COMPARISON OF THE EFFECTS OF ATROPINE AND GLYCOPYRROLATE ON COGNITIVE FUNCTION FOLLOWING GENERAL ANAESTHESIA

K. H. SIMPSON, R. J. SMITH AND L. F. DAVIES

General anaesthesia has been implicated as a cause of deterioration in postoperative cognitive function (Smith et al., 1985). Complex memory tasks remain impaired for a few days after anaesthesia, although immediate memory, tested by digit span, recovers quickly (Flatt, Birrell and Hobbes, 1984). It has been shown that cognition deteriorates independently of the level of peroperative ventilation, as long as severe hypocarbia is avoided (Blenkarn et al., 1972; Murin and Nagajan, 1974).

Memory involves central cholinergic transmission (Deutsch, 1971). Drugs acting on cholinergic systems have been evaluated in terms of their effects on the attention and memory aspects of information processing (Warburton and Wesnes, 1984). Anticholinergic agents are widely used in anaesthesia as premedicants and for the reversal of neuromuscular blockade. It is postulated that drugs affecting central cholinergic synapses may be important in the production of postoperative cognitive deficits. The involvement of central cholinergic pathways may be assessed by a comparison of atropine and glycopyrrolate, as the latter does not cross the blood–brain barrier freely (Proakis and Harris, 1978).

PATIENTS AND METHODS

Ethical approval was granted for the study which involved 72 fit patients of either sex, aged 27–87 yr, scheduled for elective major general, gynaecological or orthopaedic surgery. Patients taking anticholinergic or sedative medication were excluded, as were those who were to have “psychologically traumatic” operations such as mastectomy, or surgery for known malignancy. Patients were excluded if assessment was anticipated to be difficult or unreliable, for example because of old age or deafness.

On the day before surgery patients were given a small battery of psychometric tests by a clinical psychologist. These tests were repeated 2 days after surgery; patients who were in obvious pain or who had postoperative complications, which could interfere with testing, were then excluded.

The following tests were used:

Orientation. In order quickly and easily to assess orientation in time and place, patients were asked 17 questions and one mark was scored for each
correct answer. The questions were developed from the Wechsler Memory Scale, which has been used to study patients with organic brain damage (Wechsler, 1945). This test also detects reversible toxic confusional states and has proved sensitive to postoperative disorientation in elderly patients (Smith et al., 1985).

**Concentration.** Patients were asked to recite the months of the year backwards, starting with December. Their speed was recorded, adding 10 s for every error or omission.

**Visual memory.** The Objective Learning Test (OLT) was used to assess visual short-term memory—This involves the recall of pictures of everyday objects—presented on four cards having 10, 15, 20 and 25 items per card. After 3 s viewing time per object, subjects were asked to recall as many items as possible in any order with no time limit. The maximum score possible is 70. The OLT forms half of the Kendrick Battery for the Detection of Dementia in the Elderly (Kendrick, 1972; Gibson and Kendrick, 1979).

Patients received premedication, 1 h before anaesthesia, of papaveretum i.m. (>70 kg, 20 mg; 50–70 kg, 15 mg; < 50 kg, 10 mg), and either atropine 0.6 mg i.m. or glycopyrrolate 0.2 mg i.m.. The anticholinergic drugs were given in a double-blind randomized manner, in doses recommended for adult premedication (McCubbin et al., 1979; Mirakhur, Dundee and Connolly, 1979). Anaesthesia was induced, using thiopentone 3–5 mg kg\(^{-1}\). A competitive neuromuscular blocking drug was used to facilitate intubation of the trachea, and ventilation with 66% nitrous oxide and oxygen (minute volume 120 ml kg\(^{-1}\); tidal volume 10 ml kg\(^{-1}\)). Anaesthesia was maintained using fentanyl (> 70 kg, 0.15 mg; 50–70 kg, 0.1 mg; < 50 kg, 0.05 mg), supplemented with 0.5% halothane, if necessary. After surgery neuromuscular blockade was antagonized with neostigmine 2.5 mg. The same anticholinergic drug which had been given for premedication, either atropine 1.2 mg or glycopyrrolate 0.6 mg, was administered also. The time from induction of anaesthesia to reversal of blockade was noted. Postoperative pain was treated with papaveretum i.m., given on demand in the same dose as for premedication and, if necessary, postoperative emesis was treated with prochlorperazine.

Data were analysed using Student’s \(t\) test for independent samples, Chi-squared, Pearsons Product Moment Correlation Coefficient or two-way analysis of variance for repeated measures, followed by the Tukey test as appropriate.

### RESULTS

Twelve patients were excluded from the study after postoperative assessment: 10 were in obvious pain, one had bled during the previous night and one was pyrexial. The remaining two groups of 30 patients were analysed. The sex distribution, ages and weights of the two groups were not significantly different (table I). The doses of papaveretum (as premedication), thiopentone and fentanyl did not differ significantly between the groups. Twenty of the atropine and 22 of the glycopyrrolate group received halothane. The duration of surgery in the groups was not significantly different (table I). There were no significant differences between the groups in the number of doses of papaveretum or prochlorperazine given in the first 2 days after operation.

There were no significant changes in pre- to postoperative concentration or orientation scores in either group. Significant postoperative memory deficit was found in the atropine group \((F = 7.09, P < 0.01)\), but not in the glycopyrrolate group (table II). The performance of more patients on memory testing was worse following surgery after atropine (77%), compared with after glycopyrrolate (43%) \((P < 0.05)\). Short-term memory deficit did not correlate significantly with age \((r = 0.26)\) or duration of surgery \((r = 0.10)\).

### DISCUSSION

Several studies have suggested that learning initiates a neuronal process in which excitability at cholinergic synapses increases. When learning has
Table II. Mean (SEM) scores on cognitive testing. *Postoperative score significantly less than preoperative (P < 0.05)

<table>
<thead>
<tr>
<th></th>
<th>Atropine (n = 30)</th>
<th>Glycopyrrolate (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before surgery</td>
<td>After surgery</td>
</tr>
<tr>
<td>Orientation</td>
<td>16.3 (0.1)</td>
<td>16.2 (0.2)</td>
</tr>
<tr>
<td>(17 maximum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td>21.1 (2.9)</td>
<td>19.3 (2.4)</td>
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<tr>
<td>(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>41.1 (1.6)</td>
<td>37.3 (1.4)*</td>
</tr>
<tr>
<td>(70 maximum)</td>
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</tbody>
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finished there is a decrease in cholinergic synaptic excitability, which coincides with a natural loss of memory recall (Deutsch, 1971). If changes in cholinergic activity occur during learning it should be possible to show drug-induced facilitation or inhibition of memory.

Facilitation of memory. Animal studies have supported the involvement of cholinergic pathways in learning and memory. Learning was enhanced and errors reduced following low-dose physostigmine (Whitehouse, 1966). High doses gave the opposite effect, perhaps as a result of functional blockade of cholinergic synapses. Similarly, the intracerebral injection of a cholinesterase inhibitor, diisopropylfluorophosphate (DFP) (in rats) caused alteration of recall of learned behaviour for several days after training (Deutsch, Hamburg and Dahl, 1966). Comparable effects were produced using physostigmine (Hamburg, 1967). Because of adverse muscarinic effects, these agents are difficult to evaluate in humans.

Impairment of memory. There is evidence for impairment of the information input component of memory following cholinolytic agents such as atropine (Whitehouse, 1964) and hyoscine (Carlton and Vogel, 1965). Several studies in man have confirmed the findings in animal models. It has been suggested that there is impairment of memory storage, and possibly retrieval, following hyoscine, despite normal immediate memory span (Drachman and Leavitt, 1974). Hyoscine reduced performance on some subsets of the Wechsler Memory Scale, but not digit recall, which tests immediate memory (Ostfeld and Aruguette, 1962). Safer and Allen (1971) reported grossly impaired delayed recall of digits after hyoscine. It has also been shown that hyoscine 0.4 mg i.m. decreased ability for immediate and delayed recall of lists of words (Anderson, McGuire and McKeown, 1985). Clinically, atropine is known to produce central effects including disorientation, hallucinations and memory loss (Longo, 1966).

Atropine 2 mg i.m. affected both performance on digit span and short-term memory (Wetherell, 1980). When patients who had received atropine 0.6 mg were compared with those who had received placebo, the former showed impaired backward digit span, but normal immediate and delayed recall (Anderson, McGuire and McKeown, 1985). Cognitive effects of atropine may be dose-dependent, and more than 0.6 mg may be necessary for profound effects. Therefore, deficits may be more pronounced in patients who are paralysed and ventilated artificially, as they commonly receive atropine 0.6 mg as premedication and 1.2–1.8 mg with antagonism of neuromuscular blockade. In support of central cholinergic involvement, post-anaesthetic arousal times and recovery after glycopyrrolate have been shown to be superior to atropine (Baraka et al., 1980; Sheref, 1985).

The present study supports the envisaged role of central cholinergic mechanisms in cognitive function. Thus, in terms of postoperative cognition, glycopyrrolate may be a preferable alternative to atropine.

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References


