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Effect on cognition of galanthamine administered for neuromuscular block reversal in octogenarians undergoing cataract surgery

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Abstract

Background. The purpose of the study was to determine the possible effect of the cholinesterase inhibitor, galanthamine, on cognition when administered to antagonise neuromuscular blockade after anaesthesia.
Methods. The Wechsler Memory Scale was used to assess cognition before and after cataract surgery, carried out under general anaesthesia, in forty-five octogenarian patients. At the end of the operation, in order to reverse residual neuromuscular blockade, patients were randomly assigned to receive either galanthamine, acting on central and peripheral receptors, or neostigmine — a drug without central activity.
Results. The differences between the Wechsler Memory Scale scores obtained from both groups were not statistically significant; however, patients who received galanthamine experienced more side effects (e.g. nausea, vomiting, dysphoria) and had lower scores in memory tests performed immediately after surgery. Reduction of galanthamine doses did not improve the situation.
Conclusions. In octogenarians, impaired organ function as well as changes in body composition, are factors which affect the pharmacodynamics and pharmacokinetics of drugs.

Key words: neuromuscular blockade, reversal, galanthamine; neuromuscular blockade, reversal, neostigmine; galanthamine, side effects

Słowa kluczowe: blokada nerwowo-mięśniowa, odwracanie, galantamina; blokada nerwowo-mięśniowa, odwracanie, neostygmina; galantamina, objawy uboczne

In 1834, an article published in The Lancet by the distinguished French surgeon, Baron Guillaume Dupuytren [1], described seven postoperative cases of what he called "nervous delirium". One of the patients had undergone cataract extraction and this case became the first report on cataract surgery-related delirium. Delirium, an acute state of confusion, can affect more than 50% of hospitalised elderly patients, but often remains undiagnosed. As a result, morbidity in this group increases, and indeed at times delirium may lead to death [2]. Cataract is listed as a risk factor of delirium [2], as is being an octogenarian [3].

The risk of possible loss of sight can arouse feelings of terror in the elderly contemplating cataract removal. Such thoughts can be entertained even after surgery, inducing confusion and anxiety. Apart from the psychological aspects, there are systemic elements associated with the complex nature of postoperative delirium. One particular factor is acetylcholine, a neurotransmitter whose production in the brain diminishes with age. The issue becomes further complicated when the patients take drugs of varying central anticholinergic effects.

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Acetylcholinesterase is responsible for the hydrolysis of acetylcholine. By blocking its hydrolysis, the effect of acetylcholine should be prolonged. Galanthamine hydrobromide can be used for this purpose. Traversing the blood-brain barrier, the drug is also useful in patients with Alzheimer's disease [4] and for the neutralisation of central anticholinergic toxicity [5]. In addition, galanthamine, like neostigmine, is endowed with peripheral action, in that it antagonises the residual non-depolarising neuromuscular blockade used in anaesthesia. This latter however, being quarternary ammonium (in nature), is devoid of any central effect.

Therefore, it was thought that galanthamine might be of value if administered to patients over 80 years of age undergoing cataract surgery under general anaesthesia. In this case, the central action of galanthamine could have a positive effect on cognitive function, while its peripheral mechanism would reverse any remaining neuromuscular blockade. Thus, the present study was carried out to investigate these possibilities.

METHODS

Forty-five octogenarians living at home and preferring to have their cataract removed under general anaesthesia entered the trial. The study protocol was approved by the institutional ethics committee and oral consent was given by all the patients. All of them were seen by an anaesthetist as well as by an anaesthesia nurse before surgery. Patients with hearing difficulties, epilepsy, dementia, or those uncooperative for any reason were excluded. All prescribed drugs were noted down from the patients' charts. On the evening before surgery, the patients were given temazepam 10 mg orally, and on the following morning lorazepam 1 mg. In the operating theatre, an intravenous infusion of Ringer's acetate solution was started through which all drugs were administered. Monitoring throughout the procedure included non-invasive blood pressure, heart rate, ECG, pulse oximetry and neuromuscular blockade (TOF, *Train-Of-Four*). Following the routine induction of anaesthesia with fentanyl, thiopentone and suxamethonium, tracheal intubation was performed. Anaesthesia was maintained with isoflurane 0.25–0.5% in a mixture of N_2O/O_2 (F_IO_2 0.35), fentanyl, if needed, and vecuronium 0.1 mg kg^{-1}. The patients were mechanically ventilated with end-tidal carbon dioxide aimed at approximately 5.7%. At the end of surgery (four twitches on TOF stimulation), patients were assigned randomly to receive either neostigmine (group N) or galanthamine (group G). Galanthamine was given in the dose of 20 mg or 10 mg. In those patients who received neostigmine or galanthamine 20 mg, glycopyrrolate 0.2 mg was injected immediately before the anticholinesterase drug. Following tracheal extubation, the patients were moved to the recovery room and given oxygen through a nasal catheter with pulse oximetry being monitored. After 2–3 hours, they were transferred back to their ward.

In order to assess the patients' mental status, the psychologist had a 5–10 min conversation with every patient before each test was performed. The tests, all auditory with the subjects answering verbally, were carried out on the day before surgery, 4–6 h postoperatively, and on the following day i.e. 30–34 h after surgery. The psychologist was not aware which anticholinesterase drug a patient had received. The following tests were applied:

— subtests and current information and orientation with the Finnish version of the Wechsler Memory Scale [6], consisting of the following questions: age, date of birth, the president's name, the former president's name, the country's population, home (place) as well as year, season, month, dates of the first, middle and last day of month, and day of the week;
— categories of words, ten items each: clothing, occupations, parts of house, birds, weapons, furniture, musical instruments, kitchen utensils. Each patient was given four of these categories, separated by a short time gap. After being given 20 words from the category, the subject was asked to identify the ten words which had been given initially. Their memory was assessed by scoring immediate recall and repeated recall (the same category repeated after 10 min);
— the patient heard a short story consisting of 30 to 40 words, and thereafter was scored on: immediate recall and delayed recall (the following day);
— metamemory: during the pre-operative visit, the subjects were asked to compare their own memory to that of their peers, on the basis of a three point scale: worse than others, as good as others, or better than others;
— experienced memory deterioration: during the pre-operative visit, the patients were questioned as to whether they felt their memory had recently deteriorated, on a three point scale: has remained the same, is somewhat worse, or is much worse than earlier.

The binominal data was analysed using the Chi^2 test. As the same individual had been tested several times, the results of psychological data were tested using analysis of variance and covariance with repeated measures. $P < 0.05$ was considered as being statistically significant.

RESULTS

Forty of the initial 45 patients completed the study: 21 received neostigmine and 19 galanthamine. Apart from gender, other demographic characteristics, as well as the length of anaesthesia, were similar in both groups (Table 1). One-third of the individuals were aged 85 years and over. Although they were not questioned about the level of their education, all were literate. A large num-

Table 1. Characteristics of patients and length of anaesthesia ($\bar{x}$ ± SD, range)

Group	n	Gender (M/F)	Age (yr)	Weight (kg)	Height (cm)	Anaesthesia (min)
Group G	19	2/17	85 ± 3.1 (80–94)	62.7 ± 12.7 (47–99)	159 ± 7 (149–174)	58 ± 20.4 (25–105)
Group N	21	8/13	83 ± 2.3 (80–88)	68.6 ± 12.7 (52–92)	163 ± 6.9 (146–174)	50 ± 13.9 (25–95)

Table 2. Immediate postoperative side effects

Group	Dysphoria	Nausea	Vomiting	Tachycardia
Group G	6	8	6	5
Group N	0	3	1	1
p	0.005	0.049	0.03	NS

Table 3. Wechsler Memory Scale scores of patients during test periods

Preoperative		Postoperative 4–6 h		Postoperative 30–34 h	
Group G	**Group N**	**Group G**	**Group N**	**Group G**	**Group N**
Wechsler memory scale/current information [6]					
4.7 ± 0.95	5.1 ± 1.12	4.9 ± 0.99	5.2 ± 1.3	5.1 ± 0.64	5.1 ± 1.3
(2–6)	(3–6)	(3–6)	(2–6)	(4–6)	(2–6)
Wechsler orientation [7]					
6.6 ± 0.7	6.1 ± 1.55	6.6 ± 0.6	6.2 ± 1.66	6.5 ± 0.66	6.1 ± 1.8
(5–7)	(1–7)	(5–7)	(1–7)	(5–7)	(1–7)
Words: immediate recall (two sets of ten words each) [20]					
10.1 ± 2.08	10.2 ± 2.93	8.2 ± 2.63	8.6 ± 3.10	9.0 ± 2.08	9.1 ± 3.28
(6–14)	(5–14)	(4–15)	(2–13)	(6–12)	(4–16)
Words: repeat recall [10]					
5.2 ± 1.38	5.3 ± 2.25	4.6 ± 2.09	4.9 ± 1.62	5.6 ± 1.45	5.0 ± 1.94
(3–7)	(2–9)	(0–9)	(2–8)	(4–8)	(2–9)
Words: recognition [10]					
5.6 ± 2.63	6.2 ± 2.19	4.5 ± 3.86	6.0 ± 2.94	4.5 ± 2.63	5.1 ± 3.05
(0–9)	(3–12)	(0–10)	(0–10)	(0–8)	(0–10)
Scenario: logic memory [13]					
5.9 ± 2.12	6 ± 2.6	6.7 ± 2.73	7.2 ± 2.93	5.6 ± 1.8	5.4 ± 3.04
(1–10)	(0.11)	(0–12)	(0–12)	(3–9)	(2–12)
Scenario: delayed recall [13]					
		4 ± 2.18	4.1 ± 2.85	0.5 ± 1.66	1.6 ± 2.72
		(0–8)	(0–11)	(0–6)	(0–7)

ber of patients displayed systolic hypertension during the pre-anaesthesia visit, with 23 (57%) having values of ≥ 170 mm Hg and eight (20%) of ≥ 200 mm Hg. On entering the operating room, these figures were 17 (42%) and five (13%), respectively.

The patients were taking a wide variety of medications; one patient was receiving nine drugs. The majority of medicines were digoxin, diuretics (particularly furosemide), nitrates, oral antidiabetic agents, potassium, benzodiazepines, beta-blockers, ACE inhibitors, allopurinol and non-steroidal anti-inflammatory drugs.

After surgery, some patients who received galanthamine were extremely distressed by side effects; five of them were unable to take part in the first post-operative psychological testing and were therefore excluded from the trial. Reducing the galanthamine dose from 20 to 10 mg and withdrawing glycopyrrolate (to decrease tachycardia) did not produce any substantial reduction in the adverse side effects (Table 2).

During their first meeting with the psychologist, all the patients were well motivated to take part in the study. Some individuals spontaneously mentioned their fear of death due

to the coming operation. Comparison of the two groups of patients before surgery showed no differences in test results. In the first post-operative assessment, patients who received neostigmine obtained slightly higher values in six of the seven tests; the differences, however, failed to reach statistical significance. The scores during the second post--operative testing, although tending to favour the galanthamine group, were again statistically non-significant (Table 3).

During the first post-operative session, some of the patients, either because of the side effects (especially after galanthamine administration) and/or under the influence of residual anaesthesia, were tired and irritable. There were, however, no signs of delirium noted. In some instances, other patients sharing the room formed a social group and became hostile, accusing the psychologist of annoying them and insisted on leaving them in peace. On the following day, the patients had recovered well and were looking forward to returning home. Many of them had lost interest in the tests.

DISCUSSION

Some patients, particularly those who received galanthamine, were badly affected by the side effects of anticholinesterases, to such an extent that they were unable to take part properly in the first post-operative cognitive tests. As a result, the aim of the study was not satisfactorily fulfilled. This raises the question of whether galanthamine should be used at all in the elderly for antagonising the curare-like block. Although such trials with galanthamine have been conducted, none has been confined to octogenarians. The problem does not relate to the peripheral activity of galanthamine, but rather to the accompanying central effects, which are not seen in younger patients. To reduce this central activity, the dose of drug was reduced to 10 mg, but it did not lead to any real improvement. At the neuromuscular junction of both humans and the isolated rat diaphragm, galanthamine 20 mg is equipotent to neostigmine 1 mg. Based on these data, a further reduction in the galanthamine dose to 5 mg (equivalent to neostigmine 0.25 mg) could have left patients partially paralysed, with all the problems that such a condition entails.

The physiological changes of ageing connected with decreasing organ functions begin at about the age of 30; at 80, their functions become extensively reduced. These changes, together with the patient's chronic illnesses and medications, greatly influence the pharmacodynamics and pharmacokinetics of drugs [7]. However, of greater consequence is that such factors are related to the development of post-operative delirium. With the exception of nitrates and beta-blockers, the majority of the prescribed medications listed earlier have some anticholinergic activity [2, 8]. Moreover, the patients may have been taking other medications with this property, which were not included in the charts due to their availability without a prescription. In any case, the immense individual variations in the general condition of elderly people should always be taken into account.

Initially, many patients, despite their antihypertensive therapy, displayed disturbingly high systolic blood pressure. Although probably emotional in character, the pressure was insufficiently affected by the benzodiazepine pre-medication, and nitroglycerin was needed to lower it to the level suitable for inducing anaesthesia.

A special effort was made to avoid hypocarbia during anaesthesia by monitoring the end-tidal CO_2. In an earlier study, patients who had been normo- or slightly hypoventilated fared better in post-operative psychomotor tests than their counterparts exposed to hyperventilation. The advantage is thought to result from enhanced cerebral blood flow, which thereby prevents hypoxia [9]. In addition, great attention must be given to avoid post-operative hypoxia in elderly patients.

Unlike neostigmine, which when given to antagonise a neuromuscular block requires an anticholinergic to alleviate muscarinic effects, galanthamine may be used without an anticholinergic agent. This was the case in 12 patients in our study, who received galanthamine alone, thus preventing additional tachycardia which might develop following glycopyrrolate. However, galanthamine administered without an anticholinergic in patients with bradycardia would make them more liable to develop bradyarrhythmias and atrioventricular rhythm disturbances [10].

Interviewing the patients in the presence of their roommates was a serious, albeit unavoidable, limitation of our study (due to lack of space). However, moving the patient to another room would have also been criticised**,** since room transfer is an environmental risk factor of particular importance for delirium [11, 12]. For the elderly person, the mere admission to hospital, an uninviting place that can foster somber thoughts, can provoke confusion. It is thus not surprising that several of the patients spoke of their fear of death.

In one account, cataract extraction was performed on the patient's bed and in most cases, at their homes, with both eyes bandaged for five days. No instances of 'cataract mania' were observed and this has been attributed to patients remaining in familiar surroundings with their loved ones close at hand [13]. Interestingly, historic detailed suggestions for the prevention of delirium in such cases differ only slightly from those proposed today [14].

In our study, the Wechsler Memory Scale was chosen over the more popular Mini-Mental State Examination for the assessment of cognitive function, as the latter contains a visual component, which could have further handicapped the patients whose sight was already impaired.

In an earlier study, no difference in cognitive function was found, irrespective of whether cataract extraction was

carried out under local or general anaesthesia [15]. This result has also been noted with other types of surgery [16, 17]. This finding is difficult to explain, as general anaesthesia might be expected to affect memory: most anaesthetic drugs possess some anticholinergic activity. The list of such compounds includes propofol, benzodiazepines, pancuronium, barbiturates, atropine sulphate, opioids such as fentanyl and especially pethidine, which with its metabolite, nor-pethidine, can cause havoc in the elderly [2, 18]. Likewise, the use of isoflurane in older patients is currently under scrutiny due to findings of brain cell apoptosis in rats [19].

Cataract removal is the most frequently performed surgical procedure in relatively affluent countries [20]. With the ageing population, the number of these operations will increase and thus the procedure-related delirium will remain a problem. The refined technique of phacoemulsification under drop-form local anaesthesia and sedation is generally the method of choice. In experienced hands, it can be carried out in some 20 minutes, with the patient being discharged after a 3–4 hour hospital stay. Even so, over 4% of these patients experience delirium [21].

Failure to recognise or diagnose delirium is of the highest importance for, although usually temporary, it can become permanent, and eventually lead to death. Delirium after surgery may be the only clinical manifestation masking such conditions as sepsis, pneumonia, myocardial infarction, etc. [11].

CONCLUSIONS

1. In octogenarians undergoing general anaesthesia for cataract surgery, the central activity of galanthamine coincided with untoward postoperative side effects.
2. Postoperative side effects and lack of cooperation prevented some patients from taking part in the first post-operative cognitive tests; therefore, the desired aim of our study could not be fully realised.

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