Effects of Propofol on the Cardiac Conduction System

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Summary: Warpechowski P, Santos ATL, Pereira PJI, Lima GG – Effects of Propofol on the Cardiac Conduction System.

Background and objectives: Some studies have demonstrated that the use of propofol is occasionally associated with bradyarrhythmias or reversion of arrhythmias to sinus rhythm. This property of propofol suggests interference with the Cardiac Conduction System (CCS).

Contents: A review of the main contemporary articles on the use of propofol in the presence of cardiac arrhythmias was undertaken. The authors describe pathophysiological mechanisms of supraventricular tachyarrhythmias (SVT) and occasional interferences caused by propofol on the CCS.

Conclusions: The studies undertaken so far seem to indicate that propofol probably interferes in automatic SVT (at least in children), but not in reentrant tachyarrhythmias.

Keywords: ANESTHETICS, Intravenous: propofol; COMPLICATIONS: cardiac arrhythmia, supraventricular tachycardia.

INTRODUCTION

Several drugs used in anesthesia interfere with the cardiac rhythm. As a rule, those effects of the anesthetics on the Cardiac Conduction System (CCS), such as those promoted by drugs like acetylcholine or opioids are well known. On the other hand, careful studies on more recent drugs are lacking and their effects are not completely understood. This is the case of propofol, a well-disseminated drug in anesthesiology whose actions on the CCS require more attention, which we propose in this review. Succinylcholine, a neuromuscular blocker that is structurally similar to acetylcholine (ACh), mimics the effects of that substance on nicotinic and muscarinic receptors, leading to an increase both in parasympathetic and sympathetic tonus. This is possibly the cause of cardiac arrhythmias seen after its use. Among the main arrhythmias are: sinus bradycardia, junctional rhythm, and ventricular arrhythmias, but arrhythmias ranging from premature ventricular contractions to ventricular fibrillation have been described [1]. Sinus bradycardia is the predominant cardiovascular effect of succinylcholine. Junctional rhythm is observed when the heart rate becomes lower than the frequency of the sinus node. As a rule, this arrhythmia is related with a great cholinergic stimulus at the level of the sinus node, which causes suppression of sinus activity and leads to the appearance of the atrioventricular (AV) node pacemaker [1,2].

On the other hand, some cardiac effects of anesthetics can be beneficial, such as the vagotonic central effect and bradycardia that is seen after the administration of opioids, resulting in decreased cardiac metabolic consumption [3]. Opioids can also affect cardiac calcium and potassium channels prolonging the action potential. This supports the evidence of some antiarrhythmic activity of those drugs similar to class III antiarrhythmic agents [4,5].

Propofol, a hypnotic agent widely used as sedative, hypnotic, and auxiliary in intravenous anesthesia, occasionally promotes bradyarrhythmias and conversion of tachyarrhythmias to sinus rhythm [5,6], suggesting that this drug interferes with the CCS. Several mechanisms are mentioned for those effects, such as direct electrophysiological effects on the CCS or indirect effects like changes in the autonomous nervous system (ANS) tonus and acid-basic changes [9,10]. Clarifying the mechanism responsible for those events is highly important, since it is responsible for indicating or not this drug in specific clinical situations.

Among the arrhythmias involved in those clinical reports the most common include supraventricular tachycardias (SVTs), which will be described below.

Pathophysiological mechanisms of supraventricular tachyarrhythmia

The two basic mechanisms responsible for the generation of SVTs are the increase in automaticity and conduction abnormalities leading the reentry [7].

Change in automaticity, or increase in the generation of the impulse, can result from increased automaticity of phase 4 in normal and abnormal cells (abnormal automaticity). It can also be due to repeated post-potential stimulus, present in phase 3 or 4

of the action potential (increased triggered activity). Metabolic changes are the most common among the different factors that can cause increased automaticity. Increased circulating catecholamines, hypoxemia, hypercapnia, acute hypocalcemia, hypomagnesemia, changes in the tension of the myocardial wall, and myocardial ischemia can also be mentioned [3,7].

Reentry can be classified as anatomical, functional, or a combination of both (anisotropic). Examples of reentry include atrial fibrillation, tachycardia due to atrioventricular nodal reentrant tachycardia (AVNRT) and SVT due to an anomalous pathway (accessory). The Wolff-Parkinson-White (WPW) syndrome is an example of the last one [7,8].

Atrioventricular nodal reentrant tachycardia is caused by a reentry mechanism in the proximity of the atrioventricular node (AV). Two or more pathways with different conduction times and distinct refractory periods are necessary to trigger the mechanism. One of them is called the slow pathway (or alpha) and it has a slow conduction a short refractory period. The other with fast conduction and long refractory period is called fast (or beta) pathway. A unidirectional blockade of one of those pathways, usually the fast one, is also necessary. When a stimulus (in the majority of cases an atrial premature contraction) descends through the slow pathway and reaches the fast pathway, at a time retrograde conduction is possible, a nodal echo beat is generated. Thus, the delay in conduction and am appropriate refractory period in both pathways generate a reentrant circuit. If this occurs continuously, it will give rise to common AVNRT, characteristic of 90% of the cases of AVNRT. On the other hand, in uncommon AVNRT the stimulus descends through the fast pathway and follows retrogradely through the slow pathway [7,8].

Atrioventricular node reentry is the most common type of SVT seen in approximately 50% of the cases. It is more common in women, and it usually develops before the age of 40 years [7,8]. In this arrhythmia the heart rate can range from 100 to 280 bpm with a mean of 170 bpm. Both AVNRT and SVT due to anomalous pathways can be cured by radiofrequency ablation (RFA) through a percutaneous catheter [7,8].

Pharmacology

Propofol is an intravenous anesthetic agent widely used in general anesthesia and as a sedative in diagnostic or therapeutic procedures such as during electrophysiological (EP) studies and RFA due to its favorable pharmacokinetic properties, such as fast awakening, absence of cumulative effects, and easy titration [9,10,14]. However, it can promote a reduction in blood pressure (BP) and systemic vascular resistance (SVR), and as a rule those changes are not followed by a compensatory increase in heart rate (HR) [9,10,16].

This lack of compensation of the HR, the report of bradyarrhythmias [11], suppression of tachyarrhythmias [5,6], and conversion of other rhythms into a sinus node rhythm during the use of propofol indicate the possibility of the development of blockade of baroreceptors or depression of CCS caused by this drug [6,15]. Several reports on the development of bradycardia, blockade of CCS, and reversion of tachyarrhythmias into

sinus rhythm after the use of propofol have been published in the literature [5,6,11-13].

Some authors have suggested that propofol promotes suppression of atrial tachycardia (supraventricular) and refer that this drug should be avoided during EP procedures [14].

A systematic review on propofol between 1984 and 1995 found 65 articles and 187 reports with different degrees of evidence of induction of bradycardia totaling 1,444 cases of bradycardia, 86 asystole, and 24 deaths related to the use of this drug. Among controlled studies reviewed by those authors, propofol increased significantly the risk of bradycardia when compared with other anesthetics resulting in a number-needed-to-harm (NNH) of 11.3 (95% confidence interval of 7.7-21). During surgeries to correct strabismus in children the NNH was 4.1 (3-6.7). Those authors concluded that the risk of death related to bradycardia due to propofol was estimated in 1.4:100,000 and the risk of asystole was 15:10,000 [15].

Those facts have generated controversies about the possible direct effects of propofol on the CCS or whether those changes in rhythm are due to indirect actions of the drug.

Several studies have demonstrated that propofol has both direct and indirect cardiovascular effects [9,13,15-18].

Indirect effects include modulation of the tonus of the ANS and changes in the sensitivity of the baroreceptor reflex [9]. Since it not possible to demonstrate the central vagolytic effects of propofol, and also because it seems to exert vagotonic or sympatholytic effects, it is probable that it is responsible for the development of bradycardia in some patients [17]. Those indirect effects on the cardiovascular system were described by Deutschman et al. who observed a more intense reduction in the sympathetic tonus than that observed with the parasympathetic tonus promoted by propofol, and this could explain the bradycardia seen in some patients [18]. Similarly, Hidaka et al. when comparing the effects of propofol and midazolam on the ANS observed that propofol has a more potent sympatholytic effect on the ANS than midazolam [19].

Those studies corroborate the idea of an important indirect effect on the ANS, which could explain the development of bradycardia or suppression of tachycardia when this drug is used.

The direct effects of propofol that are basically those exerted in the CCS or on the cardiac muscle have been the objective of several studies as will be commented below.

Biological basis

The effects of propofol on the CCS have been demonstrated in several animal studies. Alphin et al. reported that propofol causes a dose-dependent delay in conduction of the AV node in guinea pigs. Besides, those authors observed that propofol reduces atrial rate and that those negative dromotropic effects are predominantly mediated by M2 muscarinic receptors. They concluded that similarly to the effects of the anti-arrhythmic agents, diltiazem and adenosine, propofol seems to generate direct and indirect effects in cardiac conduction properties [16].

A study with pigs demonstrated that propofol causes dose-dependent depression of the function of the His-Purkinje sys-

tem and the sinus node. However, those authors were not able to demonstrate effects of the drug on the AV node or on atrial or ventricular conduction tissue [20].

In studies with dogs, any effect on the CCS was not observed when in the presence of ANS blocked induced by atropine and propranolol before the administration of propofol [21].

On the other hand, Napolitano et al. investigating the anti-arrhythmic properties of the anesthetics thionembutal, ketamine, and propofol in guinea pigs concluded: 1) thionembutal prolongs the effective refractory period of the AV node while propofol and ketamine do not; 2) ketamine reduced the atrial conduction velocity (CV), but propofol and thionembutal did not affect the atrial CV; 3) all three anesthetics caused a concentration-dependent increase of the conduction interval of the Hiss bundle. The authors concluded that propofol could be more effective on preventing reentrant atrial arrhythmias [22].

Wu et al. evaluated the effects of this drug in rabbits and demonstrated that low doses of propofol promoted a significant increase in the AV conduction interval. The authors concluded that in clinical doses propofol could modify directly the AV conduction. They suggested that this drug could interfere in the induction of tachycardia during RFA and, therefore, influence the therapeutic decision during this procedure [23].

Studies in humans

Two studies that evaluated propofol during anesthesia for EP studies in humans did not demonstrate any direct effect caused by this drug on the activity of the sinoatrial node, and intra-atrial or AV conduction [24,25].

Similarly, Romano et al. [26] were not able to demonstrate effects of propofol on the CCS and they also did not observe the development of bradyarrhythmias associated with the use of this drug; on the contrary, the sinus cycle showed a statistically significant reduction during the use of propofol when compared with the control group.

However, Erb et al. when comparing propofol with isoflurane in children undergoing EP studies and RFA observed a statistically significant prolongation of the AV node conduction. However, the authors concluded that this finding did not show clinical importance. According to them both drugs would be eligible for those procedures [27].

On the other hand, Wu et al. [28] after using propofol in anesthesia for EP studies reported that, out of nine pediatric patients with ectopic atrial tachycardia, in four (44%) it was not possible to induce a sustained tachycardia and, therefore, locate its origin, avoiding ablation during anesthesia with propofol. Based on this and on studies with rabbits, in which propofol prolonged the atrial refractory period and AV conduction, the author suggested that the use of this drug in anesthesia during ablation in patients with ectopic atrial tachycardia should be avoided [28].

Similar conclusions were published by Lai et al. in a series of 150 patients in which the majority (148/152) of tachycardias remained inducible after anesthesia with propofol. However, in four out of seven pediatric patients (57%) with ectopic atrial tachycardia it stopped after the administration of propofol and

it could not be induced even after the infusion if isoproterenol – a drug used to facilitate programmed induction of those arrhythmias during EEF. The authors suggest that this anesthetic agent should be carefully used in pediatric patients with ectopic atrial tachycardia undergoing EP [29].

In a randomized study, Warpechowski et al. [30] evaluated the effects of propofol on the AV conduction system of patients with AVNRT by analyzing the refractory periods of the fast and slow pathways of the AV node during EP. The authors concluded that propofol did not promote significant changes of the electrophysiological parameters of the AV node, which was similar to the results observed by Sharpe et al. [24] and Lavoie et al. [25]. Those findings do not show evidence that propofol could have a direct action on the electrophysiological properties of the AV node in patients with AVNRT. Similarly, propofol did not prevent the induction of programmed tachyarrhythmias during EP and therefore did not interfere in the diagnosis of those tachyarrhythmias [30].

The study by Sharpe et al. [24] included patients with WPW syndrome, while that of Warpechowski et al. [30] only evaluated patients with AVNRT, i.e., both studies included patients with arrhythmias due to reentry. On the other hand, Lavoie et al. [25] investigated 20 children of which 17 had accessory pathways (WPW and occult pathways), one had junctional reciprocating tachycardia, and two had a diagnosis of AVNRT. Based on those studies, it is possible to conclude that propofol probably does not interfere with the AV conduction system in patients whose arrhythmia is due to reentry.

However, Wu et al. [23] based on a study in animals in which propofol promoted effects in the CCS and also on their observations of pediatric patients with ectopic atrial tachycardia [28] in whom it was not possible to sustain this tachycardia in four patients under propofol suggested occasional interference of this drug on the CCS in the group of patients with this arrhythmogenic substrate. This conclusion is similar to that of Lai et al. [29], who were unable to induce tachyarrhythmia even with an isoproterenol infusion, and suggested that somehow propofol interfered with the mechanism of this arrhythmia avoiding its programmed spread.

CONCLUSION

The studies undertaken so far seem to indicate that propofol somehow interferes with automatic SVTs (at least in children), but not with reentry tachyarrhythmias, such as AVNRT or tachycardia dependent on an accessory pathway.

Further studies are needed to verify the possibility of this drug interfering with automatic SVTs. Meanwhile, special attention should be given when using propofol in EP studies in patients who present this arrhythmia since it could interfere in the diagnosis and consequently interfere with the treatment with RFA.

Similarly, it is suggested that this drug should be used sparingly in the group of pediatric patients undergoing potentially arrhythmogenic procedures, especially when the development of bradyarrhythmia is possible, such as in surgeries for correction of strabismus.

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