Settings for your insulin (DIA and time-to-peak)

Contribution to the discussion among DIY loopers

The author assumes no liability   B/ V.2.4   May'24

Before doing any other tuning, make sure you are on the insulin you really want to be on, and have reasonably set the insulin-related parameters for your looping system.

In case you are just starting to loop and need to "household" with your time, all you need from this paper should be just two messages:

- Select your insulin in AAPS configuration, and refer to the data given in section 1.2.2 regarding DIA. To set it on 7 h is a fair guess for a start, if you are uncertain.

- You probably heard that Lyumjev or Fiasp are in principle *) best for looping.

    *) from an activity kinetics standpoint. References:
    figure S2 in https://github.com/bernie4375/HCL-Meal-Mgt.-ISF-and-IC-settings/blob/FCL-w/autoISF/**The**%20**Artificia**l%20**Pancreas**%20**and**%20**Meal**%20**Control**.pdf, and also
    https://github.com/bernie4375/FCL-potential-autoISF-research-/blob/FCL-book-autoISF/**Case**%20**Study**%201.2_**Insulins**%20for%20FCL_V2.1.pdf .

    In section 1.2.1 it is explained why it is a good idea to switch at the start of your looping journey, rather than at some later point.

        Changes between insulins with similar time-to-peak, like Fiasp -> Lyumjev, will be easier, and will not require much of an adjustment as in the example given in section 1.2.1.

40   But of course you can switch at any later time, as well. Many prefer actually to start
41   looping with a less reactive insulin. This enhances safety in the initial months of
42   getting to know, and tuning, the loop. (Same thought is behind the Objectives in
43   AAPS that give access to SMBs only after a couple of other steps).

44   Also, struggling with too many occlusions (and pain) can make it difficult to switch to one of the
45   fastest insulins.

46

1. Setting insulin related parameters

48 Besides time-(minutes) to-peak activity, also the duration of insulin action (DIA, hours) that
49 you select in your profile strongly influences how the loop calculates the activity from insulin,
50 as it unfolds in every 5-minute segment that your loop analyzes.

51 1.1 Mathematical model used
52

53 Especially what should be selected as duration of insulin action (DIA) is very strongly
54 influenced by the model used to figure out active insulin two, three, and more hours after
55 administration. Misunderstandings about this is often a source for disputes between loopers
56 and their treating physicians.

57   All insulin administrations (bigger and minor) add up to a insulin activity pattern.   In
58   the case of looping, with user boli, basal insulin, TBR modifications and SMBs given
59   at various times, with overlapping DIAs, this can be quite complex.

60   In AAPS you can see insulin activity in your main screen as an extra thin yellow
61   curve. Together with carb absorption is "explains" most of what you see in your
62   glucose curve.

63   This **insulin activity pattern is an extremely important basis for each of your**
64   **loop's decisions.** Having the wrong settings would give your semi-automated insulin
65   management a permanent drift towards over- or towards under-corrections.

66   The loop system can still counter-regulate, but – if you burden your's with wrong DIA
67   or time-to-peak settings in your profile – this would "use up" some of it's (limited)
68   capacity to regulate for you.

69   *Example: After heavy dinner, a DIA set <u>too short</u> "tells your loop" that active insulin is*
70   *practically gone after time X. The loop takes that info for granted, and if it sees some*

71 *insulin needed at that time X (and be it only for your profile basal need - as you also*
72 *communicate to the loop, you need to remain stable -), then, at night-time, the loop*
73 *will give you <u>more</u> insulin than you really need.*

74 *Therefore, before you tune your ISF differently, make sure to have a look at your DIA*
75 *setting.*

76 Please understand (and see to it, that your treating professionals understand) that models
77 can differ strongly:

78 • DIY looping systems use the – less common – exponential decay model.
79 • Medtronic uses non-linear capped curves (as in handbook to their pumps)
80 • Doctors / diabetes educators mostly have a rough linear model in mind
81 • xDrip uses a bilinear math ("with kinks") to model insulin activity (Caution: This info
82   might be outdated)

83 All models are working „good enough" for their (main) intended applications. But, as
84 explained above, it is worth the effort to use an exact modelling of insulin activity for a loop,
85 so it can perform optimally.

86 As pointed out already in the section 1 headline, and further explained below, the
87 mathematical model of insulin activity over time anchors on time-to-peak (minutes) and on
88 DIA (hours) in characteristic ways. This is quantitatively shown for exponential decay models
89 in <u>section 1.2.3-</u>

90 In AAPS, the insulin tab shows two curves:
91 The **pink** one starts at 1.0 (100%) and goes down to 0 (0%) when the DIA is over. It shows
92 how much of the total activity (the capacity to lower bg) is left, at any time. So, it is like the
93 iob number we always have in our AAPS home screen. The problem with that, as with the
94 pink curve, is that it may give you a false impression regarding how much "power" there
95 actually is, now, as you need it. That is where the other curve (and on your AAPS home
96 screen, the related thin yellow insulin activity curve) come in:
97 The **blue** one shows how the activity goes: Practically nothing (!) for a bunch of minutes,
98 then rapidly going high, and then slowly fading out out over the DIA period (with a maximum
99 at time-to-peak). For its calculations, AAPS adds these blue curves up for all boli, SMBs and
100 TBRs ≠ profile basal!

101

102   ## 1.2 Time-to-peak activity and DIA for various insulins

103

104   Principally, there are „correct" settings specific for each insulin type, notably regarding time-
105   to-peak activity. This is pre-programmed in the insulin choices for AAPS, for instance.

106   Regarding the DIA to set, there is more uncertainty. The following mostly cites or
107   summarizes finings published by David Burren.

108   ### 1.2.1 Insulin choice matters for profile ISF, IC

109   The following chart is *the inverse* of the pink curve in the AAPS insulin tab: *Not insulin still*
110   *there to be used*, but Insulin used up, going from 0% towards 100% in the 9 h DIA, for
111   Humalog with 75 minutes, and for Lyumjev with 45 minutes time-to-peak.

Insulin Used

BionicWookiee.com 2022

Humalog 9h/75 —— Lyumjev 9h/45

112
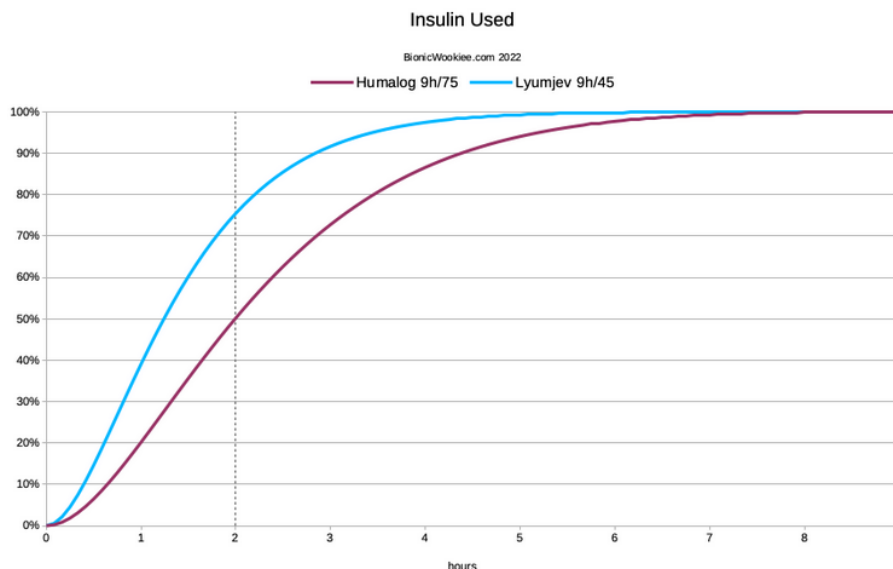
113   From a simplistic point of view, you can see that at the two-hour mark, more of the Lyumjev
114   (75.5%) should have had effect than the Humalog (50.2%).

115   So when we're calculating *how much insulin to give for a correction*, we should tell it to give
116   more Humalog up-front to get the same result after 2 hours.

117   "With the current incarnation of the oref1 algorithm I do find it helpful to scale the ISF (and IC)
118   relative to the amount of each insulin used in the first 2 hours. For Fiasp ~66% is used in the
119   first 2 hours. Lyumjev 75% (and NovoRapid/etc 50%).
120   Thus for Lyumjev I use ratios that are 15% larger than for Fiasp.
121   Basal rates are unchanged."   (D. Burren, AAPS Users 03Apr.2024)

122   The system will of course be tracking the IOB and forecasting the BG curves for hours
123   into the future, so we do have some safety built in regarding the extra insulin.

124 When going from Humalog to using Lyumjev, this must have some consequences for the

125 Insulin Sensitivity Factor (ISF) to use in the profile. If, for example, you had 1.8 mmol(l/U for

126 Humalog, you should expect a "good ISF for going with Lyumjev" in the area of 2.7 mmol/l/U.

127 According to the curves shown above (at dotted 2 hr line) a factor 75.5/50.2 applied yields

128 the same amount of insulin for a correction.

129 Likewise, the Carb Ratio (IC) may deserve an adjustment when switching insulins.

130 • The IC could be adjusted by the same factor, for instance it might go from 7.7 g/U
131 (Humalog) to 11.6 g/U (Lyumjev).

132 For a meal of 60 g, 7.8 U (=60/7.7 g/U) Humalog would have contributed 3.9 U
133 (=50.2%*7.8 U); likewise, 5.2 U (=60g/11.6 g/U) would have contributed 3.9 U
134 (=75.5%*5.2 U)

135 • For meals bigger than about 60 g you should observe that, while your insulin bolus has good
136 activity, only a limited number of carbs can get digested (30 g/h seems the limit for most).
137 Refer to the paper on IC determination (section "Determination at meal times") in:
138 https://github.com/bernie4375/HCL-Meal-Mgt.-ISF-and-IC-settings/tree/FCL-w/autoISF

139 The given example showed that switching to a "faster" insulin can have relevant

140 consequences for your key profile parameters.

141 David Burren also reports that between the two rather extreme insulin choices he tested, the

142 total amounts of insulin (TDD) did not significantly differ (- as we would expect: The same

143 amounts just gets delivered slower, even at same selected DIA, with Humalog).

144 But while the TDD has *not* changed, the instantaneous insulin levels *have*.

145 When the system is fighting post-meal "highs" the IOB will be noticeably lower with Lyumjev.

146 Although the average overall level remains similar, this might have some implications

147 for the concept of hyper-insulinaemia. This may be a subtle advantage of faster

148 insulins.

149 1.2.2 Duration of insulin action

150 The following focusses on the more uncertain topic of which duration of insulin action (DIA)

151 to use. It is largely relies on, and quotes, results from several thorough investigations done
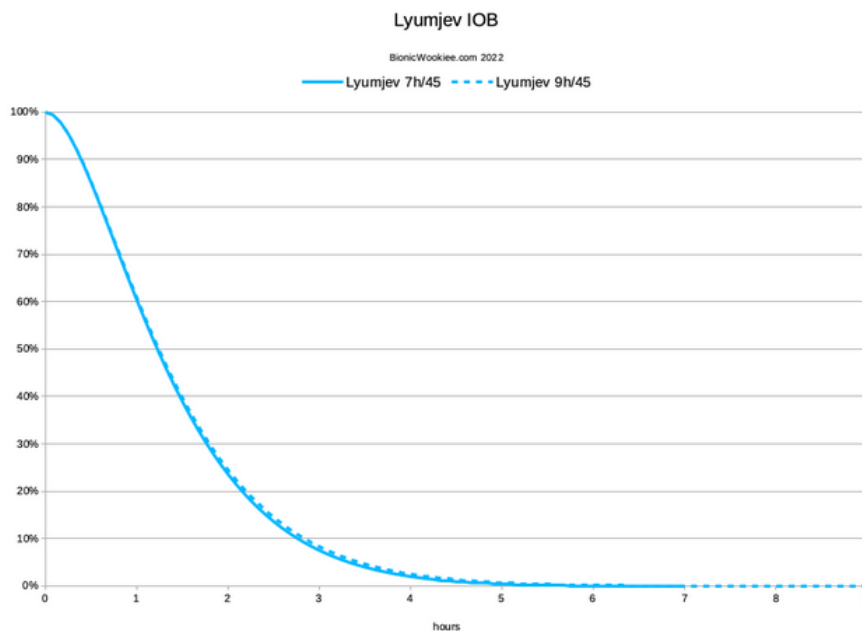
152 by David Burren: (https://bionicwookiee.com)

153 The numbers he ended up preferring are:

Insulin	Peak	Duration (DIA)
Humalog	75 minutes "Rapid-Acting Oref"	7 hours *)=
NovoRapid	75 minutes "Rapid-Acting Oref"	9 hours
Fiasp	55 minutes "Ultra-Rapid Oref"	9 hours

154   *) Later investigations https://bionicwookiee.com/2022/04/13/revised-humalog-model-in-a-closed-loop/
155   led to suggesting 9 hours DIA also for Humalog

156   The default constraints in AAPS have the duration limited to 7 hours, so he had to
157   make some local changes to the limits. It's also possible if you set your "patient type"
158   to "Pregnant", but if so you need to carefully check all the affected safety limits (listed
159   in the AAPS documentation). This may change in a future update to AndroidAPS.

160   For Lyumjev (45 minutes; Lyumjec Oref), there is not a big difference between a 7 and a 9 h
161   DIA:

162

163   However, David Burren (https://bionicwookiee.com/2022/04/13/revised-humalog-
164   model-in-a-closed-loop/) reports that, despite it's a very subtle change, he has found
165   it can make a significant difference 5-6 hours after a meal, when …the tails of the
166   earlier doses do add up, and the system had been underestimating the IOB when
167   calculating (using the shorter DIA) what was needed with new doses. With changing
168   to a longer DIA, his average Time Below Range has reduced. (Comment: This is

169   interesting for "fine-tuning extremists" but probably only a formal gain of little clinical

170   significance, assuming the bg curve just swinging a bit more often, or longer, by a few

171   mg/dl below the 70 mg/dl cut-off, that defines "below range". Judge from your own

172   data, when/if fine tuning.)

173   On the DIA topic for various insulins see also: https://www.diabettech.com/insulin/why-we-
174   are-regularly-wrong-in-the-duration-of-insulin-action-dia-times-we-use-and-why-it-matters/

175

176   1.2.3 Quantitative effects of changing DIA

177

178   Any given insulin dose comes with a defined total capacity for a certain bg lowering effect.
179   How strong or weak this unfolds over a couple of hours can be mathematically modelled.
180   In oref(1) systems, time-to-peak and DIA completely define this curve.

181   We can look on effects of increasing the set DIA in terms of how insulin activity would differ
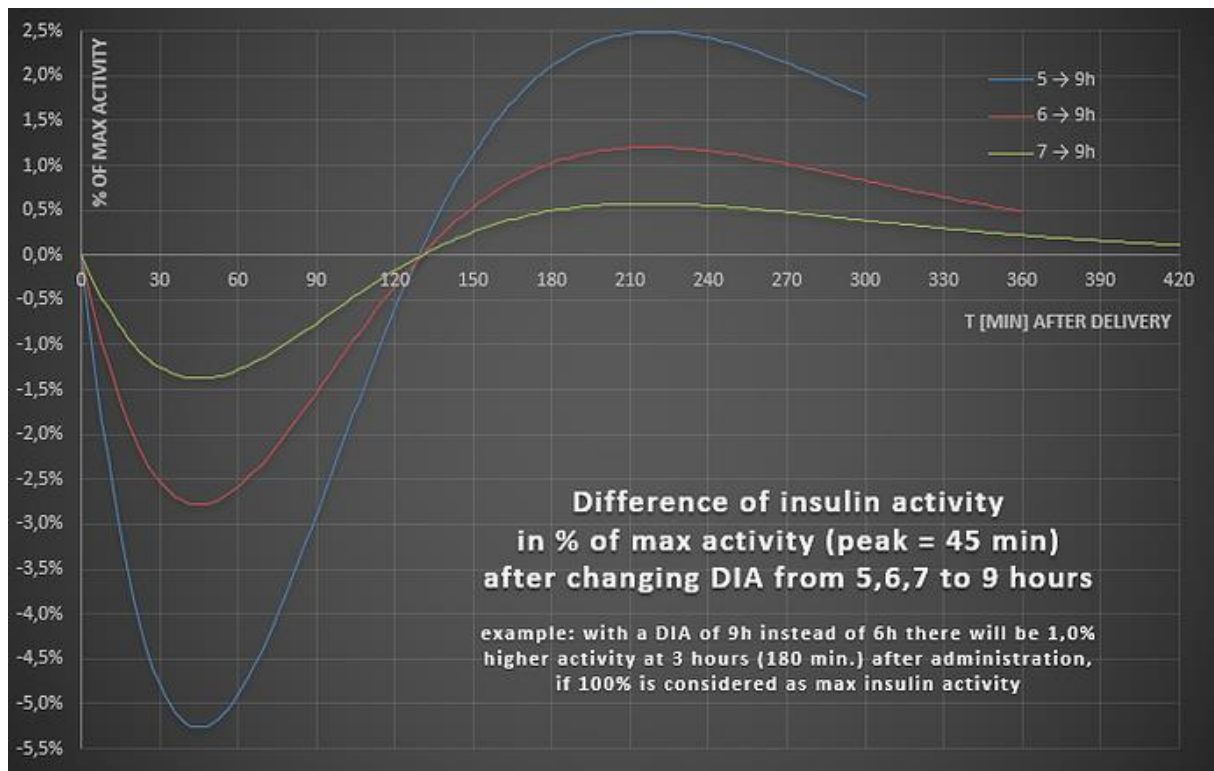182   at any moment after administering a dose.

183   The next example given (chart below) does that for going from a 5 h DIA, a 6 h DIA or a 7 h
184   DIA towards 9 h for Lyumjev

185   We see the peak going lower, and the tail activity higher when DIA is increased:
186

187   **LYUMJEV**   peak @45m   max effect on "tail" at ~ 3.5 h (220 minutes)
188   DIA 5→9h | **minus 5.5 %**   **plus 2.5%**
189   DIA 5→6h | minus 2,7 %   plus 1.3%
190   DIA 6→9h | **minus 2.8 %**   **plus 1.2%**
191   DIA 6→7h | minus 1,4 %   plus 0.6%
192   DIA 7→9h| -   **minus 1.4 %**   **plus 0.6%**
193   So, the „tail" effects differ by less than 3 percent (of peak activity=100%) in the later stages of
194   DIA:

**Difference of insulin activity
in % of max activity (peak = 45 min)
after changing DIA from 5,6,7 to 9 hours**

example: with a DIA of 9h instead of 6h there will be 1,0%
higher activity at 3 hours (180 min.) after administration,
if 100% is considered as max insulin activity

195

196   While 3 % sounds low, the significance of the problem should not be underestimated:

197   • For our Lyumjev case, note that the quoted 3% result is *3% of maximal activity.*
198   *Example: Activity at 180 minutes is about 0.0010 compared to 0.0080 at peak (blue*
199   *curve in AAPS INS tab). 2.5% of 0.0080 would be 0.0002. BUT: 0.0012 is 20 %*
200   *more than 0.0010, so* **REALLY the difference in activity at 180 minutes can be up**
201   **to 20%** *. Still, after a bolus of 8 units (and/or SMBs that reach that iob level) for a*
202   *typical meal, the max. difference from 5 -> 9 hour DIA would roughly be, whether 1.0*
203   *U or 1.2 U are active iob left at 180 minutes.* That **difference (+ 0.2 U)** should be
204   within the loop's regulating capacity from reducing basal.
205   However,it becomes much bigger for users of other insulins (with longer time-to-
206   peak):

207

208   • The delta **effects get much bigger with insulins that have a longer time-to-peak**
209   Some quantitative data for other insulins are as follows:

210   **FIASP** (peak=60m)   min/**max** differences
211   DIA **5→9h** | 6→9h | 7→9h: -10,1 **/ +6,8%** | -5,6 / +3,0% | -2,9 / +1,4%

212

213   **NOVORAPID** (peak=75m)   min/**max** differences
214   DIA 5→9h | 6→9h | 7→9h: -15,4 **/ +14,1%** | -9,1 / +7,0% | -4,8 / +3,0%

215

216 *Above example applied to Novorapid **):* The effect would be up to +14.1% *of max (!)*

217 => 2.1 U instead 1 U at 180 minutes. A ***difference of + 1.2 U*** results here, if DIA is

218 set at 5, not at 9 h, so **REALLY** it could go **up to + 120%** !)

219 More see: szantos, de.loopercommunity.org   May 2022

220 https://de.loopercommunity.org/t/naechtlicher-unterzucker/10626

221 **) 2,5% → + 0.2 U ergo 14.1% → +1,1 U stimmt insofern nicht ganz genau, als man beim
222 Novorapid Case auch die Novorapid Peak-Höhe zugrunde legen müsste (die ich aber nicht
223 greifbar habe). Wenn diese von Haus aus 20% niedriger nur kommt, hätten wir ca + 0,9U, also
224 weiterhin etwa eine Verdoppelung … die wir mit unserer Wahl eines längerem DIA unserem
225 Loop sagen könnten, damit er entsprechend weniger zu-schiesst … ergo weniger Hypogefahr
226 hinten heraus …

227

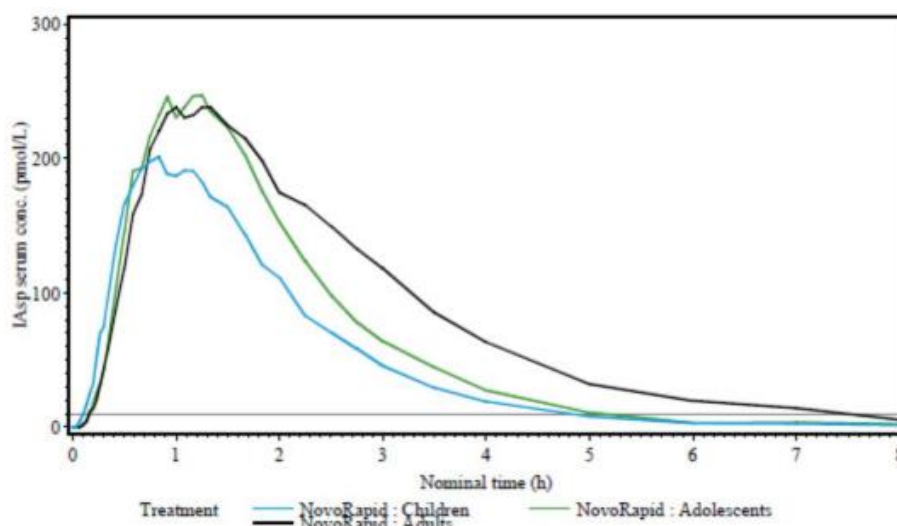228 ## 2. Other factors of potential relevance   *Source:* szantos

229 The findings reported below can give you hints in which direction to look if you attempt to

230 fine-tune your settings further, from the standard suggestion what should be suitable for your

231 insulin (section 1.2.2.).

232 ### 2.1   Age (of the diabetic)
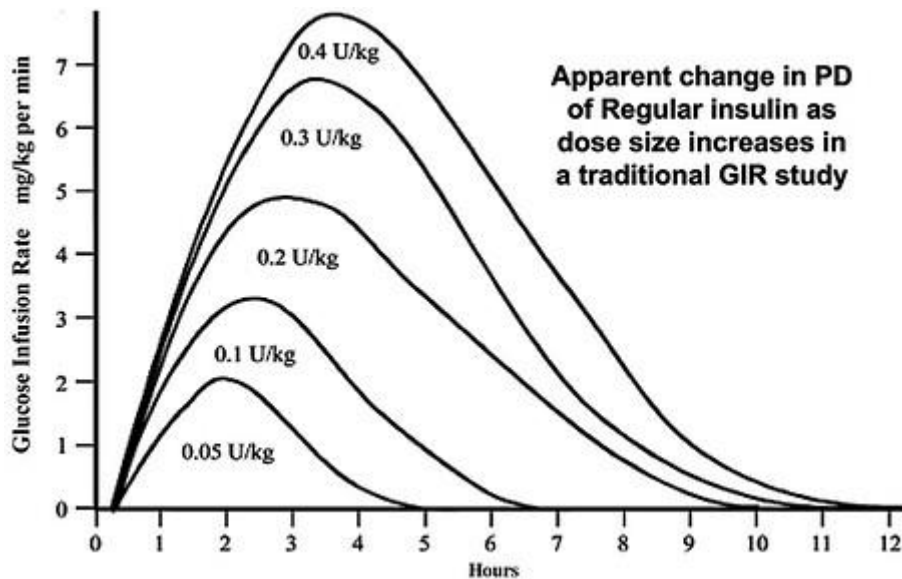
233   ema.europa.eu

234 **novorapid-h-c-258-p46-0044-epar-assessment-report_en.pdf 3**

235

236

237

238

239   ## 2.2 Dose

240
241   https://journals.sagepub.com/doi/10.1177/1932296813514319

242
243   image1000×632 78.4 KB
244
245

246   ## 2.3 Scatter (imprecision)
247

248   Individual deviations from standard suggestions could also be justified by the fact, that all

249   studies that underly the previously reported suggestions, come with very significant person-

250   to-person scatter.

251

252   All lines in the charts, as above shown from studies, are averaged data. (Some studies are

253   indicating the very significant scatter seen, as well).

254   https://www.researchgate.net/figure/Pharmacodynamic-profiles-Insulin-action-as-expressed-

255   as-GIR-required-to-maintain_fig1_41424712 2

256

3. **Mixes of two insulins**

The author did for some time successfully use a 50/50 mix of Fiasp and Novorapid, applying the time-to-peak for Fiasp, and longest of the two DIA, as was suggested at the time, for these insulins.

For a more thorough discussion see https://bionicwookiee.com/2022/03/02/mixing-insulins-theory-and-practice/

and also: https://bionicwookiee.com/2023/06/03/arcane-lyumjev-experiments/

4. **U200 insulins**

Using up-concentrated insulins, e.g. in a U200 form, is sometimes chosen by loopers

- to reduce needed daily insulin volumes and get more time from 1 pump filling (pod)
- to reduce volume per injection for getting better tolerance regarding occlusions or pain

There are no relevant effects on insulin parameters like DIA and time-to-peak.

However, dilution or up-concentration factors are highly relevant for setting profile factors like ISF and IC, and also for some important safety settings like max iob for instance.

Refer to special discussions on that topic, e.g. here re. U200 Lyumjev

https://www.diabettech.com/lyumjev/living-with-lyumjev-almost-a-year-in-review/ :

and also: https://bionicwookiee.com/2023/06/03/arcane-lyumjev-experiments/

5. **Complementary utilization of insulins with super fast bio-availability**

A core problem coming with any sub-cutaneous insulin provision (via sub-cutaneous injections, or via insulin pumps) is that time-to-peak activity can be rather long. Two faster ways to get insulin into blood are: direct venous injection, and via inhaling insulin into the lungs.

5.1 Using i.v. insulin

The "beauty" of using intra-venous insulin at around meal starts would stem from its much faster bio-availability, and also much shorter DIA

Case report: I do a basically unknown amount of insulin intravenously, let it be between 4 and 8 units (well below the size that my meal bolus would be). It really doesn't matter anyhow. What it does ,it brings me down to target within 30-40min. I record something like 4-6 units (so my loop doesn't want to get excessive insulin). Essentially, this prevents getting insulin longer than it actually has an effect (mine is gone from the system after 35min). To eliminate the false "activity tail" assigned also to the i.v. potion of insulin on bord, you can delete the i.v. insulin amount from the system *after it has done it's job* (not good for statistics/history data, but right, going forward without the DIA tail = letting your loop know the real iob).

It's an edge use (experimental) case . (source: Robert, discord FCL/iaAPS w autoISF, March 2024):

Please observe that this is not a recommendation to experiment with i.v. insulin unless in a medically supervised research context.

i.v. insulin is usually restriced to the surgical and intensive care hospital environments!

5.2 Inhaled insulin (Afrezza)

Afrezza is an inhaleable very fast (and also short) acting insulin which some find useful to correct high glucose levels.

Pro: An insulin inhalation addresses the need for a fast correction of a bg high, and even without the hours-long tail of effects.

Cons: 1) Afrezza spray is hard to dose. 2) Also it is not advisable to enter data into loop because the kinetics of this insulin are very different. => The short term problem is solved, but there are consequences in the upcoming hours from skewed calculations and eventually also (via Autotune-driven basal and factor adjustments) for the next days. ((Could partially be resolved if insulin unit equivalents coming from Afrezza are entered at bolus time, and then erased, as soon as it's activity is over)). 3) Primary approach should be to avoid high bg by finding a proper meal management strategy (pre-bolus time, EatingSoonTT).
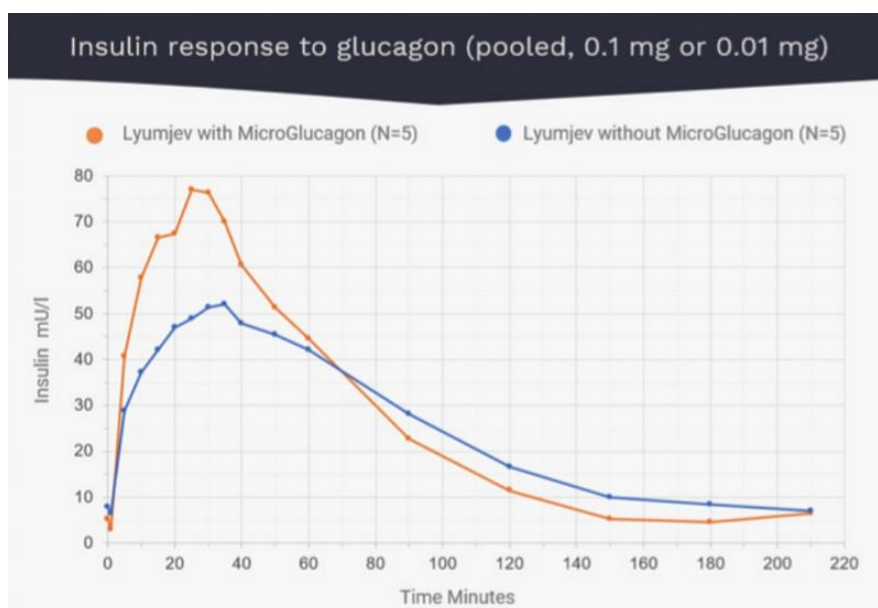
Still Afrezza can be a reasonable remedy in times. Solving the problem at hand as best as we can, even if it makes the time afterwards a bit more complicated, is the name of the

game. We and our loop do this all the time, for instance by giving more upfront insulin, then reducing basal (zero-temping).

> (from slide 38 of: Meal Mgt. Basics, https://github.com/bernie4375/HCL-Meal-Mgt.-ISF-and-IC-settings)

5.3 Lyumjev + microGlucagon mix

A highly experimental approach to further improve the kinetics of Lyumjev fro looping has been researched by a T1D physician (Dr. Carlsen, Trondheim, Norway) in self-experiments, with some promising first results.

Full article from Norwegian hospital researchers group:

https://norwegianscitechnews.com/2024/01/a-new-insulin-mixture-could-make-life-easier-for-patients-with-type-1-diabetes/

See also related discussion in "AAPS Users" FB (Alf Einar Johnsen, Jan 19, 2024)
https://www.facebook.com/groups/AndroidAPSUsers/permalink/373300557358 7499/?mibextid=W9rl1R

… and in "iAPS unchained" FB (Robban Jansson, 06 May, 2024)
https://www.facebook.com/groups/151989761311250/permalink/286074914569400/