J Anesth (2012) 26:422–428
DOI 10.1007/s00540-012-1344-3

ORIGINAL ARTICLE

Dexmedetomidine and hydroxyzine synergistically potentiate the hypnotic activity of propofol in mice

Kaori Kimura-Kuroiwa · Yushi U. Adachi · Yukako Obata · Mikito Kawamata · Shigehito Sato · Naoyuki Matsuda

Received: 22 August 2011 / Accepted: 23 January 2012 / Published online: 18 February 2012

Abstract
Purpose Investigation into the characteristics of anesthetic interactions may provide clues to anesthesia mechanisms. Dexmedetomidine, an α_2-adrenergic receptor agonist, has become a popular sedative in intensive care, and hydroxyzine, a histamine receptor antagonist, is well known as a tranquilizing premedication for anesthesia. However, no experimental or pharmacological evaluation has been reported concerning their combination with propofol. Thus, we studied their combined effect with a hypnotic dose of propofol in ddY mice.
Methods Male adult mice were intravenously administered either dexmedetomidine (30 μg/kg) or hydroxyzine (5 mg/kg) with propofol (3.75–10 mg/kg) to induce hypnosis, defined as a loss of the righting reflex (LRR). Other mice were intravenously administered propofol, dexmedetomidine (300 μg/kg), or hydroxyzine (50 mg/kg) alone, and subsequent behavioral changes were observed. The 50% effective dose (ED_{50}) for LRR was calculated, and the duration of LRR was determined.
Results The hypnotic dose of propofol was 9.95 ± 1.04 mg/kg (ED_{50} ± SEM) without combination. Dexmedetomidine and hydroxyzine reduced the ED_{50} of propofol to 5.32 ± 0.57 and 5.63 ± 0.57 mg/kg, respectively. Coadministration of dexmedetomidine significantly extended LRR duration compared with propofol alone, whereas hydroxyzine significantly shortened LRR duration. A maximal dose of dexmedetomidine or hydroxyzine alone did not induce hypnosis.
Conclusions Dexmedetomidine and hydroxyzine demonstrated no hypnotic action alone; however, their coadministration potentiated the hypnotic activity of propofol. Although reduction in the dose of propofol was similar, only dexmedetomidine prolonged the duration of hypnosis.

Keywords Dexmedetomidine · Hydroxyzine · Propofol · Synergistic · Hypnosis

Part of the results of this investigation were presented in Anesthesiology 2011, the American Society of Anesthesiologists Annual Meeting held in Chicago, IL, USA.

K. Kimura-Kuroiwa
2nd Department of Anesthesia, Nagano Red Cross Hospital, 5-22-1 Wakasato, Nagano, Nagano 380-8582, Japan

Y. U. Adachi (✉)
Department of Emergency Medicine, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
e-mail: yuadachi@med.nagoya-u.ac.jp

Y. Obata
Intensive Care Unit of University Hospital, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan

M. Kawamata
The Department of Anesthesiology and Resuscitology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan

S. Sato
Department of Anesthesia and Resuscitation, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan

N. Matsuda
Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Introduction

Many kinds of anesthetics show synergistic potentiation when two or more drugs are administered in combination

[1]. A synergistic interaction occurs with a combination of drugs when each agent acts at a different site or receptor to induce the anesthetic effect [2, 3]. Thus, the identification of interactions as additive or synergistic can be quite important in understanding the properties of drugs. Some anesthesiologists prefer to coadminister more than one drug to achieve an adequate state of hypnosis or immobility [3, 4]. One reason for coadministration may be the potential for decreasing the adverse effects of a drug, which is usually injected at a larger dose when used alone [4, 5]; however, insight as to the interaction characteristics is sometimes inadequate in practitioners.

Recently, Hendrickx et al. [1] extensively reviewed anesthetic interactions using the definitions developed in two former investigations [6, 7]. The new definition of synergy in terms of the sum of the normalized doses could be used to evaluate the interaction of drugs showing a ceiling effect [1]. Thus, comparative studies of almost all anesthetics, including intravenous and inhalational compounds [7], could be discussed. Although that review [1] may further our understanding of anesthetic interactions, a few uncertainties remain as exceptions or unsolved cases.

Dexmedetomidine is a relatively new intravenous anesthetic and one of the major sedatives used in intensive care [8] and in ambulatory and pediatric anesthesia [9]. Dexmedetomidine promotes a moderate hypnotic state, and continuous administration of this agent may be preferable for sedating patients in intensive care units [8]. The mechanism of dexmedetomidine-induced hypnosis includes inhibitory regulation of histamine release in the brain cortex [10], and the sedative state achieved with dexmedetomidine is a sleeplike hypnosis rather than true anesthesia. If the mechanism of this hypnotic action is different from that of other anesthetics, such as propofol, the combination would be expected to be synergistic.

Hydroxyzine is an anti-histaminergic drug, and drowsiness is a well-known side effect [11]. Thus, administration of hydroxyzine to a surgical patient immediately before entering the operating room has been popular as a premedication [12–14]. A series of clinical investigations studied the characteristics of hypnosis at the induction of anesthesia in patients premedicated with hydroxyzine [15–18]; however, the effect of hydroxyzine on the results was scarcely addressed.

Both dexmedetomidine and hydroxyzine are sedative agents that show weak anesthetic potency. However, the precise interactive effects on the popular intravenous anesthetic propofol were unknown. In this study, we evaluated the effect of coadministering dexmedetomidine or hydroxyzine on the hypnotic dose and duration of propofol action in ddY mice.

Methods

After obtaining approval from the Animal Ethics Committee of Hamamatsu University School of Medicine (H18-28-22-01), we studied 180 adult male ddY mice (age, 7–8 weeks; weight, 28–38 g; SLC, Hamamatsu, Japan). The animals were maintained on a 12-h:12-h light–dark cycle and fed ad libitum before the experiments. All experiments were conducted between 10 a.m. and 4 p.m. Mice were examined at least twice and had a recovery period of more than 7 days, independent of completing the drug manipulations. After 6 animals were injected, the next regimen was examined.

The mice were immobilized in a transparent animal holder to facilitate insertion of a 24-g IV plastic cannula (SurFlo; Terumo, Tokyo, Japan) into the tail vein. After confirming venous cannulation, another injection needle connected to a microsyringe was inserted into the cannula, and the prepared material was administered in 7–8 s. If the injection was irregular and extended, the data were omitted from the analysis. Mice were individually evaluated for hypnosis on a flat bed. The criterion for hypnosis was loss of the righting reflex, occurring <10 s after the start of the injection [19]. When hypnosis was confirmed, the mice were gently tilted into a lateral decubitus position, and a spontaneous righting position was defined as the end of hypnosis. The time from the start of injection to recovery of positioning was defined as the hypnotic duration.

Propofol (Diprivan; AstraZeneca, Osaka, Japan) was diluted with 10% soybean oil (Intralipid; Otsuka Pharmaceutical, Tokyo, Japan). Dexmedetomidine (Precedex; Maruishi Pharmaceutical, Osaka, Japan and Farmos Group, Turku, Finland) and hydroxyzine (Atarax P; Pfizer Japan, Tokyo, Japan) were dissolved or diluted with physiological saline. All solutions were mixed with the same volume of diluent and administered intravenously. Injection volume was set at 300 μl/30 g body weight. We tested the dose in preliminary experiments and determined the dosage that reduced the effective dose of propofol to about half of that in the control group. The investigated doses of each drug are shown in Table 1.

In the other three other groups of mice, the same volume of physiological saline as a control group and a tenfold-larger dose of dexmedetomidine (300 μg/kg) or hydroxyzine (50 mg/kg) was administered. The supplemental larger dosages were tested to explore a maximal dose for determining a ceiling effect (Table 2). Loss of the righting reflex was examined, and behavioral changes were observed using a home-cage activity test until 2 h after the injection. Locomotor activity was determined as the total count of crossing two separate lines in the cage during 30 min. These results were compared with those of the group administered a maximal dose of propofol (15 mg/kg).

Table 1 The percent ratios of responders in each treatment

	Dose of propofol (mg/kg)					
	3.75	5	7.5	10	12.5	15
Propofol alone		0	17	50	67	100
Combination of propofol and dexmedetomidine (30 μg/kg)	0	50	100	100		
Hydroxyzine (5 mg/kg)	0	33	100	100		

Ratios of responders to total number of animals ($n = 6$) are expressed as percentage (%)

Table 2 Results of larger-dose administration of dexmedetomidine and hydroxyzine

Drugs	Dose	*n*	Loss of righting reflex	Prognosis
	(μg/kg)			
Dexmedetomidine (i.v.)	300	6	No	All mice were sedated, but never lost righting reflex
	1,000	6	No	Same as above
	2,000	6	No	Same as above
	3,000	6	No	Same as above
Dexmedetomidine (s.c.)	300	4	No	Same as above
	1,000	4	No	Same as above
	3,000	4	No	Same as above
	(mg/kg)			
Hydroxyzine (i.v.)	50	6	No	No significant behavioral change was observed; however, one mouse was dead after a brief convulsion
	100	4	No	All mice were dead after a brief convulsion
	200	4	No	Same as above

To calculate the 50% effective dose (ED_{50}) for loss of the righting reflex, the standard error of the mean (SEM) of the ED_{50}, and the 95% confidence interval (CI), we determined the number of animals that lost the righting reflex from the total which received a particular pharmacological treatment and correlated the result with the probability of being under hypnosis using a nonlinear least-squares logistic regression. An analysis of variance (ANOVA) was used to compare the ED_{50} and hypnotic duration among groups, and the Newman–Keuls post hoc multiple-comparison test was used when the ANOVA showed a statistically significant difference ($P < 0.05$). The results of the dose of propofol required for each group are presented as the ED_{50}, SEM, and 95% CI. Hypnotic duration is reported as the mean and SE. All calculations were performed using a statistical software package (NCSS 2000; Number Cruncher Statistical Systems, Kaysville, UT, USA).

Results

The percentage of responders with each treatment is shown in Table 1 and Fig. 1. The $ED_{50} \pm$ SEM (95% CI) for propofol was 9.95 ± 1.04 (6.01–16.5) mg/kg. Simultaneous administration of dexmedetomidine (30 μg/kg) decreased the ED_{50} to 5.32 ± 0.57 (3.47–8.14) mg/kg. Hydroxyzine (5 mg/kg) also reduced the ED_{50} of propofol to 5.63 ± 0.57 (3.78–8.40) mg/kg (Fig. 2).

The 15 mg/kg propofol injection induced hypnosis in all animals for 88.2 ± 17.6 s. When dexmedetomidine was administered with propofol, the dose of propofol to achieve hypnosis in all mice was reduced, to 7.5 mg/kg, and the hypnotic duration was significantly prolonged, to 161.2 ± 28.5 s. Coadministering hydroxyzine with 7.5 mg/kg propofol induced hypnosis in all mice and significantly shortened the hypnotic duration to 47.3 ± 5.8 s (Fig. 3). The combination with 10 mg/kg propofol achieved hypnosis of 234.3 ± 98.1 s with dexmedetomidine and of 64.0 ± 31.5 s with hydroxyzine (Fig. 4).

Administering a maximal dose of dexmedetomidine (300 μg/kg up to 3 mg/kg) did not induce hypnosis, and no loss of righting reflex was observed throughout the experiment (Table 2). However, at a dose of 300 μg/kg, five of six animals showed no locomotor activity (0 count/30 min) 2 h after dexmedetomidine administration. Other animals were completely sedated and no locomotor activity was observed during the observation period. A maximal dose of hydroxyzine (50 mg/kg) failed to achieve hypnosis in any animal, and the mice showed no apparent behavioral

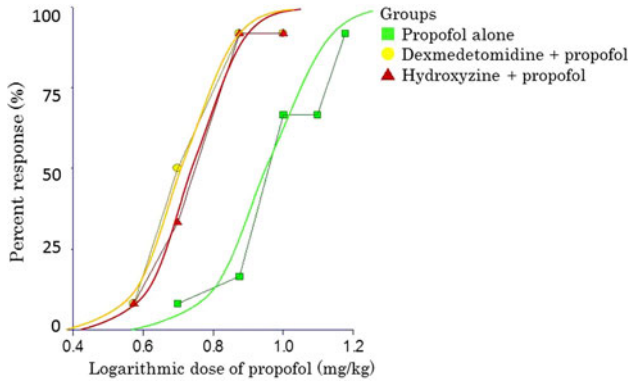

Fig. 1 Percent response of each group ($n = 6$)

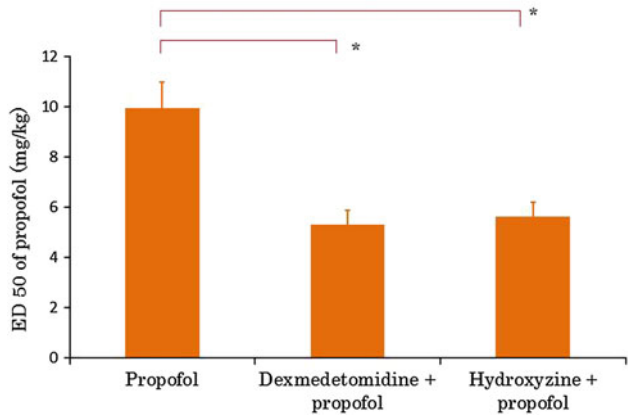

Fig. 2 Duration of loss of righting reflex (mean ± SD). All animals ($n = 6$) of each group lost the reflex. *$P < 0.05$ between groups

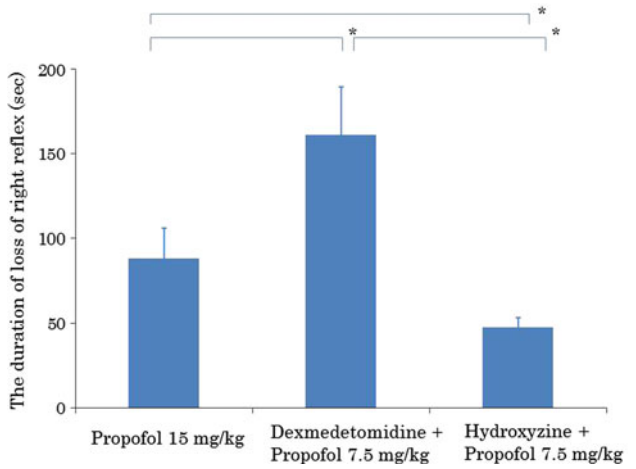

Fig. 3 Duration of loss of righting reflex (mean ± SD). All animals ($n = 6$) of each group lost the reflex. *$P < 0.05$ between groups

change (4.5 ± 2.8 counts/30 min) during the observation period compared with the activity of the control group mice (5.2 ± 2.4 counts/30 min). Administration of larger dose of hydroxyzine killed the animals after a brief and

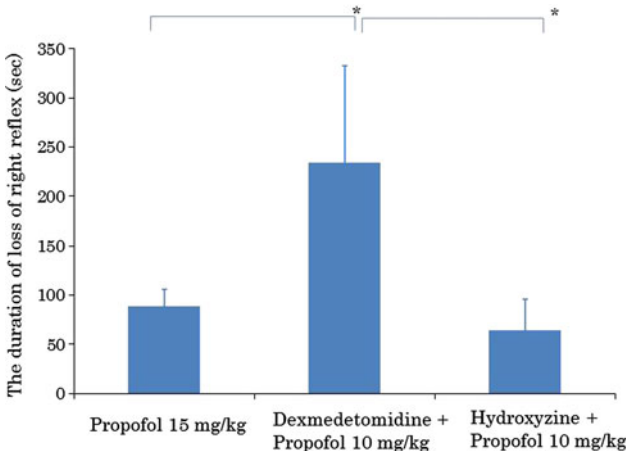

Fig. 4 Duration of loss of righting reflex (mean ± SD) when the coadministration dose of propofol was set at 10 mg/kg. All animals ($n = 6$) of each group lost the reflex. *$P < 0.05$ between groups

immediate convulsion. Administering 15 mg/kg propofol induced hypnosis in all animals, and after recovery from anesthesia, locomotor activities were the same as those of the control group (4.2 ± 3.1 and 5.2 ± 2.4 counts/30 min, respectively).

Discussion

Intravenous administration of a maximal dose of dexmedetomidine and hydroxyzine alone did not induce hypnosis in ddY mice. However, following the definition of interaction by Hendrickx et al. [1], the extrapolated maximal normalized dose was calculated as 0.63 (30/300 ± 5.32/9.95) for dexmedetomidine and propofol and 0.67 (5/50 ± 5.63/9.95) for hydroxyzine and propofol, respectively. Both values were smaller than 0.9, and the synergistic interaction in achieving hypnosis was confirmed [1].

Traditionally, preparing an isobologram has been a major and powerful tool for investigating drug interactions, defining additive or synergistic effects [20, 21]. The historical basis for predicting the effect of a combination is based on the concept of dose equivalence; that is, an equally effective dose (A) of one drug will add to the dose (B) of the other drug in the combination situation. For drugs with a constant relative potency, this leads to linear additive isobole curves of constant effect (line of additivity), whereas a varying potency ratio produces nonlinear additive isoboles. Determining the additive isobole is a necessary procedure for assessing both synergistic and antagonistic interactions of a combination. However, a practical limitation of using an isobologram is that each drug tested should alone completely achieve the endpoint: here, hypnosis. If one of the drugs in the combination fails

to induce hypnosis, determining an interaction with an isobologram is impossible. The type of interaction depends on the endpoint examined. In the current investigation, we administered an extremely larger dose of dexmedetomidine and hydroxyzine; however, no anesthetic effect determined as a loss of righting reflex was observed (Table 2). Thus, another analytical technique should be required. A comparison using the sum of "normalized dose" provides theoretical evidence for an interaction of the combination of drugs, one of which shows a ceiling effect [1, 7]. In practical settings, limiting the conclusion that a ceiling effect implies synergy to those cases in which a 10% reduction is observed at clinically relevant doses seems reasonable [1].

Generally, a synergistic interaction indicates multiple sites of action [1, 6]. Two or more different sites may be involved in synergism. Propofol is a well-known allosteric regulator of the $GABA_A$ receptor [1, 5]; however, the specific areas in the central nervous system for inducing hypnosis have not been determined. Dexmedetomidine is reported to induce hypnosis through activation of noradrenergic neurons at the locus coeruleus and of $GABA_A$ ergic neurons in the ventral lateral preoptic hypothalamus [8, 10, 22]. Finally, dexmedetomidine inhibits tuberomammillary nucleus firing and induces a sedative response. Hydroxyzine is an H_1 histamine receptor blocker. Histaminergic neurons are located primarily in the tuberomammillary nucleus, from where they project widely to several areas of the central nervous system [23]. Recently, Luo and Leung [24] reported a role of the tuberomammillary nucleus histaminergic neurons in modulating isoflurane anesthesia and that the neural circuits for isoflurane-induced hypnosis may differ from those of GABA-mediated anesthetics. Thus, a possibility exists that both dexmedetomidine and hydroxyzine promote sedative effects independent of the propofol-related GABAergic pathway in the central nervous system. If that is the case, the interaction of the drugs might be expected to be synergistic. The current study included no molecular approach, such as in vitro electrophysiological experiments, to examine action at a single receptor; however, the synergism of the drugs may be comprehensive. Further study is required to identify the mechanism through specific receptors at certain locations in the brain.

Although the pharmacokinetics and pharmacodynamics of recent agents, including propofol [25], are appropriate for new regimens, they may be limited for attaining ideal anesthesia, such as rapid induction and quick recovery [26]. Remifentanil [27, 28] and remimazolam (CNS 7056) [29, 30] have been recently developed for anesthesiology, and both drugs are quickly degraded by a nonspecific esterase with rapid hydrolysis. However, many popular anesthetic agents follow conventional pharmacokinetics, depending primarily on hepatic metabolism and clearance [25]. Thus, managing anesthesia with a single drug is complex, and a combination of drugs may provide preferable solutions in clinical settings [4, 7]. When the hypnotic activities of each drug are synergistic without clearance interference, titration of dosing for each agent may result in a faster reduction to a basal level in the blood and the effector site [4]. Thus, a combination of drugs showing a synergistic interaction may shorten the recovery time from an identical endpoint achieved by a combination of drugs with an additive interaction.

In the current investigation, dexmedetomidine and hydroxyzine showed synergistic effects on the hypnotic activity of propofol. Neither drug could induce hypnosis alone, as with narcotics [1]. Dexmedetomidine reduced the required dose of propofol [31, 32]. Although the pharmacological characteristics have not been evaluated and we determined the effect of only one dose of each drug, the results demonstrated a synergistic effect [1]. Moreover, coadministering hydroxyzine not only resulted in a reduction of the propofol dose required for hypnosis but also shortened the hypnotic duration, meaning a more rapid recovery from general anesthesia. This property is appropriate for practical settings [26], but the exact mechanism, including the quick clearance of hydroxyzine or increased clearance of propofol, were not evaluated. We suggest that reducing the propofol dose may have also impacted the results.

Hydroxyzine has been a popular premedication sedative for inducing general anesthesia [12–14]. A recent double-blind randomized trial [33, 34] demonstrated that the administration of clonidine, a classic α_2-adrenergic receptor agonist, was superior for reducing the propofol requirement during anesthesia and the hemodynamic responses against invasive stimuli compared with hydroxyzine. The interaction of clonidine and propofol was classified as additive [1, 35]. Oral clonidine premedication reduced the waking concentration of propofol [35], and clonidine may prolong the recovery time [36]. In the current investigation, a maximal dose of dexmedetomidine (300 μg/kg) reduced locomotor activity; thus, the enhanced hypnotic activity of dexmedetomidine may continue after anesthesia using propofol. Another fascinating explanation is that hydroxyzine might enhance only the induction of anesthesia using propofol without any interference against emergence. Kelz et al. [37] demonstrated the concept that emergence depends on recruitment and stabilization of wake-active regions of brain. There would be a specific neural group essential for prompt emergence from general anesthesia independent from induction of anesthesia.

We previously investigated the effect on cardiac output of a hypnotic dose of propofol at the induction of anesthesia [15]. All participants in the study were administered

hydroxyzine as a premedication to induce anesthesia. Although the evaluation of independent parameters was not affected by coadministering hydroxyzine, the absolute hypnotic dose of propofol was smaller than the dose without premedication. The results of particular investigations [16–18] require further analysis.

Our study had several limitations. First, pharmacokinetic and pharmacodynamic interactions were not evaluated [25]. The combination of drugs may have induced changes in cardiovascular parameters, and the underlying circulatory depression could have modified the pharmacological properties of the agents [15, 38]. However, any decrease in cardiac output and any induced hypotension should be followed by a delay in the drug's activity, including exposure to and disappearance of the drug effect equally [39, 40]. Thus, the findings of the present investigation would be generally acceptable [19, 41]. Second, we mentioned the development of practical regimens for clinical settings; however, the results of animal experiments should be distinguished from clinical investigations. Further studies are required, including studies on the safety of multi-agent administration [1, 7].

In summary, coadministration of dexmedetomidine and hydroxyzine significantly reduced the hypnotic dose of propofol, and, particularly, hydroxyzine shortened the hypnotic duration. This combination has the potential to accomplish rapid induction and quick recovery from general anesthesia.

Acknowledgment A part of this study was founded by Grants-in-Aid for Scientific Research from the Japan Society of the Promotion of Science, 22591706.

Conflict of interest All authors have no conflict of interest for the present investigation.

References

1. Hendrickx JFA, Eger EI II, Sonner JM, Shafer SL. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg. 2008;107:494–506.
2. Grass PS. Anesthetic drug interactions: an insight into general anesthesia—its mechanism and dosing strategies. Anesthesiology. 1998;88:5–6.
3. Rosow C. Anesthetic drug interaction: an overview. J Clin Anesth. 1997;9:S27–32.
4. Adachi YU, Watanabe K, Higuchi H, Satoh T. A small dose of midazolam decreases the time to achieve hypnosis without delaying emergence during short-term propofol anesthesia. J Clin Anesth. 2001;13:277–80.
5. Adachi YU, Watanabe K, Higuchi H, Satoh T. Flumazenil reduces the hypnotic dose of propofol in male patients under spinal anesthesia. J Anesth. 2002;16:9–12.
6. Shafer SL, Hendrickx JFA, Flood P, Sonner J, Eger EI II. Additivity versus synergy: a theoretical analysis of implications for anesthetic mechanisms. Anesth Analg. 2008;107:507–24.
7. Eger EI 2nd, Tang M, Liao M, Laster MJ, Slot K, Flood P, Jenkins A, Raines D, Hendrickx JF, Shafer SL, Yasumasa T, Sonner JM. Inhaled anesthetics do not combine to produce synergistic effects regarding minimum alveolar anesthetic concentration in rats. Anesth Analg. 2008;107:479–85.
8. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, Vedio A, Singer M, Feneck R, Treacher D, Willatts SM, Grounds RM. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia. 1999;54:1136–42.
9. Gozal D, Gozal Y. Pediatric sedation/anesthesia outside the operating room. Curr Opin Anaesthesiol. 2008;21:494–8.
10. Millan MJ, Lejeune F, Gobert A, Brocco M, Auclair A, Bosc C, Rivet JM, Lacoste JM, Cordi A, Dekeyne A. S18616, a highly potent spiroimidazoline agonist at alpha(2)-adrenoceptors: II. Influence on monoaminergic transmission, motor function, and anxiety in comparison with dexmedetomidine and clonidine. J Pharmacol Exp Ther. 2000;295:1206–22.
11. Gengo FM, Dabronzo J, Yurchak A, Love S, Miller JK. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. Clin Pharmacol Ther. 1987;42:265–72.
12. Tornetta FJ. A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. Anesth Analg. 1977;56:496–500.
13. Mojdehi E, Mauro AL, Labartino L, Reynolds B. Clinical evaluation of hydroxyzine hydrochloride in pediatric anesthesia and its effect on arousal time. Anesth Analg. 1968;47:685–8.
14. Zsigmond EK, Patterson RL. Double-blind evaluation of hydroxyzine hydrochloride in obstetric anesthesia. Anesth Analg. 1967;46:275–80.
15. Adachi YU, Watanabe K, Higuchi H, Satoh T. The determinants of propofol induction of anesthesia dose. Anesth Analg. 2001;92:656–61.
16. Hans P, Deby-Dupont G, Deby C, Pieron F, Verbesselt R, Franssen C, Lamy M. Increase in antioxidant capacity of plasma during propofol anesthesia. J Neurosurg Anesthesiol. 1997;9:234–6.
17. Hans P, Coussaert E, Cantraine F, Dewandre PY, Brichant JF, Grevesse M, Lamy M. Effects of target-controlled anesthesia with propofol and sufentanil on the hemodynamic response to Mayfield head holder application. Acta Anaesthesiol Belg. 1998;49:7–11.
18. Souron V, Delaunay L, Bonner F. Sedation with target-controlled propofol infusion during shoulder surgery under interscalene brachial plexus block in the sitting position: report of a series of 140 patients. Eur J Anaesthesiol. 2005;22:853–7.
19. Adachi YU, Watanabe K, Higuchi H, Satoh T. High-dose flumazenil potentiates the hypnotic activity of propofol, but not that of thiopental, in ddY mice. Acta Anaesthesiol Scand. 2001;45:848–52.
20. Salonen M, Reid K, Maze M. Synergistic interaction between alpha 2-adrenergic agonists and benzodiazepines in rats. Anesthesiology. 1992;76:1004–11.
21. Garfield JM, Bukusoglu C. Propofol and ethanol produce additive hypnotic and anesthetic effects in the mouse. Anesth Analg. 1996;83:156–61.
22. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha$_2$-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology. 2003;98:428–36.
23. Lin J. Brain structures and mechanisms involved in the control of cortical activation and wakefulness, with emphasis on the posterior hypothalamus and histaminergic neurons. Sleep Med Rev. 2000;4:471–503.
24. Luo T, Leung LS. Involvement of tuberomamillary histaminergic neurons in isoflurane anesthesia. Anesthesiology. 2011;115:36–43.

25. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth Analg. 1987;66:1256–63.
26. Gupta A, Stierer T, Zuckerman R, Sakima N, Parker SD, Fleisher LA. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth Analg. 2004;98:632–41.
27. Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF. Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. Anesthesiology. 1993;79:107–13.
28. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology. 1993;79:881–92.
29. Kilpatrick GJ, McIntyre MS, Cox RF, Stafford JA, Pacofsky GJ, Lovell GG, Wiard RP, Feldman PL, Collins H, Waszczak BL, Tilbrook GS. CNS 7056: a novel ultra-short-acting benzodiazepine. Anesthesiology. 2007;107:60–6.
30. Upton RN, Somogyi AA, Martinez AM, Colvill J, Grant C. Pharmacokinetics and pharmacodynamics of the short-acting sedative CNS 7056 in sheep. Br J Anaesth. 2010;105:798–809.
31. Ngwenyama NE, Anderson J, Hoernschemeyer DG, Tobias JD. Effects of dexmedetomidine on propofol and remifentanil infusion rates during total intravenous anesthesia for spine surgery in adolescents. Paediatr Anaesth. 2008;18:1190–5.
32. Peden CJ, Cloote AH, Stratford N, Prys-Roberts C. The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. Anaesthesia. 2001;56:408–13.
33. Boussofara M, Bracco D, Ravussin P. Comparison of the effects of clonidine and hydroxyzine on haemodynamic and catecholamine reactions to microlaryngoscopy. Eur J Anaesthesiol. 2001;18:75–8.
34. Guglielminotti J, Descraques C, Petitmaire S, Almenza L, Grenapin O, Mantz J. Effects of premedication on dose requirements for propofol: comparison of clonidine and hydroxyzine. Br J Anaesth. 1998;80:733–6.
35. Higuchi H, Adachi Y, Arimura S, Ogata M, Satoh T. Oral clonidine premedication reduces the awakening concentration of propofol. Anesth Analg. 2002;94:609–14.
36. Richards MJ, Skues MA, Javis AP, Prys-Roberts C. Total i.v. anaesthesia with propofol and alfentanil: dose requirements for propofol and the effect of premedication with clonidine. Br J Anaesth. 1990;65:157–63.
37. Kelz MB, Sun Y, Chen J, Cheng Meng Q, Moore JT, Veasey SC, Dixon S, Thornton M, Funato H, Yanagisawa M. An essential role for orexins in emergence from general anesthesia. Proc Natl Acad Sci USA. 2008;105:1309–14.
38. Du C, Tully M, Volkow ND, Schiffer WK, Yu M, Luo Z, Koretsky AP, Benveniste H. Differential effects of anesthetics on cocaine's pharmacokinetic and pharmacodynamic effects in brain. Eur J Neurosci. 2009;30:1565–75.
39. Kent AP, Dodson ME, Bower S. The pharmacokinetics and clinical effects of a low dose of alfentanil in elderly patients. Acta Anaesthesiol Belg. 1988;39:25–33.
40. Mertens MJ, Olofsen E, Burm AG, Bovill JG, Vuyk J. Mixed-effects modeling of the influence of alfentanil on propofol pharmacokinetics. Anesthesiology. 2004;100:795–805.
41. Norberg A, Hahn RG, Li H, Olsson J, Prough DS, Børsheim E, Wolf S, Minton RK, Svensén CH. Population volume kinetics predicts retention of 0.9% saline infused in awake and isoflurane-anesthetized volunteers. Anesthesiology. 2007;107:24–32.