“CRIME SCENE INVESTIGATION” AT AN ANESTHETIC COCKTAIL PARTY WITH ATRIOVENTRICULAR DISSOCIATION

CHRISTOPH J. SCHLIMP* AND FRANZ J. WIEDERMANN**

Abstract

A healthy 21-year old female patient received midazolam, propofol, fentanyl, rocuronium, nitrous oxide in oxygen, ranitidine, diclofenac, neostigmine and glycopyrrolate during the anesthetic process for elective knee arthroscopy and developed a complete AV dissociation with a P-wave frequency of 40 and a “small” QRS-complex frequency of 55 beats/min. Based on this typical case of poly-pragmatic anesthetic drug administration causing a complete atrioventricular dissociation in a young healthy patient we will discuss the possible pharmacodynamic mechanisms of all used drugs with regard to the cardiac conduction system.

Keywords: atrioventricular heart block, general anesthesia, midazolam, fentanyl, propofol, ranitidine, neostigmine, rocuronium, glycopyrrolate, nitrous oxide.

Financial support and conflict of interest: None.

Introduction

Poly-pragmatic drug administration during balanced anesthesia is commonly used to reduce high doses and side effects of one drug or to antagonize (side) effects of other drugs. Typically used poly-pragmatic anesthetic drug administrations are e.g. different hypnotics: benzodiazepines for pre-medication, barbiturates for induction and a volatile anesthetic for sustaining anesthesia; or e.g. different opioids: fentanyl for induction of anesthesia, remifentanil for accurate controllable analgesia during the operation and a less potent agent like morphin or piritramid for postoperative analgesia. In addition to hypnotics and opioids, neuromuscular blocking agents and their antagonist (acetyl-cholinesterase inhibitor again combined with its own vegetative antagonist: an anticholinergic) are commonly used. Histaminic H2-receptor antagonists are also often administered to minimize gastric volume and for gastric protection in combination with non-steroidal anti inflammatory drugs. However, the advantages of this poly-pragmatic drug administration may lead to difficult allocation of possible side effects due to the higher potential of drug interaction. Based on a “crime scene” of a complete atrioventricular (AV) dissociation after administration of nine different drugs in a young healthy patient we will investigate and discuss the scene and review the possible pharmacodynamic mechanisms of all used drugs with regard to its influence on the AV conduction system.

* Dept. of Anesthesiology and Critical Care Medicine, Trauma Hospital Klagenfurt, Austria.
** Associate Professor. Dept. of Anesthesiology and Critical Care Medicine, Medical University Innsbruck, Austria.
Corresponding Author: Dr. Christoph Schlimp, Department of Anesthesiology and Critical Care Medicine, Trauma Hospital Klagenfurt, Waidmannsdorferstrasse 35, A-9021 Klagenfurt, Austria. Tel: +43-463-5890-1035, Fax: +43-463-5890-1038. E-mail: c.schlimp@gmx.at
“Crime Scene”

A 21-year-old woman, 65 kg and 168 cm, ASA status I, presented for an elective knee arthroscopy of about 45 min anesthesia. Medical history and physical examination were without pathological findings, the patient took no medication, and preoperative routine laboratory results were within the normal range. The following drugs were given to the patient during the anesthetic process: midazolam (7.5 mg orally), propofol (200 mg bolus + 400 mg/h), fentanyl (0.15 mg), rocuronium (25 mg), nitrous oxide (66%) in oxygen (33%), ranitidine (50 mg), diclofenac (75 mg), neostigmine (3.2 mg) and glycopyrrolate (0.6 mg). Suddenly the monitoring ECG showed a complete A V dissociation, with a P-wave frequency of 40 and a “small” QRS-complex frequency of 55 beats/min, hemodynamical stable and resolving during emergence.

C.S.I. “Crime Scene Investigation”

Investigator: At the scene currently under investigation, we saw the appearance of a complete AV dissociation during anesthesia. Nine drugs (midazolam, fentanyl, propofol, rocuronium, nitrous oxide, ranitidine, diclofenac, neostigmine, glycopyrrolate) have been spotted on the scene. Which drug used has the potential to elicit AV dissociation?

Anesthesia Expert: Midazolam was reported to have a dose-dependent depressing effect on the AV node in isolated guinea pig hearts. Fentanyl is known to have central vagal effects and might probably posses direct depressing effects on the AV conduction. Clinical evaluation of cardiac electrophysiological effects of midazolam combined with fentanyl, however, did not show significant changes in the electrophysiological variables.

Propofol’s mechanism of action on the AV conduction system is not completely known and literature is quite dissolute on this topic. Propofol is supposed to have a central vagotonic and/or sympatholytic mechanism and was held responsible for the occurrence of a second degree AV Mobitz I block reversible by anticholinergic drug administration. In a child, a single bolus of propofol elicited a complete AV block, but this child was suffering from Ondine’s curse, characterized by a generalized disorder of autonomic function. The combination of propofol and neostigmine in a patient also caused a complete heart block. In all of the cases described above, the AV block was thought to be caused by a vagotonic (cholinergic) mechanism. Recently, propofol was associated with antiarrhythmic properties in the cardiac conduction system, but the indirect vagotonic or direct influence of propofol on the electrophysiological properties of the heart are controversial and may depend on the species investigated and the specific conditions of study. The negative dromotropic effects of propofol in the isolated guinea pig heart were suggested to be mediated by muscarinic M2-receptors, an idea which would be supported by a study that found no direct effect of propofol on the canine cardiac conduction system under autonomic blockade. This is in contrast with the results of a study of isolated rabbit hearts, in which under complete autonomic blockade at clinically relevant propofol doses, a direct frequency-dependent effect on the AV node was found. A study in closed chest pigs showed that propofol causes a dose-related depression of the sinus node and the His-Purkinje system but has no effect on the AV node function whereas studies in isolated guinea pig heart revealed dose-or frequency-dependent AV nodal effects of propofol. On the cellular level, propofol suppressed directly the sodium, calcium and potassium currents in rabbit heart myocytes. However, clinical studies have shown that propofol does not affect the effective refractory periods of the AV node in patients with Wolff-Parkinson-White syndrome and children undergoing radiofrequency ablation.

Ranitidine blocks histaminic H2-receptors and inhibits the G-protein mediated rise in cyclic adenosine monophosphate, and thus decreases the heart rate. Furthermore, by blocking competitively H2-receptors, free histamine molecules can now activate more H1-receptors leading to a G-protein-mediated rise in calcium decreasing cardiac dromotropy. Extremely rare cardiovascular side effects are reported to occur especially after rapid infusion, and it has been mentioned in association with AV block.

Neostigmine, a peripheral acetyl-cholinesterase inhibitor is strongly parasympathomimetic by increasing the acetyl-cholin concentration also at the muscarinic M2-receptor in the heart. Therefore, neostigmine was reported to cause AV conduction...
Investigator: What effects do the other drugs exert on the cardiac conduction system?

Anesthesia Expert: Glycopyrrolate, a peripheral blocking drug at the muscarinic M2-receptor in the heart, enhances parasympatholytic effects and therefore is a cardiac conduction-stimulatory agent. Rocuronium is also known to have weak parasympatholytic activity. Nitrous oxide was mentioned in a case of AV dissociation with AV junctional rhythm but its influence on the heart’s automaticity and conduction is not easy to define and might rather be a change in sympathetic nervous activity. Diclofenac is not known to have any direct impact on cardiac arrhythmia, besides the possible hyperkalemia after non-steroidal anti-inflammatory drug-induced renal dysfunction.

Investigator: What do you think was the combined effect of all these drugs and which drug should be held most responsible regarding the onset of AV dissociation in this patient?

Anesthesia Expert: Probably minor complices on the scene but inevitably present in almost all anesthetic scenes were midazolam and fentanyl. Due to its previously discussed properties, propofol is a very interesting possible culprit present during the whole act. Another potential offender present and to be considered is ranitidine. All these drugs were finally topped up with neostigmine. We have previously discussed, that midazolam, fentanyl, propofol, ranitidine and neostigmine have all depressing effects on the AV conduction and may therefore conclude in the first place that their combination might have elicited this AV dissociation.

Timing of the appearance of neostigmine shortly before the onset of the AV dissociation would also suggest that it played the major role in this act. Furthermore, due to the well known parasympathomimetic effect of neostigmine to induce bradycardia, it is usually combined with glycopyrrolate a parasympatholytic. Some would now advocate that the simplest explanation for the heart block in this patient is a relatively high dose of neostigmine and a relatively low dose of glycopyrrolate. Rocuronium that has weak vagolytic side effects was apparently not much of a help to support glycopyrrolate in this case. We do, however, not know whether a higher dose of glycopyrrolate would have made any difference in the occurrence of the AV dissociation and can conclude that midazolam, fentanyl, propofol and ranitidine had at least a very high potential for enhancing this side effect of neostigmine.

Investigator: Well, then is there anything, that could have prevented AV dissociation?

Anesthesia Expert: With regard to this patient, it is of interest that post-operative evaluation of pre-operative existing electrocardiography (ECG) showed a borderline AV block grade I with a PQ interval of 212 ms.

Pre-operative consideration of this fact would probably have changed the poly-pragmatic drug administration in this case, but routine ECG evaluation in young patients is not common and its outcome and cost effectiveness with regard to the prevention of such adverse events would be subject to further discussion and investigation? However its knowledge might lead to a more critical use of the previously discussed agents in such patients. Furthermore, routine use of intra-operative relaxometry might help to reduce or avoid the routine use of acetyl-cholinesterase inhibitors and their mentioned side effects. Routine use of ranitidine in every patient should be carefully considered and restricted to especially indicated cases. Maybe, where possible, regional anesthesia would be preferable reducing drug interaction and its potential to cause AV dissociation in such patients.

Final pleading

The combination of many drugs routinely used during general anesthesia may have caused the complete AV dissociation in this scene. It appears that the cardiac conduction-stimulatory agent glycopyrrolate was not effective enough to compensate for the cardiac conduction-depression, provoked by the cumulative drug interaction due to combination of midazolam, fentanyl, propofol, ranitidine and neostigmine. Anesthetists should be aware of the cardiac conduction side effects of routinely used drug cocktails and should adapt poly-pragmatic drug administration with regard to possible AV conduction abnormalities evident on available ECGs even in young healthy patients. Current poly-pragmatic drug administration should be generally reconsidered.
References