38. Elimination half-life vs. effect half-life

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Because the literature sometimes contains inaccuracies and ambiguities, I would like to highlight the difference between the elimination half-life and the effect half-life of a drug. The **elimination half-life** corresponds to the ***time required for the plasma concentration of a drug to decrease by half*** after reaching its peak concentration or steady state. In contrast, the **effect half-life** refers to the ***time required for the pharmacological effect to decrease by half***, which may or may not have a direct relationship with the plasma concentration.

> For many years, I was intrigued by the way this topic was addressed in our pharmacology "bible" (Mihic & Mayfield, 2023). In this edition, it was stated that "Drugs active at the benzodiazepine receptor may be divided into four categories based on their elimination half-life ($t_{1/2}$) (P.430): ultra-short-acting benzodiazepines, short-acting agents ($t_{1/2}$ <6 h), intermediate-acting agents ($t_{1/2}$, 6-24 h), long-acting agents ($t_{1/2}$ >24 h)*".* However, this classification appears to be in apparent contradiction with another statement on the same page, according to which "the durations of action of many benzodiazepines bear little relationship to the $t_{1/2}$ of elimination of the parent drug". The case of flurazepam illustrates this discrepancy well: although the parent drug has a short plasma half-life ($t_{1/2} \approx 2.3$ h), its duration of action is long ($t_{1/2}$ of effect: 47-100 h) due to the formation of an active metabolite, N-des-alkyl-flurazepam, which has a prolonged elimination half-life.

Having outlined the problem, let us now examine some of the mechanisms that may explain such discrepancies between pharmacokinetics and pharmacodynamics. This is a topic addressed quantitatively by researchers studying PK/PD relationships, who seek to integrate drug plasma concentration data with the observed effect through modeling.

1. Active metabolites

The situation illustrated above with flurazepam is also found beyond the classic example of benzodiazepines. One example is losartan, which has a relatively short plasma elimination half-life (≈ 2.5 hours), but whose duration of action is longer due to the formation of the active metabolite EXP3174, which is more potent and has a longer elimination half-life (≈ 5.4 hours).

2. Irreversible inhibition

Irreversible enzyme inhibitors produce effects that last much longer than would be predicted from their persistence in plasma. This is illustrated by acetylsalicylic acid (Aspirin®), whose elimination half-life is very short (≈ 15-20 min), but whose antiplatelet effect at low doses has a much longer duration (up to 7-10 days), due to irreversible inhibition of cyclooxygenase (COX-1) in platelets and the slow turnover of these cells. A similar situation occurs with proton pump inhibitors in gastric parietal cells (e.g., omeprazole) and with the active metabolite of clopidogrel.

3. Receptor residence time

As discussed in a previous glossary entry (*Drug-receptor complex residence time*), the factor determining *in vivo* pharmacological activity and its duration may, in some cases, be the lifetime of the drug-receptor complex, as determined by its dissociation rate. This is particularly relevant when the residence time is longer than the plasma half-life, as illustrated by A_{2A} receptor agonists (Guo et al., 2012).

4. Post-receptor processes (signaling, protein synthesis, etc.)

To illustrate this case, we can cite systemic corticosteroids (e.g., dexamethasone), whose plasma half-life is short (≈ 3-6 h), but whose anti-inflammatory effect is prolonged (36-72 h). This occurs because of their genomic effects, which reduce the expression of cytokines, chemokines, adhesion molecules, and other inflammatory proteins, thereby preventing the recruitment of inflammatory cells to sites of inflammation.

5. Physiological adaptation (desensitization, receptor regulation, etc.)

In the case of selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g., paroxetine), the relatively short plasma half-life (≈ 17 h) does not explain the very slow onset of the therapeutic effect (after 3-4 weeks), even though inhibition of the serotonin transporter occurs within minutes. The explanation lies in the progressive desensitization of presynaptic 5-HT_{1A} autoreceptors (Kulikov et al., 2018).

Finally, it is worth remembering the different uses of these two parameters. The **elimination half-life** is used to determine the dosing interval, estimate the time required to reach steady state (≈ 4-5 half-lives), establish the sampling schedule in bioavailability studies (3-5 half-lives), and predict how long the drug will remain detectable in plasma, thereby allowing estimation of the interval required between two administrations in crossover studies (*washout*), generally 5-7 half-lives, at least for drugs exhibiting linear pharmacokinetics. By contrast, the **effect half-life** is useful for predicting the time required for the pharmacological effect to disappear after treatment is discontinued. In this case, this time also corresponds to approximately 5-7 **effect half-lives**, rather than elimination half-lives, because the effect disappears when the plasma concentration of the drug, or of its active metabolite, falls below the minimum effective concentration, well before the drug is completely eliminated from the body or its plasma concentrations become undetectable.

References

Guo D, Mulder-Krieger T, Ijzerman AP, Heitman LH. Functional efficacy of adenosine A2A receptor agonists is positively correlated to their receptor residence time. *Br. J. Pharmacol.* 166:1846-1859, 2012.

Kulikov AV, Gainetdinov RR, Ponimaskin E, Kalueff AV, Naumenko VS, Popova NK Interplay between the key proteins of serotonina system in SSRI antidepressants efficacy. *Expert Opin. Ther. Targets* 22(4):319-330, 2018.

Mihic S.J., Mayfield J. Hypnotics and sedatives, ch. 22, em: Brunton L.L., Knollmann B.C. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition, 2023. McGraw Hill LLC, New York, USA.