Pharmacological interactions: Synergism, or not synergism, that is the question

To date there is no final agreement on the definition of drug-drug interaction (DDI). However, it can be generally defined as the pharmacologic or clinical response to the administration of a drug combination that differs from the known effect of the drugs when administered alone. In other words, DDI may elicit change in the effects of one drug by the presence of another or more drugs. The terms additivity, synergism and antagonism should be used with care, unless the specific pharmacological pathways of the investigated drugs are known (Goldoni and Johansson, 2007; Ciracì et al., 2014).

In this respect, the main point of DDI is to correctly identify additive effects, as synergy leads to an effect that is markedly greater than the additive effect, whereas antagonism leads to an effect smaller than the additive effect or the effect of either drug alone. Unfortunately, translating this concept into a suitable methodological approach is challenging due to the lack of universal definition of additivity: for decades researchers have been looking for a formal solution that has been not yet found (Foucquier and Guedj, 2015). Certainly, an additive effect is not represented by the arithmetic sum of the effect of each single component (Calzetta et al., 2015; Chou, 2006).

Despite the several equations and theories proposed to correctly identify additivity, the most frequently used methods provide effective results characterized by minimal differences each other. For instance, the expected additive effect resulting from the Bliss Independence equation, a statistical analysis of DDI, is only $\simeq 5$ % different than the outcome provided by the isobologram approach, a method representative of the Unified Theory that permits quantification of the magnitude of DDI (Calzetta et al., 2015; Chou, 2006). Interestingly, both the Bliss Independence and Unified Theory methods have been extensively validated in human pharmacology, by providing consistent and biologically plausible results (Calzetta et al., 2018a).

Current medicine is mainly driven by the identification of new molecules with beneficial pharmacological activity. Nevertheless, the probability of success in discovering new molecules with potential therapeutic action is becoming more and more difficult (Rai et al., 2021). Thus, combining two or more agents may have multiple favourable impacts in pharmacotherapy. While administering one drug at high doses could improve the efficacy, this approach may lead to higher frequency and greater severity in adverse events. Furthermore, it may also increase the emergence of resistance to monotherapy (Yang et al., 2020). Conversely, acting on parallel pharmacological pathways linked at intracellular level by cross-talk networks may induce beneficial DDI, thereby amplifying the benefits of either drug alone to produce a strong synergistic effect (Calzetta et al., 2015, 2018a). Overall, synergistic interaction across different drugs allows optimization of efficacy towards achieving the maximal biological effect.

DDI has also another relevant advantage: when synergy is elicited by combining two or more drugs, the same pharmacological response can be achieved by administering lower doses of each single component (Calzetta et al., 2018b). Indeed, this intrinsic characteristic of DDI can be used to elicit a clinically detectable effect by reducing the risk of adverse events (Calzetta et al., 2015, 2018a). Interestingly, the possibility of dose-reduction mediated by synergistic DDI seems to be related with the number of single components included in the combination, at least in pre-clinical investigations performed in human isolated tissue (Calzetta et al., 2018c; Rogliani et al., 2020).

In the light of these data, the current virtual special issue (VSI) entitled "Pharmacological interactions: synergism, or not synergism, that is the question" provides valuable information concerning DDI in the context of the following disease areas: chronic obstructive respiratory disorders, chronic kidney disease, anti-infective treatments, cancer, cardiovascular and neurodegenerative disorders.

In asthma and chronic obstructive pulmonary disease (COPD), the use of bronchodilators and corticosteroids has been a mainstay treatment for disease. Rogliani et al. (2021) detailed the mechanisms of synergism between inhaled corticosteroids (ICS), long-acting β_2 adrenergic receptor agonists (LABA), and long-acting muscarinic receptor antagonists (LAMA). In chronic kidney disease, there is an exceedingly high level of DDI, thus Papotti et al. (2021) described the mechanisms underlying DDI in patients that are being treated with multiple therapeutics.

With respect to pathogen exposure, some of the therapies utilized have the capability to significantly affect normal processes in the patient in order to rid the body of the microorganism. Riccardi et al. (2021) reported on treatment of tuberculosis, noting ways in which to optimize treatment to effectively manage infection while minimizing any negative effects of treatment on patients. With respect to virus exposure, HIV treatments are varied in their mechanisms of action to combat infection and spread of the virus. Lu et al. (2021) described how integrase strand transfer inhibitors, a first-line treatment for HIV, differ in how the drugs are metabolized, and how this can potentially affect interactions with other therapeutics that the patient may be taking concomitantly.

While primarily being known for regulation of cellular antioxidant responses in a large number of disorders, Wang et al. (2021) specifically detailed the role for the Nrf/Keap1 signaling pathway in anti-cancer treatments and how other therapeutic regimens may modulate the pathway.

Since cardiovascular disorders are so multifaceted, different aspects been given particular attention in this VSI. Bellia et al. (2021) described the effects of interactions between anti-coagulants and medications prescribed for cardiometabolic diseases of the elderly. With respect to heart failure due to cardiac fibrosis, Garoffolo and Pesce (2021) detailed

the mechanisms of action underlying anti-fibrotic therapies, and how by targeting these pathways both contractile dysfunction and progression of heart failure can be slowed. With a different perspective on cardiac disease, Geng et al. (2021) summarized evidence showing interactions between cardiovascular drugs with respect to pharmacogenomics and the effect of circadian rhythms.

Neurodegenerative disorders, like cardiovascular diseases, are multifaceted in their etiology. Khatri et al. (2021) described the concert of signaling pathways by which neurodegenerative diseases occur and how the targeting of multiple pathways provides better ways to treat these disorders, but with special attention paid to DDI.

The goal of this VSI was to increase our understanding of how drug interactions may be beneficial as well as detrimental to the health of patient in order to treat the underlying disease. Overall, in order to elicit benefits from DDI, it is important that drugs characterized by different mechanisms of action reach the same site of action at balanced dose-ratio (Calzetta et al., 2018d, 2019). Finally, but no less important, the assessment of DDI should be carried via validated reference analysis framework at any stage of drug development, from bench-to-bedside, in order to optimize the final formulation by considering to combine also more than two drugs (Foucquier and Guedj, 2015; Calzetta et al., 2019).

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