Is Synergy the Rule? A Review of Anesthetic Interactions Producing Hypnosis and Immobility

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BACKGROUND: Drug interactions may reveal mechanisms of drug action: additive interactions suggest a common site of action, and synergistic interactions suggest different sites of action. We applied this reasoning in a review of published data on anesthetic drug interactions for the end-points of hypnosis and immobility.

METHODS: We searched Medline for all manuscripts listing propofol, etomidate, methohexital, thiopental, midazolam, diazepam, ketamine, dexmedetomidine, clonidine, morphine, fentanyl, sufentanil, alfentanil, remifentanil, droperidol, metoclopramide, lidocaine, halothane, enflurane, isoflurane, sevoflurane, desflurane, N_2O, and Xe that contained terms suggesting interaction: interaction, additive, additivity, synergy, synergism, synergistic, antagonism, antagonistic, isobologram, or isobolographic. When available, data were reanalyzed using fraction analysis or response surface analysis.

RESULTS: Between drug classes, most interactions were synergistic. The major exception was ketamine, which typically interacted in either an additive or infra-additive (antagonistic) manner. Inhaled anesthetics typically showed synergy with IV anesthetics, but were additive or, in the case of nitrous oxide and isoflurane, possibly infra-additive, with each other.

CONCLUSIONS: Except for ketamine, IV anesthetics acting at different sites usually demonstrated synergy. Inhaled anesthetics usually demonstrated synergy with IV anesthetics, but no pair of inhaled anesthetics interacted synergistically.

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All general anesthetics produce two critical clinical end-points: hypnosis and immobility. Two or more drugs are often combined to achieve these end-points, producing interactions labeled as "synergistic," "additive," or "infra-additive" when their combined effect exceeds, equals, or is less than that of the sum of the effects of the individual drugs, respectively. Infra-additive is also referred to as "antagonistic."

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Synergistic interactions may be clinically useful because they allow the use of smaller doses of the individual drug and thus potentially decrease side effects. However, synergy can also be associated with adverse effects, such as profound ventilatory depression when midazolam is combined with fentanyl.[1] Documentation of net benefit or risk with synergy is scant, with ". . . very few studies that demonstrate that a particular anesthetic drug interaction makes a meaningful improvement in cost, safety, or patient comfort."[2]

Beyond clinical uses, drug interactions may provide insights into mechanisms of anesthetic action. Strictly additive interactions must occur when anesthetics act identically at a single site. Thus, strict additivity supports, but does not prove, a single site of action. Deviations from strict additivity suggest different sites of action.[2–8]

This review summarizes published interaction data for the end-points of hypnosis and immobility (particularly suppression of movement after "supramaximal" noxious stimulation). We will define common trends in drug interactions between different drug classes, and identify where new information is needed to guide clinical care and studies of mechanism of action.

METHODS

We searched the entire PubMed database for animal and human data describing anesthetic combinations

producing hypnosis and immobility. We considered drugs that act on γ-aminobutyric acid type A ($GABA_A$) receptors (propofol, etomidate, methohexital, thiopental, midazolam, and diazepam), an *N*-methyl-D-aspartate (NMDA) receptor antagonist (ketamine), α_2 adrenoceptor agonists (dexmedetomidine, clonidine), μ-opioid receptors (morphine, fentanyl, sufentanil, alfentanil, and remifentanil), dopamine receptor antagonists (droperidol and metoclopramide), and a sodium channel blocker (lidocaine). We added inhaled anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane, nitrous oxide [N_2O], and xenon [Xe]), compounds whose site of action is less clear. Every pair of these drugs was entered as a search term, combined with each of these terms: interaction, additive, additivity, synergy, synergism, synergistic, antagonism, antagonistic, isobologram, isobolographic, regression, movement, minimum alveolar concentration (MAC), incision, awareness, hypnosis, and memory.

In humans, we defined hypnosis as loss of appropriate response to verbal command or as "syringe drop," and immobility as suppression of movement in response to surgical incision or tetanic electrical pulses. In animals, we defined hypnosis as loss of the righting reflex, and immobility as suppression of movement in response to tail clamping or electrical stimulation.

We applied the definitions of addition, synergy, and infra-additivity used in the two companion studies.[9,10] After determining the dose (or concentration) that abolishes the target response (e.g., movement) in 50% of subjects (ED_{50}) for each of two paired drugs A and B individually, we analyzed the dose (or concentration) of both drugs given together that produced exactly the same effect. The doses of each of the two drugs, A and B, were normalized to the ED_{50} for each drug ($ED_{EP,A}$ and $ED_{EP,B}$) when given alone. The normalized doses were summed: $\frac{Dose_A}{ED_{EP,A}} + \frac{Dose_B}{ED_{EP,B}}$. A normalized sum <0.9 was defined as synergy. A normalized sum between 0.9 and 1.1 was defined as additivity. A normalized sum more than 1.1 was defined as infra-additivity or antagonism. Although such a sum supplies only one point on the isobologram, it is particularly attractive because that single number provides a simple and clear definition applicable to most published data. Using these criteria, we reanalyzed the data from all studies identified in our literature search. When full dose–response data for both drugs and their combination were published (an infrequent event), our reanalysis also applied response surface modeling.[11] Raw data supplied by several investigators allowed a more accurate reanalysis. All analyses are available as a web supplement to this manuscript (available online at www.anesthesia-analgesia.org).

When one or both drugs could not produce the target response alone (i.e., a ceiling effect was found), but the drugs given together could produce the target response, this was considered synergy by definition. An example is the relationship between inhaled anesthetics and opioids. Opioids can reduce the MAC of inhaled anesthetics, but they cannot reduce it to 0. There is a ceiling on the interaction. The Appendix explains why a ceiling effect by definition demonstrates synergy.

Some data (e.g., measures of the time to loss of consciousness when using drug X with or without drug Y) did not permit assessment of the nature of the interaction, and we excluded these studies. We also excluded studies that only examined a single dose of either drug, because a single dose cannot imply the nature of an interaction (i.e., in the absence of a knowledge of the ED_{50} for the test compound). Studies of inhaled anesthetics provide an exception because the ED_{50} (MAC) for these drugs is known.

For our presentation of results, absence of a description of interactions of a particular compound with other study compounds indicates that no such interaction reports were found. Similarly, the absence of statements for results with animals or with humans indicates that no interpretable data were found.

RESULTS

The text below describes the interaction between individual drug pairs. An excel spreadsheet summarizing the detailed results by study is available as a web supplement (available at www.anesthesia-analgesia.org). Figure 1 presents the interaction grid between drugs in various drug classes for human and animal studies.

One or Both Drugs Acting at the $GABA_A$ Receptor (But Not Necessarily at the Same Site on the Receptor)

Propofol

In humans, propofol and thiopental interact additively[12,13] or synergistically[14] for hypnosis, and synergistically for movement in response to noxious stimulation.[12] Propofol and midazolam reportedly interact synergistically for hypnosis in humans,[11,15–18] and where sufficient data were available, our reanalyses confirm some of these findings.[11,15,16] Midazolam and propofol interact synergistically to produce immobility as indicated by a left shift in the dose–response curve[15,16] more than 10% (since midazolam cannot produce immobility on its own, if the dose versus response relationship is left shifted by more than 10%, this is synergy by definition, as described in the Appendix). Propofol and ketamine reportedly interact additively in humans to produce hypnosis and immobility.[19] On reanalysis, the interaction term for both hypnosis and immobility indicates infra-additivity, a finding significant for immobility ($P = 0.02$), but not hypnosis ($P = 0.17$). Propofol and clonidine appear to produce additivity for hypnosis in humans.[20] In 11 of 13 studies, propofol and opioids produced hypnosis synergistically

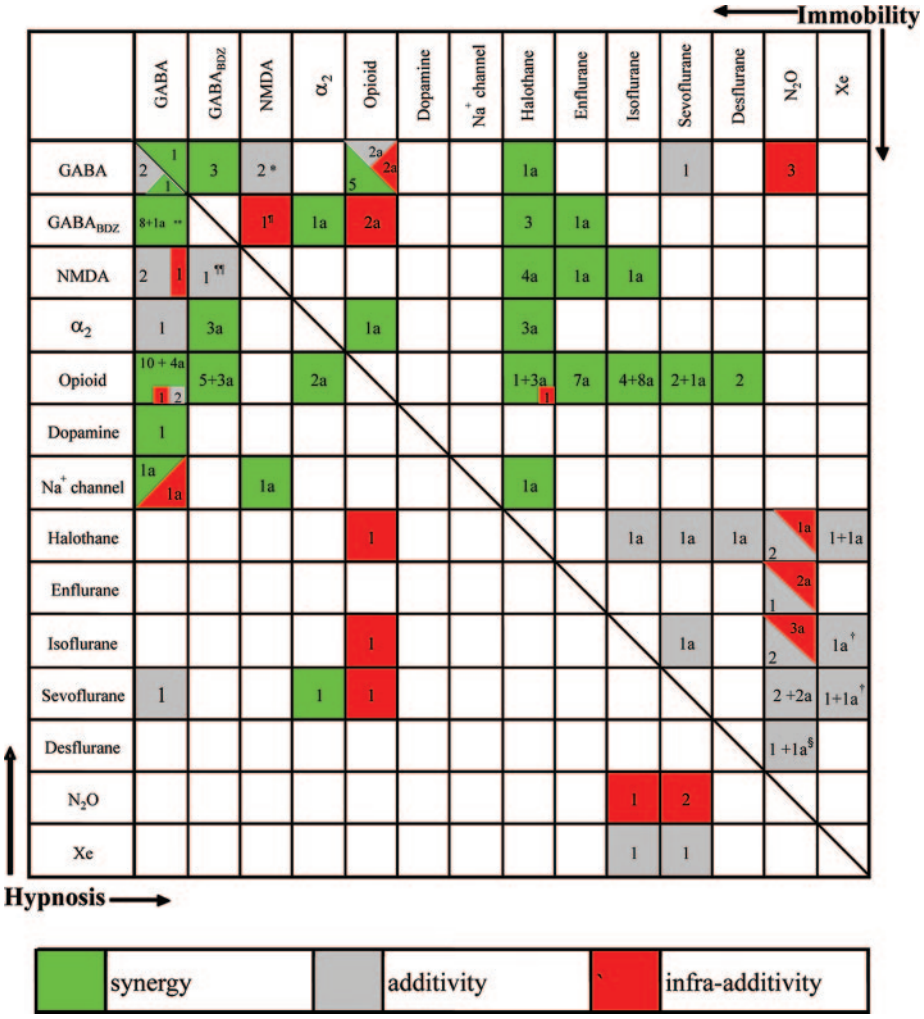

Figure 1. Interaction grid summarizing the available data on drug interactions in humans and animals for hypnosis and immobility. Drugs are organized by pharmacological class. Gamma-aminobutyric acid (GABA) = GABA acting drugs (propofol, thiopental, methohexital, and etomidate); $GABA_{BDZ}$ = agents acting at the benzodiazepine binding site (midazolam, diazepam); *N*-methyl-D-aspartate (NMDA) = NMDA receptor antagonist (ketamine); α_2 = α_2 adrenergic agonists (dexmetedomidine, clonidine); opioid = drugs acting at μ-opioid receptor (morphine, alfentanil, fentanyl, sufentanil, and remifentanil); dopamine = dopamine antagonists (droperidol, metoclopramide); Na^+ channel = sodium channel blockers (lidocaine, bupivacaine); and anesthetic gases. The right upper half of the grid (above the thick diagonal) summarizes interactions for the end-point of immobility; the left lower half (below the thick diagonal) summarizes interactions for the end-point of hypnosis. Synergy is coded as green, additivity as gray, and infra-additivity as red. The number refers to the number of studies attesting to a particular interaction; if one study documents two interactions (e.g., isoflurane with both fentanyl and alfentanil), they are counted separately. Animal data carry the suffix "a" after the number of studies, human data have no suffix. *Reanalysis: propofol–ketamine interaction in humans is infra-additive for immobility.[19] **Reanalysis: thiopental – midazolam interaction in humans is additive for hypnosis.[37] ¶, ¶¶Reanalysis: ketamine–midazolam interaction in humans is infra-additive for hypnosis and additive for immobility.[51] †Because the MAC of Xe in swine is uncertain, data in swine[149,150] are not included (see Discussion). §Infra-additivity between desflurane and N_2O has been suggested in a small subgroup of 18–30-yr old patients.[139]

in humans (fentanyl,[21] alfentanil,[11,16,18,22,23] remifentanil[24,25]). Because fentanyl has a ceiling effect (i.e., in the absence of propofol no dose of fentanyl can exert a full hypnotic effect), the interaction in two studies[26,27] is labeled "synergy by definition." Two studies found additivity, one for fentanyl[28] and one for sufentanil.[29] Why these results differ from most results is unknown. For immobility, the 50% probability of a no-response isobole for the interaction of propofol with fentanyl[19,26] and remifentanil[30,31] bends towards the origin, demonstrating synergy. This is expected, of course, since no dose of opioid suppresses movement in all patients (i.e., the ability of opioids to produce immobility has a ceiling). In a study limited by muscle rigidity, the investigators interpreted the interaction of propofol with alfentanil[16] as synergistic. These authors noted that interactions with drugs that are not full anesthetics (e.g., the ED_{50} of opioids, benzodiazepines cannot be defined for immobility) cannot have an isobologram applied to them to define the nature of their interactions. Therefore, the authors resorted to interpreting the shift in dose–response curves (shift and change in slope) to assess the nature of the interaction. As explained in the Methods section, these studies demonstrate synergy by definition. In

the single available study on propofol and lidocaine's interaction, synergy was found for hypnosis in animals.[32]

The propofol–sevoflurane interaction was additive for hypnosis and immobility[33] in humans. At 67% N_2O or at least half of MAC, N_2O decreased the propofol concentration that inhibited movement after skin incision in humans by 25% to 35%,[34,35] indicating an infra-additive interaction.

Etomidate

In rats, etomidate is synergistic with morphine and with fentanyl for hypnosis and additive for suppression of movement from noxious stimulation. We would expect the interaction for suppression of movement to be "synergy by definition" because opioids cannot alone suppress movement, but data are insufficient to allow reanalysis.*

Methohexital

Methohexital interacts synergistically with midazolam for hypnosis in humans.[36]

Thiopental

Thiopental's interactions with propofol were described above. In humans[37,38] and animals,[39] thiopental and midazolam reportedly act synergistically for hypnosis. We confirmed synergy for one study in humans,[38] but found additivity in another[37] whereas the authors considered their findings a demonstration of synergy. The reason for the discrepancy is unclear. The limited effect of midazolam given alone, hampers studies of interaction on immobility, but a left shift in the thiopental dose–response relationship more than 10% (Appendix) is synergy by definition for immobility in humans.[38] One study[40] in humans described the interaction between thiopental and ketamine as additive both for hypnosis and immobility, but another study found infra-additivity for hypnosis.[41] Reanalysis confirmed the findings of the latter study (infra-additivity, $P < 0.001$); raw data were unavailable for the former. Analgesic concentrations of fentanyl in humans do not affect the hypnotic concentration of thiopental, suggesting either no interaction (if one assumes that sedation and hypnosis are unrelated effects) or at most infra-additivity.[42] Alfentanil decreases the dose of thiopental for hypnosis and immobility,[43] but the nature of the interaction was not examined. In rats, thiopental and morphine or fentanyl interact synergistically for hypnosis[44] and infra-additively for immobility.[45] Droperidol has a ceiling in its ability to induce hypnosis, i.e., no dose of droperidol can induce full hypnotic drug effect.[46] Since droperidol reduces the dose of thiopental for loss of consciousness by more than 10%,[46] the interaction is synergistic by definition (Appendix). IM administration of lidocaine and bupivacaine decreases the dose of thiopental required to produce hypnosis in humans,[47] but the nature of the interaction is unknown. In rats, the thiopental–lidocaine interaction is infra-additive for hypnosis.[48] Thiopental decreases halothane MAC in rats, but with a ceiling according to the authors' Figure 3.[49] In humans, the interaction between N_2O and thiopental appears to be infra-additive on MAC.[50]

Midazolam

The interactions of midazolam with propofol, methohexital, and thiopental are discussed in previous sections. The interaction between midazolam and ketamine in humans is reported as additive for hypnosis and infra-additive (no effect) for immobility.[51] Reanalysis shows infra-additivity for hypnosis ($P < 0.006$) and additivity for immobility ($P > 0.99$). In rats, midazolam interacts synergistically with clonidine on hypnosis[52] and synergistically with dexmedetomidine on both hypnosis and immobility.[53] Opioids and midazolam interact synergistically to produce hypnosis in humans (fentanyl,[54] alfentanil[11,16,18,55]) and animals (morphine[56]). Lidocaine increases the effect of midazolam on hypnosis in humans, but the nature of the interaction is unknown.[57]

Midazolam decreases the MAC of potent inhaled anesthetics in humans (halothane[58,59]) and animals (enflurane[60]). Again, the inability of midazolam to function as a full agonist by itself (i.e., a ceiling effect) combined with its reduction of the inhaled anesthetic concentration required for immobility demonstrates synergy by definition.

Diazepam

Diazepam interacts synergistically with dexmetedomidine[61] and morphine on hypnosis[61,62] in rats. In dogs, it decreases the amount of fentanyl that produces immobility, but the nature of the interaction is unclear.[63] In rats, it produces an infra-additive interaction with fentanyl and morphine for immobility.[64] The study in dogs used isoflurane MAC decreases to measure the interaction, whereas the study in rats may not have applied a supramaximal stimulus (400 g tail pressure).

Diazepam decreases the MAC of halothane in humans[65,66] and animals,[67] with only one study[65] examining two diazepam doses instead of one. This last study suggests, within the limitations of exploring only two doses, that diazepam cannot function as a full agonist for immobility, again suggesting a ceiling effect and synergy by definition.

NMDA Receptor Antagonists—Ketamine

Ketamine's interactions with propofol, thiopental, and midazolam were described above. A study of ketamine and lidocaine interactions found synergy for hypnosis in mice.[32] Ketamine decreases the MAC of halothane[68,69] and enflurane[70] in animals, with the

*Kissin I, Brown PT, Bradley EL. Morphine and fentanyl anesthetic interactions with etomidate. Anesthesiology 1987:67;A383 [abstract].

isobolographic data bending towards the origin, indicating synergy.[68,69] The study that explored doses of ketamine up to 100% MAC reduction (i.e., immobility with ketamine alone)[70] found the best fit to the isobole was a log-linear relationship, one intrinsically curved towards the origin, demonstrating synergy. In dogs, ketamine clearly demonstrated synergy with isoflurane on MAC.[71] Note that ketamine blocks more than NMDA receptors, perhaps explaining why ketamine alone can produce immobility, but MK-801, an NMDA antagonist that can completely block NMDA receptors, does not produce immobility by itself.[72]

α_2-Adrenergic Agonists

Dexmetedomidine

Dexmedetomidine's interactions with propofol, midazolam, and diazepam were outlined above. Dexmedetomidine interacts synergistically with fentanyl to produce hypnosis in rats[61] and immobility in dogs.[73]

In humans, dexmedetomidine decreases isoflurane and sevoflurane MAC by 35%–50%[74,75] and 0%–17%,[76] respectively. The type of interaction is unclear because of the lack of a full dose-response curve for dexmedetomidine.[74–76] The concomitant use of alfentanil confounds the results of one study.[74] In animals, dexmedetomidine decreases the MAC of potent inhaled anesthetics by 81%–100%,[73,77–80] with the report by Vickery et al.[77] showing synergy.

Clonidine

Studies of clonidine's interactions with propofol and midazolam were mentioned earlier. Although several studies describe interactions between opioids and clonidine for pain, no adequate studies examined the end-point of immobility. One study investigated the interaction of fentanyl and clonidine on hypnosis in animals. Alone, these two drugs did not provide hypnosis but did when combined,[81] implying synergy by definition (the logical extension of the analysis in the Appendix for the case where neither drug can reach the given end-point).

Although several studies found that clonidine decreases MAC (immobility) and MAC_{awake} (hypnosis) of inhaled anesthetics, the nature of the interaction remains unclear because of the limited dose ranges used (1 or 2 doses only). Clonidine decreases MAC_{awake} for isoflurane (30%)[82] and sevoflurane (17%–21%)[83,84] in humans. Clonidine alone cannot produce immobility, at least at doses explored clinically, as demonstrated by a study finding that doubling the dose of clonidine did not further decrease sevoflurane MAC_{awake} in children.[85] If there is a ceiling to clonidine's effect on MAC_{awake}, the ability of clonidine to reduce MAC_{awake} of inhaled anesthetics demonstrates synergy by definition. Clonidine decreases the MAC of isoflurane[86] and sevoflurane[83,84] in humans by 30% and 17%–34%, respectively; this decrease is linear for sevoflurane over the limited dose range (two doses only) studied.[87] In animals, clonidine decreases the halothane MAC by 16%–48%,[88–90] with one study showing no further MAC reduction over a four-fold range[89] and another over a 100-fold dose range,[90] again showing a ceiling effect, and synergy by definition.

μ Opioid Receptor

Numerous studies have examined the interactions of morphine and the opioids fentanyl, alfentanil, sufentanil, and remifentanil with other drugs. Interaction data with IV anesthetics were described above.

Morphine does not affect MAC_{awake} for halothane,[91] isoflurane,[92] and sevoflurane[93] in humans, suggesting an infra-additive relationship. In humans, morphine decreases halothane MAC by an unknown interaction.[94] However, unpublished data from one of us (EIE) indicates a ceiling effect of morphine on halothane MAC in humans, indicating synergy by definition. In animals, morphine decreases the MAC of potent inhaled anesthetics,[95–102] an effect that often reaches a ceiling.[96–98,101]

The nature of the interaction between fentanyl and sevoflurane on hypnosis in humans remains unclear. Although fentanyl decreased the MAC_{awake} of sevoflurane in humans in two studies,[103,104] it had no effect at lower doses in one[103] and caused a dose reduction described as "parabolic without manifest ceiling" in the other.[104] All human interaction data for opioids and potent inhaled anesthetics show a dose-dependent decrease of MAC with a ceiling effect,[103–111] thus demonstrating synergy. This has been shown for fentanyl, alfentanil, sufentanil, and remifentanil with isoflurane,[105,106,110,111] and for fentanyl with isoflurane,[105,106] sevoflurane,[104,107] and desflurane.[108,109] In animals, the effect on MAC is less consistent, but most studies find a decrease in MAC,[63,73,96,112–120] usually demonstrating that opioids cannot produce immobility in the absence of some inhaled anesthetic,[96,113–119] again demonstrating a ceiling and synergy in the ability of opioids alone to suppress movement. One exception found no effect of alfentanil on halothane MAC in horses.[121] Although N_2O and Xe can prevent awareness in studies determining the ED_{50} for opioids for several clinical endpoints, these studies reveal little about the nature of the interaction between N_2O or Xe, as these studies examined one fixed end-tidal concentration of Xe or N_2O.[122–126]

Dopamine Antagonists

Droperidol and Metaclopromide

The interaction of droperidol and metaclopromide with thiopental for hypnosis in humans is synergistic by definition (see above).[46]

Sodium Channel Blockers

Lidocaine

Interactions with propofol, thiopental, midazolam, and ketamine were described above. Lidocaine administration decreases the MAC of halothane,[127,128]

enflurane,[129] and isoflurane[130,131] in animals, an effect usually described as additive.[128–131] However, these studies explored lidocaine concentrations <10 μg/mL, probably because of the risk of seizure, and no study demonstrated more than a 70% reduction in halothane MAC. This could represent either additivity or synergy, depending on the unknown (and possibly unknowable) concentration of lidocaine given alone that produces immobility. However, one paper described a ceiling of 50% in halothane MAC with lidocaine concentrations ranging from 12 to 20 μg/mL in dogs[127] and another presented similar data for rats for cyclopropane, halothane, isoflurane, and *o*-difluorobenzene.[132] This constitutes synergy by definition. This finding of synergy is not inconsistent with the other studies suggesting additivity, because only these latter studies investigated high doses of lidocaine in an attempt to identify whether lidocaine alone could produce immobility (i.e., could produce 100% reduction in MAC). In humans,[127] 70% N_2O was used to ensure hypnosis in a study of the ED_{50} of lidocaine for suppression of movement on incision. However, we do not know the effect of lidocaine alone because of the limited dose-range of lidocaine applied. Thus this study did not define the nature of the interaction between lidocaine and N_2O.

Inhaled Anesthetics

Studies describing interactions of inhaled anesthetics with IV anesthetics were described previously.

In rats, interactions between inhaled anesthetics are additive for MAC for halothane with isoflurane,[133] desflurane, and sevoflurane[10] and for isoflurane with sevoflurane.[10] Most human data show an additive effect of N_2O on MAC for potent inhaled anesthetics (halothane,[94,134] enflurane,[135] isoflurane,[136,137] sevoflurane,[107,138] and desflurane[139]). Infra-additivity has been suggested between desflurane and N_2O in 18 to 30-year old patients (only 45% MAC reduction) from the previously mentioned desflurane study in which the overall results showed additivity,[139] and in pediatric patients (only a 25% MAC reduction) in a study flawed by the use of historical controls for the O_2 only group.[140] In contrast to the human data, older animal data suggest that higher concentrations of N_2O act infra-additively with enflurane,[141,142] halothane,[142] and isoflurane.[142,143] Recent animal studies find additivity with N_2O for all inhaled anesthetics tested (sevoflurane in lizards[144] and sevoflurane and desflurane in rats),[10] except for isoflurane [infra-additivity in rats].[10] In humans, the interaction between N_2O and isoflurane[145] and sevoflurane[145,146] on hypnosis is infra-additive. Interaction studies between Xe and volatile inhaled anesthetics find additivity for hypnosis (isoflurane and sevoflurane[145]) and immobility (halothane,[147] sevoflurane[148]) in humans. Although the results in the last study might statistically deviate from additivity, the deviation is <10%, and thus by our definition is additive. Two studies in swine by the same group of investigators came to opposing conclusions for immobility, showing additivity with sevoflurane[149] but infra-additivity with isoflurane.[150] The companion report to this paper[10] finds additivity for Xe with isoflurane, sevoflurane, and halothane in rats.

DISCUSSION

What Trends Do the Data Reveal?

The grid in Figure 1 reveals several underlying trends. Opioids act synergistically with both IV and inhaled anesthetics,[11,16,18,19,22–27,30,31,44,54,61–63,73,81,96–98,101,112–120] with two exceptions. In humans, opioids do not affect the MAC_{awake} of inhaled anesthetics (i.e., they are infra-additive).[91–93] In animals, they are additive* (abstract only) or infra-additive for suppression of movement when combined with GABA-enhancing drugs,[45,64] a finding possibly attributable to use of low (pronociceptive) concentrations of IV thiopental,[45] acute opioid tolerance,[151] or inframaximal stimulus intensities.[64]

Synergy is common when drugs acting on $GABA_A$ receptors are combined with drugs acting on non-$GABA_A$ receptors, but there are exceptions to this rule. As mentioned in the previous paragraph, GABA-enhancing drugs are additive or infra-additive on immobility with opioids in animals. The interaction with $GABA_A$-enhancing drugs is also additive to infra-additive with N_2O and with ketamine (see next paragraph).

In animals, ketamine acts synergistically with inhaled anesthetics on movement[68–70] and with lidocaine[32] on hypnosis, yet does not show synergy with drugs acting on $GABA_A$ receptors in any study. The interaction between ketamine and $GABA_A$ agonists ranges from additivity[19,20,40] to infra-additivity[19,41,51] (on reanalysis). Plausible explanations include the presence of an active ketamine metabolite (the effects of which may be difficult to account for without measuring blood concentrations), indirect effects (orthosympathic stimulation), and the fact that the methods used tended to skew the data towards additivity ["additivity by default"—see companion paper by Shafer et al.[9]].

All combinations of potent inhaled anesthetics (halothane with isoflurane, desflurane, and sevoflurane or isoflurane with sevoflurane) are additive on MAC in rats.[133] MAC for volatile anesthetics with N_2O[94,107,134–139,145,147,148] and Xe[107,135–139,145,147,148] are usually additive in humans. The N_2O/isoflurane interaction is infra-additive in rats,[142] and this is the only exception to the general finding of additivity between inhaled drugs. Although the MAC of N_2O in humans had been determined in 1982,[152] older animal data on the interaction between N_2O and volatile anesthetics had to be interpreted with caution because many of these studies estimated the MAC of N_2O by extrapolation, possibly causing N_2O MAC to be under-estimated and

biasing the results towards infra-additivity.[6] Nevertheless, when using hyperbaric conditions to determine the MAC of N_2O, Russell and Graybeal[143] confirmed the infra-additive nature of the isoflurane-N_2O interaction, a finding corroborated in the companion paper.[10] Studies in swine find additivity of MAC for the Xe/sevoflurane pair[149] but infra-additivity for Xe/isoflurane.[150] Again these results are difficult to interpret because the MAC for Xe in swine is unclear. In a subsequent study by the same authors, the MAC for Xe was found to be higher than previously estimated, but the MAC was determined using halothane MAC reduction assuming additivity for the halothane/Xe interaction.[149,150,153] The companion report to this paper[10] found additivity of MAC for Xe/isoflurane and Xe/sevoflurane pairs in rats, and for all potent inhaled anesthetic interactions tested (including pairs that were not part of our literature search), except for the combination of isoflurane with N_2O where infra-additivity was found.[10] Interestingly, N_2O has significant NMDA antagonistic properties, and thus the failure to find synergy with isoflurane (which has more potent $GABA_A$ effects) parallels the lack of synergy observed with ketamine and IV hypnotics.

Interest in quantifying drug interactions and appropriate analysis methodology developed after 1980. This explains the limited data for older drugs like lidocaine, which is likely synergistic with inhaled anesthetics, as suggested by the demonstration of a ceiling effect,[127] even though most studies examined modest doses and referred to the interaction as "additive."[128–131] Lidocaine has been shown to interact synergistically with cyclopropane.[154] Some other older, but extensively used drug combinations, such as the opioid-droperidol combination to provide neuroleptanesthesia, have not been formally analyzed.

What Is Missing from Our Understanding of Drug Interactions

A study often provides interaction data for a single drug pair, and external validation (duplication or the use of a parallel drug pair) for many such studies is lacking. We compensated for this deficiency by combining data from drug pairs from the same drug classes (Fig. 1). Even this approach fails to cover interactions between certain drug classes. For other classes, only animal data are available, necessitating extrapolation from one species to another. There is a risk in such extrapolation since data from different species can produce conflicting results as illustrated by the different interaction between isoflurane and N_2O on immobility in animals versus humans.

Only two studies investigated the interaction between volatile anesthetics and $GABA_A$ receptor-enhancing drugs: in animals, halothane, and thiopental are synergistic for immobility,[49] whereas sevoflurane and propofol are additive for hypnosis and immobility in humans.[33] Although both propofol and midazolam act on the $GABA_A$ receptor and additivity might therefore be expected, various evidence suggests that they affect different receptor sites.[155–158] Propofol alone can produce immobility,[23,25,26,31] whereas midazolam alone cannot completely obliterate movement to noxious stimulation.[59,60] Thus, perhaps, the finding of synergy should not be surprising.

No human data were found for ketamine/volatile anesthetics and α_2 adrenergicagonist/benzodiazepine combinations despite the clinical interest in the use of ketamine as an analgesic adjunct[159] and the use of dexmedetomidine as a sedative in the intensive care setting.[160]

Our data apply to *in vivo* interactions in which specific responses potentially result from actions on multiple receptors. We have not examined *in vitro* effects for actions on a single receptor. In a companion paper exploring this issue, additivity was the predominant finding.[161]

We may not have retrieved some published interaction data because of the limitations of our search terms. Nevertheless, the large number of studies identified presents a clear overall picture of what we know and where future research efforts may be warranted.

What Can Interaction Studies Tell Us About the Underlying Mechanism of Action

Except, possibly, for ketamine, IV anesthetics that work at different receptors or receptor subtypes usually show synergy for hypnosis and suppression of movement from noxious stimulation. Our review supports the widely held belief that IV anesthetics that work at different receptors or receptor subunits usually, but not always, exhibit synergy to the end-point of interest, and that IV anesthetics that act at identical receptors show additivity.[2–7]

Our review findings may also allow some deductions regarding the mechanism of action of inhaled versus IV anesthetics, particularly as regards immobility. First, consistent with the analysis in the first companion paper[9] suggesting that additivity should be an uncommon finding for drugs acting at different sites of action, IV anesthetics with known differing receptor effects usually, but not always, exhibit synergy for movement. Second, IV anesthetics acting at identical receptors or receptor subunits almost always show additivity, again supporting the analysis presented by Shafer et al.[9] Third, the consistent lack of synergy among inhaled anesthetics on MAC, demonstrated in our literature review, and reinforced in the companion manuscript by Eger et al.,[10] strongly suggests that inhaled anesthetics act at a common site to produce immobility despite considerable differences in receptor effects.

Clinical Implications

This analysis has only considered two clinically desirable interactions: hypnosis and immobility.[162] The widespread practice of combining opioids with inhaled or IV hypnotics suggests that clinicians find

the resulting synergy clinically useful. However, nothing in our analysis speaks to synergy for adverse events. There can be synergy for ventilatory depression,[1] hypotension, loss of airway reflexes, and other common adverse effects. Little research has compared clinically useful with clinically undesirable forms of synergy.[2]

Summary

Interactions between drugs of different pharmacological classes often result in synergy. The type of interaction depends on the end-point examined. It also depends on the analysis technique, with "additivity by default" having different implications from clear demonstrations of additivity.[9] The absence of synergy among inhaled anesthetics regarding MAC has no parallel with IV drugs with known mechanisms of action. This would support the notion that the mechanism of inhaled anesthetic action underlying immobility may result from an effect at a single, presently unidentified site of action.

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APPENDIX: WHY A "CEILING EFFECT" IS SYNERGY BY DEFINITION

Consider the interaction of inhaled anesthetics and opioids on the end-point of movement in response to a noxious stimulation (e.g., incision). By definition, inhaled anesthetics produce this effect in 50% of patients at 1 MAC, which is defined as the steady-state end-tidal concentration associated with 50% likelihood of no movement response to incision. Opioids can decrease the concentration of inhaled anesthetic required to ablate the response to noxious stimulus. Thus, there is an interaction. Is it synergistic, additive, or infra-additive?

Multiple studies demonstrate that opioids alone cannot suppress movement in 50% of patients. Figure 2 superimposes the results of two studies of inhaled anesthetic interaction with fentanyl on MAC: one studying the interaction between isoflurane and fentanyl,[105] and one studying the interaction between desflurane and fentanyl.[109] Both studies show the "ceiling effect" of opioids on MAC. Even with very large doses of fentanyl there is some requirement for inhaled anesthetic. The interaction plots are not straight lines, as would be seen with additivity, instead, curving in a concave manner towards the origin. It is visually obvious that the isobole bows towards the origin when describing a ceiling effect, such as the relationship between an inhaled anesthetic and an opioid. This concave bowing suggests synergy. However, can one demonstrate that it "proves" synergy in a statistically rigorous manner?

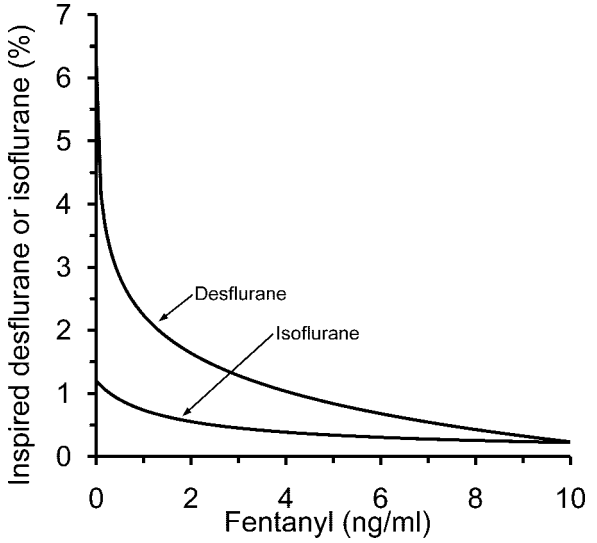

Figure 2. The graph shows the interaction between isoflurane and fentanyl,[105] desflurane, and fentanyl.[109] Both studies show the "ceiling effect," in that even with very large doses of fentanyl there is some requirement for inhaled anesthetic to prevent movement in response to incision.

We defined synergy in terms of the sum of normalized "doses" (broadly defined to also include concentrations, if the experiment was conducted using concentrations rather than doses). Let $ED_{EP,A}$ be the "effective dose" of drug A associated with a given end-point, and $ED_{EP,B}$ be the effective dose of drug B associated with exactly the same end-point. There is synergy when, for some dose of drug A and some dose of drug B taken together, and producing exactly the same end-point, $\frac{Dose_A}{ED_{EP,A}} + \frac{Dose_B}{ED_{EP,B}} < 0.9$. This is readily applied to the relationship between two drugs that intersect the *X* and *Y* axes at $ED_{EP,B}$ and $ED_{EP,A}$.

Assume that drug B has a ceiling (e.g., the ceiling for fentanyl effect in decreasing MAC seen in Fig. 2). That is, drug B cannot produce the given end-point without at least Δ units of drug A, regardless of the concentration of drug B. This is shown in Figure 3. The problem is that it does not intersect the *X* axis, so the definition of synergy given in $\frac{Dose_A}{ED_{EP,A}} + \frac{Dose_B}{ED_{EP,B}} < 0.9$ cannot be applied directly.

We can redraw our graph with different axes by subtracting Δ from all of the concentrations of drug A, as shown in Figure 4. Consider two choices of Δ. Δ_1 yields an intersection with the *X* axis at infinity, and Δ_2 yields in an intersection with the *X* axis at something less than infinity. This produces the set of three graphs, shown in Figure 5. Note that all three graphs describe exactly the same relationship. However, in the top graph the curve never intersections the *X* axis. In the middle graph Δ has been chosen to that the curve intersects with the *X* axis at infinity, and in the bottom graph Δ has been chosen so that the graph

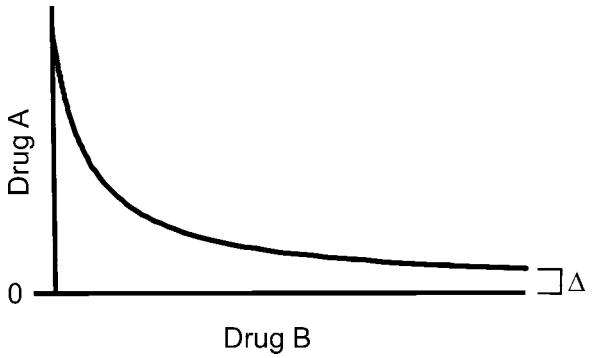

Figure 3. Drug B cannot cause the defined effect on its own. At least Δ units of drug A are required to produce the drug effect. Thus, drug B demonstrates a ceiling in its ability to produce the drug effect of interest.

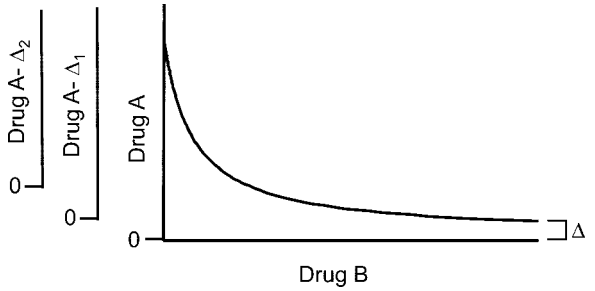

Figure 4. The graph from Figure 3 can be redrawn using different *Y* axes, in which some fixed amount, Δ_1 or Δ_2, is subtracted from the dose (concentration) of Drug B. This does not change the underlying relationship between Drug A and Drug B. It simply changes how it is graphed, and the interpretation of the figure.

intersects with the curve at something less than infinity.

The three curves in Figure 5 all reflect exactly the same relationship between drugs A and B. However, because of the positioning of the axes on the relationship, there is a difference in interpretation. The middle and lower graphs in Figure 5 show the relationship between drug B and incremental doses of drug A above Δ_1 and Δ_2, respectively, always given in the presence of Δ_1 and Δ_2 units of drug A, respectively. For example, were this the relationship between isoflurane (drug A) and fentanyl (drug B), then we might have chosen $\Delta = 0.2\%$ (Fig. 2) as the asymptope for the middle figure, and $\Delta = 0.4\%$ for the lower figure. Thus, the middle figure would show the relationship between doses of isoflurane larger than 0.2% (*Y* axis) and fentanyl concentrations (*X* axis), given in the presence of the isoflurane dose on the *Y* axis plus an additional. 0.2% isoflurane. The lower figure would show the relationship between doses of isoflurane larger than 0.4% (*Y* axis) and fentanyl concentrations (*X* axis), given in the presence of the isoflurane dose on the *Y* axis plus an additional 0.4% isoflurane.

Our definition of synergy was deviation from the straight line isobole. We can generalize our synergy equation to permit adjustment of the *Y* axis as in

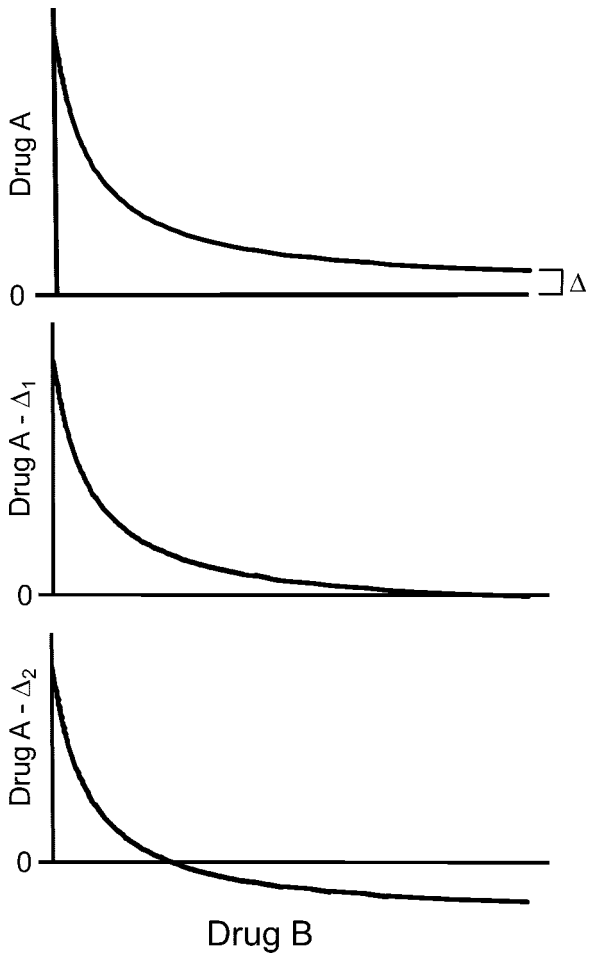

Figure 5. Three ways of drawing the relationship between drug A and drug B. In the top graph, the ceiling effect is evident. In the middle graph, Δ from Figure 3 has been subtracted from the *Y* axis, producing a graph that intersects with the *X* axis at $X = \infty$. In the lower graph, a larger Δ has been subtracted, resulting in a graph that intersects the *X* axis. Although all three graphs depict exactly the same relationship between drugs A and B, the middle and lower graphs are most easily interpreted as the relationship between Drug B and incremental doses of drug A in excess of Δ_1 and Δ_2, respectively.

Figure 5 by adjusting the dose of drug A, and the *X* intercept of drug A, by Δ: $\frac{\text{Dose}_A - \Delta}{\text{ED}_{EP,A} - \Delta} + \frac{\text{Dose}_B}{\text{ED}'_{EP,B}} < 0.9$. In our isoflurane/fentanyl example, $\Delta = 0$ for the top graph, 0.2% isoflurane in the middle graph, and 0.4% isoflurane in the lower graph. Notice the different definition of the "effective dose" of drug B. A prime has been added to the term, $\text{ED}'_{EP,B}$, because here the term ED is the effective dose of drug B in the presence of at least Δ units of drug A.

We will analyze the middle graph in Figure 5, because the dose of drug B conveniently disappears. Recall that in the middle graph, Δ_1 was chosen so that the figure intersected with the *X* axis at infinity. Since $\text{ED}'_{EP,B} = \infty$, $\frac{\text{Dose}_B}{\text{ED}'_{EP,B}} = 0$. Our equation for

synergy thus reduces to $\frac{\text{Dose}_A - \Delta}{\text{ED}_{EP,A} - \Delta} + 0 < 0.9$. This can be rearranged as $\text{Dose}_A - 0.1\Delta < 0.9\ \text{EDEP,A}$. If this equation is satisfied, then synergy exists.

Positive values of Δ decrease the left side of the equation, making the relationship more likely to be true and hence favoring a finding of synergy. Let's take the most conservative setting in which the equation is least likely to demonstrate synergy: $\Delta = 0$. This reduces the relationship to $\text{Dose}_A < 0.9\ \text{ED}_{EP,A}$. This means is that if ANY dose of drug B can reduce the dose of drug A required to reach the stipulated end-point by 10%, then there is synergy for the relationship $\frac{\text{Dose}_A - \Delta}{\text{ED}_{EP,A} - \Delta} + \frac{\text{Dose}_B}{\text{ED}'_{EP,B}} < 0.9$. Since this relationship describes exactly the same relationship between the two drugs as described by $\frac{\text{Dose}_A}{\text{ED}_{EP,A}} + \frac{\text{Dose}_B}{\text{ED}_{EP,B}} < 0.9$, a demonstration of synergy for one relationship describes synergy for all. Since this conclusion is based on our definition of synergy, we refer to this as "synergy by definition."

In some settings, it might be possible to pick a theoretical dose of drug B, well beyond the measured data, and extrapolate from the measured data to predict that a high dose of drug B would yield a 10% reduction in the dose of drug A. As a practical matter, it seems reasonable to limit the conclusion that a ceiling effect implies synergy to those cases where the 10% reduction is observed at clinically relevant doses.

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