ASPECTS OF ANAESTHESIA*

Cardiovascular changes during induction of anaesthesia

Influence of three anticholinergic premedicants

R K Mirakhur MD PhD FFARCS
Research Fellow

J W Dundee MD PhD FFARCS MRCP
Professor of Anaesthetics, The Queen's University of Belfast

Summary

The effects on cardiovascular changes during induction of anaesthesia and intubation of routine premedication with three different anticholinergic drugs, atropine, hyoscine, and glycopyrronium, were compared in a double blind trial. Administration of both atropine and hyoscine, whether intramuscularly or orally, was found to be associated with a high incidence of dysrhythmias. With glycopyrronium the incidence was much lower, but control patients receiving no anticholinergic premedication had no dysrhythmias. The heart rates and blood pressures were similar in all the groups during intubation and cuff inflation. A single dose of suxamethonium was not associated with any bradycardia. The need for routine anticholinergic drug administration should be reconsidered. However, if necessary, glycopyrronium appears to have an obvious advantage over atropine and hyoscine.

Introduction

Anticholinergic drugs have traditionally been used in preanaesthetic medication mainly for their antisialogogue and parasympatholytic actions, atropine and hyoscine being the most commonly used drugs[1]. Both have some disadvantages, such as short duration of action and undesirable central effects. Atropine is also known to give rise to cardiac dysrhythmias[2-4]. More recently glycopyrronium (glycopyrrolate USNF), a quaternary ammonium compound, has been evaluated and found to be a potent antisialogogue agent with no central action or serious cardiovascular effects[5].

The present study compared the effects of atropine, hyoscine, and glycopyrronium when given intramuscularly in premedication. Their effects on cardiovascular changes at the time of induction of anaesthesia and at tracheal intubation were studied. The effects of orally administered atropine and hyoscine were also studied since these drugs are absorbed to a significant extent from the gastrointestinal tract[6,7]. Some of the findings of this study have been described previously[8] but are included here for the sake of completeness.

Material and methods

The study was carried out on adult patients free from any intercurrent systemic disease and undergoing elective surgery.

Heart rate and blood pressure were measured before the premedication was administered. This consisted of pethidine hydrochloride 1 mg/kg body weight and one of the following anticholinergic drugs: atropine 1.0 mg intramuscularly (i.m.) or 2.0 mg orally, hyoscine 0.5 mg i.m. or 1.0 mg orally, or glycopyrronium 0.2 mg i.m. (Oral glycopyrronium was not evaluated as a previous study[5] had shown its poor absorption.) The anticholinergic drugs were administered by random selection under double blind conditions and the whole premedication was given 90–120 min before operation. A control group of patients received no anticholinergic premedication. The patients received the routine nursing supervision usually given to premedicated patients.

Electrocardiographic (lead II) monitoring in the theatre was started from 1 min before induction of anaesthesia and was carried on until induction was completed. Arterial pressure

The Editor would welcome any observations on this paper from readers.
*Fellows and Members interested in submitting papers for consideration with a view to publication in this series should first write to the Editor.

TABLE I *Physical characteristics of patients*

Anticholinergic drug	*M*	*F*	*Age (years) (mean ± SEM)*	*Weight (kg) (mean ± SEM)*
Atropine				
1.0 mg i.m.	10	10	40.5 ± 2.91	62.9 ± 1.85
2.0 mg oral	10	10	39.5 ± 2.72	64.2 ± 1.88
Hyoscine				
0.5 mg i.m.	8	12	41.1 ± 3.85	59.9 ± 1.92
1.0 mg oral	12	8	37.8 ± 3.23	65.3 ± 2.15
Glycopyrronium				
0.2 mg i.m.	8	12	42.7 ± 3.00	64.8 ± 2.90
No anticholinergic drug	10	10	37.9 ± 3.19	63.5 ± 2.90

was measured before and immediately after induction of anaesthesia, which was achieved with 2.5% thiopentone 4–6 mg/kg. Intubation was facilitated by giving suxamethonium 1.0 mg/kg, ventilation being assisted as soon as any depression was evident, with a mixture of 50% nitrous oxide in oxygen. Once relaxation was achieved laryngoscopy and tracheal intubation were carried out with an appropriate-sized cuffed tube lubricated with non-anaesthetic jelly. Ventilation was resumed and the cuff of the tracheal tube inflated with the minimum amount of air necessary to effect a seal.

Oropharyngeal secretions were assessed at the time of intubation and during the course of operation and were arbitrarily classified as dry, moderately dry, or wet.

Anaesthesia was maintained with nitrous oxide, oxygen, and halothane or neuroleptanalgesic drugs, myoneural blocking agents with positive pressure ventilation being employed as necessary. The electrocardiograms were analysed in detail for changes in cardiac rate and rhythm.

The serial changes in heart rate and blood pressure in each group were analysed by means of a paired-*t* test. Student's *t* test was used for comparison between the groups and non-parametric observations were subjected to a χ^2 test.

Results

There were 20 patients in each of the six groups, which were broadly comparable with regard to their physical characteristics (Table I).

CHANGES IN HEART RATE

The preoperative heart rates were similar in all the groups (Table II). Following premedication 1.0 mg atropine i.m. produced the highest rise (48%) in the heart rate. This was statistically significant ($P<0.01$), as were the rises produced by orally administered atropine and by glycopyrronium, though the rises following the last two were much smaller. The patients given no anticholinergic premedication showed a small rise. Hyoscine by both routes produced changes of a very small magnitude. Heart rates monitored before induction are henceforth referred to as the 'control' values. These reflect the effect of premedication.

As seen from Table II, the whole process of induction of anaesthesia and tracheal intubation was associated with significant ($P<0.05$–<0.01) increases in the heart rates in comparison with their control values except in the group given intramuscular atropine. The maximum heart rates were observed at the time of intubation and cuff inflation. The rates were similar 1 min later, when they started to decrease. By now, however, inhalational agents or other adjuvants were being administered to keep the patients anaesthetised. The serial changes are shown in Figure 1. The changes in heart rate following intubation and cuff inflation were almost instantaneous in comparison with those following administration of thiopentone and suxamethonium.

CHANGES IN BLOOD PRESSURE

Average systolic, diastolic, and mean blood pressures were similar in all the groups preoperatively and before induction (Table III).

TABLE II *Heart rate per minute (mean ± SEM) at specific events during process of induction*

Anticholinergic drug	*Preoperative*	*Before induction (control value)*	*Thiopentone*	*Suxamethonium*	*Fasciculations*	*Relaxed state following fasciculations*	*Laryngoscopy*	*Intubation*	*Cuff inflation*	*½-1 min after cuff inflation*
Atropine 1.0 mg i.m.	72.6 ±1.56	107.5* ±4.45	109.1 ±3.89	106.3 ±3.76	106.3 ±3.41	107.0 ±3.08	106.7 ±2.62	109.1 ±2.86	115.5 ±2.81	115.9 ±2.97
Atropine 2.0 mg oral	72.6 ±1.37	89.7* ±4.34	97.7† ±4.09	95.2† ±3.59	93.2 ±3.28	95.0 ±2.93	92.3 ±3.09	100.0† ±3.93	109.9† ±4.15	111.0† ±4.09
Hyoscine 0.5 mg i.m.	76.1 ±1.97	73.7 ±3.74	85.7† ±3.81	88.6† ±3.25	93.3† ±3.58	94.4† ±4.46	85.9† ±3.90	85.9† ±4.77	93.8† ±4.00	92.9† ±3.92
Hyoscine 1.0 mg oral	71.5 ±1.36	73.0 ±3.49	90.4† ±3.94	87.4† ±3.57	90.0† ±3.13	90.8† ±3.61	90.5† ±3.01	93.3† ±3.32	94.1† ±2.93	94.5† ±3.25
Glycopyrronium 0.2 mg i.m.	74.0 ±2.13	82.7* ±3.65	95.4† ±3.12	94.9† ±2.86	98.0† ±3.27	97.1† ±3.28	98.5† ±3.54	100.3† ±3.86	107.7† ±3.63	108.5† ±3.28
No anticholinergic drug	72.9 ±1.86	81.5* ±3.56	92.6† ±3.41	87.6† ±3.43	89.6† ±3.96	88.8 ±3.96	83.8 ±3.68	92.6† ±3.32	100.5† ±3.21	100.1† ±3.42

*Rate significantly higher ($P<0.01$ - <0.001) than preoperative value.
†Rate significantly higher ($P<0.05$ - <0.001) than control value.

Immediately after induction these were significantly raised ($P<0.01$) in all the groups when compared with the preoperative or pre-induction values. However, there were no significant differences between the groups.

CHANGES IN CARDIAC RHYTHM

These were observed in 28 patients (23%). The incidence varied in different groups. (Table IV). Of the patients receiving anticholinergic drugs, this was lowest in those

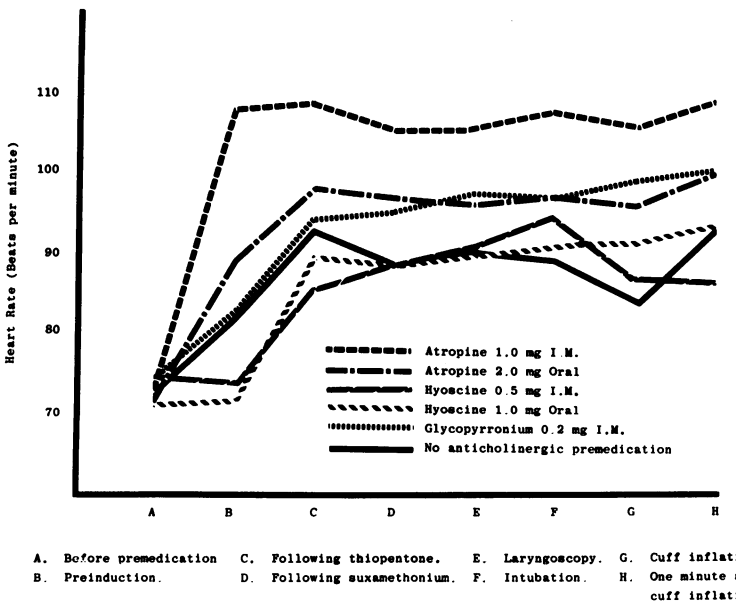

FIG. 1 *Heart rate changes after premedication and induction of anaesthesia.*

TABLE III *Blood pressure (mm Hg; mean ± SEM) during induction of anaesthesia*

Anticholinergic drug	*Preoperative*			*Preinduction*			*Postinduction**		
	Systolic	*Diastolic*	*Mean*	*Systolic*	*Diastolic*	*Mean*	*Systolic*	*Diastolic*	*Mean*
Atropine 1.0 mg i.m.	124.7 ±3.31	74.7 ±1.75	91.4 ±2.18	132.0 ±4.88	79.5 ±1.95	97.0 ±2.86	153.2 ±4.47	90.5 ±2.04	111.4 ±2.76
Atropine 2.0 mg oral	119.5 ±2.87	73.0 ±1.82	88.5 ±2.01	123.2 ±2.97	77.7 ±1.42	92.9 ±1.76	153.3 ±5.19	92.2 ±2.06	112.6 ±3.02
Hyoscine 0.5 mg i.m.	118.5 ±2.90	73.2 ±1.99	88.3 ±2.11	120.0 ±3.22	76.2 ±1.69	90.8 ±2.10	151.2 ±5.30	89.8 ±2.49	110.2 ±3.34
Hyoscine 1.0 mg oral	122.2 ±2.72	73.8 ±1.91	89.9 ±2.08	122.7 ±3.04	74.5 ±1.53	90.5 ±1.94	145.7 ±5.01	85.5 ±2.17	105.4 ±3.04
Glycopyrronium 0.2 mg i.m.	123.3 ±2.28	75.3 ±1.22	91.3 ±1.40	123.5 ±2.64	75.2 ±1.28	91.3 ±1.60	157.5 ±4.36	90.5 ±2.31	112.8 ±2.92
No anticholinergic drug	125.5 ±4.25	75.7 ±2.12	92.3 ±2.74	127.0 ±4.60	77.5 ±2.00	94.0 ±2.80	157.7 ±4.96	94.2 ±2.24	115.4 ±3.02

*All values here are significantly higher ($P<0.001$) than the corresponding preoperative and preinduction.

given glycopyrronium. All other groups showed a significantly higher incidence in comparison with the control group, in whom no dysrhythmias were observed.

The dysrhythmias observed are shown in Table V. In addition, 4 patients receiving no anticholinergic premedication, 3 given 0.5 mg hyoscine i.m., 2 given 1.0 mg hyoscine orally, and 1 given glycopyrronium exhibited sinus arrhythmia. The majority of dysrhythmias occurred following intubation and cuff inflation. However, ventricular ectopic beats were noticed in 3 patients following injection of thiopentone and in another 3 during fasciculations following suxamethonium administration. In 1 patient premedicated with intramuscular hyoscine 16 consecutive ventricular ectopic beats were noted at intubation.

SECRETIONS

The incidence of the three degrees of dryness in each group is shown in Figure 2. The incidence of acceptable dryness (dry and moderately dry) was higher in all the groups receiving anticholinergic drugs in comparison with the control group, though the difference from

TABLE IV *Incidence of arrhythmias*

Anticholinergic drug	*No showing arrhythmias (No of cases in each group)*	*Incidence of arrhythmias (%)*	*Statistical comparison between groups*
Atropine 1.0 mg i.m.	7 (20)	35	
Atropine 2.0 mg oral	6 (20)	30	
*Hyoscine 0.5 mg i.m.	5 (19)	26	
Hyoscine 1.0 mg oral	8 (20)	40	
Glycopyrronium 0.2 mg i.m.	2 (20)	10	
*No anticholinergic drug	0 (19)	0	

NS; $P<0.005$; $P<0.025$; $P<0.02$; $P<0.005$

*One patient in each of these two groups had pre-existing arrhythmias (see Table V) and were therefore omitted from the statistical evaluation.

TABLE V *Arrhythmias encountered during induction of anaesthesia (Figures represent numbers of cases.)*

	Atropine 1.0 mg i.m.	*Atropine 2.0 mg oral*	*Hyoscine 0.5 mg i.m.*	*Hyoscine 1.0 mg oral*	*Glycopyrronium 0.2 mg i.m.*	*No anticholinergic drug*
Ventricular ectopic beats (unifocal or multifocal and including bigeminy)	5	5	2	5		
Nodal (junctional) rhythm	1		1	2		
Atrial ectopic beats	1		2	2	1	
Wandering pacemaker			1			
Supraventricular tachycardia		1			1	
Pre-existing atrial ectopic beats persisting during induction			1			
Pre-existing atrial and ventricular ectopics persisting during induction but disappearing 2 min later						1

the group receiving oral atropine was not statistically significant. Intramuscularly administered drugs produced more intense dryness. The course of induction and maintenance of anaesthesia was smooth in all the groups.

Discussion

Tachycardia and a hypertensive response during induction of anaesthesia and tracheal intubation have been reported previously[9-11]. The present study demonstrates this reflex effect once again except in the group receiving 1.0 mg atropine i.m. This group showed only the pressor response. The mean heart rate before induction was, however, maximal in this group and the subsequent rise was minimal. This can be explained on the basis of a negative correlation between the initial heart rate and the subsequent rise. Such a negative correlation has been demonstrated following administration of atropine alone and atropine–neostigmine mixtures[12,13]. Moreover, the heart rate in the atropine group was similar to those in the other groups at the time of intubation and cuff inflation.

From the present study it appears that anticholinergic premedication does not alter the

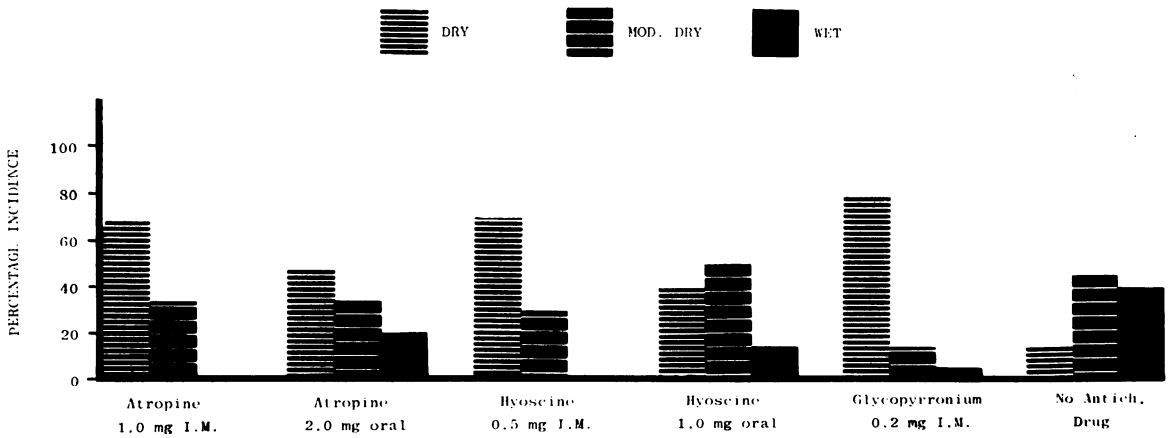

FIG. 2 *Histogram showing the various grades of secretions assessed during induction of anaesthesia and the operative period.*

pressor response to tracheal intubation. The failure of atropine to abolish the rise in blood pressure was demonstrated by De Vault and his colleagues[14]. However, they showed its abolition by phentolamine, confirming that the changes were due to sympatho-adrenal stimulation, a view already held by other workers[9,15]. In fact, it has been suggested that atropine itself can give rise to sympathetic overactivity[16,17].

The difference in the incidence of dysrhythmias following the three anticholinergic premedicants is mostly related to their cardiovascular effects. Tachycardia and dysrhythmias following atropine administration are well known[2-4]. Hyoscine is generally thought to have weaker cardiac effects[18]. Although the rise in heart rate following hyoscine administration was less, the incidence of dysrhythmias was similar to that with atropine. It is probable that the dosage of intramuscular hyoscine used here was slightly higher than usual and thus the cardiac effects were more obvious. The studies of Stephen *et al*[19] and Gravenstein, Andersen, and De Padua[20] showed tachycardia following hyoscine administration, though List and Gravenstein[21] found it to be short-lasting. Insignificant cardiovascular changes have been a feature of glycopyrronium administration in various studies[5,22,23].

The dosages used in this study were based on our previous studies on volunteers and patients[5,7,24], though it is possible that hyoscine was used in a relatively larger dose. A previous study[22] had suggested that glycopyrronium was twice as potent an antisialogogue as atropine, but a more accurate assessment from dose–response curves in our volunteer studies referred to above showed the potency ratio to be 5 : 1. Indeed, this is reflected in the rather similar incidence of dryness following various anticholinergic premedicants in the present study.

The absence of dysrhythmias in the control group and the similarity of the course of anaesthesia to that seen in the other groups suggests the desirability of reconsideration of routine anticholinergic drug administration. This is perhaps reflected by the trends shown in a recent survey[1] in the British Isles which showed that nearly 40% of anaesthetists had stopped using anticholinergic premedicants routinely. There is usually no bradycardia following the administration of a single dose of suxamethonium[25] except perhaps in children[26]. If, however, antisialogogue action is the main aim of administering anticholinergic drugs glycopyrronium would appear to have advantages over the other two drugs tested here. Patients could be saved a lot of unnecessary discomfort and if necessary intravenous administration of such drugs could be resorted to.

We thank our surgical and anaesthetist colleagues and nursing staff for all their help and co-operation. A H Robins Co provided generous supplies of glycopyrronium (Robinul).

References

1 Mirakhur, R K, Clarke, R S J, Dundee, J W, and McDonald, J R (1978) *Anaesthesia, 33,* 133.
2 Averill, K H, and Lamb, L E (1959) *American Journal of Medical Sciences, 237,* 304.
3 Eger, E I (1962) *Anesthesiology, 23,* 365.
4 Eikard, B, and Andersen, J R (1977) *Acta anaesthesiologica Scandinavica, 21,* 245.
5 Mirakhur, R K, Dundee, J W, and Jones, C J (1978) *British Journal of Clinical Pharmacology, 5,* 77.
6 Innes, I R, and Nickerson, M (1975) in *The Pharmacological Basis of Therapeutics,* ed. L S Goodman and A Gilman, 5th edn, p 154. London, Baillière.
7 Mirakhur, R K (1978) *British Journal of Anaesthesia, 50,* 591.
8 Mirakhur, R K, Clarke, R S J, Elliott, J, and Dundee, J W (1978) *Anaesthesia, 33,* 906.
9 King, B D, Harris, L C jr, Greifenstein, F E, Elder, J D, and Dripps, R D (1951) *Anesthesiology, 12,* 556.
10 Wycoff, C C (1960) *Anesthesiology, 21,* 153.
11 Forbes, A M, and Daly, F G (1970) *British Journal of Anaesthesia, 42,* 618.
12 Baraka, A (1968) *British Journal of Anaesthesia, 40,* 30.
13 Boba, A (1972) *Canadian Anaesthetists' Society Journal, 23,* 92.
14 De Vault, M, Greifenstein, F E, and Harris, L C jr (1960) *Anesthesiology, 21,* 360.
15 Rollason, W N, and Hough, J M (1957) *British Journal of Anaesthesia, 29,* 363.
16 Holt, A T (1962) *Lancet, 2,* 984.
17 Thurlow, A C (1972) *Anaesthesia, 27,* 429.
18 Orkin, L R, Bergman, P S, and Nathanson, M (1956) *Anesthesiology, 17,* 30.
19 Stephen, C R, Bowers, M A, Nowill, W K, and Martin, R C (1956) *Anesthesiology, 17,* 303.
20 Gravenstein, J S, Andersen, T W, and De Padua, C B (1964) *Anesthesiology, 25,* 123.

21 List, W F, and Gravenstein, J S (1965) *Anesthesiology, 26,* 299.
22 Wyant, G M, and Kao, E (1974) *Canadian Anaesthetists' Society Journal, 21,* 230.
23 Mirakhur, R K, Dundee, J W, and Clarke, R S J (1977) *British Journal of Anaesthesia, 49,* 825.
24 Mirakhur, R K, Dundee, J W, and Connolly, J D R (1979) *British Journal of Anaesthesia, 51,* 339.
25 Lupprian, K G, and Churchill-Davidson, H C (1960) *British Medical Journal, 2,* 1774.
26 Leigh, M D, McCoy, D D, Belton, M K, and Lewis G B (1957) *Anesthesiology, 18,* 698.

NOTICE TO CONTRIBUTORS

The attention of all intending contributors to the Annals *is drawn to the statement published in our issue of July 1979 (p. 321) on the subject of* 'Uniform requirements for manuscripts submitted to biomedical journals'. *This announced the intention of this journal, as from January 1980, to adhere to the recommendations on style made by the International Steering Committee of Medical Editors. These have been published in full in the* British Medical Journal *and the* Lancet *(24th February 1979) and in several other journals and should be studied by all authors before submitting papers for publication in the* Annals. *Particular attention should be paid to the requirement for the provision of 3–10 'key words' for indexing purposes and to the recommended style for the citation of references, which differs substantially from that hitherto used in this journal, notably in including the titles of papers cited and both first and last page numbers. The section of the Steering Committee's recommendations dealing with references, with examples, was reproduced in the article in the* Annals *together with notes on certain special requirements and suggestions.*

It must be repeated that it will regrettably be necessary in future to return papers for amendment to authors who omit to provide key words or whose references fail to meet the requirements of the new style.