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Insulin Pump Occlusions: For Patients Who Have Been Around the (Infusion) Block

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Insulin pump occlusions are felt by many diabetes professionals to impair blood glucose control,[1] although a definite link between occlusion frequency and elevation of A1C has not been demonstrated.[2,3] If a pump cannot maintain a set flow rate either because of a total or partial occlusion of the insulin infusion set (IIS), then the pressure inside the IIS/insulin cartridge will increase (and will induce an occlusion alarm), the flow rate of insulin delivery will decrease (probably down to zero), and if the occlusion is not relieved, then blood glucose levels will rise. The two main risks induced by a pump occlusion are:

1. hyperglycemia due to failure of insulin delivery; and
2. hypoglycemia if an occlusion is due to kinking or compression and if the insulin infusion rate is increased to overcome the occlusion and maintain normoglycemia, then after the occlusion is relieved, a relatively large volume of noninfused insulin that was not infused during the occlusion will suddenly be delivered.[4]

Causes of Occlusion

Occlusion can occur gradually because of progressive factors or can occur acutely: Progressive occlusion can be due to either a true obstruction of the IIS caused by insulin fibrils at the cannula outlet or in the tubing, progressive kinking of the cannula, compression of the skin around the infusion site due to local inflammation or a hematoma at the insertion site, or displacement of the IIS. In either gradual or acute occlusion, a predictive algorithm can analyze the rise of pressure and deliver an occlusion alarm. Most occlusion detection technology is proprietary. The patent literature contains information about occlusion detection systems from at least 400 patents from 1971 through 2016.[5] Whether or which such patents are currently being used by any pump manufacturers at this time cannot be determined. Occlusion detection by infusion pumps may depend on detecting increased pressure in the tubing, increased radial diameter of the tubing, lack of a temperature gradient of heated fluid, lack of optical signals from an inline piston, or an unexplained rise in the concentration of interstitial fluid glucose.[5] In some cases like with the Medtronic 670G (Medtronic, Dublin, Ireland) the programmed insulin delivery rate could increase in a failing attempt to maintain target glycemia and in some cases the patient will notice a rising glucose level and reprogram the pump to deliver a higher infusion rate. This can occur either if the IIS is disconnected or dislodged or else if the insulin stream is not being fully delivered, in which case there can be back pressure from the occluded catheter tip. Increasing back pressure is generally detected by measuring the maximum pressure and the shape of the pressure wave for each pump stroke in the reservoir and/or IIS to look for evidence of an increased pressure pattern indicative of an occlusion.

Frequency and Significance of Pump Occlusions

In one of the earliest studies of the frequency of insulin pump occlusion, reported in 2001, over a 24-week period, approximately 66% (38 of 58) subjects with type 1 diabetes using an insulin pump had an episode of hyperglycemia and 36% of the episodes were caused by an occlusion of the IIS. There was no significant difference in the occlusion rate when these patients used either insulin lispro (LIS) or buffered regular insulin (BRI).[6] In a follow-up study reported in 2002 by some of the same investigators, occlusion rates were reported with the use of either insulin aspart (ASP), LIS, or

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BRI in insulin pumps, over 16 weeks among 146 subjects with type 1 diabetes who were randomized to one of these types of insulin. A subset of subjects (25%, 36%, and 22% of those in the ASP, LIS, and BRI groups, respectively) reported four or more clogs or blockages of the pump or IIS during the treatment period. Only a small percentage of clogs or blockages (9% [15/158], 6% [5/81], and 7% [9/136] for ASP, LIS, and BRI, respectively), coincided with a hyperglycemic episode.[7]

In a study of 59 subjects with type 1 diabetes receiving either ASP or insulin glulisine (GLU) via insulin pump for 16 weeks the median (minimum-maximum) catheter occlusion rate was low for both GLU and ASP (0 [0-0.7] vs 0 [0-1.1] occlusions/month). The median occlusion rate was 0% for both groups, but based on a slight difference in the maximum (but not the minimum or median) occlusion rates of subjects in the two groups, there was a slight trend toward fewer IIS occlusions with GLU. Unexplained hyperglycemia occurred more frequently in the ASP-treated cohort.[8] In a follow-up study comparing the occlusion rate of pumps delivering GLU against those of both APS and LIS, 256 subjects with type 1 diabetes received three sequences of insulin analogs, each for 13 weeks for a total of 39 weeks. At the end of the study they had each used all three analogs. Percentages of subjects with at least one unexplained hyperglycemia and/or IIS occlusion were not significantly different between GLU and ASP (68.4% vs 62.1%, $P = .04$) and between GLU and LIS (68.4% vs 61.3%, $P = .03$). For the multivariate statistical analysis, P was set at the .025 level for treatment effect.[2]

Bode et al used an insulin pump in a laboratory-based nonclinical comparison of occlusion rates using ASP, LIS, and GLU in IIS over five days using low flow rates. In all, 24 pumps were used—eight each infusing each of the three insulins. Over the five-day infusion period, the probabilities of occlusion for each insulin were 9.2% for ASP, 40.9% for GLU, and 15.7% for LIS. All occlusions occurred after 48 hours of pump use and all occlusions, except for three, occurred during a bolus infusion.[9]

Detection

Occlusions are not necessarily noted immediately and interruptions of insulin flow during infusion often appear to not trigger occlusion alarms[10] as it takes time to build up sufficient back pressure until an occlusion is detected and an alarm sounds. One study has assessed the amount of time needed from setting a clear IIS occlusion to detection, as recognized by an occlusion alarm sounding. In this study, five brands of insulin pumps, each delivering insulin at two different flow rates, through two different lengths of IIS were occluded with a clip over the catheter. There were $5 \times 2 \times 2$ or 20 different combinations of pump brands, flow rates, and IIS lengths. The time from occlusion to alarm ranged from 1.5 hours to 24 hours; most combinations were in the range of 2-4 hours. The fact that any type of occlusion could take as much as 24 hours to be detected was part of the impetus for this editorial. The time from occlusion to alarm was approximately double for an infusion rate of 0.5 U/hour than with an infusion rate of 1.0 U/hour.[11] Zisser demonstrated in 2008 that when an insulin pump is shut off blood glucose level rises by approximately 1 mg/dl/minute for the first 30 minutes of occlusion. By extrapolation assuming that the relationship of glucose increase to time without insulin remains linear, then an occlusion typically does not lead to an alarm until the glucose level has risen by approximately 120-240 mg/dl.[12] Such a rise in glycemia can be difficult to correct later by correction boluses. This amount of time of that insulin delivery is suspended, if not greater than two hours, is still unlikely to lead to ketoacidosis;[13] however, many pump occlusions were not detected for far more than two hours.

To determine pump performance following an IIS occlusion, an experimental full IIS occlusion was created with a surgical clamp compressing the cannula of five different insulin infusion pumps. A bolus was then programmed. Eventually the alarm sounded for each system—two patch pumps and three traditional pumps. The volume of noninfused insulin was measured subsequently. The lowest and highest volumes of uninjected insulin when the alarm sounded were recorded by the two patch pumps; the three traditional pumps performed in the midrange between the two patch pumps. The alarm threshold (defined as the time between occlusion and alarm) was then tested for one patch pump and three traditional pumps at two different basal rates. The patch pump had the fastest alarm threshold of the four pumps.[14]

Prediction

In vitro simulations of patients using insulin pumps with rising glucose levels have been generated to create models of such patterns associated with total disconnections of the insulin pump or complete occlusions of the IIS in simulated patients. A fault detection algorithm for complete suppression of insulin infusion due to disconnection of the IIS was applied to 100 in silico scenarios (ten patients' times ten faults per patient). With a predefined upper safety limit for blood glucose of 300 mg/dl all 100 scenarios detected the fault below the safety limit except for two false negatives. There was a single false positive alert in one scenario after 1,257 hours of nonfaulty simulation.[15] A failure detection algorithm applied to 100 in silico pump patients with type 1 diabetes detected a total occlusion or dislocation in 75% of patients within 63 minutes with a 10% false positive rate.[16]

Recently, Cescon et al reported an algorithm designed to alert a patient to the onset of either clinically significant partial or total IIS failure and tested the predictive value algorithm with actual patients with type 1 diabetes.[17] This formula

is tuned to recognize a combination of both a rising trend in average daily continuous glucose monitor glucose reading along with increasing daily doses of insulin being programmed into the pump. The method was tested in a clinical trial with nine subjects who wore an IIS for seven days or until occlusion occurred. An occlusion was defined as one of three outcomes:

1. BG monitor glucose >250 mg/dl and a correction dose fails to decrease the glucose by 50 mg/dl in one hour;
2. meter BG >250 mg/dl and serum ketones ≥0.6 mmol/l in the absence of infection at the infusion site; or
3. an infection at the infusion site.

Eighteen weeks of wear data from nine subjects were analyzed to assess how well the algorithm predicted IIS failure. The algorithm achieved 50% sensitivity and 66% specificity. If the IIS failure alarm had been activated in real time, a potential 29% reduction in the time spent >180 mg/dl (from 82.7 hours/week/patient to 58.8 hours/week/patient) would have been achieved, assuming that the patient would have acknowledged the alert and reacted with appropriate actions.

Prevention

To avoid occlusions, IIS must be properly inserted, maintained, and removed. If a patient delays IIS replacement beyond the manufacturer's recommended interval for changing these IIS, then there is increased risk of site inflammation or infection. This type of problem will be manifested by recurrent hyperglycemia in spite of steady or increasing does of insulin with or often without an alarm.

In 2016 two separate studies were reported to compare the in-line pressure profiles and occlusion rates using a novel IIS with a 6 mm, 28-gauge polymer, dual-ported catheter (called the BD FlowSmart™; Becton Dickinson and Co, Franklin Lakes, NJ) with those of an existing IIS (Quick-set®; Medtronic MiniMed, Northridge, CA).[1] These studies involved administering insulin diluent infusions over 2.5- to 4.5-hour periods to healthy adults without diabetes. Study 1, a pilot study (n = 25), compared the occurrence of flow interruption events (silent occlusions and/or occlusion alarms) between the two IIS and between manual or device-assisted insertion methods. Study 2 (n = 60) was designed to show ≥50% reduction in flow interruption events with the new IIS after manual insertions. In the first study, significantly fewer silent occlusions occurred with the novel IIS than with the traditional IIS for both manual (3 of 22 [13.6%] vs 12 of 24 [50%]; $P = .012$) and mechanical (2 of 24 [8.3%] vs 9 of 25 [36%]; $P = .037$) insertions. In the second study, flow interruption events occurred in 3 of 117 (2.6%) and 12 of 118 (10.2%) novel and traditional IIS, respectively. The difference in occlusion rates represented a 75% risk reduction (95% CI, 20-92%; $P = .030$) with the novel technology.

Conclusions

Insulin infusion pumps are an attractive technology for patients with diabetes; however, an occlusion of IIS can massively interfere with glycemic control and degrade patients' confidence in this type of technology. Occlusions do occur frequently and often without an alarmed warning or this provided too late. There is a need to improve this situation by either: 1) proper education of patients with respect to IIS management; or 2) development of insulin pumps/IIS with robust predictive alarms for detection of occlusions and other technological solutions for the avoidance of occlusions.

Abbreviations

ASP, insulin aspart; BRI, buffered regular insulin; GLU, insulin glulisine; IIS, insulin infusion set; LIS, insulin lispro.

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