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## Safety and Potency of ANQ 9040 in Male Volunteers

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**Background:** ANQ 9040 is an experimental nondepolarizing neuromuscular relaxant. Initial investigations in animals had indicated a rapid onset of action comparable to that of succinylcholine. The purpose of this study was to assess the safety and potency of ANQ 9040 in humans.

**Methods:** ANQ 9040 was assessed in 41 male volunteers. Anesthesia was induced with propofol and maintained with a propofol infusion and 60% N<sub>2</sub>O/40% O<sub>2</sub>. Neuromuscular function was measured by mechanomyography using train-of-four stimulation of the ulnar nerve every 12 s. After an initial pilot study, 23 volunteers received a single dose of ANQ 9040 of between 0.5 and 1.1 mg/kg to determine the dose-response relationship. The final 10 volunteers were given twice the estimated ED<sub>95</sub> of ANQ 9040 as a single bolus dose.

**Results:** The estimated ED<sub>50</sub> and ED<sub>95</sub> of ANQ 9040 were 0.6 and 1.3 mg/kg, respectively. Apart from an increase in heart rate, no important adverse effects were noted after ANQ 9040 administration in the dose range 0.5–1.1 mg/kg. In the volunteers who received 2.6 mg/kg ANQ 9040, a substantial increase in plasma histamine was observed. This was associated with a 12% decrease in mean arterial pressure and a 49% in-

crease in heart rate. In this group, the mean onset time to neuromuscular block was 51.3 s.

**Conclusions:** ANQ 9040 is a rapid-onset neuromuscular blocking agent. However, twice the ED<sub>95</sub> dose is associated with significant histamine release and tachycardia. This finding suggests that this drug will not be useful in clinical practice. (Key words: Complications: histamine release. Neuromuscular relaxants: ANQ 9040.)

ANQ 9040 is a nondepolarizing neuromuscular relaxant of the steroid class (fig. 1). Preclinical investigations in animals had indicated that ANQ 9040 possesses an onset of action at least as fast as that of succinylcholine. The duration of action was reasonably short, and its cardiovascular effects were primarily vagolytic. The purpose of the current study was to determine its safety and potency in humans.

We divided the study into two phases. The aim of the first phase, involving 31 volunteers, was to estimate the effective dose that results in 50% (ED<sub>50</sub>) and 95% (ED<sub>95</sub>) neuromuscular blockade. In the second phase, we hoped to demonstrate the safety of ANQ 9040 in the dose range that might be used in clinical practice. The 10 volunteers in this phase received twice the estimated ED<sub>95</sub> as a single bolus dose.

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 27A.

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### Materials and Methods

After institutional ethics committee approval and written informed consent were obtained, we studied 41 ASA physical status 1 male volunteers. All volunteers were aged between 18 to 30 yr, were within 20% of their ideal body weight, and had taken no medication for the previous 7 days. Before recruitment into the study a complete medical history was taken, physical examination performed, and 12-lead electrocardiogram (ECG) recorded. Blood and urine samples were taken for analysis of hematologic and biochemical variables and screened for hepatitis B and C and illicit drugs. Volunteers were admitted to the drug research unit on the day before the study and the laboratory tests, ECG, and physical examination repeated and confirmed normal.

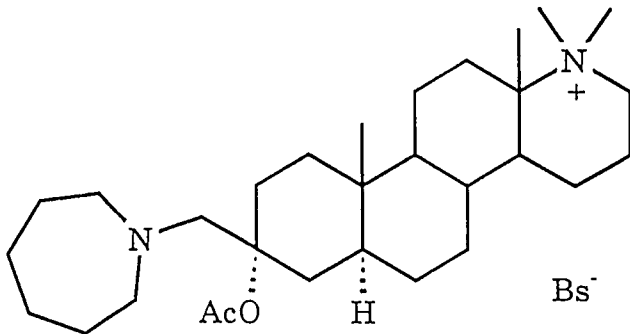


Fig. 1. ANQ 9040, a nondepolarizing neuromuscular relaxant. AcO = acetoxy; Bs = benzene sulphonate.

Volunteers were fasted for a minimum of 6 h before the study. During the hour before induction of anesthesia, at least 3 ml/kg intravenous Hartmann's fluid was administered to ensure normovolemia. The ECG, axillary temperature, end-tidal CO<sub>2</sub>, and hemoglobin O<sub>2</sub> by pulse oximetry were monitored continually throughout the experiment and for 3 h afterward. Arterial blood pressure was measured by automated oscillometry at 5-min intervals during anesthesia and at 15-min intervals for 3 h afterward. The blood pressure also was measured at 1-min intervals each minute for 5 min before and after administration of ANQ 9040.

Blood samples were obtained for plasma histamine and tryptase determination before induction of anesthesia, just before administration of ANQ 9040, and at 2, 5, 10, 15, and 30 min afterward. The plasma was separated immediately and the histamine and tryptase concentration measured by radioimmunoassay.<sup>1,2</sup> A urine sample was collected as soon as possible after recovery from anesthesia to determine methylhistamine and creatinine concentrations.

After recording baseline vital signs, volunteers breathed O<sub>2</sub> for 3 min. Anesthesia was induced with propofol and maintained with a propofol infusion and 60% N<sub>2</sub>O/40% O<sub>2</sub>. A laryngeal mask was inserted and ventilation controlled to maintain an end-tidal CO<sub>2</sub> between 33 and 47 mmHg. Surface electrodes were positioned over the ulnar nerve at the wrist. Responses were evoked with repetitive train-of-four stimulation (four supramaximal stimuli of 0.2 ms duration delivered at 2 Hz every 12 s) generated by a Biometer Myotest nerve stimulator (Odense, Denmark). The force of thumb adduction was measured and recorded with a Biometer Myograph 2000. ANQ 9040 was administered when the control twitch tension, pulse, and blood pressure had been stable for at least 10 min.

The first six volunteers received ANQ 9040 in a 1-mg/ml formulation, but the potency of the drug was less than anticipated and large volumes of solution were necessary to achieve neuromuscular blockade. It was considered impractical to continue with this formulation because volumes exceeding 100 ml might be required to obtain 95% twitch suppression. Therefore, the remaining volunteers received ANQ 9040 in a 10-mg/ml formulation.

The first phase of the study was designed to determine the potency of ANQ 9040 using a cumulative dose technique. However, the rapid recovery from neuromuscular blockade in an additional two volunteers indicated that a single-bolus technique would be more appropriate. Consequently, the next 23 volunteers received a single bolus dose of ANQ 9040. The dose given was administered rapidly and adjusted up and down between volunteers in 0.1-mg/kg increments to approach 95% block but to avoid complete abolition of the twitch response.

In the second phase of the study we wished to give a single large dose to assess the safety of ANQ 9040 in the dose range that might be used in clinical practice. It was our original intention to give five volunteers a 2 × ED<sub>95</sub> dose and the subsequent five volunteers a 3 × ED<sub>95</sub> dose. However, as a result of unexpected cardiovascular effects, we limited the dose of ANQ 9040 to just 2 × ED<sub>95</sub>. The drug was administered over 30 s in the first seven volunteers. The final three volunteers received the drug as an infusion over 1 min in an attempt to minimize cardiovascular changes. The progress of the study and changes in experimental protocol were discussed with the ethics committee and approved.

Anesthesia was continued until full recovery of neuromuscular function had been determined. If spontaneous recovery to a fourth-to-first-twitch (T<sub>4</sub>/T<sub>1</sub>) ratio of 0.7 had not been achieved by 60 min, neostigmine 0.05 mg/kg with glycopyrrolate 0.1 mg/kg was administered. On awakening, each volunteer was asked to raise his head for 5 s to confirm full recovery. All volunteers remained under observation for a further 24 h and were discharged when final physical examination, ECG, and laboratory tests were confirmed normal.

#### Statistical Techniques

The data obtained from the 23 volunteers in the first phase of the study who had received a single bolus dose were used to estimate the ED<sub>50</sub> and ED<sub>95</sub> by log-probit transformation and linear regression analysis. The paired

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**Table 1. Dose-Response, Onset, and Recovery Data from the First Phase of the Study**

Dose (mg/kg)	n	Maximum Block (%)	Time to Maximum Block (s)	Recovery (min)
0.5	3	33 20-40	85 70-97	7.6 6.3-8.3
0.6	5	53 10-96	82 54-103	12.4 4.9-31.1
0.7	2	73 54-92	73 62-84	13.5 13.4-13.5
0.8	3	80 56-98	96 63-113	15.0 14.9-17.8
0.9	5	76 50-100	90 72-105	14.1 11.5-21.4
1.0	3	78 73-84	68 47-88	14.8 12.8-16.4
1.1	2	81 76-86	74 67-80	17.8 14.0-21.5

Results are expressed as the mean and range.

Recovery is defined as a T4/T1 ratio greater than 0.7.

*t* test or two-way analysis of variance was used to assess changes in variables from baseline. Statistical significance was defined as  $P < 0.05$  (two-sided test).

## Results

In the first phase of the study, all volunteers recovered uneventfully. There were no adverse reactions, al-

though some mild erythema was noted around the injection site of one volunteer who had received the 1 mg/ml formulation. This was attributed to the rapid infusion of a large volume of solution into a small vein. Results from the dose-finding part of the study are summarized in table 1. The estimated ED<sub>50</sub> for neuromuscular blockade is 0.6 mg/kg (95% confidence limits 0.5-0.7), and the ED<sub>95</sub> is 1.3 mg/kg (1.0-1.7). The onset of the block was rapid and was associated with marked fade in the train-of-four response. Spontaneous recovery also was fast except in one volunteer, in whom the duration of blockade exceeded 30 min.

The predominant cardiovascular effect was a tachycardia that developed concurrently with neuromuscular blockade (table 2). The increase in heart rate was most evident in the volunteers with a slow resting pulse rate and was not dose-dependent. A small increase in arterial blood pressure was recorded. There were no clinical signs of histamine release in these volunteers. In one volunteer (subject 13, given 0.6 mg/kg ANQ 9040), plasma histamine increased and peaked at 10 min. The histamine concentrations in the other 22 volunteers who received a single bolus dose of ANQ 9040 are summarized in table 3. The small increase in plasma histamine after 2 min was significant at the 5% level (paired *t* test). Urinary methylhistamine was not increased.

Table 4 documents the onset and recovery times of neuromuscular blockade in the ten volunteers who re-

**Table 2. Cardiovascular Data from the First Phase of the Study**

Dose (mg/kg)	n	Arterial Pressure (mmHg)			Heart Rate (beats/minute)		
		Pre-ANQ 9040	Post-ANQ 9040	Change (%)	Pre-ANQ 9040	Post-ANQ 9040	Change (%)
0.5	3	71 63-77	75 65-83	5.8	75 65-89	88 77-100	16.8
0.6	5	67 57-75	69.0 62-78	2.7	73 63-81	87 76-97	18.5
0.7	2	70 65-75	75 73-76	6.7	68 47-88	80 65-95	23.5
0.8	3	62 61-62	72 66-78	16.2	64 57-74	77 66-91	19.1
0.9	5	64 58-73	67 61-73	5.2	67 62-79	79 71-88	17.9
1.0	3	76 66-94	80 69-98	5.1	70 68-74	77 71-85	10.0
1.1	2	62 54-70	64 55-73	3.2	75 72-79	89 82-96	17.7

Results are expressed as the mean and range.

Heart rate and blood pressure were recorded at 1-min intervals for 5 min before and after administration of ANQ 9040. The results in the table are the mean values for these periods.

**Table 3. Plasma Histamine after 0.5–1.1 mg/kg ANQ 9040**

Time (min)	Plasma Histamine (ng/ml)		Subject 13
	Mean	Standard Deviation	
Baseline	0.21	0.10	0.19
0	0.20	0.10	0.15
2	0.25	0.11	0.20
5	0.19	0.08	0.93
10	0.20	0.10	1.91
15	0.19	0.08	0.45
30	0.20	0.07	0.13

The data from subject 13, who received 0.6 mg/kg, are depicted separately.

ceived twice the estimated ED<sub>95</sub> of ANQ 9040. The times recorded are measured from the end of administration until 100% block was observed (*i.e.*, 12 s after the last discernible T1). In the final volunteer, 100% blockade had been achieved before completion of injection. There was marked fade in the train-of-four response during onset. Volunteers 33 and 41 were given neostigmine 0.5 mg/kg with glycopyrrolate at 60 min. In both cases T1 had fully recovered, and the T4/T1 ratio was greater than 0.5 but less than 0.7. Within a min of administration of neostigmine, the T4/T1 ratio exceeded 0.7. The time to a T4/T1 ratio of 0.7 was not determined in volunteer 34 because of recording difficulties, but recovery was not prolonged.

In all ten volunteers a faint red flush appeared within 1 min of administration. The flush was widespread although most noticeable on the face and upper trunk. There was no localized skin eruption at the injection site and no cutaneous wheals. No audible wheeze could be heard on auscultation of the chest, and there was no change in ventilator inflation pressures. Volunteer 36 coughed once approximately 1 min after ANQ 9040 administration. The plasma histamine and tryptase levels are recorded in table 5. There was a significant increase in plasma histamine at 2 and 5 min but no change in plasma tryptase concentration. Methylhistamine concentrations in the urine were not increased.

The cardiovascular changes are summarized in table 6. At 1 min after administration of ANQ 9040, a 16% increase in heart rate was observed and was associated with a 3% increase in mean blood pressure. At 2 min, the heart rate increased to 49% above baseline and the mean arterial pressure decreased by 12%. The mean arterial pressure had returned to baseline by 4 min, but the heart rate remained increased for the duration of the experiment.

After recovery from anesthesia, two volunteers complained of a sensation of chest tightness. No abnormalities were detected on physical examination. Both their forced vital capacity and their forced expiratory volume in 1 s were within the normal range. On further questioning, one of these volunteers was found to have a history of childhood asthma and was an former smoker who occasionally experienced chest tightness in association with upper respiratory tract infections. This volunteer was treated with salbutamol and beclomethasone for 7 days. The other volunteer with chest tightness recovered without treatment within 2 h.

In all volunteers exposed to ANQ 9040, there were no significant abnormalities in the measured laboratory variables, physical examination, or ECG. The volunteers reported no other adverse effects.

## Discussion

The results from this study support the findings of the preclinical work in animal models. ANQ 9040 is a neuromuscular blocking agent with a rapid onset. The presence of fade in the train-of-four response is characteristic of nondepolarizing relaxants.

Determination of an ED<sub>95</sub> dose is a difficult and imprecise exercise when there is considerable individual variation in response and a limited number of volunteers. A cumulative dose study would be an alternative method to obtain dose–response data and may be accomplished with fewer subjects.<sup>3</sup> The potency of a relatively short-acting drug may be underestimated, however, by a cumulative dose technique.<sup>4,5</sup> Moreover, the

**Table 4. Characteristics of ANQ 9040 after 2× ED<sub>95</sub>**

Volunteer	Time to Maximum Block (s)	Time to T4/T1 = 0.7 (min)
1	67	36.3
2	46	60.6
3	52	ND
4	48	43.6
5	59	37.5
6	47	47.0
7	40	35.6
8	28	41.5
9	35	44.9
10	–3	60.8

Onset and recovery times in ten volunteers who received 2.6 mg/kg ANQ 9040. Volunteers 1–7 received ANQ 9040 over 30 s, and volunteers 8–10 received ANQ 9040 over 1 min. In volunteer 10, 100% blockade was achieved before completion of injection. ND = not determined.

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**Table 5. Plasma Histamine and Tryptase after 2 × ED<sub>95</sub> ANQ 9040**

Time (min)	Histamine (ng/ml)		Tryptase (ng/ml) Mean (SD)
	Mean (SD)	Range	
Baseline	0.22 (0.05)	0.15–0.35	0.92 (0.27)
0	0.30 (0.35)	0.14–1.28	0.92 (0.31)
2	3.82 (3.12)	0.50–7.98	0.91 (0.32)
5	1.05 (0.81)	0.20–2.08	0.98 (0.24)
10	0.42 (0.23)	0.20–0.75	0.97 (0.26)
15	0.27 (0.10)	0.16–0.51	0.98 (0.24)
30	0.23 (0.05)	0.16–0.30	0.97 (0.26)

Ten volunteers received 2.6 mg/kg ANQ 9040.

primary objective of our study was to evaluate the safety of ANQ 9040, and a single bolus injection enables physiologic changes to be seen more clearly. The variable up-and-down method of determining the next dose reduced the risk of obtaining 100% twitch suppression, which is of limited use in constructing a dose–response graph. Propofol was chosen as the anesthetic agent in this study because it does not appear to interact with neuromuscular relaxants.<sup>6</sup>

In a dose of 2.6 mg/kg (2 × ED<sub>95</sub>), ANQ 9040 has an onset of action at least as fast as that of succinylcholine 1 mg/kg.<sup>7</sup> The mean onset time for 0.6 mg/kg (ED<sub>50</sub>) was 1.4 min. This is much faster than an equivalent dose of mivacurium (0.05 mg/kg, 5.3 min<sup>8</sup>), atracurium (0.10 mg/kg, 4.4 min<sup>9</sup>), or vecuronium (0.021 mg/kg, 5.1 min<sup>10</sup>). The ED<sub>95</sub> of ANQ 9040 is relatively high compared with other neuromuscular blocking agents except gallamine. Rapid receptor blockade is more likely to occur with drugs of low potency. This is expected because the greater number of drug molecules injected will reduce the time taken to occupy sufficient receptors for neuromuscular blockade. This theory is supported in a study of some desacetoxy analogues of pancuronium and vecuronium in the cat, in which the least potent compound was associated with the fastest onset.<sup>11</sup> In a clinical study comparing equipotent doses of pancuronium, gallamine, and tubocurarine, an inverse linear relationship was demonstrated between the log of the ED<sub>95</sub> and the log of onset time to 50% twitch depression.<sup>12</sup> More recently, this relationship between onset times and potency was confirmed in a laboratory study that measured the speed of action of various muscle relaxants at a frog muscle end-plate.<sup>13</sup>

We do not know whether the low potency of ANQ 9040 entirely accounts for its rapid onset. Different

investigators use disparate methods for determining relaxant potency. Consequently, it is not possible to compare directly our results with the potency and onset times of other nondepolarizing drugs. In a comparison with atracurium and vecuronium, ORG 9426 (rocuronium) appeared to have an onset time to 50% blockade that was faster than predicted from its molar potency.<sup>14</sup> This suggests that other factors may be important in determining onset times. In the dose-finding phase of this study, fade in the train-of-four response was prominent during the onset of block, with disappearance of T<sub>4</sub> before T<sub>1</sub> had reached 25% of control. Fade usually develops more slowly than depression of T<sub>1</sub> tension and consequently is normally more noticeable during recovery. This observation has provided evidence for the theory that neuromuscular blocking agents may bind to more than one type of receptor with differing actions and time courses.<sup>15</sup> It is possible that ANQ 9040 has a relatively high affinity for “fade” receptors and that this influences the onset of blockade. However, fade may be more apparent during onset when small doses are administered.<sup>16</sup> In addition, it has been suggested that the difference between the degree of fade during onset and recovery and its relationship with T<sub>1</sub> suppression may be a consequence of different equilibration times within the muscle rather than different receptors.<sup>17</sup> When 2.6 mg/kg ANQ 9040 was given, usually only one train-of-four response with fade was recorded before total block was achieved. Consequently, a comparison of the fade profiles during onset with other neuromuscular blocking agents is difficult. The fade profile during recovery was unremarkable.

There was no clear evidence of histamine release by ANQ 9040 in first phase of this study using the dose range 0.5–1.1 mg/kg. A statistically significant increase in plasma histamine was detected at 2 min. However, almost any substance given intravenously, including saline, may cause minor mast cell degranulation.<sup>18</sup> Although a greater increase in plasma histamine was measured in one volunteer (subject 13), the long time course for increase and decay was not typical of drug-induced histamine release. An increase in plasma histamine was measured in all volunteers after the administration of 2.6 mg/kg ANQ 9040. There was also much variability in the peak plasma histamine. Our results are comparable to the histamine release observed after a rapid bolus of 0.6 mg/kg of D-tubocurarine.<sup>19</sup> The mechanism of this histamine release is likely to be non-immunologic because all volunteers were affected to

**Table 6. Hemodynamics after 2× ED<sub>95</sub> ANQ 9040**

	Time (min)								
	0	1	2	3	4	5	10	15	30
Blood pressure (mmHg)									
Systolic	99 (9.0)	111 (12.0)	86 (19.3)	90 (17.4)	91 (16.4)	95 (15.1)	99 (13.3)	99 (11.4)	99 (13.6)
	88–112	99–132	63–122	70–124	71–122	74–126	81–127	82–122	83–124
Diastolic	49 (5.5)	46 (7.5)	44 (6.7)	44 (7.9)	47 (6.8)	47 (7.8)	51 (7.6)	50 (7.3)	53 (9.1)
	41–57	36–61	36–54	40–57	39–61	39–61	38–65	40–63	37–64
Mean	66 (6.1)	68 (8.1)	58 (10.4)	60 (11.0)	62 (9.7)	63 (10.1)	67 (9.0)	66 (8.1)	68 (9.8)
	66–74	58–84	50–77	47–79	50–79	50–81	55–86	57–83	60–84
Heart rate (beats/min)	71 (9.5)	83 (11.5)	106 (16.1)	104 (15.5)	103 (16.0)	101 (15.3)	95 (13.0)	94 (13.4)	91 (11.3)
	52–87	64–104	87–123	85–124	84–126	84–125	80–121	79–125	79–120

Results are expressed as the mean (with SD in parentheses) and range.

Ten volunteers received 2.6 mg/kg ANQ 9040.

some extent. Steroidal muscle relaxants, in contrast to the benzyloquinoline compounds, usually are not associated with histamine release in typical clinical doses.<sup>20,21</sup> ANQ 9040 evidently has a low therapeutic index between the dose causing histamine release and the dose required for neuromuscular blockade. This probably results from its low potency, which requires the use of a larger dose to effect neuromuscular blockade and leads, consequently, to a reduced margin of safety for other side effects.

Tryptase is a neutral protease that is stored in mast cell granules. It is released with histamine and other mediators during mast cell degranulation. Measurement of plasma tryptase has been suggested as a means of investigating drug-induced hypotensive reactions.<sup>22</sup> We did not detect any increase in tryptase levels. This may be because ANQ 9040 induced histamine release from basophils rather than mast cells or because we failed to take blood samples at appropriate time intervals. Human basophils contain very little tryptase in comparison with tissue mast cells.<sup>23,24</sup> However, drugs that release histamine in humans by nonimmunologic mechanisms appear to act selectively on cutaneous mast cells.<sup>25</sup> Although the effect of ANQ 9040 on basophils has not been investigated, basophils seem an unlikely source of ANQ 9040-induced histamine release. Plasma tryptase concentrations have been reported to peak at 1–2 h after anaphylactic shock, and elevated concentrations may not be detected in the first 15–30 min.<sup>26</sup> However, after anaphylactic reactions to muscle relaxants, high tryptase concentrations have been detected within 30 min.<sup>27</sup> This study suggests that plasma tryptase concentration measured in the first 30 min may

not be a sensitive marker of nonimmunologic histamine release.

Urinary methylhistamine excretion is used as an indicator of histamine release in investigations of anaphylactoid reactions during anesthesia.<sup>28</sup> No difference was detected in urinary methylhistamine concentration (corrected for creatinine) between the first sample voided after recovery and a sample taken before induction. Although some neuromuscular blocking drugs are known to inhibit histamine N-methyltransferase, the effect of ANQ 9040 on this enzyme is unknown.<sup>29</sup> In contrast to the quantity of histamine released during anaphylaxis, it is probable that insufficient histamine was released to significantly increase the excretion of methylhistamine.

The tachycardia induced by ANQ 9040 in the dose range 0.5–1.1 mg/kg confirms the vagolytic effect seen in animals. At a dose of 2.6 mg/kg, the immediate effects of ANQ 9040 on the cardiovascular system cannot be distinguished from the effects of histamine release. However, the persistent tachycardia after 5 min until the end of the experiment indicates vagolytic activity. Although ANQ 9040 has an onset of action comparable to that of succinylcholine, the adverse effects demonstrated in this study indicate an inadequate safety margin for clinical practice.

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