Physostigmine increases the dose of propofol required to induce anaesthesia

Argyro Fassoulaki MD PhD DEAA,*
Constantine Sarantopoulos MD DEAA,†
Ch Derveniotis MD

Purpose: This prospective, randomized, double-blind study was performed to determine the effect of administration of physostigmine on the dose of propofol required to produce loss of consciousness.

Methods: Forty female unpremedicated patients were assigned in a random blind design to receive either 2 mg physostigmine or equal volume of normal saline *iv*, five minutes before induction of anaesthesia with propofol. All patients received general anaesthesia for breast surgery. Propofol was infused at a constant rate of 200 $ml \cdot hr^{-1}$ while patients were breathing oxygen 100% via a face mask. In each patient the dose of propofol required to produce loss of the ability to grasp a 20 ml syringe was recorded as the end-point of loss of consciousness. At this point the protocol was terminated and, after intubation of the trachea, anaesthesia was maintained with a nitrous oxide-isoflurane or sevoflurane mixture in oxygen, increments of an opioid and a muscle relaxant. Doses of anaesthetic drugs and duration of anaesthesia varied and depended on the type of breast surgery, determined by frozen section.

Results: The mean ± SD dose of propofol required to produce loss of consciousness was 2.4 ± 0.6 $mg \cdot kg^{-1}$ and 2.0 ± 0.4 $mg \cdot kg^{-1}$ in the physostigmine and in the normal saline groups respectively ($P = 0.014$).

Conclusion: Physostigmine pretreatment increases the dose of propofol required to produce loss of consciousness.

Objectif : Cette étude prospective, aléatoire et en double insu visait à déterminer l'influence de l'administration de la physostigmine sur la dose de propofol requise pour provoquer la perte de conscience.

Méthodes : Cette étude aléatoire et à l'insu regroupait quarante femmes non prémédiquées et programmées pour une chirurgie du sein sous anesthésie générale. Elles ont reçu soit 2 mg de physostigmine soit un volume égal de sol. phys. *iv* cinq minutes avant l'administration du propofol. Une perfusion de propofol de 200 $ml \cdot h^{-1}$ était mise en marche à débit constant alors que les patientes respiraient de l'oxygène à 100% par masque facial. On enregistrait chez chacune des patientes la dose de propofol requise pour produire la perte de la capacité de préhension d'une seringue de 20 ml, méthode adoptée comme critère de la perte de conscience. À ce moment, le protocole prenait fin et, après l'intubation de la trachée, l'anesthésie était maintenue avec un mélange de protoxyde d'azote et d'isoflurane ou de sévoflurane en oxygène associé à des doses répétées de morphiniques et de relaxants musculaires. Les doses d'agents anesthésiques et la durée de l'anesthésie variaient et dépendaient de la chirurgie mammaire déterminée par la coupe en congélation.

Résultats : La dose moyenne (± ÉT) de propofol requise pour faire perdre conscience était de 2,4 ± 0,6 $mg \cdot kg^{-1}$ pour le groupe physostigmine et de 2,0 ± 0,4 $mg \cdot kg^{-1}$ pour le groupe contrôle ($P = 0,014$).

Conclusion : Le prétraitement à la physostigmine augmente la dose de propofol requise pour provoquer la perte de conscience.

From the Department of Anaesthesia,* St Savas Hospital, 171 Alexandras Ave, 11522 Athens, Greece and the Department of Anesthesiology† Medical College of Wisconsin, Milwaukee, WI, USA.
Address correspondence to: A. Fassoulaki MD, 57-59 Raftopoulou street, 11744 Athens, Greece.
Accepted for publication July 23, 1997.

STIMULATION of the central nervous system cholinergic pathways leads to generalized arousal. The anticholinesterase physostigmine salicylate is a tertiary amine which, unlike neostigmine, penetrates the blood brain barrier. Physostigmine has been shown to antagonize the depressant effects of a variety of drugs including morphine,[1] benzodiazepines,[2] and ketamine.[3] The arousal produced by physostigmine may be useful postoperatively, if prolonged sedation occurs.

The effect of physostigmine on propofol anaesthesia has not been investigated. The purpose of the present study was to determine whether pretreatment with physostigmine affected the dose of propofol required to induce anaesthesia.

Methods

This randomized prospective investigation was approved by the Local Ethics Committee and informed consent was obtained in all patients. Forty female patients ASA physical status I and II scheduled for breast surgery were studied. Premedication was not given. Noninclusion criteria were impairment of hepatic or thyroid function, history of asthma or ischaemic heart disease, previous exposure to drugs known to affect anaesthetic requirements, history of chronic alcoholism and/or drug abuse, and pregnancy potential. Preoperative laboratory tests included haemoglobin, blood urea, creatinine, alanine aminotransferase and aspartate aminotransferase concentrations.

The experimental subjects were assigned at random using a table of random numbers obtained from a computer created table. Twenty envelopes containing odd and twenty envelopes containing even random numbers were prepared. An envelope was opened when each patient arrived at the operating room and 2 mg physostigmine or an equal volume of normal saline solution was prepared for each odd or even number respectively. The envelope was opened and the solution prepared by an anaesthetist who was not involved in the anaesthetic administration or in the evaluation of the results. The solution was administered five minutes before induction of anaesthesia.

All patients breathed 100% oxygen for three to five min via a face mask before induction of anaesthesia. Two 16 g peripheral venous catheters were inserted, one in each antecubital fossa, and propofol was administered at a constant rate 200 $ml \cdot hr^{-1}$ (33.3 $mg \cdot min^{-1}$) by means of two infusion pumps (DSP, Johnson and Johnson). The maximum infusion rate for each pump was 100 $ml \cdot hr^{-1}$. This rate was chosen after several trials, as slower rates were associated with excitation or/and involuntary movements interfering with the precise time of "syringe dropping."

A 20 ml plastic syringe filled with water was placed between the patient's forefinger and thumb of the right hand. Both arms were supported by arm-boards. This test for loss of consciousness has been described previously.[4] When the patient dropped the syringe the propofol infusion was stopped and the total dose of propofol was recorded. Then, the protocol was terminated and, after intubation of the trachea, anaesthesia was maintained with isoflurane or sevoflurane in a nitrous oxide/oxygen mixture, a muscle relaxant (rocuronium or mivacurium) and an opioid. Doses of anaesthetic drugs and duration of anaesthesia varied as the surgery might be excision of breast tumour with or without dissection of axillary glands. All patients were treated with antiemetics (metoclopramide and ondansetron) intraoperatively.

The estimated sample size in each group required to ensure power 0.95 ($\beta = 0.05$) of detecting a clinically relevant difference of 0.5 $mg \cdot kg^{-1}$ was found to be 15 patients for $\alpha = 0.05$. An estimated SD of 0.53 was used based on initial pilot measurements. Equal number of subjects were initially distributed in each group to maximize power.[5] The Statgraphics® statistical package (Statistical Graphics Corporation) was used for sample size estimation and statistical analysis. We studied 20 patients in each group in case some were lost. Results are expressed as mean ± SD. Statistical comparisons of demographic data and of the doses of propofol required to produce loss of consciousness in each group were performed using Student's t tests for unpaired observations. $P < 0.05$ was considered significant.

Results

No differences were found between the physostigmine and the control groups in age, body weight or height.

The laboratory test values (haemoglobin, alanine and aminotransferases, urea and creatinine) were normal and did not differ between the two groups.

The mean total dose for positive response was 117 ± 23 mg in the control group and 140 ± 37 mg in the physostigmine group, and the average duration of propofol infusion was 3.5 min and 4.2 min respectively.

The propofol requirements for loss of consciousness were 20% higher in the physostigmine pretreated group than in the group who received normal saline, 2.4 ± 0.6 *vs* 2.0 ± 0.4 $mg \cdot kg^{-1}$ ($P = 0.014$) (Table I).

Discussion

Our results demonstrate that the dose of propofol required to produce loss of consciousness in patients pretreated with physostigmine was increased by 20% compared with saline pretreated patients.

Physostigmine, the centrally acting cholinesterase inhibitor, when given *iv*, reverses the respiratory depressant effect of morphine and restores the sensi-

TABLE I Demographic data of patients and the dose of propofol required to produce loss of consciousness in the physostigmine and in the control group. Mean ± SD.

	Physostigmine group (n = 20)	*Control group (n = 20)*
Age (yr)	41 ± 10.5	37 ± 9.6
Weight (kg)	60 ± 9.8	60 ± 8.2
Height (cm)	164 ± 6.2	162 ± 6.7
Dose of propofol ($mg \cdot kg^{-1}$) to produce loss of consciousness	2.4 ± 0.6*	2.0 ± 0.4*

*$P = 0.014$

tivity of the respiratory centre to CO_2.[1] Prolonged postoperative somnolence following induction of anaesthesia with midazolam was rapidly reversed by physostigmine after other measures to awake the patients, like naloxone administration, had failed.[2]

Ketamine is also antagonized by physostigmine. Toro-Matos *et al.* in a double blind cross-over trial in healthy volunteers demonstrated that physostigmine shortens the recovery from ketamine anaesthesia.[3] Mimura *et al.* administered either physostigmine or oxotremorine or 4- aminopyridine in rats after anaesthesia with ketamine. The three cholinergic agents have a central muscarinic action but different peripheral actions. All antagonized ketamine-induced anaesthesia. This antagonism was attenuated by pretreatment with l-hyoscyamine, which produces sedation due to central muscarinic inhibition.[6] Reversal by physostigmine is not accompanied by reversal of analgesia. It has been shown that ketamine at clinically relevant concentrations inhibits muscarinic signalling through M1 receptors.[7]

Propofol, at clinically relevant concentrations, potentiates GABA-mediated transmission in the rat olfactory cortex probably by an interaction with the GABA receptor complex.[8] Propofol facilitates GABA-receptor interaction and GABA stimulated chloride channel conductance in the rat brain.[8] However, its site of action appears to be different from that of benzodiazepine and $GABA_A$ receptor recognition sites.[9] In selected lines of mice the $GABA_A$ receptor did not mediate propofol sleep time, thus the effect of propofol on $GABA_A$ receptor may not be related to loss of consciousness.[10] These may be reasons that flumazenil had no effect on propofol anaesthesia.[11]

No data are available concerning inhibition of central muscarinic transmission by propofol, or reversal of propofol anaesthesia by physostigmine. The excitatory neurotransmitter acetylcholine is associated with the maintenance of consciousness, and muscarinic signalling is one of several systems affected by anaesthetics.[12] However, it is not clear whether the effect of physostigmine on propofol depends on muscarinic or nicotinic receptors. Anaesthetics interfere with muscarinic signalling.[12] At the same time, an effect on nicotinic receptors cannot be excluded. It has been shown recently that propofol potentially inhibits the α4ß2 but not the α7-type nicotinic acetylcholine receptors in a clinically relevant range.[13,14] Nevertheless, the role of inhibition of nicotinic acetylcholine receptors in producing anaesthesia is unclear.

It is possible that physostigmine-induced bradycardia and decreased cardiac output prolonged loss of consciousness in the physostigmine group. Nonetheless, our patients were relatively young, healthy and unpremedicated. The rate of infusion we used, 33.3 $mg \cdot min^{-1}$, is slow enough to allow a sleep dose of propofol unaffected by possible changes in cardiac output.

If propofol shares, with other anaesthetics, an effect on cholinergic transmission, physostigmine may reverse the depression associated with propofol administration by inhibiting acetylcholine hydrolysis and raising acetylcholine concentrations in the brain. In this way more acetylcholine becomes available. Cholinergic agonists with greater specificity may allow wider perioperative manipulation of CNS cholinergic systems.

We conclude that physostigmine pretreatment increases the dose of propofol required to produce loss of consciousness. Further studies are needed to establish the clinical importance of reversing propofol anaesthesia as well the precise mechanism(s) of a possible antagonism by physostigmine.

References

1 *Snir-Mor I, Weinstock M, Davidson JT, Bahar M.* Physostigmine antagonizes morphine-induced respiratory depression in human subjects. Anesthesiology 1983; 59: 6–9.

2 *Caldwell CB, Gross JB.* Physostigmine reversal of midazolam-induced sedation. Anesthesiology 1982; 57: 125–7.

3 *Toro-Matos A, Rendon-Platas AM, Avila-Valdez E, Villarreal-Guzman RA.* Physostigmine antagonizes ketamine. Anesth Analg 1980; 59: 764–7.

4 *Fassoulaki A, Farinotti R, Servin F, Desmonts JM.* Chronic alcoholism increases the induction dose of propofol in humans. Anesth Analg 1993; 77: 553–6.

5 *Lerman J.* Study design in clinical research: sample size estimation and power analysis. Can J Anaesth 1996; 43: 184–91.

6 *Mimura M, Namiki A, Kishy R, Ikeda T, Miyake H, Iwasaki H.* Central cholinergic action produces antagonism to ketamine anesthesia. Acta Anaesthesiol Scand 1992; 36: 460–2.

7 *Durieux ME.* Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesth Analg 1995; 81: 57–62.
8 *Collins GGS.* Effects of the anaesthetic 2,6-diisopropylphenol on synaptic transmission in the rat olfactory cortex slice. Br J Pharmacol 1988; 95: 939–49.
9 *Peduto VA, Concas A, Santoro G, Biggio G, Gessa GL.* Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. Anesthesiology 1991; 75; 1000–9.
10 *Simpson VJ, Blednov Y.* Propofol produces differences in behavior but not chloride channel function between selected lines of mice. Anesth Analg 1996; 82: 327–31.
11 *Fassoulaki A, Sarantopoulos C, Papilas K.* Flumazenil reduces the duration of thiopentone but not of propofol anaesthesia in humans. Can J Anaesth 1993; 40: 10–2.
12 *Durieux ME.* Muscarinic signaling in the central nervous system. Anesthesiology 1996; 84: 173–89.
13 *Flood P, Ramirez-Latorre J, Role L.* α4ß2 neuronal nicotinic acetylcholine receptors in the central nervous system are inhibited by isoflurane and propofol, but α7-type nicotinic acetyicholine receptors are unaffected. Anesthesiology 1997; 86: 859–65.
14 *Violet JM, Downie DL, Nakisa RC, Lieb WR, Franks NP.* Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. Anesthesiology 1997; 86: 866–74.