lower A1C levels. To my surprise (I was mostly wrong on this score!), although better A1C levels have been observed in some studies, the overall picture is essentially neutral. A study by Hörnquist et al[17] found that metabolic control improved only for a few patients in the study—those who had previously been receiving 1 or 2 injections daily. Although this is seemingly encouraging, Wikby et al[18] found that patients in their study who transitioned from syringe to pen showed significant metabolic deterioration over time, despite enhanced quality of life. One group who clearly experienced metabolic benefit from pen use is the homeless. A study conducted in this difficult-to-treat population in Dallas, Texas[19] reported that improvement in A1C levels was seen at 3- and 6-month follow-up visits.