Journal of Diabetes Science and Technology
2021, Vol. 15(3) 705–709

DOI: 10.1177/1932296821999080
journals.sagepub.com/home/dst
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Advances in Insulin Pump Infusion Sets Symposium Report

Jennifer Y. Zhang, BA[1], Trisha Shang, BA[1], Sarnath Chattaraj, PhD, MS[2], Ohad Cohen, MD[3], Matthias Heschel, PhD[4], Robert A. Vigersky, MD[2], Lutz Heinemann, PhD[5], Kirsten Nørgaard, MD, DMSc[6], Jannet Svensson, MD, PhD[7], Bruce Buckingham, MD[8], and David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE[9]

Abstract

Continuous subcutaneous insulin infusion (CSII) is becoming increasingly used for achieving target glycemic control as well as providing flexibility in lifestyle. In a widely used version of CSII, the insulin pump itself is attached to one end of an insulin infusion set (IIS), which delivers insulin via a thin flexible plastic tube to the patient's body via a cannula or needle that is inserted under the skin at the other end of the IIS. Despite the increased use of CSII by patients with diabetes, there have been few recent advances in IIS technology, especially when compared to the many recent advances made in insulin pump technology and in insulin pharmacokinetics. To discuss recent developments in, and future plans for IIS development, Diabetes Technology Society virtually hosted the Advances in Insulin Pump Infusion Sets Symposium on December 1, 2020. This symposium featured experts in the field of IISs, including representatives from Medtronic and ConvaTec (which are two manufacturers that are currently developing IISs), Stanford University, Steno Diabetes Center Copenhagen, and Science Consulting in Diabetes. The webinar's six speakers covered (1) patient burden, (2) extended wear technology, and (3) future directions in IIS development.

Keywords

adhesive, diabetes, infusion set, insulin, occlusion, pump

Introduction

An insulin pump allows flexible manual adjustment of insulin dosing as well as automated algorithm-controlled insulin delivery as part of a closed loop system. An insulin infusion set (IIS) delivers insulin from the insulin pump to the subcutaneous tissue of a patient with diabetes. An IIS consists of thin plastic tubing connected to a cannula or needle which is inserted in the patient's skin and typically held in place at the infusion site by an adhesive.[1] The other end of the IIS is connected to the pump via a universal or proprietary connecto r. IISs must be changed every few days in most patients to avoid skin problems, such as infections and lipohypertrophy.[2] It is preferable that a person with diabetes chooses a new infusion site every time they reposition their IIS.[1] The purpose of continuous subcutaneous insulin infusion (CSII), compared to multiple daily injections, is to reduce the patient burden associated with frequent subcutaneous insulin injections as well as deliver continuous infusion of insulin to mimic physiologic insulin production. However, studies have shown the current generation of IISs is not popular among people with diabetes who are interested in CSII.[3] Users express multiple reasons for dissatisfaction, ranging from various issues that arise at the insertion site to malfunctions in the IIS.[4] The current generation of IISs are prone to such malfunctions as occlusion which stops the flow of insulin, air bubbles in the tubing which interferes with the flow of

[1]Diabetes Technology Society, Burlingame, CA, USA
[2]Medtronic Diabetes, Northridge, CA, USA
[3]Medtronic Diabetes EMEA, Tolochenaz, Switzerland
[4]ConvaTec Infusion Care, Taastrup, Denmark
[5]Science Consulting in Diabetes GmbH, Neuss, Germany
[6]Steno Diabetes Center, Copenhagen, Gentofte, Denmark
[7]Department of Pediatrics and Adolescent Medicine, Herlev and Gentofte Hospital, Herlev, Denmark
[8]Stanford University, Stanford, CA, USA
[9]Mills-Peninsula Medical Center, San Mateo, CA, USA

Corresponding Author:
David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE, Mills-Peninsula Medical Center, 100 South San Mateo Drive, Room 5147, San Mateo, CA 94401, USA.
Email: dklonoff@diabetestechnology.org

insulin, kinking of the catheter which can interfere with or halt the flow of insulin, and the need for priming, which can interfere with correct dosing of insulin, all of which degrade their appeal and cause some patients to turn to insulin patch pumps, which do not use IISs, but have their own advantages and disadvantages.[5] All pump types (both patch and conventional) have been associated with cases of allergic dermatitis caused by the adhesive maintaining their insertion site in place.[4] Acrylates are a commonly used ingredient in adhesives for securing many diabetes devices, including IISs. In 2020, one specific widely used acrylate, isobornyl acrylate,[6] was named Allergen of the Year by the American Contact Dermatitis Society.[7] 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate, which is used as an ingredient in adhesive for some pumps, has also been implicated as a potential cause of contact allergy.[8]

There is a need for new ideas, new technologies, and new products for IISs. This three-part report characterizes (1) the patient burden associated with using current IISs, (2) new developments in extended wear technology, and (3) future directions for IIS developments that would be well received.

Section 1: Patient Burden

Lutz Heinemann, PhD

Science Consulting in Diabetes GmbH, Neuss, Germany

Key Points:

- IISs are critically important for successful insulin pump therapy. More attention should be paid to them in order to support patients with diabetes to achieve their therapeutic goals in a safe and efficient way.
- Insulin pump therapy has made great progress in recent decades, mainly driven by many different improvements in pump technology. The progress made with respect to IISs is less prominent.
- Scientific focus on IIS is mainly driven by the manufacturer of insulin pumps/IISs. Basic research is needed with respect to factors that influence insulin absorption in the subcutaneous tissue.

Jannet Svensson, MD, PhD

Chief Physician in Paediatrics, Department of Pediatrics and Adolescent Medicine, Herlev and Gentofte Hospital, Herlev, Denmark

Key Points:

- Skin reactions with respect to IISs are much more common than should be expected and receive little clinical attention, which is why they tend to be chronic. Checking for skin reactions at insertion sites of IISs should be part of routine care.
- Itching or skin reactions add to the mental burden of wearing an insulin pump; developing better IISs may help ease the burden.
- The constituents and design of IISs are important factors affecting the risk of developing skin irritation and eczema. Mandatory legislation requiring disclosure of adhesive constituents may help identify toxic or allergic material in the housing of the IIS or the adhesive used to fix the IIS on the skin.

Summary

The number of insulin pump users is over 500 000.[9] While the insulin pumping technology has been progressively improving, there has not been similar advances in IIS technology, despite the important role of IISs in ensuring optimal insulin delivery. Patients often complain of skin irritation or allergic reactions when employing CSII therapy, typically from the adhesive component of their IIS. Patients can also experience insertion anxiety resulting from the pain associated with piercing the skin and they might link pain to the sound from their IIS inserter. Other acute IIS problems can include complete pullout, insulin leakage hematoma, occluded tubing, a kinked cannula, a loose hub, or a punctured line. Currently, IISs are recommended to be replaced every two to three days and are not suitable for extended wear in the majority of patients. If current IISs remain in the subcutaneous tissue for more than three days, then inflammation, irritation, or a local infection can occur at the insertion site. The result is that insulin absorption is hampered, the IIS has to be pulled out, and a new IIS has to be inserted at another infusion site. Local skin problems may occur because of the insulin itself, rather than the IIS, ie, lipohypertrophy in the skins take place. The absorption of insulin in the subcutaneous tissue related to various types of IISs used for CSII has not been extensively-researched. The kinetics of insulin absorption from skin with lipohypetrophic changes have also not been extensively studied. All of these factors based on inadequate research and unsolved problems with current IISs contribute to the patient burden associated with the use of CSII. Further research is needed to develop safer adhesive materials, better product designs, and longer lasting IISs to decrease the current patient burden.

Section 2: Extended Wear Technology

Ohad Cohen, MD

Director of Medical Affairs, Medtronic Diabetes EMEA, Tolochenaz, Switzerland

Key Points:

- There is an unmet need for longer IIS wear duration in pump users.
- Medtronic solutions for reducing inflammation and improving adhesive with IISs were assessed in a clinical trial.
- The results of the trial demonstrate that these solutions resulted in an Extended Wear Infusion Set (EWIS) that has had 80% survival for seven days.

Sarnath Chattaraj, PhD, MS

Senior Research Director, Medtronic, Northridge, California, USA

Key Points:

- Decreased insulin-induced chronic inflammation is an important target for lengthening the duration of IIS wear.
- Loss of preservative and insulin aggregation are major contributors in causing insulin-induced chronic inflammation.
- Medtronic research has developed novel approaches for IISs that mitigate the loss of preservative and insulin aggregation as well as improve adhesive performance.

Summary

IISs are currently indicated for two to three days of wear.[10] The goal of developing an extended wear IIS is about twice that duration. Extending the IIS wear duration satisfies patients' interests in longer wear-times, which can allow previous infusion sites more time to rest and heal. In vitro Humalog/Novolog stability testing have demonstrated that less than 50% of the preservative content from the insulin reservoir is actually pumped with traditional IISs and even after twelve days, over 50% of the initial preservative added to the insulin by the pharmaceutical manufacturer was still in the reservoir.[10] Preservatives are important to prevent aggregation of insulin and prevent local inflammation. Aggregates can be characterized in two ways: chemical and physical. (a) Chemical aggregates have a United States Pharmacopeial specification of no more than 1.5% for both Insulin Aspart (Novolog) and Insulin Lispro (Humalog) injection. (b) There are no standard specifications for physical aggregates of insulin. Increased aggregates lead to more pro-inflammatory cytokines formation and reduced wear duration. Dynamic light scattering showed that the pumped insulin with low preservative content contains an increased number of insulin aggregates and that such aggregates cause increased pro-inflammatory cytokine production in murine macrophage cultures.[10] IIS survival at three days in a diabetic porcine model was reduced from 77% using insulin containing a normal preservative concentration to 15% with a low preservative concentration. These data suggest that loss of preservative and insulin aggregation are major contributors to insulin-induced site inflammation. Testing of seven adhesive variants in human subjects identified one variant with both a long wear-time and good comfort.[11] Medtronic has designed a novel IIS that maintains better insulin formulation stability in the fluid path. This new IIS also benefits from parallel research studies designed to identify the best performing adhesive. The safety and efficacy of this newly designed EWIS in 21 subjects was compared to published results of the MiniMed™ Quick-set™.[12] The trial demonstrated that the newly designed EWIS has an 80% survival for seven days compared to 33% for the comparator without a change in the total daily insulin dose. EWIS permits people with diabetes to change their IISs half as often and to rest their preferred infusion sites, as well as reduce insulin and plastic waste.[13]

Section 3: Future Directions

Matthias Heschel, PhD

Vice President, R&D, ConvaTec Infusion Care, Taastrup, Denmark

Key Points:

- IIS innovation must be patient-centric to accommodate whatever conditions the patient may exert on it and not put constraints or limitations onto the patient, which means the product should not be designed primarily for functionality, but rather for usability.
- System-level innovation thinking is a prerequisite for enhancing patient care.
- Early-stage collaborative efforts by pharmaceutical companies and technology providers can bring CSII to the next level.

Bruce Buckingham, MD

Stanford University, Stanford, California, USA

Key Points:

- The length of IIS wear is being extended and the insertion sites are becoming more comfortable to wear.
- Inserters are improving to provide easier insertion of the needle of an IIS with less medical waste.
- There remain many unanswered questions:
  - What causes the underlying biologic process that results in individual variability in the length of IIS wear?
  - How well will new, Ultra Rapid insulin analogs work with EWIS?
  - Is it practical to have a single site with a combined glucose sensor and IIS lasting seven to ten days?

Summary

A main goal for developing new types of IISs is to reduce patient burden as much as possible without sacrificing their efficiency or function. Three methods to implement this goal would be to: (1) develop a smaller discreet inserter to permit easier insertion of the needle of the IIS and improve portability, (2) extend the wear time of the IIS to reduce medical waste, and (3) modify adhesives to minimize adverse skin reactions as well as IIS insertion failures. Dr Heschel from ConvaTec emphasized that company's most recent innovations, which include a novel IIS (Minimed™ Mio™ Advance). This IIS provides an excellent patient experience and user

comfort.[14] The system uses a soft cannula utilizing what the company calls Lantern technology, which contains a catheter coating and multiple slits intended to reduce foreign body response and occlusion from bending or kinking to enables consistent flow of medication even in kinked/bent cannula situations.[15,16] Going forward, the focus on future IIS innovation should be on extending the wear time of IISs. Whereas promising results have already been presented for IISs with an average wear time of eight days (using coated soft cannulas),[15] the whole system, including the reservoir and insulin-on-board calculations, must be considered in order to provide a true extended-wear experience. Technology developers and pharmaceutical companies should collaborate on future Automated Insulin Delivery (AID) systems. In recent years, the number of publications in PubMed-referenced journals on this topic have leveled off, which suggests that basic technical knowledge about insulin delivery to and absorption from the subcutaneous space has not advanced much in recent years, despite the increased number of patents on the topic.[17]

The interactions between insulin and subcutaneous tissue must also be better characterized to account for unexplained infusion set failures that may result from insulin aggregation or issues with excipients.[18] IISs should be modified to work with various insulin formulations to facilitate the implementation of CSII.

Conclusion

Extended wear technology is important to create successful and improved IISs. It is now time to alleviate CSII users' burden currently caused by infusion site-induced local skin problems and inconsistent insulin absorption. The key outcomes from improving IIS technology must include: (1) reducing patient burden and (2) extending wear duration. Achieving these two goals will definitely upgrade the performance of IISs. These two outcomes of IIS research must be prioritized.

Abbreviations

AID, automated insulin delivery; CSII, continuous subcutaneous insulin infusion; EWIS, extended wear infusion set; IIS, insulin infusion set.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JYZ and TS have nothing to disclose. SC is an employee of Medtronic. OC is an employee of Medtronic. MH is an employee of Convatec Infusion Care (Unomedical A/S). RAV is a full-time employee of Medtronic Diabetes. LH is a partner of Profil Institut für Stoffwechselforschung in Neuss, Germany. He is a member of advisory boards for Roche Diagnostics, Zense, and Medtronic. He is also on the Board of Directors for Lifecare. KN is a shareholder in Novo Nordisk, has received research support from Novo Nordisk, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk, and Dexcom, and has served on advisory panels for Medtronic, Abbott, and Novo Nordisk. JS serves as an adviser to Medtronic, Janssen, and Novo Nordisk. She owns shares in Novo Nordisk, and has received fees for speaking on behalf of Medtronic, Sanofi, Novo Nordisk, and Bayer AG. BB is on medical advisory boards for Convatec and Medtronic. BB receives research support from the NIH, Medtronic, Insulet, Tandem, Beta Bionics, and Dexcom. DCK is a consultant to EOFlow, Fractyl, Lifecare, Novo Nordisk, Samsung, and Thirdwayv.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Medtronic provided grant support for the meeting and publication of this article.

ORCID iDs

Jennifer Y. Zhang https://orcid.org/0000-0002-3374-9777
Trisha Shang https://orcid.org/0000-0001-9687-9336
Sarnath Chattaraj https://orcid.org/0000-0003-0409-0886
Ohad Cohen https://orcid.org/0000-0003-4337-1795
Matthias Heschel https://orcid.org/0000-0003-1278-0772
Robert A. Vigersky https://orcid.org/0000-0002-3546-3385
Lutz Heinemann https://orcid.org/0000-0003-2493-1304
Kirsten Nørgaard https://orcid.org/0000-0003-1620-8271
Jannet Svensson https://orcid.org/0000-0002-9365-0728
Bruce Buckingham https://orcid.org/0000-0003-4581-4887
David C. Klonoff https://orcid.org/0000-0001-6394-6862

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