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Research Article

Isobolographic analysis of sedative and hypnotic interactions of propofol with ketamine and xylazine in chicks

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Abstract. Objective: Propofol is an ultra-short acting anesthetic agent used in humans and animals. Ketamine, a dissociative anesthetic and xylazine, a sedative-analgesic agent can be used with propofol to improve the quality of sedation and anesthesia. The purpose of the present study was to apply an isobolographic analysis to examine the sedative and hypnotic interactions of propofol (given intraperitoneally) with ketamine and xylazine (given intramuscularly) in young chick model. Methods: The up-and-down method was used to determine the median effective sedative and hypnotic doses (ED50s) of propofol, ketamine and xylazine administered alone, or propofol-ketamine and propofol-xylazine combinations (50:50 ED50 values) in 7-10 day-old chicks. Isobolographic analysis was applied to determine the type of interaction between them. Results: The ED50 values for propofol, ketamine and xylazine were 1.83, 5.39 and 0.18 mg/kg for the induction of sedation, and they were 5.71, 12.24 and 3.83 mg/kg for the induction of sleep, respectively. Combined administration of propofol and ketamine or xylazine resulted in ED50 values of 0.63 + 2.63 and 0.86 + 0.09 mg/kg for sedation and 4.12 + 8.12 and 2.92 + 1.92 mg/kg for sleep, respectively. The ED50 values of propofol, ketamine and xylazine in the drug combinations decreased by 28 to 66% for the induction of sedation and sleep. Isobolographic analysis of the ED50 values of the three drugs revealed synergistic interactions between propofol and ketamine or xylazine for the induction of sedation in chicks. For the induction of sleep in chicks, no interaction (additive effect) occurred between propofol and xylazine and it was antagonistic between propofol and ketamine. Conclusion: The interaction reduced dose ratio of propofol with ketamine or xylazine (50:50 ED50 values) which produced the required end points of sedation and sleep in chicks. This could be of value clinically in the avian species or could be extended after further studies to mammals.

Key Words: anesthesia, ketofol, xylafol, isobolography, ketamine, propofol, xylazine.

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Introduction

Propofol is a non-narcotic ultra short acting anesthetic agent used in humans (Smith et al 1994; Lundström et al 2010; McGrane et al 2012) and various animal species (Short & Bufalari 1999; Glowaski & Wetmore 1999; Papich 2011). The drug modulates the inhibitory effect of gamma-aminobutyric acid via GABAA receptors and potentiates glycinergic neurotransmission in the central nervous system (CNS) and the spinal cord to produce sedation, analgesia and anesthesia (Dong & Xu 2002; Vasileiou et al. 2009). Xylazine is a centrally acting alpha-2 adrenoceptor agonist which induces sedation, analgesia, sleep and muscle relaxation in animals (Greene & Thurmon 1988; Lizarraga & Chambers 2012; Coetzee 2013). Ketamine is a dissociative anesthetic agent widely used in humans and animals for anesthesia and pain management (Carter & Story 2013; Persson 2013; Tawfic 2013). More recently, it has been used against treatment-resistant depression in humans (Browne & Lucki 2013). Ketamine antagonizes N-methyl-D-aspartate receptors in the CNS (Persson 2013; Tawfic 2013). Ketamine combinations with sedatives, tranquilizers and analgesics are also widely used as balanced anesthetics and restraining agents in animals (Short 1992; Carter & Story 2013; Coetzee 2013).

Ketamine has the limitations of producing emesis, agitation during recovery from anesthesia with long recovery time (White et al 1982). Xylazine is not an anesthetic agent (Greene & Thurmon 1988), but it rather improves the quality of anesthesia or its recovery, including those of propofol, in animals (Short & Bufalari 1999; Frias et al 2003; Wagner et al 2012). Propofol on the other hand causes hypotension and depresses respiration (Smith et al 1994; Mortero et al 2001). Many studies have reported the beneficial procedural sedation, analgesia and hypnosis of ketamine and propofol combination, named ketofol, in humans (Willman & Andolfatto 2007; Andolfatto et al 2012; Coulter et al 2014) and animals (Lerche et al 2000; Ravasio et al 2012) including the avian species (Fitzgerald & Cooper 1990; Lierz & Korbel 2012). The rationale for using ketofol is to reduce the dose of either drug required to produce procedural sedation, analgesia and hypnosis or anesthesia; hence the reduction of the adverse effects of both drugs (Slavik 2007; Coulter et al 2014). However, concerns appeared regarding the best anesthetic combination ratio of propofol and ketamine or xylazine and the type of drug interactions between them, whether it is a simple additive or synergistic or even none at all (Lerche et al 2000; Frias et al 2003; Mair et al 2009; Andolfattoet al 2012;

Coulter et al 2014). There is no clear-cut evidence of the optimum dose of either drug in the combinations as it depends on the clinical requirements (Lerche et al 2000; Frias et al 2003; Slavik 2007; Hendrickx et al 2008).

Isobolographic analysis of the interactions of propofol with sedatives or anesthetics might result in a better understanding of the type of drug interaction in producing sedation or anesthesia (Vinik et al 1990; Hendrickx et al 2008). Additive effects were reported when propofol and ketamine were combined for the induction of sedation or for the endpoint of immobility (Hui et al 1995; Kil et al 1999; Hendrickx et al 2008). The purpose of the present study was to further apply an isobolographic analysis to assess the interaction between propofol and ketamine or xylazine (xylafol- a new name for the combination we propose for the first time here) using a model of young chicks.

Materials and methods

Animals and drugs

A total of 60 one-day old Ross broiler chicks (Gallus domesticus) of both sexes were obtained from a certified hatchery (Mosul, Iraq). The chicks were raised at a temperature ranging between 32 to 35°C in a room with 23h light-1 h dark cycle and wood shavings as floor litter. The birds had free access to drinking water and feed until the age of 7-10 days when the experiments were conducted. A commercial propofol solution (10 mg/ml injection formulation, Astra, Zeneca, UK) was diluted with distilled water to obtain the required concentrations of the drug to be injected on the basis of mg/kg body weight, intraperitoneally in a volume of 10 ml/kg body weight. Ketamine (50 mg/ml, Rotexmedica, Germany) and xylazine (20 mg/ml, Sanofi, France) were further diluted with physiological saline solution to obtain the required concentrations for intramuscular injection at 5 ml/kg body weight. All drug solutions were freshly prepared before each experiment. The Committee of Graduate Studies at the College of Veterinary Medicine, University of Mosul reviewed and approved the present study. Experiments and animal handling were according to our institutional regulations and guidelines addressing animal use, attention and humane care. They were based on the guidelines of National Research Council (2011).

Determination of the median effective doses (ED50s) of propofol, ketamine and xylazine for the induction of sedation and hypnosis (sleep) in chicks

Using the up-and-down method (Dixon 1980), we determined in separate experiments (n=5–8/each ED50 experiment) the individual ED50s of propofol, ketamine and xylazine as well as the combinations of propofol-ketamine and propofol-xylazine (50:50 of their individual ED50 values) for the induction of sedation and sleep in chicks. Sedation in chicks was manifested by drooping of the head, closed eyelids, reduced motility or immotility, decreased distress calls, or recumbency (Al-Zubaidy and Mohammad, 2005; Mohammad et al. 2012). The onset of sleep was manifested as loss of righting reflex when the chick was gently placed on one side (Hsu 1981; Mohammad and Faris 2006; Mohammad et al. 2012). Each chick was observed for 20 minutes after drug injection for the occurrence of sedation or sleep. The experiments were conducted between 9–11 a.m.

The ED50s of propofol, ketamine and xylazine together with the combinations of propofol and ketamine or xylazine were subjected to isobolographic analyses to determine the type of interaction in producing sedation and sleep in chicks (Tallarida 1992; Puig et al 2000; Mohammad et al 2007). The ED50 point of propofol was represented on the y-axis and those of ketamine and xylazine on the x-axis. A straight diagonal line was drawn for the isobolographic analysis between isoeffective ED50s of propofol and ketamine or xylazine given alone to chicks. The line of additive effect (zero interaction) is the straight line between the individual ED50 values of propofol and ketamine or xylazine alone, and the combination points on the left (below) and right (above) sides of the line represent synergistic and antagonistic interactions, respectively (Tallarida 1992; Puig et al 2000; Mohammad et al 2007). The interaction index (Y) was calculated by the equation da/Da+db/Db (Puig et al 2000). Da and Db are the individual ED50s of propofol and ketamine or xylazine for the induction of sedation or sleep, respectively, whereas da and db are combined ED50s of propofol and ketamine or xylazine in producing sedation or sleep. A Y value of 1 is an additive effect (no interaction), < 1 synergy, and > 1 antagonism (Tallarida 1992; Puig et al 2000; Mohammad et al 2007). In all the experiments, each bird was subjected to sedative or hypnotic tests only once.

Results

The ED50 values, as determined by the up-and-down method, for propofol, ketamine and xylazine were 1.83, 5.39 and 0.18 mg/kg for the induction of sedation, and they were 5.71, 12.24 and 3.83 mg/kg for the induction of sleep, respectively. Combined administration of propofol and ketamine or xylazine resulted in ED50 values of 0.63 + 2.63 and 0.86 + 0.09 mg/kg for the induction of sedation and 4.12 + 8.12 and 2.92 + 1.92 mg/kg for the induction of sleep, respectively. The ED50 values of propofol, ketamine and xylazine in the drug combinations decreased by 50 to 66% for the induction of sedation and by 28 to 50% for the induction of sleep (Table 1).

Isobolographic analysis of the ED50 values of the three drugs (either alone as well as propofol and ketamine or xylazine combinations) revealed synergistic interactions between propofol and ketamine or xylazine for the induction of sedation in chicks (Figure 1). For the induction of sleep in chicks, no interaction (additive effect) occurred between propofol and xylazine and it was antagonistic between propofol and ketamine (Figure 2). The synergistic sedative effect was indicated by the location of the points representing the combined sedative ED50s of propofol with ketamine or xylazine below the diagonal line that connect their isoeffective sedative ED50 values given alone (Figure 1). The additive hypnotic effect of propofol and xylazine was indicated by the location of the point representing the combined hypnotic ED50 values of both drugs on the diagonal line (Figure 2). Further, the antagonistic hypnotic effect of propofol and ketamine was indicated by the location of the point representing the combined hypnotic ED50 values of both drugs above the diagonal line (Figure 2). The calculated interaction indices for the induction of sedation and sleep in chicks treated with propofol and ketamine or xylazine are shown in table 1. These indices further support the types of interaction seen between propofol and ketamine or xylazine in inducing sedation or sleep in chicks.

Table 1. Interaction indices (Y) and percentages of decrease in median effective doses (ED50s) of propofol with ketamine or xylazine for the induction of sedation and sleep in chicks

Drug combination	Sedation		Sleep	
	Y*	% decrease in ED50	Y	% decrease in ED50
Propofol+ketamine	0.83	66+51	1.4	28+34
Propofol+xylazine	0.97	53+50	1	49+50

* Y: 1 additive (no interaction), < 1 synergy, and > 1 antagonism. n=5–8 chicks/each ED50 experiment.

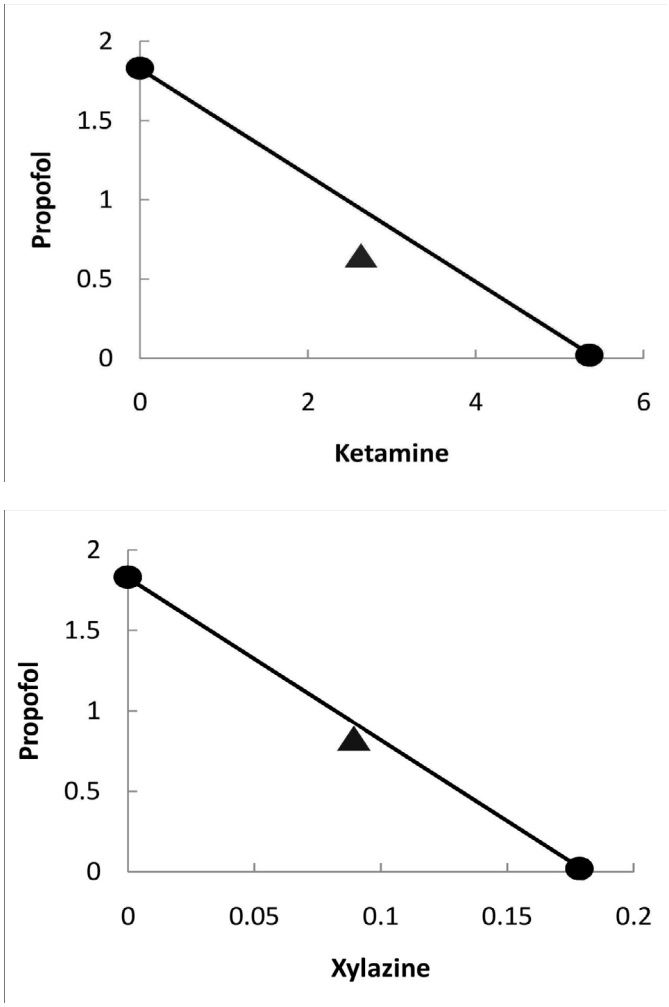

Figure 1. Isobolographic analysis of the sedative interaction of propofol and ketamine or xylazine in chicks. Propofol was injected intraperitoneally, whereas ketamine and xylazine were given intramuscularly. Points on x- and y-axes represent median sedative doses (ED50s, mg/kg) of the drugs given alone, whereas the triangular point represents 50:50 of ED50 combinations of both drugs. The diagonal line between the individual ED50s of propofol and ketamine or xylazine is additive (no interaction), and the triangular point indicates synergistic interaction. n=5–8 chicks/each ED50 experiment.

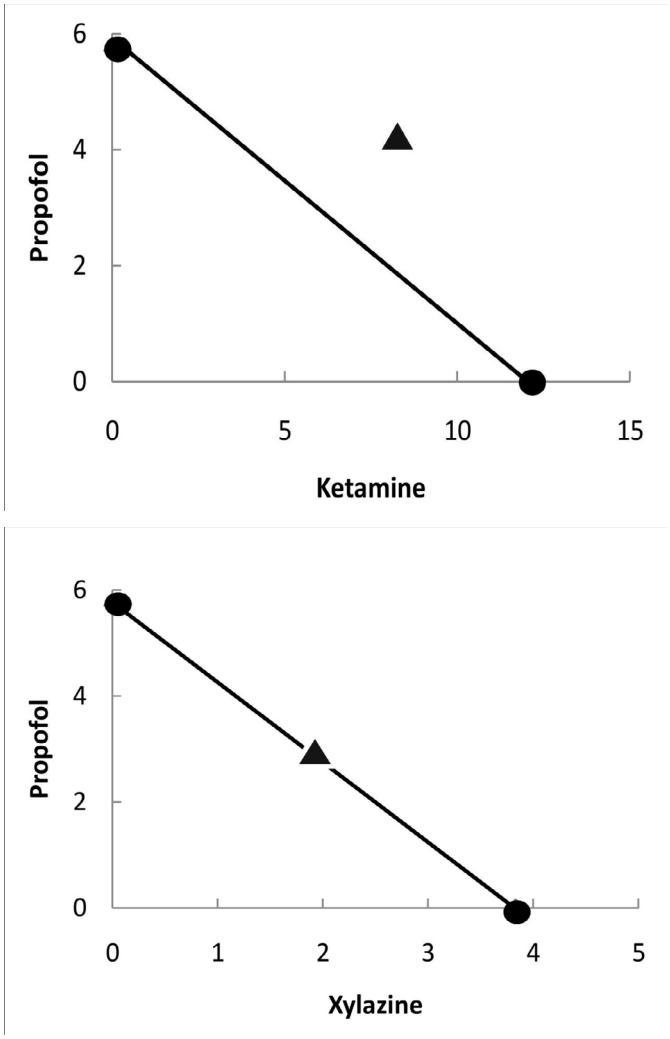

Figure 2. Isobolographic analysis of the hypnotic interaction of propofol and ketamine or xylazine in chicks. Propofol was injected intraperitoneally, whereas ketamine and xylazine were given intramuscularly. Points on x- and y-axes represent median hypnotic doses (ED50s, mg/kg) of the drugs given alone, whereas the triangular point represents 50:50 of ED50 combinations of both drugs. The diagonal line between the individual ED50s of propofol and ketamine or xylazine is additive (no interaction), and the triangular point above the line indicates antagonistic interaction. n=5–6 chicks/each ED experiment.

Discussion

In the present study, propofol, ketamine and xylazine induced sedation and hypnosis as the chicks became docile and lost the righting reflex. These effects of the three drugs are in accordance with their depressant actions resulting in sedation, hypnosis or anesthesia (Hsu 1981; Greene & Thurmon 1988; Short 1992; Short & Bufalari 1999). The central pharmacological actions of propofol, ketamine and xylazine vary with regards to receptors and neurotransmitters involved (Greene & Thurmon 1988; Vasileiou et al. 2009; Persson 2013).

Several studies explored the combined effects of propofol-ketamine in humans and animals or propofol-xylazine in animals in order to reduce side effects and decrease doses for better depressant (e.g. anesthetic) actions of the drugs (Short 1992; Short & Bufalari 1999; Mortero et al 2001; Mair et al 2009; Ravasio et

al 2012; Coulter et al 2014). Our isobolographic analysis of the interaction between fixed ratio (50:50 ED50 values) of propofol-ketamine and propofol-xylazine in chicks revealed mixed findings depending on the end point measured. At the level of sedation, where the chicks retained the righting reflex ability, synergistic interaction occurred between propofol and ketamine or xylazine. For the induction of sleep in chicks, an additive effect occurred between propofol and xylazine and an antagonistic interaction between propofol and ketamine. These interactions were further substantiated by the calculation of interaction indices (Table 1). The synergistic interaction was thought to result when two drugs act by different mechanisms of action, as in the case of propofol and ketamine or xylazine, producing opposing physiologic effects (Vinik et al 1990; Hendrickx et al 2008; Andolfatto et al 2012). However, a similar argument about the additive effect which results from interaction of drugs with similar mechanisms of action does not hold true for the present additive hypnotic effect seen between propofol and xylazine (Vinik et al 1990; Hendrickx et al 2008; Andolfatto et al 2012) or even for the antagonistic one between propofol and ketamine. Additive effect between drugs of different mechanisms of action is not an uncommon finding (Puig et al 2000; Hendrickx et al 2008). The reason for this discrepancy is not clear at present. It might be related to multiple receptor types and neurotransmitters affected by the drugs we used in the present study (Greene & Thurmon 1988; Vasileiou et al. 2009; Tawfic 2013). In accordance with the findings of our study, however, ketamine was not additive with propofol for the induction of anesthesia in dogs (Mair et al 2009) and propofol-ketamine combination produced anesthesia in dogs comparable to that of propofol alone without any reported interaction (Lerche et al 2000). Furthermore, Shah et al (2011) reported that ketofol was not superior to ketamine in producing procedural sedation in children, but without any adverse event. Our findings are in agreement with the reported reductions of propofol-drug combination dosages in reaching the end points of sedation and anesthesia (Hui et al 1995; Mortero et al 2001). In our study, the ED50 values of propofol, ketamine and xylazine were reduced by 50 to 66% for the induction of sedation and by 28 to 50% for the induction of sleep.

Various combinations of propofol with ketamine or xylazine at different dose ratio have been successfully used in humans or animals (Short 1992; Frias et al 2003; Vasileiou et al. 2009; Shah et al 2011; Wagner et al 2012; Persson 2013). Generally, the outcome was superior sedation and anesthesia as well as reduced drug side effects. The limitation of our study, as found in other reports (Willman & Andolfatto 2007; Andolfatto et al 2012; Ozgul et al 2013), was that only fixed dose ratio of propofol-drug combinations was used. We do stress, therefore, that the interactions we reported in the present study are limited to the ratio of propofol-ketamine and propofol-xylazine dosages used in the chicks and the conclusion cannot be generalized to other combination levels or animal species. There are also mixed evidence regarding the best clinically effective dosage combinations of propofol with ketamine or xylazine (Lerche et al 2000; Frias et al 2003; Slavik 2007; Mair et al 2009; Coulter et al 2014).

Conclusions

Our findings indicated that reduced dose ratio of propofol with ketamine or xylazine (50:50 ED50 values) produced the required end points of sedation and sleep in chicks. We also report here a new interaction of propofol-xylazine combination for the induction of sedation (synergism) and sleep (additive). We propose the name of xylafol for this drug combination. These findings could be of value clinically in the avian species or it could be extended after further studies to mammals.

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