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CASE REPORT

Physostigmine: going . . . going . . . gone? Two cases of central anticholinergic syndrome following anaesthesia and its treatment with physostigmine

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Summary

Two patients presented with very different signs of central anticholinergic syndrome following general anaesthesia for which they had received premedication with hyoscine. Both responded dramatically to 1 mg of intravenous (i.v.) physostigmine, which produced a rapid return to a normal level of consciousness. The aetiology of central anticholinergic syndrome is multi-factorial, but the diagnosis should be considered in all patients who demonstrate abnormal post-anaesthetic awakening. It is recommended that 1 mg of intravenous physostigmine is a safe and effective treatment for central anticholinergic syndrome, and that a supply of this important drug must be kept readily available in the recovery area of the operating theatre department.

Keywords: CENTRAL ANTICHOLINERGIC SYNDROME, hyoscine; ANAESTHESIA, general (complications); PHYSOSTIGMINE.

Introduction

Physostigmine is a centrally acting anticholinesterase which increases acetylcholine levels in the brain, but has minimal effects elsewhere [1,2]. It is the treatment of choice for central anticholinergic syndrome (CAS), a condition not widely recognized following anaesthesia, which results from an imbalance in the widespread cholinergic pathways in the central nervous system (CNS) [3,4]. Clinical features of CAS include alterations in the level of arousal and response to external stimuli, producing a range of effects including agitation, delusions, somnolence, coma and convulsions. Anticholinergic premedication has long been known to be a cause of CAS in a minority of patients [3], and despite the reported decline in the use of this type of premedication in current UK anaesthetic practice [5], it is important to recognize that CAS may still occasionally occur following anaesthesia.

Two cases of CAS following anaesthesia which responded dramatically to physostigmine are reported below. Unfortunately, despite being the drug of choice in CAS, physostigmine appears to have become less readily available in recovery areas in recent years. We wish to reiterate the value and effectiveness of physostigmine for the treatment of CAS, and highlight the clinical importance of maintaining supplies of this important drug in the recovery room.

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Case histories

Case one

A fit, muscular 93 kg, 26-year-old male underwent general anaesthesia for a nephropyeloplasty because of asymptomatic ureteric obstruction. The patient had

previously undergone an uneventful general anaesthetic as a child to enable a lacerated arm to be sutured, and was not a known drug abuser. Following premedication with papaveretum 20 mg and hyoscine 0.4 mg 1 h before operation, anaesthesia was induced with midazolam 3 mg and thiopentone 300 mg i.v. After muscle relaxation and intubation with alcuronium 20 mg, anaesthesia was maintained with enflurane 1% and 60% nitrous oxide in oxygen. An intrapleural block was performed using 30mLs of 0.5% bupivacaine with 1: 200 000 adrenaline to provide post-operative analgesia.

At the end of an uneventful anaesthetic and 3 h surgical procedure, metoclopramide 10 mg was given prior to adequate reversal with neostigmine 2.5 mg and glycopyrronium bromide 0.5 mg, confirmed with the use of a peripheral nerve stimulator. Despite this the patient remained deeply unconscious and did not respond to an initial dose of doxapram 50 mg. A total dose of doxapram 150 mg and naloxone 400 μg were required i.v. before he started breathing. The patient was extubated and taken to the recovery room, but remained unrousable. The patient maintained an oxygen saturation of 100% with oxygen 4L min^{-1} via a Hudson facemask. Pulse, blood pressure, ECG, plasma electrolyte and glucose levels were all normal. Flumazenil was not given because of the small initial dose of midazolam and the time lapse involved.

One hour post-operatively, his clinical condition was unchanged but blood gas analysis showed a respiratory acidosis (pH 7.15, $PaCO_2$ 10.2 kPa, PaO_2 58.3 kPa, BE −3 mmol L^{-1}), and as a result the patient was reintubated and ventilated. Over the next hour the patient became more responsive, although continued to tolerate the endotracheal tube without sedation. With an uncertain diagnosis, the patient was reviewed by a neurosurgeon, and had a computerized tomogram (CT) scan of his head which was normal. Three hours post-operatively the possibility of central anticholinergic syndrome was raised, and he was given 1 mg of physostigmine i.v., following which he regained full consciousness, immediately extubating himself. There was no evidence of neurological deficit, and his clinical response was maintained without the need for further treatment.

Case two

A 90 kg, 60-year-old female underwent general anaesthesia for a lateral sphincterotomy. The patient was taking atenolol 50 mg for hypertension and amitriptyline 50 mg daily for depression. Following premedication with papaveretum 20 mg and hyoscine 0.4 mg 1 h before operation, anaesthesia was induced with propofol 200 mg, fentanyl 50 μg i.v and the airway was established with a size 3 laryngeal mask. Anaesthesia was maintained with isoflurane 1% and nitrous oxide 70% in oxygen, breathing spontaneously. The patient was treated with i.v. atropine 0.3 mg for an episode of bradycardia, and ketorolac 10 mg i.v. was given for post-operative analgesia.

The anaesthetic was terminated 20 min after induction, the patient awoke rapidly on the operating table in an extremely agitated and confused state, and pulled out her laryngeal mask. The patient's cardiovascular system was stable, ECG was normal, she was pink and making good respiratory efforts with an oxygen saturation of 94% on air. The patient required sedation with propofol 50 mg and midazolam 2 mg i.v. for transport to the recovery area.

Twenty minutes after arrival in the recovery room she required resedation with propofol and midazolam. During this time oxygen saturation remained at 98%, with oxygen 4 L min^{-1} via a Hudson facemask, her cardiovascular status remained unchanged, central temperature was 36.5°C, plasma electrolytes and blood sugar level were normal, there were no localizing neurological signs and her bladder was empty. A total of 200 mg propofol and 8 mg midazolam were used over three occasions to provide intermittent sedation.

Ninety minutes after the end of surgery the possibility of central anticholinergic syndrome was considered and physostigmine 1 mg was given i.v. The response was immediate, the patient awoke and asked rational questions of the recovery staff. This effect was sustained with no further doses of physostigmine.

Discussion

These two patients demonstrate both ends of the clinical spectrum of CAS, the diagnosis taking some time to reach and being confirmed by the rapid response to physostigmine. Despite the increasing use of short-acting anaesthetic agents and less sedative premedication, it is not uncommon to encounter patients who do not recover from general anaesthesia as expected. In the vast majority of cases this will

simply be the result of the variable individual response to anaesthetic drugs. The diagnosis of CAS may only be made after a process of elimination, and important treatable causes of abnormal awakening from anaesthesia must be considered, particularly hypoxia, over-sedation with opioids or volatile agents, persistent neuromuscular blockade, bladder distension and pain.

In clinical practice CAS is caused by the use of drugs with anticholinergic properties which cross the blood-brain barrier, commonly atropine and hyoscine. However, most anaesthetic drugs probably interfere to some degree with central cholinergic transmission [3] and over 500 drugs have been implicated in CAS, including anti-histamines, anti-depressants, benzodiazepines, and anti-psychotic and anti-parkinsonian drugs [4].

The variation in presentation of CAS is partly agent-specific: atropine is generally stimulant and hyoscine depressant [3], although larger doses of hyoscine may also produce an excitatory response. However, this can also occur with normal doses of hyoscine, particularly in the elderly [6]. In their landmark paper of 1976, Rupreht and Dworacek reported CAS to occur in up to 9.4% of patients following anticholinergic premedication and general anaesthesia [7], and an element of CAS may well be a contributory factor in a number of patients who show varying degrees of post-operative confusion in the recovery room.

These two case studies demonstrate that CAS is not just a problem of inappropriate premedication in the elderly, but can effect the young as well. It is likely that CAS developed in the first patient presented here as a result of the anticholinergic effects of hyoscine premedication, with possible additive effects from midazolam and metoclopramide; in retrospect flumazenil might have been useful. In the second patient CAS probably developed as a result of the combined effects of amitriptyline, the hyoscine premedication and intra-operative atropine.

The use of anticholinergic premedication is currently declining in the UK: in a survey of the members of the Association of Anaesthetists of Great Britain and Ireland in 1991 only 36% of anaesthetists reported using anticholinergic premedication routinely [5]. Avoidance of anticholinergic premedication, particularly in the elderly and patients already taking drugs with anticholinergic effects, and the use of glycopyrronium bromide as an alternative to hyoscine or atropine, will minimize the risk of CAS [7]. However, whilst the overall effect of this may be to reduce the incidence of CAS following anaesthesia, it may also reduce awareness of the possible diagnosis in specific cases.

Physostigmine, is the anticholinesterase of choice for the treatment of CAS. It is an alkaloid originally obtained from the Calabar bean of West Africa [8]. Unlike neostigmine which contains a quaternary amine group, physostigmine contains a tertiary amine group and therefore is able to cross the blood-brain-barrier, increasing the amount of acetylcholine available for neuro-transmission by reducing endogenous cholinesterase activity. It produces a wide range of effects, chiefly those of parasympathetic stimulation including nausea, salivation, sweating, abdominal colic and bronchospasm. However, these are reported to be of minor significance [1] and there is little effect on the neuromuscular junction [2], although some authors recommend the concomitant use of glycopyrronium bromide to avoid these peripheral effects [8]. Physostigmine has recently been shown to significantly reduce the recovery time from ketamine anaesthesia in military practice, although it made no difference to the incidence of ketamine side effects [9]. Central stimulation may cause bradycardia, hypertension and convulsions, and physostigmine should therefore be used with caution in patients with epilepsy, Parkinson's disease and avoided in asthmatic patients since bronchospasm may be a problem [10].

Physostigmine is usually presented as a clear solution, does not require refrigeration and has a shelf-life of 2 years [10]. It has an onset of action of 3–8 min and a short plasma elimination half-life of 20–30 min, giving a duration of action of up to 120 min [8]. The recommended initial dose is 0.04 mg kg^{-1} (given by slow i.v. injection over several minutes with ECG monitoring) which may need to be followed by further repeated doses [3]. However, this was not our experience since a relatively small single dose (0.015 mg kg^{-1}) produced rapid and long-lasting reversal of CAS.

Physostigmine currently has no licence for i.v. use in the UK, does not appear in the current Data Sheet Compendium or British National Formulary, other than as eye drops for the treatment of glaucoma, and is manufactured in the UK only in special licensed centres. Whilst the use of drugs outside of Product

Licence is controversial [11], anaesthetists may be reassured that physostigmine is both safe and the treatment of choice for post-operative CAS [3,6]. However, as with any limited small market, there is now a real danger that the use and availability of i.v. physostigmine may fall into obscurity. Indeed, many hospitals already appear to have removed it from their local formulary. We believe that physostigmine should be available in the recovery room of every hospital and that anaesthetists must insist that the supply of this useful and important drug must be maintained.

Whilst rarely recognized, CAS almost certainly occurs more commonly now than is generally appreciated. Anaesthetists should consider this possible diagnosis when faced with a confused or unexpectedly sedated patient in the recovery room, particularly when an anticholinergic premedicant has been given. If CAS is suspected, i.v. physostigmine should be used, whereupon a dramatic return to normal consciousness may be anticipated.

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