**Improved Outcomes and Ease-of-Use when closed looping with Lyumjev**

Oct 13, 2020 / BerNie @ loopercommunity.org

**Introduction**

A new ultra-rapid insulin (Lyumjev, Eli Lilly, USA) might offer advantages for looping over currently used insulins like Fiasp, Novorapid (Novo, Denmark) or Humalog (Eli Lilly, USA). This is a (n=1) pilot study investigating the outcomes when switching to the new insulin in a closed loop.

**Method**

Closed Loop with AndroidAPS 2.6.1 using the oref(1) algorithm with „SMB always“ setting, the Accu-Chek Combo insulin pump (Roche, Germany) and Dexcom G6 CGM using factory calibration code (Dexcom, USA).

Trial period was 1 week in each of three modes:

**(A)** Looping with **50/50** mix of Fiasp/Novorapid (both: Novo, Denmark), in a mode that the user had thoroughly „tuned“ by adjusting factors and settings for good performance over a period of many months.

The same settings as in (A) were used in AndroidAPS for (B) and (C), except for entering the shorter time-to-peak for the new insulin (45 minutes), and shorter DIA (5 hours):

**(B)** Lyumjev (Eli Lilly, USA) was used for **standard looping** as in (A)

**(C)** Lyumjev (Eli Lilly, USA) was used in a totally different mode of looping called **UAM** (unannounced meals). Here, the user does not make any inputs about carbohydrates, nor is he/she doing any bolusing. The max. allowed size of a SMB was elevated from 90 to 120 minutes basal for this mode.

Especially in (C) it was important to use a smoothly performing CGM system. It was monitored for values eventually getting „jumpy“, and values were checked at least daily against a blood glucose measurement, to determine eventual need for a new sensor.

The study was done by a male person in the age group 60-70 who is retired, has normal body weight, and has a moderately active lifestyle (biking and walking regularly with his big dog, garden work). He has been on pump therapy for nearly 20 years, and on AndroidAPS closed loop for 2 years and 3 months. TDD 37 U, and basal 13 U/d. Time in range (70-180 mg/dl) in 3 months prior to
this study was 93% (with 1% under 70 mg/dl), and recent laboratory HbA1c was 5.8%.

Daily caloric intake around 2200 kcal came from 165g carbs, 85g protein, 90 g fat and 40 g alcohol. Lunch was the main meal; very minor breakfast. In all investigated modes, meal management involved pressing EatingSoonTT one hour before meals. (This sets a low temporary glucose target).

In (A) and (B) a bolus was given for max.60g carbs. Later absorbed carbs, also from FPU, were announced via numeric input into AndroidAPS, including the estimated absorption time window.

In (C) no carb inputs were made, and also no boli were done by the user.

Autosense was used in the range 0.6 to 1.5. In all three studied modes, a user-defined „automation“ was implemented which (in case of AS<130%) elevates profile to 130% if glucose rises above 170 mg/dl.

The study data were evaluated as 7 day statistics in the xDrip+ software (V.2020-09-04) which every 5 minutes captures the „native“ glucose values from the Dexcom CGM transmitter, and sends them into the AndroidAPS looping software. Results were cross-checked using the statistics section of the AndroidAPS software (V. 2.6.1).
**Results**

**Chart 1, A-C** shows the results from 7 days each of closed looping in modes:

(A) Fiasp/Novorapid „tuned”looping  (B) Lyumjev @ standard looping  (C) Lyumjev @ UAM

Lyumjev usage (B) reduced highs by 66% (70->24) and lows by 55% (42 -> 19).

In a usage mode without any carb inputs or user-triggered boli (C), highs were reduced by 39% (70->43) and lows by 88% (42 -> 5)

TIR (70-180 mg/dl) improved with Lyumjev from 94% (A) to 97% (B and C).

**Chart 2 A-C** shows the scatter of glucose values by time of day, for 7 days each (10-90% of all value are in the dark-blue areas; 25-75% light-blue; mean white. Colored lines = 70 resp. 180 mg/dl range limits.). In the UAM mode increased scatter is seen after the main meal (lunch), with values exceeding 180 mg/dl up to about 200 mg/dl for the 90% dark-blue mark.

This also results in slightly higher mean and median value, higher Std.Dev., and higher HbA1c in the pure UAM mode (C), compared to Lyumjev standard looping (B). Also, only marginal improvements are seen with (C) when compared to (A), regarding these metrics (chart 1).
In the UAM mode, the lowest incidence of low values under 70 mg/dl was found (5 compared to 42 in mode (A), and 19 in mode (B); chart 1). This finding contributes to the UAM mode (C) receiving a PGS rating of 4.16 which is comparable to the 3.81 value found in mode (B).

Site reactions (hematoma) were seen in 1 of 4 cannula sites with Lyumjev in (B). No site reactions were observed in (A) or (C).

There is an indication that daily insulin requirement was reduced in the UAM mode with Lyumjev (chart 3: 34.81 U/d, compared to 37 U mean in (A) and (B)). However, this study was not thoroughly controlled for evaluating this aspect.

Charts 4 and 5 show how the TIR findings would change if applying a narrower range of 70-140 mg/dl.

In the first week on Lyumjev (B), 13% of values were above 140 mg/dl, and 14% were above this threshold in 30 days, which included the 7 days in mode (B).

In the week on Lyumjev in UAM mode (C), 20% of values were above 140 mg/dl (chart 5).
Discussion

The observation period of only 14 days using Lyumjev in total allows only very cautious, preliminary conclusions. Hopefully, we quickly will see further investigations into the sketched very promising new modalities of looping.

Site reactions (hematoma) as seen in (B) were not observed in (C), probably because 1) cannula utilization was strictly limited to 48 hours and 2) in the UAM mode (C), never any big boli are released, but every 5 minutes some smaller amount (if any) is administered by the loop.

Because of low tolerance and a tendency towards occlusion due to hematoma the study participant was unable to use 100% Fiasp but diluted it with Novorapid. It could be hypothesized that using 100% Fiasp in (A) would narrow the relative advantage seen in this pilot study for Lyumjev.

Of note, mode (A) was what the patient had routinely used for a couple of months, with occasional attempts to optimize results by “tuning“ factors and settings. There was no such attempt made to optimize any settings for looping with the new insulin. Therefore, also bigger advantages than those described here are imaginable.

This report has a problem in that – within the selected standard reporting range 70-180 mg/dl – there was not really much room for improvement, starting out from a 94% TIR in mode (A).

However, the results seem meaningful as it does become exponentially more difficult to reach improvements when going towards 100% TIR.

It remains to be seen, whether loopers with lower starting TIR also can find a comparable pattern to the one described in this report.

The movement towards target after midnight, to early morning (chart 2), works slightly better (with less scatter, at same ISF setting) with Lyumjev. The shorter DIA of the new insulin (5.0 h vs. 6.7 h for the 50/50 mix (A)) might contribute to that finding.

Regarding the effect on glucose curves, noon to midnight: This is after the two main meals, where in mode (B) the faster onset of active insulin seemed to help curb glucose rises. Likewise, we can expect faster corrections of high values, something to investigate in other studies where users might encounter values above 200 mg/dl more frequently.
In this pilot study no efforts were made to check diet-related limitations, notably in the new UAM mode (C). Further investigations are needed about the net glucose-elevating effects of deliberately consuming a big amount of rapidly digested carbohydrates. Also, no meals above 100 g carbs were included (although the latter would seem less of a challenge, as the physiological absorption seems to be limited around 30 g per hour, and the UAM algorithm might be able to keep up with that).

In the UAM mode (C), the algorithm cannot give any meal-related insulin before it sees the glucose rising. On top of the effects owed to glucose absorption physiology, there is the additional delay of a few minutes coming from the CGM system, which only can measure glucose in tissue but not in blood. Therefore, not unexpectedly, we see in the glucose curves in (C) more incline and scatter in post-meal hours. This is probably the prime reason behind the slightly higher average glucose and HbA1c in (C) compared to (B).

As a consequence, mode (C) performance in terms of TIR is also more dependent on the selected upper threshold, than modes (A) or (B) (chart 4-5). It could be argued that, as state of art progresses towards better glucose control, metrics based on the conventional definition of a 70-180 mg/dl range should be abandoned in favour of, for instance, 70 – 140 mg/dl. This would put the UAM method at a disadvantage: Due to the fact that no early bolus before a glucose rise is possible in that mode, it needs a certain „wiggle room“ around and also above 140 mg/dl. Advantages of UAM (C), compared to the other modes, will become visible more above 180 or 200 mg/dl, and highlight the differences focussed on an area of certainly more valid medical concerns.

The PGS is supposed to give a good overall medical assessment of each mode. Here we in fact see (chart 1), despite the difference in HbA1c, a similar evaluation of 4.16 in mode (C) and 3.81 in mode(B) , compared to 8.73 in mode (A).

The UAM mode can make up for some deficiencies in the upper-normal glucose range with the very small incidence of low values <70 (5 vs. 19 in (B) and 42 in (A)), chart 1). If the loop runs with well-adjusted factors, this finding really makes sense: In the two other modes, users can and will give boli with the potential of leading to low values (that the loop will try to counter, but it’s capabilities cannot go beyond shutting off basal in so-called zero-temping). In mode (C), the algorithm just fights glucose rises, using the caution inherent in the algorithm.
Overall this pilot study shows the following pattern:

- Using Lyumjev in a closed loop (B) improves TIR (70-180 mg/dl) and HbA1c. High and low glucose values are reduced. Of note, advantages are less prominent if a 140 mg/dl threshold is used instead of the 180 mg/dl standard.

- Using Lyumjev in an UAM mode (C) undisputably would bring a big relief in sharply reducing the daily mental burden (and often health hazards) associated with carb counting, determining size and timing of meal-related boli, and of correction boli. However, in the UAM mode only a small reduction of average glucose value and HbA1c was realized. The medical value of the UAM mode seems to lie rather in avoidance of low values, and is reflected in the excellent PGS rating achieved.
Conclusion

As expected, the most rapidly acting insulin offers potential for an improved outcome in terms of time in range, and lower average glucose.

Still, the UAM mode might disappoint patients who strive for HbA1c values well inside the range seen in healthy subjects, i.e. below 5.8%, even at a certain risk of hypoglycemia (which they might consider manageable, as with CGM and loop they can be rapidly detected and nearly always averted). It remains to be seen whether some tuning of settings, or the advent of even faster insulins, could in the future bring further improvements.

Some daily user interaction will also remain in the UAM mode for setting temporary glucose targets before meals and before sports, but some of that could also be automated within AndroidAPS (which offers to formulate and activate user programmable automation routines).

In the end it comes down to a personal choice, which TIR is good enough, so it does not become an obsession to permanently „feed“ and „tune“ the loop.

When „good enough outcome“ is achieved, not having to bother with meal inputs, boli, or even pre-boli any longer has been kind of everyone’s dream. Based on this brief observation period, Lyumjev seems to be well suited for the fine regulation of the AndroidAPS loop, and should bring the UAM mode, which, among available solutions, closest resembles an artificial pancreas so far, into reach for more people with diabetes.

Closing remark

This paper does not constitute medical advice. Any attempts to use unregulated products like the open source software AndroidAPS, or to reproduce what seemed to work for another patient, would be on own risk. Speak to your doctor. Learn about the system before you use it. Do not test out the limits, like with a really big meal, before you saw your system work at moderate challenges. And always safeguard yourself by making use of the alarm options integrated in all open source systems, as well as in the commercially sold components of it.

Closing remark especially for users of iOS Loop and of commercial closed loops

The reported study was done using AndroidAPS which uses core OpenAPS algorithms. iOS Loop (and also most commercially available loop systems) differ
significantly in their core algorithms, and rely much heavier on input about amount and kind of carbs consumed.

While all loopers are likely to gain benefits from using a more rapid and “more short tailed” insulin, it is probably not sensible to attempt an “unannounced meals (UAM)” study with such systems. (Compare also Univ.Stanford pig study in which iOS Loop showed much inferior performance compared to AndroidAPS in an experimental UAM mode comparison).

The developmental FreeAPS (ivan branch to iOS Loop) seems to come closest to what OpenAPS and AndroidAPS offer. It is advised to wait for an official release with instructions how to use, in order to assess potential of running it without carb inputs (in some sort of UAM mode).

Lastly, I like to point to the fact that AndroidAPS loopers are instructed to use a (“circadian”) basal rate that truly keeps glucose steady without food and other special effects. This seems important, so factors are not carrying a bias for basal-correction, and to allow the loop optimal regulating capacity.

Different philosophies prevail regarding basal rates (and factors) used for looping. It will be interesting to see how they do in an “UAM“ challenge.

Next steps
Meanwhile AAPS 2.7 (which has changes in Autosense) has become available and should be used in further investigations.

For usage of Lyumjev replacing other insulins in a „normal“ looping mode (B), tuning the breakfast and lunch IC settings (carb ratios) could be important. 
(Footnote)
„Tuning“ settings for „UAM“ utilization should be investigated. As there are not really many settings involved in UAM, this would mainly mean looking at ISF.
Also Autosense settings seem of very high importance, especially in the UAM mode (C).
More investigation on the UAM mode (C) are planned using moderate carb load meals, to gain more experience and understanding, before checking out limitations that may come with challenging high carb meals.
Footnote:

„Regarding carb ratio IC it could be expected that milder (higher) values would result when using an insulin with more rapid onset and shorter DIA.

With reference to extensive discussions in the German loopercommunity.org site on how carb absorption and insulin activity are principally out-of-sync in the hours following any meal, and therefore, how an optimal IC would be set, I rather expect the following:

With Lyumjev we see a shortened window of high insulin activity. Less grams of carbs will be absorbed in this time. Therefore, ideally less carbs should be entered for determining a user-triggered initial meal bolus (while more goes into the so-called extended carbs input for the later absorption time window).

As a result, the „old“ IC value might still be valid with Lyumjev: A bit less insulin is bolussed (in mode B) than with the previously used insulin(s) (in mode A). But also less carbs are being absorbed in the window of strong activity from that bolus.„