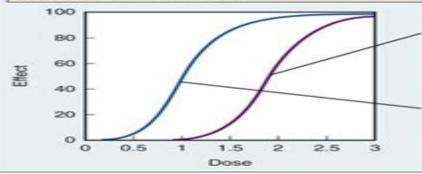


The standard dose response curve for a single drug is shifted to the left along the horizontal axis by the presence of a second drug.

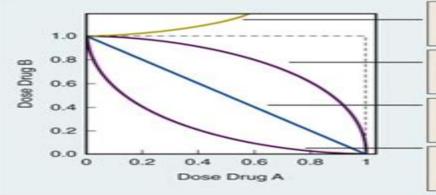


**Drug A alone,** for example:  $ED_{50}$  Drug A = 1.9 This is a standard *sigmoid*  $E_{max}$  dose-response curve. (e.g., Propofol for immobility)

Drug A + Drug B e.g., ED50 Drug A = 1.0 in presence of drug B In the presence of Drug B, dose requirements of Drug A are reduced. (e.g., Propofol in the presence of fentanyl 1  $\mu$ /kg at an endpoint of immobility)

#### The isobologram

An isobologram is an iso-effect line whereby all the combinations of each drug along the line give the same observed effect. Multiple isobolograms can be drawn for different effect levels such as ED50 or ED95. The doses required of each drug individually are on the X and Y axes respectively.



Antagonistic

Drug A increases dose of drug B to achieve the same effect

(e.g., Naloxone and fentanyl for analgesia)

Infra-additive e.g., >0.5 + >0.5 = 1 Together the individual doses of each drug are slightly reduced to achieve the same effect (e.g., Ketamine and midazolam for sedation)

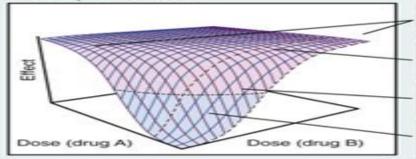
Additive e.g., 0.5 + 0.5 = 1 Together, half the dose of each drug will achieve the same effect (e.g., Isoflurane and nitrous oxide for immobility)

Synergistic e.g., <0.5 + <0.5 = 1Together, less than half the expected dose of each drug is required to achieve the same effect (e.g., Propofol and midazolam for hypnosis)

#### The response surface

The response surface is a three dimensional graph with drugs A and B on the horizontal axes and effect on the vertical axis. The concept embraces shift in dose-response curves and the isobologram, and describes effects for the complete set of doses for the endpoint in question. Responses may be either continuous such as bispectral index and blood pressure, or quantal such as a sedation scale, awake/sleep and movement/immobility.





#### Dose-response curve

Drug A alone is on one axis and drug B in the other axis

#### Shift in dose response

Drug B in the presence of a constant concentration of Drug A

#### Isobologram

The 50% effect isobole is shown.

Outward bowing of the surface indicates synergy

#### Response surface

All doses of drug A and B and their responses are shown (e.g., Sevoflurane and remifentanil for immobility)

# **Drug Interactions In Anesthesia**

Kurt A. Grimm, William J.
Tranquilli, Leigh A. Lamont

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