2. Synergism vs. additivity and potentiation

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Since Brazilian legislation has restricted the use of fixed-dose combinations (ANVISA, 2004), some of which lacked a sound scientific rationale, it is important to emphasize the existence and justification of **combinations** (different active principles in the same pharmaceutical dosage form) and **associations** (different active principles in different dosage forms) with proven efficacy. The best-known example is certainly the fight against AIDS (Sühnel, 1990), traditionally based on the use of drug "cocktails" (associations of different medicines). Illustrating a strategic shift (from associations to fixed-dose combinations), the Food and Drug Administration approved in 2012 a medication (Stribild®) formulated as a tablet containing a fixed-dose combination of four anti-AIDS drugs (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate).

In light of the above, we consider it important to review some notions on additivity and synergism, topics seldom addressed in pharmacology textbooks and even by the International Union of Basic and Clinical Pharmacology (Neubig et al., 2003). This helps explain the imprecision in the use of these terms, as illustrated by the provocative title of the article "What is synergism?" published in one of the most traditional pharmacology journals (Berenbaum, 1985).

We speak of **synergism** when the effect of a combination (or association) of two drugs is greater than that expected from simple additivity. The first step, therefore, is to define precisely what is meant by **additivity** (null interaction), which may seem straightforward but becomes more complex in practice, especially given the lack of consensus. For simplicity, two alternatives can be considered: **effect additivity** and **dose additivity** (Tallarida, 2001; Groten et al., 2001; Chou, 2006). Effect additivity (used by ANVISA, unfortunately) means that the resulting effect of a drug association/combination is the arithmetic sum of the individual effects. In the case of dose additivity (Loewe additivity, commonly used in basic and clinical pharmacology through isobolographic analysis – see Tallarida, 2012), the effect of the association/combination is the predicted effect based on the potencies (and doses) of the two drugs; in this case, additivity is assumed when one drug (the less potent) behaves as if it were merely a diluted form of the other.

Once the meaning(s) of this phenomenon are understood, we can reflect on the nature of the mechanisms involved in synergism between two drugs. In practice, interactions may occur at the pharmacokinetic level (usually during metabolism) or at the pharmacodynamic level. In the former case, the most frequent example is enzymatic inhibition, when one drug inhibits the metabolism of another, as in the association between ritonavir and saquinavir. Here, ritonavir inhibits the extensive metabolism of saquinavir via the CYP3A4 enzyme, thereby increasing its plasma concentration and half-life. In the latter case, the final effect may result from the action of two drugs on distinct

molecular targets, as in the marked synergism observed for the antinociceptive effects of phentolamine and paracetamol (Tallarida, 2001).

Finally, the question remains of how, in practice, to assess the type of interaction present when a combination of two (or more) drugs is used. Empirical models are generally employed, requiring only information on the doses (or concentrations) used and the observed effects of the two drugs, in addition to a quantitative dose-response relationship selected empirically (Tallarida, 2001; Groten et al., 2001). Once the criterion for defining a null interaction is established, effects greater than expected indicate synergism, whereas identical and smaller effects indicate additivity and antagonism, respectively (Tallarida, 2001; Groten et al., 2001). If the dose-additivity criterion is chosen, the classical isobolographic analysis introduced by Loewe can be used. An isobologram is a two-dimensional plot with the doses of drugs A and B on the axes, where different lines, the isoboles, connect dose combinations that produce the same effect intensity (Tallarida, 2001; 2012). The situation is somewhat more complex due to the need for statistical testing in addition to qualitative graphical assessment (Tallarida, 2001; 2012).

To conclude, it is important to emphasize that the term **"potentiation"** should be used only in the case of an association/combination between a drug A that has an effect and a drug B with no intrinsic effect, when the resulting effect is greater than that of drug A alone (Chou, 2006).

References

ANVISA, Resolução - RDC Nº 210, de 2 de Setembro de 2004.

ANVISA, Guia para Registro de Novas Associações em Dose Fixa. 1ª edição, 2010.

Berenbaum M.C. What is synergism ? *Pharmacol. Rev*. 41: 93-141, 1989.

Chou T.C. Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies. *Pharmacol. Rev.* 58: 621– 681, 2006.

Groten J.P., Feron V.J., Sühnel J. Toxicology of simple and complex mixtures. *Trends Pharmacol. Sci*. 22: 316-322, 2001.

Neubig R.R., Spedding M., Kenakin T., Christopoulos C. International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. XXXVIII. Update on Terms and Symbols in Quantitative Pharmacology. *Pharmacol. Rev.* 55: 597–606, 2003.

Sühnel J. Evaluation of synergism or antagonism for the combined action of antiviral agents. *Antiviral Res*. 13: 23–39, 1990.

Tallarida R.J. Drug Synergism: Its Detection and Applications. *J. Pharmacol. Ther*. 298: 865–872, 2001.

Tallarida R.J. Revisiting the Isobole and Related Quantitative Methods for Assessing Drug Synergism. *J. Pharmacol. Exp. Ther.* 342: 2–8, 2012.