Pharmacodynamic Drug–Drug Interactions

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Contents

Abstract

Concomitant medications with similar or opposite pharmacological effects can cause pharmacodynamic drug interactions. Pharmacodynamic interactions generally fall into three categories: additive, antagonistic and synergistic. This chapter describes the commonly used

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empirical methodologies to evaluate pharmacodynamic interactions. Due to knowledge and data gaps in the systems involved, pharmacodynamic interactions are difficult to predict. Quantitative systems pharmacology models are emerging recently as promising approaches that integrate knowledge from multiple disciplines including drug pharmacology, systems biology, physiology, mathematics and biochemistry. Readers are referred to other sources for more detailed discussions on such novel methodologies.

General Considerations

Drug–drug interactions (DDIs) can occur during polypharmacy therapies. DDIs can be the results of pharmacokinetic interactions, e.g., metabolic or transporter-mediated, or pharmacodynamic interactions. Pharmacokinetic interactions are the topic of discussion in another chapter in this book. Pharmacodynamic interactions can occur between coadministered drugs with similar or opposite pharmacological effects from direct interactions at drug receptors or targets. Pharmacodynamic interactions due to drug exposure changes as the result of pharmacokinetic interactions are not discussed here.

The resulting pharmacodynamic interactions can be generally classified into three categories: additive, antagonistic, and synergistic. Additive DDIs describe the resulting effect of the two coadministered drugs that is greater than the effect of each drug given alone. Examples of additive DDIs include sleeping aid medicines taken with alcohol which can result in greater drowsiness than caused by either sleeping aid or alcohol taken alone, or aspirin (antiplatelet) plus heparin (anticoagulant) which may increase bleeding risk. In antagonistic DDIs, one drug reduces or eliminates the effect of the other coadministered drug. Antagonistic DDIs can be beneficial to reverse dangerous drug effects. For example, vitamin K is a reversal agent for anticoagulant warfarin, and naloxone is used an antidote for narcotic overdose.

Synergistic DDIs describe the situations when the combined effect of two drugs is greater than the sum of the effects of each drug given alone. Synergistic DDIs are commonly employed in drug therapies. Drug cocktails have been developed and often used for treatment of diseases from HIV to cancer. Anti-HIV drugs are almost always combined to minimize the development of drug-resistant HIV virus. Harvoni® combines two HCV direct-acting agents, ledipasvir and sofosbuvir, that have significantly reduced the length of treatment compared to the previous interferon-based therapy. In the more recent exciting areas of immuno-oncology, immune check point inhibitors for different immune targets are combined to enhance the immune responses against tumors (Allard et al. 2018). For example, in patients with metastatic melanoma and less than 1% PD-L1 expression, exploratory subgroup analysis showed that the combination of PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab had higher progression-free survival than either agent given alone (Opdivo® Package Insert, March 2018).

Unlike pharmacokinetic interactions where one may be able to predict the direction or magnitude of the DDIs based on the known disposition mechanisms of the drugs involved using mechanistic static or dynamic models (e.g., physiologically-based pharmacokinetic models) (FDA 2017; Jones et al. 2015; EMA 2012), it is far more difficult to predict pharmacodynamic interactions due to knowledge and data gaps in the systems involved. Quantitative systems pharmacology models are emerging recently as promising approaches that integrate knowledge from multiple disciplines including drug pharmacology, systems biology, physiology, mathematics, and biochemistry (Abernethy et al. 2011; Leil and Ermakov 2015; Gadkar et al. 2016). These models allow in silico hypothesis testing that would otherwise need to be evaluated experimentally and potentially prospective predictions following drug therapies either as a single agent or combination. The readers may refer to the above references for more detailed discussion of these approaches.

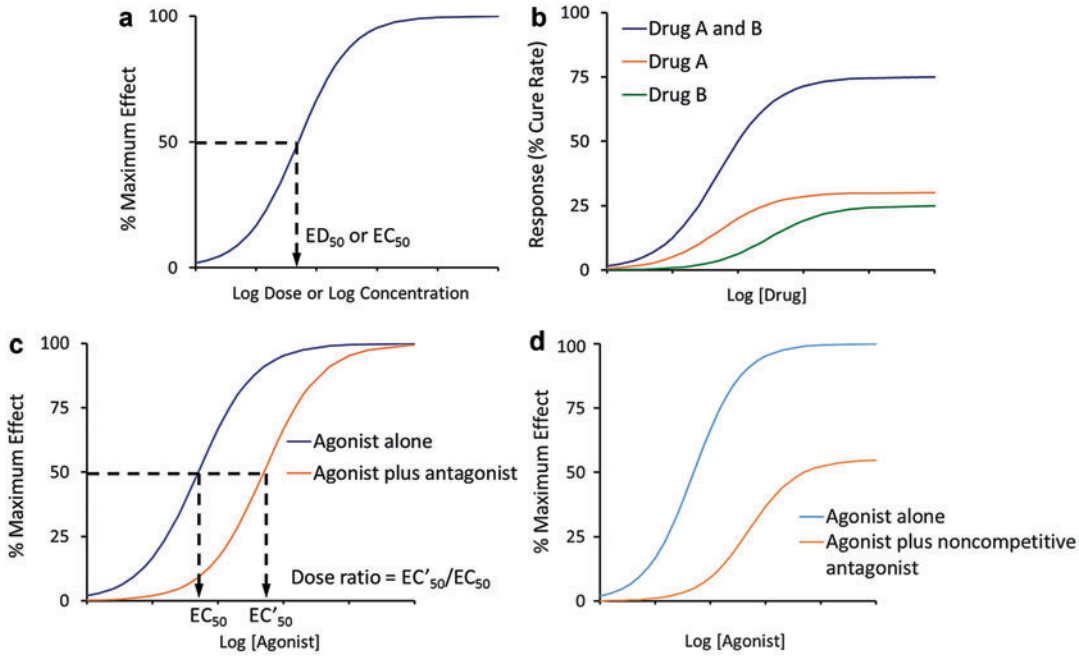

Fig. 1 (**a**) Semilogarithmic dose- or concentration-response curve. Log dose or concentration scale is for illustration purpose only and does not represent any actual values. (**b**) Concentration-response curves when Drug A or B is administered alone or combined. (**c**) Right shift of a concentration-response curve in presence of a competitive antagonist. (**d**) Change in concentration-response curve in presence of a noncompetitive antagonist

Dose- or Concentration-Response Curve Analysis

Purpose and Rationale

Analysis of the dose- or concentration-response curves and comparison of the curves from Drug A alone and Drug A and B combined allow exploration of pharmacodynamic interactions of the two drugs.

Procedure

Observed responses are plotted on the y-axis against the respective doses or concentrations where the responses were obtained on the x-axis. Response can be expressed as a percentage of the maximum response or change from baseline. The doses or concentrations on the x-axis are usually log-transformed so the corresponding dose- or concentration-response curve becomes sigmoidal (Fig. 1a). Log-transformation is helpful; especially, the dose or concentration range is relatively wide. Comparison of the resulting curves from Drug A alone and Drug A and B combined can yield useful insights on the nature of the pharmacodynamic interaction.

Evaluation

The dose- or concentration-response curve allows estimation of the maximum effect (E_{max}) and the dose or concentration at which half of the maximum effect is observed, ED50 or EC50, respectively. If the E_{max} of combined Drug A and B is greater than Drug A alone, an additive or synergistic effect can be assumed (Fig. 1b). However, unless the dose- or concentration-response curve is known for Drug B alone, additive or synergistic effect from the combination cannot be differentiated.

In the case of competitive antagonistic effect, the curve shifts to the right and Drug A needs to be at higher doses or concentrations to reach the E_{max} (Fig. 1c). In the presence of noncompetitive antagonism after combining Drug A and B, not only the curve shifts to the right but the E_{max} is also decreased (Fig. 1d).

The linear part of the log-transformed concentration-response curve, between 20% and 80% of the maximum effect, can be described by the following equation (Gibaldi and Perrier 1982):

$$E = m \times \log C + b$$

where E is the response, m the slope of the linear portion of the plot, b the intercept.

Critical Assessment of the Method

Comparison of dose- or concentration-response curves is an empirical method to explore pharmacodynamic interactions. The ability to successfully conduct such analysis relies on the completeness of the available data. To be able to establish a good dose- or concentration-response relationship, it is important to conduct the study over a wide range of doses or concentrations. Due to obvious practical concerns over cost and time, studies meeting such criteria were not widely conducted. However, the advent of model-informed drug development in recent years predicts that more better quality studies will be conducted as well as more mechanistic modeling approaches as mentioned earlier.

Isobolograms

Purpose and Rationale

Direct comparison of the dose- or concentration-response curves from Drug A or B alone versus combination is not able to readily distinguish additive from synergistic effect. Isobologram allows a graphical analysis whether the pharmacodynamic interaction is additive, synergistic/supra-additive, or sub-additive. The basis of this analysis was based on the concept of dose equivalency where an equally effective dose of Drug A would add to the dose of Drug B. When the potency ratio of the two drugs is constant, the isobole is linear and shows an additive effect. Varying potency ratio leads to nonlinear additive isobole indicating synergistic or sub-additive effect (Chou 2006; Tallarida 2006, 2011, 2016).

Procedure

First the ED50 or EC50 is determined from the dose- or concentration-response curve for both Drug A and B when administered alone (Fig. 2a). The ED50 or EC50 values for the two drugs on the x- and y-axis are connected by a linear line when the potency ratio is constant (Fig. 2b). Any dose combination of Drug A and B based on the linear line can be tested to determine the combined effect.

In addition to 50% effect, other desired effect levels, e.g., 30%, 40%, 70%, etc., can also be studied and the resulting lines will be parallel to the 50% effect line.

Evaluation

The linear line in the isobologram (Fig. 2c) implies an additive effect from the combination. When different combinations of Drug A and B along the linear line in Fig. 2b are tested, if the combination results in synergism, then the 50% effect will fall below the linear line of additivity. On the other hand, the 50% effect from sub-additivity will fall above the linear line.

The linear additive isobole is commonly expressed as (Tallarida 2006):

$$\frac{a}{Ai} + \frac{b}{Bi} = 1$$

$$(0 \le a \le Ai, 0 \le b \le Bi)$$

where a and b are the dose pairs of Drug A and B, respectively, along the isobole, and Ai and Bi are

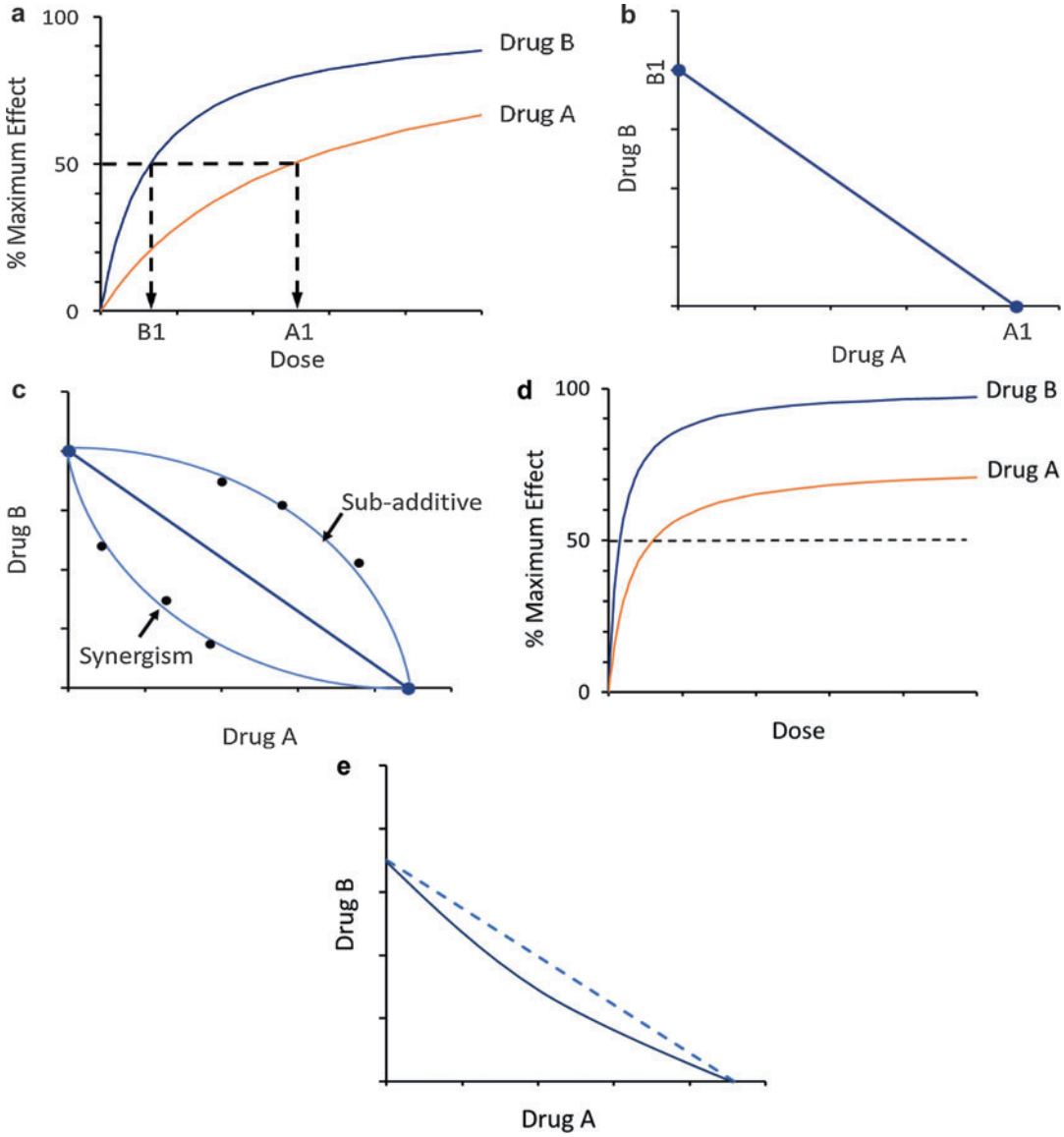

Fig. 2 (**a**) Determination of ED50 from dose-response curves of Drug A and B when administered alone. (**b**) Linear additive isobole when Drug A and B have a constant potency ratio. (**c**) Isobologram showing additive, synergism, and sub-additive effect from drug combinations. The black dots depict experimental data. (**d**) Dose-response curves from Drug A and B with different maximum effects. (**e**) A curvature isobole deviates from linearity when potency ratio of the two drugs is not constant

intercept with the x- and y-axis and equivalent to the ED50 or EC50 of Drug A and B. As mentioned earlier, the additive isobole can also be drawn for other effective levels and the above equation still applies. The resulting isoboles will be parallel to the 50% effect line.

Critical Assessment of the Method

An isobologram has only two dimensions for two-drug combinations. For combinations of three or more drugs, it is not convenient to construct multidimensional isobologram. Secondly,

accurate determination of synergism or subadditivity requires accurate determinations of ED50 or EC50 for each drug as well as the effects after combinations. Large variabilities in these determinations can lead to uncertainties in drawing the correct conclusion. Finally, there is also no general rule as to how far the combined effect should be from the isobole to conclude nonadditivity.

Modifications of the Method

As the actual determined ED50 or EC50 values from studies always have a variance, there is also a variance for the total additive dose. Consequently, every point on the isobole has an error. Calculation of variance or confidence intervals for isoboles can be incorporated for proper statistical comparison with the observed data points (Tallarida 2006, 2016).

As mentioned earlier, the additive isobole is linear if the potency ratio of the two drugs is constant. When two drugs have different maximum effect (Fig. 2d), the potency ratio is no longer constant. In this case, the additive isobole will show a curvature (Fig. 2e). Therefore, it is very important to first establish the relationship of the potency ratio of the two drugs before drawing conclusion from the shape of the isobole. The equations and calculations to derive the additive isobole when the two drugs have variable potency ratios were discussed in detail by Tallarida (2011).

Schild Plots

Purpose and Rationale

In the presence of an antagonist, it can be expected that there will be a rightward shift of the dose- or concentration-response curve of an agonist. In the case of competitive antagonism, the rightward shift is parallel to the original curve (Fig. 3a). For noncompetitive antagonism, there is a rightward shift as well as a decrease of the maximum effect (Fig. 1d). By testing with the antagonist over a wide range of doses or concentrations, one can quantify the potency of the antagonist (Schild 1957; Arunlakshana and Schild 1959).

Procedure

First a series of separate experiments are conducted, one without the antagonist, the others with the antagonist and increasing doses or concentrations of the agonist (Fig. 3a). The log-transformed dose- or concentration-effect curves are plotted. If the curves are parallel, competitive antagonism can be presumed. Next the constants of the following equation describing competitive antagonism are determined (Schild 1957; Arunlakshana and Schild 1959):

$$\log(x-1) = \log K2 - n\ pAx$$

where x is the dose/concentration ratio, K_2 the dissociation equilibrium constant for the antagonist, n the slope, and pAx the negative logarithmic molar concentration of the antagonist that produces the fold rightward shift of the agonist dose- or concentration-response curves. For a two-fold shift, pAx is expressed as pA_2. For competitive antagonism, $n = 1$. The dose/concentration ratio x is the ratio of agonist dose/concentration needed to achieve the same effect, e.g., half maximum effect, in the presence and absence of the antagonist. It is worth noting that the above relationship describing competitive antagonism is independent of the fraction of active receptors, i.e., receptors bound to the agonist.

The Schild plot is constructed by plotting log (x-1) against the negative logarithmic molar concentrations of the antagonist, which is pAx by definition (Fig. 3b).

Evaluation

The Schild plot intersects with –log[molar antagonist] when dose ratio is 2, i.e., $\log(x\text{-}1) = 0$. This value corresponds to pA2 which is a measure of the potency of the antagonist. When $n = 1$, $pA2 = \log K_2$, and $pA2 - pA10 = 0.95$. The $pA2 - pA10$ difference of 0.95 can be used as a simple test for competitive antagonism. Several

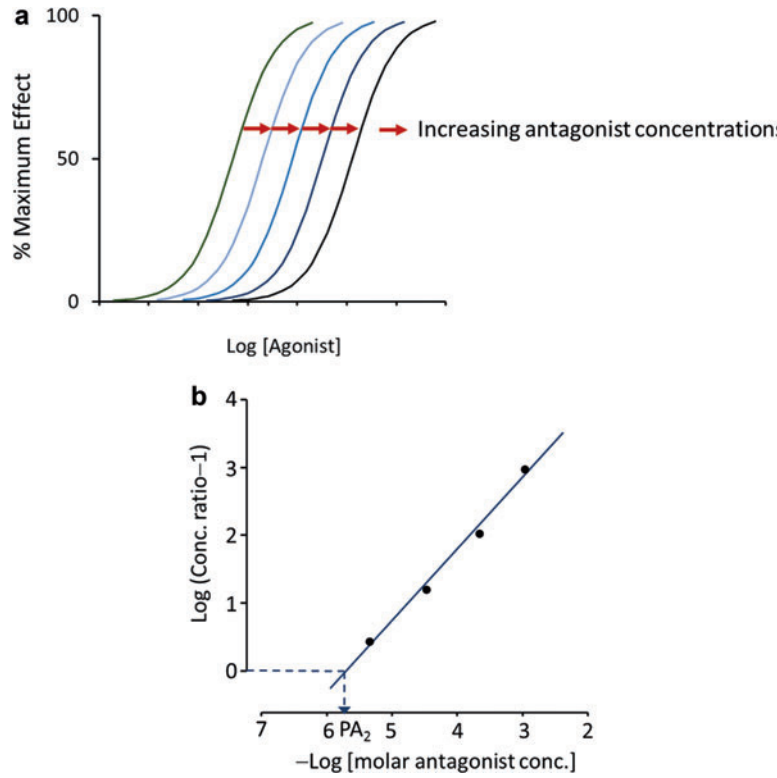

Fig. 3 (**a**) Right shift of concentration-response curves with increasing concentrations of competitive antagonism. The green curve is in the absence of an antagonist. (**b**) Schild plot

sources of errors may lead to underestimation of the pA2−pA10 difference: depression by a maximum agonist dose, a change in effect and receptor relationship (e.g., due to desensitization), and failure or delay of the antagonist to reach equilibrium (Schild 1957).

Critical Assessment of the Method

The application of Schild plots requires exhaustive tests of administering the agonist and antagonist at various combinations of doses. This is possible under in vitro experimental settings but impractical under clinical settings due to ethical, safety, cost, and time restrictions.

Modifications of the Method

pAx is suitable for determining and comparing activities of antagonists which do not alter the slopes of the logarithmic dose- or concentration-effect curves of an agonist. In the case of noncompetitive antagonism where the curves are not parallel but become gradually flattened and the maximum effect declines with increasing doses of the antagonist, the pAx values vary with the concentrations of the agonist. In addition, both pAx and pAx differences, e.g., pA2–pA10, depend on the fraction of active receptors. One way is to describe the noncompetitive antagonistic activity in terms of the concentration required to produce a given reduction of the maximum effect, e.g., the concentration which reduces the maximum effect by half (Schild 1957). pAh was introduced to describe the negative logarithm of this molar concentration.

Factorial Design Trials

Purpose and Rationale

Factorial design trials are used to assess two or more interventions (i.e., independent variables) on the same endpoint in the same study. In a

factorial design, two or more interventions are tested simultaneously using varying combinations. The main advantage of a factorial design is its efficiency which potentially reduces the sample size of the study, up to one-half, compared to two separate two-arm parallel studies (Pandis et al. 2014). Factorial design may allow evaluation of interactions only when the study is properly powered (Montgomery et al. 2003; Pandis et al. 2014; Pocock et al. 2015).

Procedure

The simplest example is a two-treatment 2×2 factorial design. In this design, subjects are randomly allocated to one of the four possible combinations of Intervention A and B: A alone, B alone, combination of both A and B, and neither A nor B (placebo or control group). In a 2×2 factorial design (Table 1), subjects are randomized twice: once to either the experimental or control arm for Intervention A and again to either the experimental or control arm for Intervention B. Alternatively, subjects may be randomized simultaneously to the four groups (Pandis et al. 2014).

There are three hypotheses one may want to test in a 2×2 factorial design: (1) the hypothesis on the effect of Intervention A, (2) hypothesis on the effect of Intervention B, (3) interaction hypothesis that the effect of Intervention A depends on the level of Intervention B, or vice versa. Factorial design trials are most commonly powered to detect the main effect of each intervention, on the assumption that there is no interaction between the interventions (Montgomery et al. 2003). A main effect refers to the effect of one intervention, either Intervention A or B, on the endpoint, regardless of the effect of the other intervention. As factorial design trials are powered to detect the main effects, they are under powered to detect interactions (Montgomery et al. 2003).

A real-world 2×2 factorial design study can be illustrated with the CURRENT-OASIS 7 study

Table 1 An example of a 2×2 factorial design

		Intervention B	
		Yes	No
Intervention A	Yes	A + B	A only
	No	B only	Neither A nor B

(CURRENT–OASIS 7 Investigators 2010). The CURRENT-OASIS 7 study randomized 25,086 patients with acute coronary syndrome to either double-dose clopidogrel or standard-dose clopidogrel and either higher-dose aspirin or lower-dose aspirin. The primary outcome was cardiovascular death, myocardial infarction, or stroke at 30 days. The study was powered assuming no interaction between the two study-drug comparisons. The patients were first randomly assigned in a double-blind fashion to a double-dose clopidogrel or standard-dose clopidogrel regimen. This was followed by a second randomization in an open-label fashion to higher-dose aspirin or lower-dose aspirin. As summarized in Table 2, main effect analyses showed that there was no significant difference between a double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to the primary outcome of the study. There was a nominally significant interaction between the clopidogrel and aspirin dose comparisons (Table 3). Since the interaction was not expected based on a known biological mechanism, the authors suggested that it was due to the play of chance. However, had there been a known mechanism, as the study was powered to only detect the main effects, the authors would not be able to draw conclusion on the interaction.

Interaction from a 2×2 factorial design may be visualized in a line graph. Using the CURRENT-OASIS 7 results, the interactions may be represented in Fig. 4. If the two lines are parallel, it may be interpreted that there was no interaction, whereas if the lines are not parallel, there may be an interaction. In this particular, as explained previously, since there is not a plausible biological explanation, it may be due to the play of chance.

Table 2 Results from CURRENT-OASIS 7 study

Main effect of clopidogrel dose on primary outcome			
	Double dose clopidogrel (percent rate)	Standard dose clopidogrel (percent rate)	P value
Primary outcome	4.2	4.4	0.30
Main effect of aspirin dose on primary outcome			
	Higher dose aspirin (percent rate)	Lower dose aspirin (percent rate)	P value
Primary outcome	4.2	4.4	0.61

Table 3 Interaction test of clopidogrel dose regimen according to aspirin dose regimen

	Primary outcome rates		
	Double dose clopidogrel	Standard dose clopidogrel	P value for interaction
Higher dose aspirin	3.8	4.6	0.04
Lower dose aspirin	4.5	4.2	

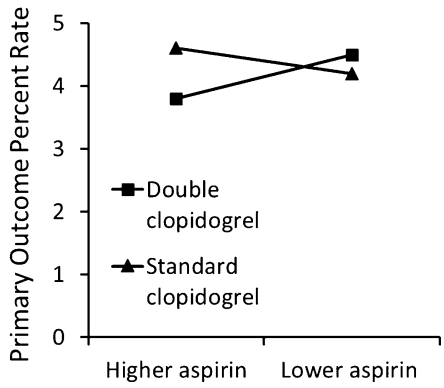

Fig. 4 Graphical interaction analysis of clopidogrel and aspirin

Critical Assessment of the Method

The efficiency of reduced sample size from factorial designs is only realized if there is no interaction between the interventions. A study that is designed to specifically test interactions requires a much larger sample size, thus has no advantage compared to a multiarm parallel trial (Montgomery et al. 2003; Pandis et al. 2014; Pocock et al. 2015). It is therefore critical during the design stage to ascertain the assumption about interaction. If absence of interaction cannot be ascertained and the study is powered to detect main effects, then it is not possible to draw conclusion on interaction. Because factorial design trials are most commonly powered to detect main effects, it has limited power to detect interaction.

Modifications of the Method

In a 2×2 factorial design, two independent variables and two levels (two levels per independent variable) are investigated. In the above CURRENT-OASIS 7 study, the two independent variables were clopidogrel and aspirin, and each had two dose levels. Factorial designs are also able to investigate multiple independent variable and multiple levels. For example, a 3×3×2 factorial design is a design with three independent variables, the first two independent variables with three levels and the last with two levels.

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