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PATTERN OF CNS RECOVERY FOLLOWING REVERSAL OF NEUROMUSCULAR BLOCKADE

Comparison of Atropine and Glycopyrrolate

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SUMMARY

Recovery from anaesthesia was compared, in a group of patients (n = 25) receiving a mixture of glycopyrrolate and neostigmine (to reverse non-depolarizing neuromuscular blockade), with recovery in a group of patients (n = 25) receiving an atropine–neostigmine mixture. Recovery following anaesthesia was more rapid in the patients receiving the glycopyrrolate–neostigmine mixture.

Glycopyrrolate has been shown to have certain advantages over atropine: when used as an adjunct in the reversal of residual neuromuscular blockade, it is associated with a lower initial increase in heart rate and less secondary bradycardia (Ostheimer, 1977; Mirakhur, Dundee and Clarke, 1977; Cozanitis et al., 1980; Heinonen, Salmenpera and Takkunen, 1982). Moreover, since it is a quaternary ammonium compound, only limited amounts of glycopyrrolate penetrate the blood–brain barrier (Proakis and Harris, 1978) and, as a result, it has no significant central anticholinergic effects.

In a preliminary study, Baraka and colleagues (1980) suggested that arousal from anaesthesia was more rapid in patients receiving glycopyrrolate when compared with a similar group receiving atropine. Heinonen, Salmenpera and Takkunen (1982) demonstrated that, when residual neuromuscular blockade was antagonized with a glycopyrrolate–neostigmine mixture, return of consciousness was more rapid than in a similar group of patients who had received an atropine–neostigmine combination.

We have studied the pattern of recovery of central nervous system (CNS) function in patients in whom residual neuromuscular block was antagonized with a mixture of neostigmine and either atropine or glycopyrrolate.

PATIENTS AND METHODS

Fifty adult patients (ASA Grade I or II) undergoing general surgical or gynaecological procedures took part in the study. Any patient receiving, at the time of the study, phenothiazines, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants or any atropine-like drugs, was excluded from the study, as were patients with a known psychiatric history.

Pre-anaesthetic medication consisted of papaveretum 0.2–0.3 mg kg^{-1} i.m., depending on the individual patient, approximately 60 min before the start of surgery. Anaesthesia was induced with a sleep dose of thiopentone 3–4 mg/kg body weight; intubation of the trachea was performed immediately after the administration of either suxamethonium 1 mg kg^{-1} or 2–3 min after the administration of pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen from a high-flow open circuit (Cape Waine ventilator), with a minute volume of 150 ml/kg body weight. Tidal volume was measured periodically (Wright's respirometer). Incremental doses of pancuronium 0.02 mg kg^{-1} or papaveretum 5 mg, or both, were administered when necessary. The last incremental dose was given 30 min before the end of surgery. Halothane 0.5%, whenever used, was discontinued approximately 15–20 min before the anticipated end of surgery.

At the end of surgery, and before withdrawal of the nitrous oxide, the patients received a mixture of neostigmine methylsulphate 3.75 mg with either glycopyrrolate 0.6 mg or atropine 1.2 mg. The anticholinergic component of the mixture was administered "double-blind" from specially pre-

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pared coded ampoules, the order of administration being randomized. Nitrous oxide was discontinued after administration of the reversal mixtures. As soon as the patient opened his eyes, oropharyngeal toilet was performed, the tracheal tube removed, and the patient transferred to the recovery ward.

Patients were assessed by the investigator before the induction of anaesthesia, and questioned about their name and exact date of birth, which served as a baseline for the post-anaesthetic pattern of CNS recovery. They were also questioned at the following times after administration of the reversal mixtures: 5, 10, 15, 20, 25, 30, 40, 50, 60 and 120 min. The five-point scoring system used is shown in table I and is a modification of that described by Bidwai, Cornelius and Stanley (1976). Patients who complained of pain following surgery received papaveretum i.m.

TABLE I. *Post-anaesthetic CNS recovery scoring system*

Level	Description
0	Well orientated and initiates conversation
1	Orientated, feels drowsy or falls asleep Gives exact date of birth
2	Disorientated Responds to verbal and painful stimuli Does not give EXACT date of birth (some dissociation)
3	Disorientated Responds to painful but not to verbal stimuli Does not give exact date of birth (in a state of complete dissociation from surroundings)
4	Unresponsive to verbal or painful stimuli No signs of respiratory depression and adequate reversal of muscle blockers

The CNS scores were analysed using the Chi-squared test.

RESULTS

Both groups were similar in regard to age, weight, ASA status and duration of anaesthesia (table II).

The distribution of CNS scores at all times of assessment following reversal is shown in table III. The main differences between atropine and glycopyrrolate occur from the 10th minute onwards. There was a significantly greater number of patients in the glycopyrrolate group with a score of 0 at 15–120 min inclusive (except at 60 min) (table III). The only patient who consistently presented with a score of 2 was a patient who had received atropine in the reversal mixture. There were no patients with a score of 3 in either study group.

TABLE II. *Physical characteristics of the patients in the study (mean values (± SEM))*

	Atropine	Glycopyrrolate
No. of patients	25	25
Age (yr)	47.6 ± 2.48	40.0 ± 2.40
Weight (kg)	61.4 ± 2.62	66.6 ± 2.42
Physical status		
ASA I	20	20
ASA II	5	5
Sex		
Male	5	7
Female	20	18
Median duration of anaesthesia (min)	98.3	95.6

Several of the patients received postoperative analgesia in the first 60 min after reversal, and it was considered that this analgesic (papaveretum) could have influenced the CNS score by virtue of its analgesic–sedative effect. Accordingly, a separate analysis was made of the 34 patients who did not receive postoperative analgesia in the first 60 min (17 patients in each group). Figure 1 shows the CNS scoring pattern for these patients. Significant differences were noted between the two groups, at 10, 20, 40, 50 and 120 min ($P < 0.05$).

DISCUSSION

The problems of "somnolence" and "disorientation" following anaesthesia have been recognized for some time, and atropine has been considered responsible (Longo, 1966; Greene, 1971; Lapan and Smith, 1977; Smith et al., 1979). However, few controlled studies have been carried out to test this hypothesis.

At 2 h after operation, the number of patients with a score of 0 (table III) was significantly higher in the glycopyrrolate group. Thus, although atropine does have a short duration of action peripherally, it may have a longer duration of action centrally or, at least, its central after-effects may last longer than was appreciated previously. This observation may have clinical implications, especially if atropine is prescribed for day-case surgery. Further studies are needed to test this.

The central anticholinergic syndrome was first appreciated by Longo (1966). The syndrome consists of confusion, hallucination, agitation, somnolence, delirium, convulsions and decreased ability to

TABLE III. *Post-anaesthetic CNS recovery pattern at various times: number of patients scoring 0, 1, 2 or 4. (No patient presented with a score of 3 in either study group.) Significantly greater than atropine group: * P < 0.05; ** P < 0.01*

	Atropine group (n = 25)				Glycopyrrolate group (n = 25)			
Time (min)	(0)	(1)	(2)	(4)	(0)	(1)	(2)	(4)
5	4 (16%)	13 (52%)	7 (28%)	1 (4%)	9 (36%)	13 (52%)	2 (8%)	1 (4%)
10	5 (20%)	17 (68%)	3 (12%)	0	11 (44%)	14 (56%)	0	0
15	4 (16%)	19 (76%)	2 (8%)	0	10* (40%)	15 (60%)	0	0
20	3 (12%)	21 (84%)	1 (4%)	0	12* (48%)	12 (48%)	1 (4%)	0
25	5 (20%)	19 (76%)	1 (4%)	0	13* (52%)	12 (48%)	0	0
30	5 (20%)	19 (76%)	1 (4%)	0	14* (56%)	11 (44%)	0	0
40	4 (16%)	20 (80%)	1 (4%)	0	16** (64%)	9 (36%)	0	0
50	4 (16%)	20 (80%)	1 (4%)	0	13* (52%)	12 (48%)	0	0
60	6 (24%)	19 (76%)	0	0	14 (56%)	11 (44%)	0	0
120	9 (36%)	16 (64%)	0	0	20* (80%)	5 (20%)	0	0

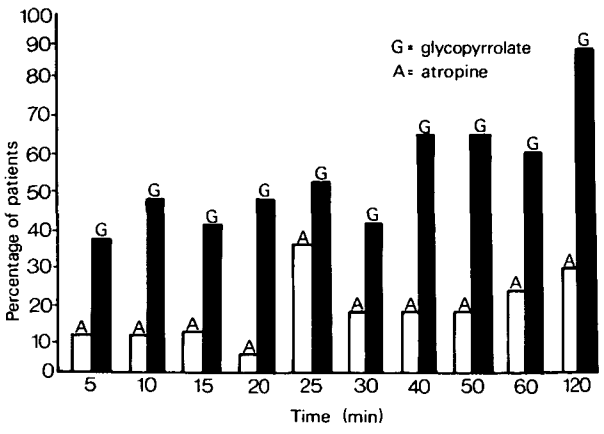

FIG. 1. Percentage of patients who had not received postoperative analgesia in the first 60 min with a CNS score of zero at each assessment time.

concentrate (Longo, 1966; Bidwai, Cornelius and Stanley, 1976). The syndrome is triggered by various drugs that exhibit central anticholinergic activity, including atropine (Greene, 1971; Lapan and Smith, 1977; Smith et al., 1979), hyoscine (Longo, 1966), phenothiazines (Bernards, 1973), tricyclic antidepressants (Burk, Walton and Rumack, 1974), thalamonal (Innovar) (Bidwai, Cornelius and Stanley, 1976), butyrophenones (Duvoisin and Katz, 1968), and ketamine (Hill, Stanley and Sentkar, 1977). Since these different groups of drugs are unrelated pharmacologically, it has been assumed that the centrally-acting anticholinesterase, physostigmine, which is used to reverse this syndrome, acts by non-specific mechanisms (Greene, 1971; Bidwai, Cornelius and Stanley, 1976; Hill, Stanley and Sentkar, 1977).

Electrophysiological studies confirmed that central cholinergic pathways are potentiated by physostigmine and depressed by atropine and general anaesthetics (Kinjevic, 1967). Two mechanisms have been suggested: either a decreased sensitivity to acetylcholine during deep general anaesthesia, or a decrease in acetylcholine release (MacIntosh and Oborin, 1953; Mitchell, 1963).

Since glycopyrrolate is a quaternary ammonium compound, it penetrates minimally through the blood–brain barrier (Proakis and Harris, 1978). Therefore, it can be assumed that glycopyrrolate does not affect the acetylcholine pathway in the brain. This may be the explanation why, in this study and in previous work (Baraka et al., 1980; Heinonen, Salmenpera and Takkunen, 1982),

arousal from anaesthesia was significantly more rapid in the patients in the glycopyrrolate groups compound, it penetrates minimally through the

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