ANTICHOLINERGIC DRUGS IN PREANESTHETIC MEDICATION

C. R. Stephen, M.D., M. A. Bowers, M.D.
W. K. Nowill, M.D., R. C. Martin, M.D.

For many years the anticholinergic drugs, atropine or scopolamine, have been employed in premedication to reduce the undesirable effects of excessive parasympathetic stimulation. Reduction of salivary secretions, prevention of laryngospasm or bronchospasm and suppression of cardiovascular vagal reflexes are the principal attributes ascribed to these alkaloids in anesthetic practice. The clinical effectiveness of these compounds is believed limited to from one and a half to two hours following subcutaneous injection (1).

Two anesthetic developments in recent times have created problems associated with such premedication: (1) the advent of muscle relaxant drugs has permitted satisfactory operating conditions in light planes of anesthesia at levels where the anesthetic drugs themselves do not depress parasympathetic reflexes, and (2) many operative procedures now last for several hours. The net result of these changes, particularly if atropine or scopolamine is given one hour or more before the induction of anesthesia, is to leave the patient unprotected from parasympathetic reflexes during a major portion of anesthesia. This state of affairs can lead to dangerous episodes during operation (2).

Several approaches may be made toward this problem: Repeated doses of the alkaloids may be given during operation; this procedure is worth while but is not practiced commonly. Anesthesia may be carried in deeper planes, but it is questionable if the advantages of such a decision outweigh the disadvantages to the patient. A third possibility is to employ anticholinergic drugs which are maximally effective over longer periods of time. With this latter aim in view, an investigation has been conducted into the feasibility of employing certain synthetic compounds which were recommended originally for the treatment of peptic ulcer.

Animal Investigation

The effects of atropine, methantheline bromide (Banthine®), diphenmethanil methylsulfate (Prantal®) and oxyphenonium bromide (Antrenyl®) on salivation, cardiac rate and the electrocardiogram were compared in animals. Five mongrel dogs were anesthetized with open drop ether, intubated, and the sublingual duct cannulated with a small

The authors are in the Division of Anesthesia of the Duke University Hospital and School of Medicine in Durham, North Carolina. The paper was read before the annual meeting of the American Society of Anesthesiologists in Boston, November 1, 1955, and accepted for publication December 22, 1955. The work was supported by a grant from Ciba Pharmaceutical Products, Summit, New Jersey.

polyethylene catheter. Anesthesia was maintained at as constant a level as possible with ether-air and the rate of flow of saliva (drops per minute) was recorded. Salivary secretion was found to be relatively constant for each dog from day to day. Electrocardiographic tracings were recorded on a Visocardiette intermittently throughout each experiment.

Following a baseline control, a parasympatholytic drug was injected intravenously. The speed with which salivation ceased and the duration of its absence were recorded. The return of salivation was the end point of any particular experiment. No attempt was made to determine the duration of partial blockade.

All dogs first received 1 mg. of atropine. This dosage abolished secretions completely for an average of seventy-eight minutes, the

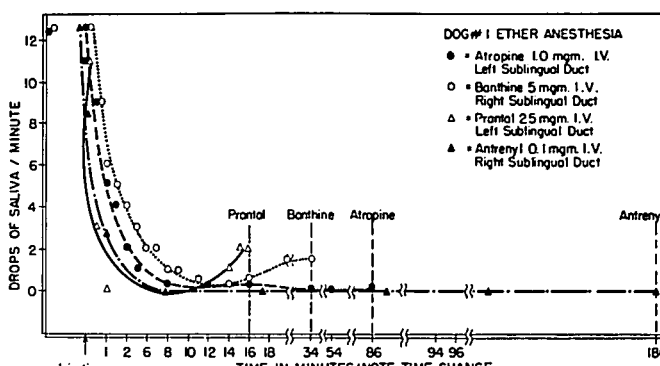

FIG. 1. Showing return of salivation in dogs after intravenous injection of anticholinergic compounds.

extremes being sixty-six and ninety minutes. The pulse rate increased from an average of 142 to 164 per minute.

On succeeding days the same dogs were reanesthetized in similar fashion and were given Banthine, 5, 10, 15 and 25 mg., Prantal, 25 and 50 mg., and Antrenyl, 0.5, 1.0 and 1.5 mg. Figure 1 shows the relative effectiveness of these drugs in blocking secretions in one dog. Atropine, 1 mg., abolished salivation for eighty-six minutes; Banthine, 5 mg., for thirty-four minutes; Prantal, 25 mg., for 16 minutes, and Antrenyl, 1 mg., for 186 minutes. Other dogs reacted in a similar manner.

The effect on cardiac rate is shown in figure 2. After anesthetization the control rate was 144 per minute. With the intravenous doses noted above, atropine increased the rate to 164, Banthine to 176, Prantal

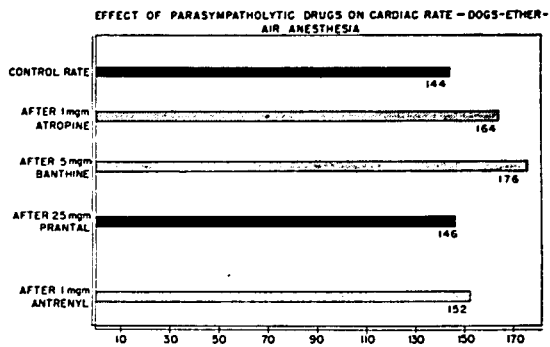

FIG. 2. Showing effect of anticholinergic drugs on cardiac rate of dogs during anesthesia.

to 146 and Antrenyl to 152 per minute. Abnormal cardiac rhythms were not seen in any of the animals before or after administration of the drugs.

It has been shown that other vagal reflexes may be blocked in the dog following Antrenyl. Electrical stimulation of the peripheral vagus nerve does not cause the rapid and pronounced fall in blood pressure which occurs in the control state. Total protection may last two or three hours (3).

CLINICAL INVESTIGATION

In an effort to evaluate some subjective and objective effects of anticholinergic drugs, five members of the anesthesia department were given on different days atropine, 0.6 mg.; Banthine, 50 mg. in divided doses, and Antrenyl, 1.0 mg. intravenously (fig. 3). The subjects knew what class of compound was being given but not the name of the drug. Cardiac rate was counted from the electrocardiogram. As

PARASYMPATHOLYTIC DRUGS
EKG DATA - CONTROLS

VOLUNTEER	ATROPINE 0.6 MG. I.V. CONTROL	MAX.		BANTHINE 50 MG. I.V. CONTROL	MAX.		ANTRENYL 1 MG. I.V. CONTROL	MAX.	
P.S.	85	140	64%	95	132	39%	95	130	37%
B.W.	78	92	18%	90	150	64%	85	85	0%
R.S.	78	81	3%	74	95	28%	71	82	15%
M.A.B.	84	93	10%	80	120	50%	74	78	5%
W.K.N.	70	76	8%	96	115	19%	83	94	13%

FIG. 3. Effect of anticholinergic drugs on cardiac rate human volunteers. Note variation in individual response.

might be expected, there was a wide individual variation in the response to each of these drugs. However, the increase in pulse rate after atropine and Antrenyl was of the same order, whereas that with Banthine was considerably higher. A maximal increase in pulse rate was achieved with Banthine after the administration of 15 mg. In these five volunteers minimal dryness of the mouth occurred with atropine, moderate dryness with Antrenyl and intense dryness with Banthine. The subjective effects of atropine were short-lived (less than one hour), but prolonged for three to four hours with Antrenyl and Banthine. Urinary retention was a problem for several hours in each individual receiving Banthine, but was not troublesome with the other two compounds.

ATROPINE 0.6 MG. I.V.
CARDIOVASCULAR EFFECTS

PATIENT	CONTROL PULSE	MAXIMUM PULSE	% INCREASE	B.P.	REMARKS
D46764	98	160	63	120/80	
D42324	90	134	49	110/78	
D50547	100	105	5	110/70	
D49010	103	130	26	120/80	
C49287	138	162	17	110/60	
A76939	85	143	68	102/70	
B43862	80	130	63	100/40	
D48080	65	84	23	150/100	nodal rhythm
D51865	90	140	56	120/80	
38125	86	130	51	140/90	
49800	85	88	3	126/55	
D50077	52	62	19	100/60	

FIG. 4. Effect of atropine intravenously on cardiac rate of 12 patients. Note variation in individual response.

In an effort to assay the effects of each drug on patients without subjective bias, a "blind study" was conducted. Fresh stock solutions were made of the following: atropine, 0.6 mg. per cc.; Banthine, 10 mg. per cc.; scopolamine, 0.4 mg. per cc., and Antrenyl, 1.0 mg. per cc. These were labelled only A, B, C and D and the labels were alternated frequently. One cubic centimeter of a solution was administered intravenously ten to thirty minutes prior to induction of anesthesia. In many cases electrocardiographic tracings were taken before and after injection. In all cases pulse rates were noted carefully by palpation. There was no selection of patients except that infants were excluded to avoid dosage variations. In each case the anesthetist noted the efficiency of the drug in suppressing secretions and the effect on the cardiovascular system.

Figure 4 shows the effect of atropine, 0.6 mg. intravenously, on the

SCOPOLAMINE 0.4 MG. I.V.
CARDIOVASCULAR EFFECTS

PATIENT	CONTROL PULSE	MAXIMUM PULSE	% INCREASE	B.P.	REMARKS
D46558	115	150	30	110/70	B.P. to 95/70
D25604	90	118	31	110/70	B.P. to 90/60
D46538	110	140	27	120/80	
D3538	82	60		130/80	
D43218	47	64	36	100/60	
D46752	110	160	46	110/80	
C86282	82	90	10	110/74	
D38008	108	144	30	118/78	
D24905	78	88	13	124/60	
A10702	103	140	36	118/80	

FIG. 5. Effect of scopolamine intravenously on cardiac rate of 10 patients. Note variation in individual response.

cardiac rate of 12 patients. The maximum increase was 68 per cent, with an average increase of 30.7 per cent. One patient developed nodal rhythm after atropine. Blood pressures were not affected.

In 10 cases in which the patients received scopolamine, 0.4 mg. (fig. 5), the maximum increase in pulse rate was 48 per cent, with the average being 28.5 per cent. One patient developed a decrease in pulse rate. Two patients had slight falls in blood pressure.

With Banthine, 10 mg., administered to 7 patients (fig. 6), the maximum increase in pulse rate was 76 per cent, the average being 41.7 per cent. In two patients electrocardiographic changes were noted.

Antrenyl was administered in the blind study to 14 patients (fig. 7). The maximum increase in pulse rate was 124 per cent (58 to 130 beats

BANTHINE 10 MG. I.V.
CARDIOVASCULAR EFFECTS

PATIENT	CONTROL PULSE	MAXIMUM PULSE	% INCREASE	B.P.	REMARKS
C15857	83	156	76	118/80.	
D30736	80	96	20	126/70	
83397	70	120	71	150/90	
C84962	130	175	35	150/90	B.P. to 120/80 Multiple premature ventricular contractions
D42666	144	185	28	144/90	B.P. to 154/90
D51396	130	175	35	150/90	
A40030	70	89	27	140/70	ST segment depressed

FIG. 6. Effect of Banthine® intravenously on cardiac rate of 7 patients. Note variation in individual response.

ANTRENYL 1 MG. I.V.
CARDIOVASCULAR EFFECTS

PATIENT	CONTROL PULSE	MAXIMUM PULSE	% INCREASE	B.P.	REMARKS
A95767	82	104	26	90/58	
D45431	92	132	44	118/70	B.P. to 130/80
C57669	100	116	16	100/60	
80224	118	160	36	180/100	
D43466	92	140	52	108/60	B.P. to 128/80
B43201	85	140	67	140/60	B.P. to 120/56
C79514	58	130	124	110/70	B.P. to 140/100 nodal rhythm
D54651	105	135	29	170/100	
D54443	84	96	14	160/90	
D54262	116	144	24	120/70	
D52538	95	133	40	118/70	
B43896	74	104	41	140/70	
A18113	110	190	73	110/80	17 years
47221	120	200	67	110/70	18 years

FIG. 7. Effect of Antrenyl® intravenously on cardiac rate of 14 patients. Note variation in individual response.

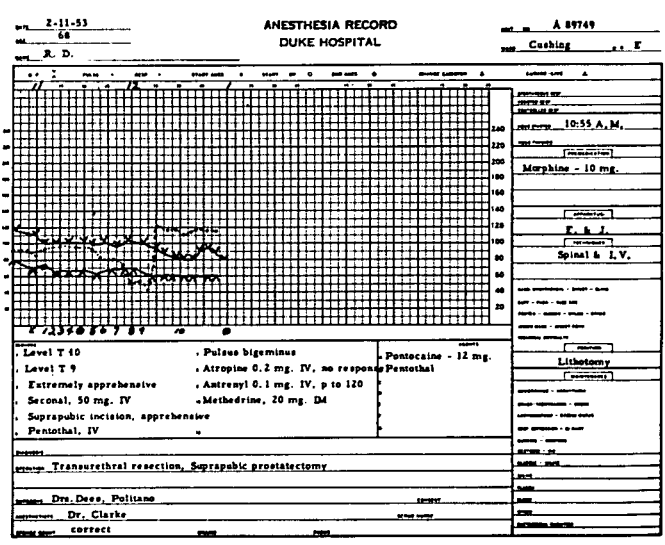

FIG. 8. Showing ineffectiveness of atropine, 0.2 mg. I.V. at (8) and effectiveness of Antrenyl®, 0.1 mg. I.V. at (9) in correcting bradycardia during spinal analgesia.

per minute), while the average rate increase was 40.7 per cent. The blood pressure increased moderately in three patients and decreased in one case. Nodal rhythm developed in one patient.

The anesthesiologists evaluating these drugs were impressed with the lack of salivary secretions associated with what turned out to be the synthetic compounds Banthine and Antrenyl.

To evaluate these synthetic compounds further, specific instances of what were believed to be marked parasympathetic reflexes during operation were treated with intravenous injections of these anti-

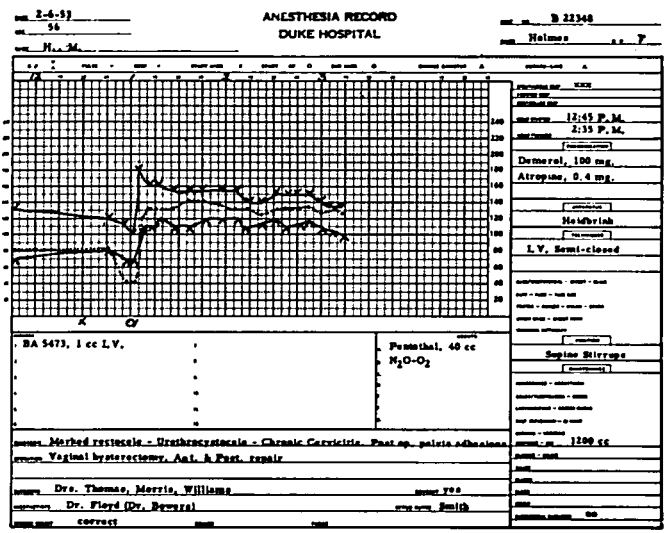

FIG. 9. Showing sympathotonic-like effects of Antrenyl®, 1.0 mg. I.V. during general anesthesia. Note atropine, 0.4 mg. S. C. for premedication and persistence of Antrenyl® action

cholinergic drugs. It was found that each drug would tend to reverse an undesirable situation, but Antrenyl tended to be more reliable than atropine and productive of less tachycardia than Banthine. In figure 8, during a suprapubic prostatectomy under spinal analgesia, the pulse rate fell gradually to 46 per minute, being preceded by pulsus bigeminus. The intravenous injection of atropine, 0.2 mg., produced no response, but the subsequent administration of Antrenyl, 0.1 mg., provoked an immediate increase in rate to 120 per minute which persisted for the duration of the operation. Another interesting reaction which has been seen frequently with Antrenyl is shown in figure 9.

In this 56 year old patient a fall in pulse rate to 40 per minute, associated with minimal decrease in blood pressure, was noted at the beginning of operation. The intravenous injection of Antrenyl (BA 5473), 1 mg., produced an increase in pulse rate to 130 per minute, associated with a decided rise in blood pressure. Both these alterations persisted with little change until the end of the operation 130 minutes later. The end result here was akin to overactivity of the sympathetic nervous system (4).

PHARMACOLOGY OF ANTRENYL®

Of the three synthetic compounds, it was believed that Antrenyl was worthy of continued investigation. This quaternary compound, first prepared in 1944 (3), is diethyl (2-hydroxyethyl) methylam-

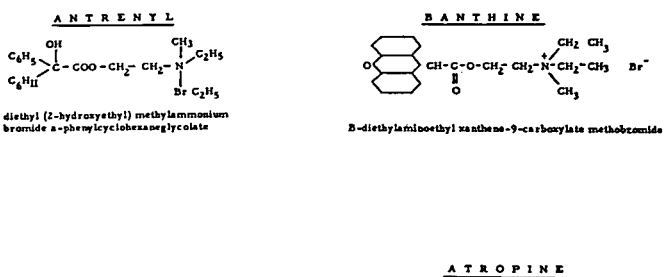

FIG. 10. Structural formulas of Antrenyl®, Banthine® and atropine.

monium bromide a-pheny-cyclohexaneglycolate. The structural formulas of Antrenyl, Banthine and atropine are shown in figure 10 for comparison.

Antrenyl is a white crystalline substance which is freely soluble and stable in aqueous solution, and is absorbed readily on oral, subcutaneous, intramuscular or intravenous administration. Effective action is noted ten to fifteen minutes after subcutaneous injection. It has been suggested (5) that the relatively long duration of action of Antrenyl (three to four hours) may be due to the fact that it is quite resistant to the esterases found in human plasma. Only about 5 per cent is hydrolyzed in four hours as compared to 50 per cent for Banthine.

The anticholinergic effect of Antrenyl on the cardiovascular system

is marked. In the dog or cat, 10 to 20 micrograms per kilogram prevents completely cardiac slowing and depressor effects from electrical stimulation of the right vagus nerve for two to three hours (3). Vagal activity is not fully recovered for six hours. The intravenous injection of 1 mg. per kg. in the dog shows no change in mean arterial pressure. With large doses of 8.5 mg. per kg. and above, a drop in systolic pressure of 40 to 60 mm. of mercury occurs for five to fifteen minutes. This effect is believed due to blockade at the level of the autonomic ganglia and is similar to that seen with large doses of atropine or Banthine. In the heart-lung preparation, no adverse effect is seen with the intraventricular injection of Antrenyl, 1 mg.

Acute toxicity studies in rats show the LD_{50} of intravenous administration is 13.2 mg. per kg. Death occurs with respiratory paralysis. Chronic toxicity studies on dogs given 2 to 6 mg. per kg. daily for three months showed no adverse effects.

The parenteral dosage of this compound for effective anticholinergic action in humans is believed to be in the same range as that for atropine, that is, up to 0.75 mg., depending on age, size and general condition.

CLINICAL TRIAL

In the last two and a half years approximately 6,000 patients have received Antrenyl as the anticholinergic preoperative medication in Duke University Hospital. The drug has been administered intravenously, subcutaneously or intramuscularly in the anesthetic room five to thirty minutes prior to the induction of anesthesia. It is felt that parenteral injection is effective within ten to fifteen minutes. Solutions containing 1 mg. per cc. have been employed, and these have proved to be non-irritating on injection and stable at room temperatures over long periods of time. Dosage range has been from 0.1 to 1.5 mg., depending on individual circumstances. With experience the usual dosage for adults has narrowed to 0.5 to 0.75 mg. Administration just prior to anesthesia induction has prevented the complaint that many patients express preoperatively concerning dryness of the mouth.

It is difficult to be didactic about the prophylactic value of a drug like Antrenyl used for purposes of preliminary medication. However, it is believed that this compound meets adequately the requirements of preanesthetic anticholinergic medication. Troublesome salivary secretions have been uncommon, even with inexpert open-drop ether administrations. Laryngospasm and bronchospasm have been rare, although these complications have not been eradicated. Parasympathetic reflexes involving the cardiovascular system during operation have been infrequent, and it is our impression that their incidence has been reduced with Antrenyl as compared with atropine. Certain

it is that vagal reflexes when present, can be abolished rapidly and with some permanence by Antrenyl in small doses.

As employed in premedication, Antrenyl produced no cerebral sedation. In certain patients a moderately rapid tachycardia followed injection. In the series, 4,400 anesthetic records were examined carefully, and of these 2.3 per cent showed an average increase in pulse rate of 30 per minute, 2.0 per cent showed an increase of 40 per minute, and 1.2 per cent showed the pulse rate increasing 50 or more per minute. Those patients in whom a definite tachycardia occurred demonstrated the length of action of Antrenyl in a clear manner. In most instances the effect persisted for three to four hours, the pulse rate then returned toward normal gradually.

DISCUSSION

One of the interesting observations in this study of anticholinergic drugs was the wide variation in response to similar dosages of a drug from one patient to another. Predictability is a word to be employed with caution, as has been found with other drugs which act predominantly on the autonomic nervous system (6).

To explain these variations, it may be necessary to accept the thesis that each human individual at any given moment is striking a balance between his sympathetic and parasympathetic nervous systems. The extent to which one system predominates over the other will vary from one person to another and in the same person from time to time.

Since the rate of the heart is controlled primarily by variations in vagal tone, it is reasonable to believe that, with injection of an anticholinergic drug, the rate will increase markedly in patients with minimal vagal tone and, conversely, may vary little in patients with marked vagal tone.

Under these circumstances an anticholinergic drug which consistently produces some increase in heart rate is serving its function well. On the other hand, a drug which increases the heart rate to a marked degree in a majority of patients may have some hazard associated with its use. In older patients, particularly those with advancing cardiovascular disease and coronary sclerosis, a pronounced tachycardia may increase the work load of the myocardium to such an extent that irreparable damage may ensue. Taking these factors into consideration, it is felt that Antrenyl provides a relatively safe means of providing optimum anticholinergic effect in humans for periods of several hours.

SUMMARY

1. Effect of anticholinergic drugs on salivation and heart rate was studied in dogs.

2. Action of atropine, scopolamine, Banthine and Antrenyl were compared in humans by means of a "blind study."

3. Ability of Antrenyl to reverse cholinergic reflexes was shown.

4. Prolonged length of action of Antrenyl was noted.

5. Experiences with Antrenyl as an anticholinergic drug for premedication in 6,000 patients were described.

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