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LETTER TO THE EDITOR

When can weekly anti-obesity peptides be used for monthly administration?

To the Editor,

I would like to comment on what appears to be a growing trend of using short-acting anti-obesity peptides over prolonged periods; as examples, using peptides intended for weekly dosing for monthly dosing intervals.

There is a renaissance of interest in incretin-based peptides as treatments for obesity—exemplified by GLP-1 receptor agonists (RA). However, peptides have short in vivo half-lives of minutes to hours and require some form of half-life extension to make them practical for use as therapeutics. The most common half-life extension technologies used for such peptides are lipidation[1] and Fc fusions,[2] but these usually only allow weekly administration unless high dosing is used.[3] Additionally, there is an anti-obesity monoclonal antibody AMG133—a GLP-1 agonist/GIP antagonist mAb—that has a half-life of ~2 weeks and is administered QWk.[4]

To optimize efficacy and minimize toxicity, it is necessary to maintain the concentration of a drug within its therapeutic window—the concentration range between the minimum level necessary to achieve efficacy—often the C_{min} in a C versus t profile—and the maximal tolerable concentration attainable without unacceptable side effects—often the C_{max} in the profile. This concept is illustrated by the C versus t profiles for semaglutide—with a half-life of ~1 week—administered either QWk or QMo (Figure 1), both at doses necessary to maintain the presumed therapeutic C_{min} of 50 nM. As shown, to maintain C_{min} at 50 nM at steady state the C versus t profile of semaglutide dosed at the recommended 2.5 mg QWk, the C_{max} is 90 nM (Figure 1A). But, to maintain the steady-state C_{min} at 50 nM with QMo dosing, the C_{max} is 720 nM (Figure 1B), some 8-fold higher than with the 2.5 mg/week dose. In contrast, using a recently reported slow-release microsphere depot with a half-life of 1 month to maintain the drug at a C_{min} of 50 nM, the C_{max} is only 62 nM (Figure 1A).[5] This optimized delivery system gives a C_{max} that is 12-fold lower than the QMo dosing of semaglutide needed to maintain a 50 nM C_{min}. Hence, while a sufficient amount of a QWk peptide can be dosed QMo to maintain a therapeutic C_{min}, the price paid is a high C_{max} which likely exceeds the safe level; regardless, it is clearly advantageous to use a drug with a half-life close to the dosing interval.

To keep a peptide above a minimal therapeutic level, C_{min}, the optimal half-life is about equal to the dosing interval, and the optimal dose maintains plasma concentrations above C_{min} while minimizing C_{max} and C_{max}/C_{min}. With peptides having half-lives shorter than their dosing interval, it is a common practice to maintain the concentration above C_{min} by increasing dose and risking C_{max}-related GI side effects. For example, although AMG133 has a half-life of 14 days, it is dosed

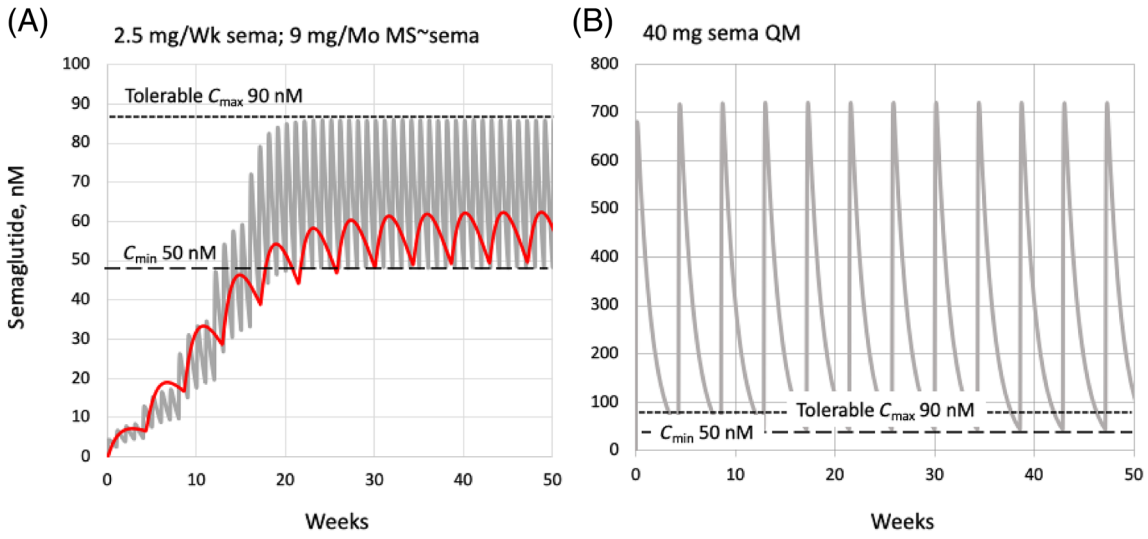

FIGURE 1 C versus t profiles of plasma semaglutide. (A) After ascending doses, steady-state levels of dosing 2.5 mg/week semaglutide (grey) or 9 mg/month microsphere-semaglutide depot (red)[5]; (B) steady-state level upon dosing 40 mg/month semaglutide. Dashed lines show 50 nM C_{min}, and dotted lines show the known tolerable C_{max} of 90 nM.

TABLE 1 GLP-1 receptor agonist half-lives versus dosing frequencies.[a]

Product	Company	Receptor target	Drug type	Half-life, days[c]	Current dosing interval, weeks	Fold dose and C_{max} increase for QMo dosing[d]
PG-102	Progen	GLP-1/GLP-2	Fc fusion	5	1	32
Efpeglenatide	Hanmi	GLP-1/GLP-2	Fc fusion	6	1	13
MBX4291	MBX	GLP-1/GIPR	Acyl-peptide[b]	6	1	16
VK2735	Viking	GLP-1/GIPR	Acyl-peptide[b]	9	1	5
ZT002	QL Bio	GLP-1	Acyl-peptide[b]	11	1	3
AMG133	Amgen	GIP(ant)/GLP-1	mAb	14	4	2
MET-097	Metsera	GLP-1	Acyl-peptide[b]	16	1	2

[a]Data sources: Progen, Diabetes 2024;73 (Supp1):1859-LB; Hanmi, Diabetes Care 2022, 45, 1592; MXB, SEC 08/023/24, as in tirzepatide; Viking, Investor's Business Daily 08/27/2024, 07/25/2024; QL Bio, Diabetes 2024;73(Supp. 1):119-OR; Amgen, Nat Metab 2, 290, 2024; Metsera, Fierce Biotech 9, 24, 2024.
[b]Lipidated peptide.
[c]Half-lives as reported or estimated from available data; median t1/2 if range is reported.
[d]Calculated as 2^(30/t1/2)/2.

every month,[4] which requires a 2-fold higher dose than would be needed for 14-day intervals, and a resultant 2-fold higher C_{max}. This higher dose of AMG133 causes tolerable side effects, but the same may not be the case for shorter acting QWk agonists that dominate the anti-obesity treatment menu. If a drug has a tight pharmacokinetic-pharmacodynamic relationship, increasing dose to lengthen dosing intervals much longer than the half-life could be problematic.

Regardless, it is speculated that many of the current investigational QWk agonists can be used for QMo dosing. Table 1 shows GLP-1RA-containing anti-obesity agents with half-lives of 5 to ~14 days that have been posited to be suitable for QMo dosing. Also shown are the estimated dose and C_{max} increases that would be necessary to keep the drug over a therapeutic C_{min} for 1 month compared to those needed for dosing intervals equal to the half-life. It can be seen that the monthly doses are inversely related to the half-life of the drug: the shorter the half-life, the higher the dose and the higher the risk for C_{max}-related adverse effects. As with the approved anti-obesity agents semaglutide and tirzepatide, a slow up-titration of dosing can improve tolerability but this has not yet been shown with QWk peptides dosed QMo. Hence, while some peptides might tolerate overdosing to achieve QMo dosing intervals, many would likely breach their tolerance barrier and cause unacceptable side effects. A much safer solution would be to develop technologies that could overcome the barriers to QMo and longer administration.

In summary, administration of GLP-1 agonists with short half-lives in monthly dosing intervals require increases in dose and C_{max} to maintain therapeutic levels. Typical anti-obesity peptides or Fc fusions currently using weekly dosing intervals that are dosed QMo would require ~2- to 32-fold higher dose requirement and give ~2- to 32-fold higher C_{max} values. If the undesirable adverse effects of GLP-1 agonists are indeed related to C_{max} effects, prolonging the dosing interval of short-acting agonists to 1 month could have undesirable consequences.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16134.

DATA AVAILABILITY STATEMENT

Data is available to all.

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