

Dose-response for Atropine and Heart Rate in Infants and Children Anesthetized with Halothane and Nitrous Oxide

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The dose recommendations for atropine in anesthetized children vary, and the dose-response for heart rate has not been defined. We determined the dose-response for atropine and heart rate in 181 healthy children anesthetized with halothane and nitrous oxide. After induction of anesthesia, atropine in a dose of 5, 10, 20, 30, or 40 $\mu\text{g} \cdot \text{kg}^{-1}$ was administered by rapid intravenous infusion to each subject. The effects of atropine on heart rate, heart rhythm, and systolic blood pressure were compared among dosage groups, and a dose-response curve for peak heart rate was constructed. The effects of atropine were compared also between younger and older subjects. For the group of all 181 subjects, atropine increased heart rate in a dose-related manner up to 30 $\mu\text{g} \cdot \text{kg}^{-1}$. Fifty percent maximal response corresponded to 9 $\mu\text{g} \cdot \text{kg}^{-1}$, and 90% maximal response corresponded to 26 $\mu\text{g} \cdot \text{kg}^{-1}$. Some subjects had nonsinus supraventricular rhythms before atropine, but none had nonsinus rhythm after atropine except after the smallest dose, 5 $\mu\text{g} \cdot \text{kg}^{-1}$. Systolic blood pressure increased significantly after all doses of atropine except 5 $\mu\text{g} \cdot \text{kg}^{-1}$. Subjects < 6 months old had higher control and peak heart rates than did subjects ≥ 2 yr old, but the older subjects had greater change in heart rate after atropine. For subjects ≥ 2 yr old, all doses of atropine produced a significant increase in heart rate. The same was true for younger subjects, < 6 months old, except that 5 $\mu\text{g} \cdot \text{kg}^{-1}$ did not increase heart rate. Control and response systolic blood pressures were higher for subjects ≥ 2 yr than for those < 6 months old. Systolic blood pressure did not change after any dose of atropine for subjects < 6 months old, but for subjects ≥ 2 yr systolic blood pressure increased after doses of atropine 10 $\mu\text{g} \cdot \text{kg}^{-1}$ or greater. Atropine in doses $\geq 10 \mu\text{g} \cdot \text{kg}^{-1}$ increased heart rate and systolic blood pressure and promoted sinus rhythm in children anesthetized with halothane and nitrous oxide. For infants < 6 months old, systolic blood pressure did not change significantly after atropine. (Key words: Anesthesia, pediatric. Heart, rate; drug effects. Anesthetics, volatile: halothane. Anesthetics, gases: nitrous oxide. Parasympathetic nervous system, anticholinergic drugs: atropine.)

ATROPINE is one of the most commonly used drugs in the practice of pediatric anesthesiology. Although much has been written about the use of atropine¹⁻¹⁰ in anesthetized children, still pertinent today is the statement made in 1962 by Gaviotaki and Smith: "The doses of atropine that have been employed clinically in pediatric anesthesia have varied so tremendously that the situation makes little sense and begs investigation. Not only has there been inconsistency among different authorities, but

there has been a striking tendency to give what appears to be a huge amount to infants and homeopathic doses to adults."¹¹ Published dose recommendations range from 10 to 40 $\mu\text{g} \cdot \text{kg}^{-1}$, and a minimum dose of 0.1 mg also has been recommended.¹²⁻¹⁴ A more precise definition of the dose-response relationship will help the clinician achieve desired effects and possibly avoid troublesome side effects. The purpose of this study was to define the dose response for atropine and heart rate in children anesthetized with halothane and nitrous oxide.

Materials and Methods

This study was approved by the Human Research Review Boards of Children's Hospital of Wisconsin and the Medical College of Wisconsin. Subjects were ASA physical status 1 or 2 infants and children scheduled for elective surgical procedures. Anesthesia was induced with 60-70% nitrous oxide and halothane in concentrations judged to be clinically appropriate (sufficient to prevent movement on insertion of an intravenous cannula without causing excessive depression of blood pressure). An intravenous catheter was inserted at a peripheral site and atropine (Elkins-Sinn, Cherry Hill, NJ) in a dose of 5, 10, 20, 30, or 40 $\mu\text{g} \cdot \text{kg}^{-1}$ was injected into the catheter of the swiftly flowing intravenous infusion. Atropine was administered when the heart rate had been stable for at least 20 s and the anesthetic depth had been judged sufficient to proceed to tracheal intubation or preparation for the surgical procedure. For most subjects, the dose of atropine was determined at random, but for some subjects the dose was determined by the clinician's "usual" practice, *i.e.*, administration of 10 or 20 $\mu\text{g} \cdot \text{kg}^{-1}$ to every patient.

For each subject, lead II of the ECG was continuously monitored (78200 series monitor, Hewlett-Packard, Palo Alto, CA) and permanently recorded (model 8373-20, Cole-Parmer Instrument, Chicago, IL; model 78172A Hewlett-Packard; or model 90651A, Spacelabs, Redmond, WA). From the R-R interval we determined control heart rate immediately before atropine was injected and peak heart rate within 1 min after atropine injection. We also noted rhythm before and after atropine and recorded one systolic blood pressure measurement immediately before atropine injection and another when the heart rate was stable at peak value. Blood pressure was measured by automated oscillometry (Dinamap[®] Vital Signs Monitor, Critikon, Tampa, FL).

Comparisons of variables were made among and within

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TABLE 1. Age and Weight

Dose ($\mu\text{g} \cdot \text{kg}^{-1}$)	n	Age (yr)	Weight (kg)
5	40	3.0 ± 0.5	15 ± 1
10	40	3.1 ± 0.5	15 ± 2
20	41	3.0 ± 0.5	16 ± 2
30	38	2.6 ± 0.4	13 ± 1
40	22	2.3 ± 0.5	12 ± 2

Age and weight values are means \pm SEM.Age and weight are not different between dose groups ($P > 0.60$).

the dosage groups of 5, 10, 20, 30, and 40 $\mu\text{g} \cdot \text{kg}^{-1}$. To ensure that subjects in the different dosage groups were similar, the groups were compared by age, weight, and control variables (heart rate, heart rhythm, and systolic blood pressure). To determine the effect of atropine dose on heart rate, peak heart rate was compared within (*vs.* control) and among dosage groups. Also, a dose-response curve relating atropine dose to percent maximal response was constructed, and doses corresponding to 50 and 90% maximal responses were determined. The effect of atropine dose on heart rhythm was examined by comparing the occurrence of sinus and nonsinus rhythms within and among dosage groups. Likewise, the effect of dose on systolic blood pressure was determined by comparing blood pressures within and among dosage groups. Rhythms were compared with chi-squared analysis, with Yates's correction when appropriate. For all other variables, comparisons within dosage groups were made by Student's paired *t* test, and comparisons among dosage groups were made by analysis of variance or analysis of covariance when a covariate was expected to affect the data. For example, age was expected to affect control values, and age and control values were expected to affect response values. Specific groups that were the source of intergroup differences were identified by the Student-Newman-Keuls test. Statistical significance was determined at $P < 0.05$.

It was expected that age would effect heart rate.¹⁵ Therefore, control heart rate was compared among age groups, as follows: <0.5 , 0.5 – 0.99 , 1 , 2 , 3 , 4 , 5 , 6 , 7 , and 8 – 12 yr. The results of this comparison were used to de-

fine a "younger" group and an "older" group. Heart rates and blood pressures then were analyzed separately for younger and older subjects, and the groups were compared to each other. Comparisons were made as above with analysis of variance or covariance, the Student-Newman-Keuls test, and Student's paired and unpaired *t* tests.

Results

One hundred eighty-one infants and children between 1 month and 12 yr of age were enrolled in the study. The dose groups were not different in age, weight, control heart rate, control blood pressure, or occurrence of sinus rhythm before atropine (tables 1–3). Peak heart rate was significantly greater than control for all dose groups ($P = 0.0001$), and peak heart rate increased with increasing dose up to 30 $\mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.05$) (table 2). From the dose-response curve it was determined that 50 and 90% maximal responses corresponded, respectively, to doses of 9 and 26 $\mu\text{g} \cdot \text{kg}^{-1}$ (fig. 1). Heart rate decreased after atropine in 6 of 40 subjects who received 5 $\mu\text{g} \cdot \text{kg}^{-1}$, but the maximum decrease was only 7 beats per min. There were no occurrences of nonsinus rhythms after atropine except after the smallest dose, 5 $\mu\text{g} \cdot \text{kg}^{-1}$, which made this dose significantly different from all other doses ($P = 0.0001$) (table 2). Nonsinus rhythms were supraventricular atrial and nodal rhythms and atrioventricular dissociation. There were no occurrences of ventricular dysrhythmia. Systolic blood pressure increased significantly after atropine ($P \leq 0.001$) except after the smallest dose, 5 $\mu\text{g} \cdot \text{kg}^{-1}$, which made this group significantly different from all other doses ($P < 0.05$) (table 3).

Control heart rate was significantly affected by age ($P = 0.0001$): subjects < 0.5 yr old were significantly different from all older subjects ($P < 0.05$), and those ≥ 2 yr were significantly different from all younger subjects ($P < 0.05$) (fig. 2). Subjects < 0.5 yr old were therefore defined as the younger group and those ≥ 2 yr as the older group. Control heart rate was significantly higher for younger than for older subjects ($P = 0.0001$), and peak heart rate after each dose of atropine was also significantly higher for younger subjects ($P \leq 0.01$) (fig. 3). The change in heart rate (peak minus control), however, was greater

TABLE 2. Heart Rate and Rhythm

Dose ($\mu\text{g} \cdot \text{kg}^{-1}$)	n	Heart rate (beats per min)		Sinus Rhythm (n/total)	
		Control	Peak after Atropine	Control	After Atropine n
5	40	103 ± 3	$115 \pm 3^{*}\dagger$	31/39	27/39 ^{*†}
10	40	106 ± 4	$142 \pm 3^{*}\dagger$	32/38	38/38 [*]
20	41	104 ± 4	$156 \pm 2^{*}\dagger$	34/41	41/41 [*]
30	38	107 ± 4	$164 \pm 3^{*}$	33/38	38/38 [*]
40	22	111 ± 6	$167 \pm 3^{*}$	20/22	22/22 [*]

Heart rate values are means \pm SEM.* Different from control ($P = 0.0001$).† Different from all other doses after atropine ($P < 0.05$).

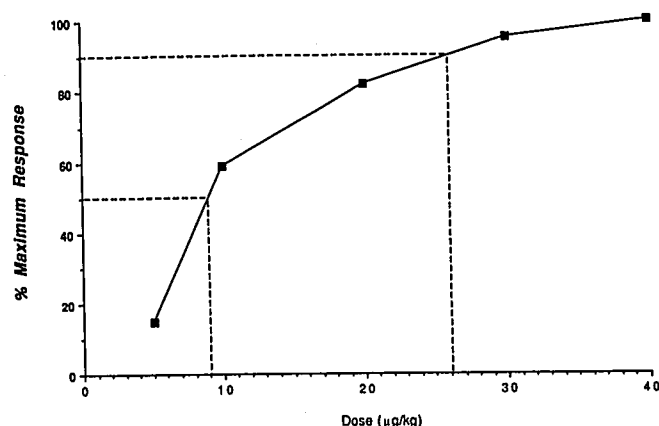


FIG. 1. Dose-response curve for atropine dose and peak heart rate. Fifty percent of maximal response corresponds to $9 \mu\text{g} \cdot \text{kg}^{-1}$, and 90% of maximal response corresponds to $26 \mu\text{g} \cdot \text{kg}^{-1}$.

in older than in younger subjects for all doses of atropine except $10 \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.05$). The dose response for atropine and heart rate were similar between younger and older ages in that peak heart rate increased with increasing dose, up to $30 \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.05$). Also, from dose-response curves it was determined that 50 and 90% maximal responses corresponded, respectively, to 9 and $26 \mu\text{g} \cdot \text{kg}^{-1}$ for the younger group and to 8.5 and $23.5 \mu\text{g} \cdot \text{kg}^{-1}$ for the older group. The dose response was dissimilar between age groups when peak heart was compared to control (fig. 3). For older subjects peak heart rate was different from control for all doses ($P = 0.0001$), whereas for younger subjects peak heart rate was different from control ($P = 0.0001$) for all doses except $5 \mu\text{g} \cdot \text{kg}^{-1}$.

Blood pressure variables differed between younger and older subjects (fig. 4). Control blood pressure was significantly greater for older than for younger subjects ($P = 0.0001$), and blood pressures after each dose of atropine were also significantly greater for older subjects ($P < 0.01$). For older subjects, systolic blood pressures after atropine were greater than control for all doses ($P \leq 0.01$) and were dose-related. Blood pressures after 30 or 40

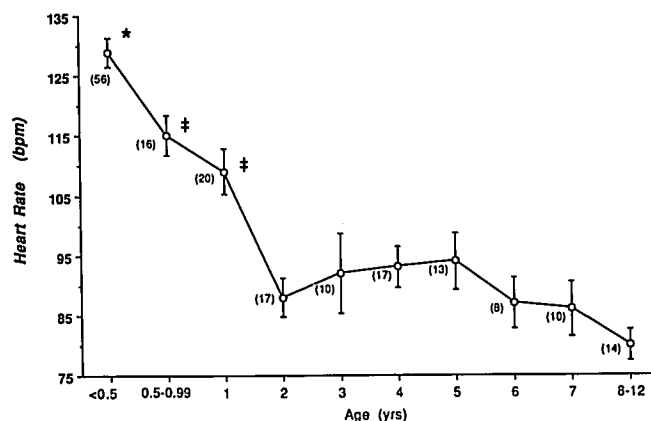


FIG. 2. Control heart rate and age. Values are means \pm SEM. Numbers in parentheses are number of subjects in each group. *Significantly different from all higher ages ($P < 0.05$). †Significantly different from ages < 0.5 and ≥ 2 yr ($P < 0.05$).

$\mu\text{g} \cdot \text{kg}^{-1}$ were greater than those after 10 or $20 \mu\text{g} \cdot \text{kg}^{-1}$, which were higher than those after $5 \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.05$). For younger subjects, systolic blood pressures after atropine were not different from control for any dose and were not dose-related, except that after $5 \mu\text{g} \cdot \text{kg}^{-1}$ blood pressure was significantly less than after all other doses ($P < 0.05$). The change in blood pressure was greater in older than younger subjects for all doses of atropine except $30 \mu\text{g} \cdot \text{kg}^{-1}$ ($P \leq 0.01$). For subjects 6 months–2 yr of age (those not included in the younger and older age groups), atropine in doses of 10 – $30 \mu\text{g} \cdot \text{kg}^{-1}$ significantly

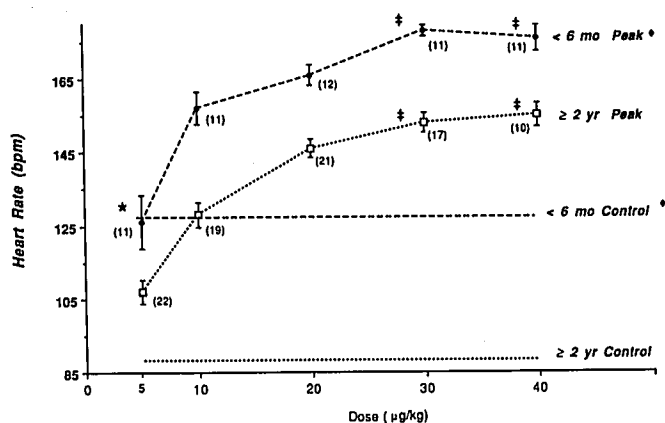


FIG. 3. Dose-response curves for atropine and peak heart rate for infants < 6 months old and children ≥ 2 yr old. Values are means \pm SEM. Numbers in parentheses are number of subjects in each group. Peak heart rates are greater than control ($P < 0.0001$) for all doses in both age groups except $5 \mu\text{g} \cdot \text{kg}^{-1}$ in the < 6 months group. For both age groups, peak heart rates are different among doses ($P < 0.05$) except for ± 30 and $40 \mu\text{g} \cdot \text{kg}^{-1}$, which are not different from each other. Control and peak heart rates for all doses are greater for infants < 6 months old than for children ≥ 2 yr (indicated by diamonds; $P < 0.01$). (Control SEM = 2 for both age groups.)

TABLE 3. Blood Pressure

Dose ($\mu\text{g} \cdot \text{kg}^{-1}$)	n	Systolic Blood Pressure (mmHg)	
		Control	After Atropine
5	33	85 ± 3	$86 \pm 3^*$
10	34	87 ± 2	$93 \pm 2^\dagger$
20	35	82 ± 2	$93 \pm 2^\dagger$
30	34	88 ± 3	$97 \pm 3^\dagger$
40	18	82 ± 4	$93 \pm 4^\dagger$

Blood pressure values are means \pm SEM.

* Different from all other doses after atropine ($P < 0.05$).

† Different from control ($P \leq 0.001$).

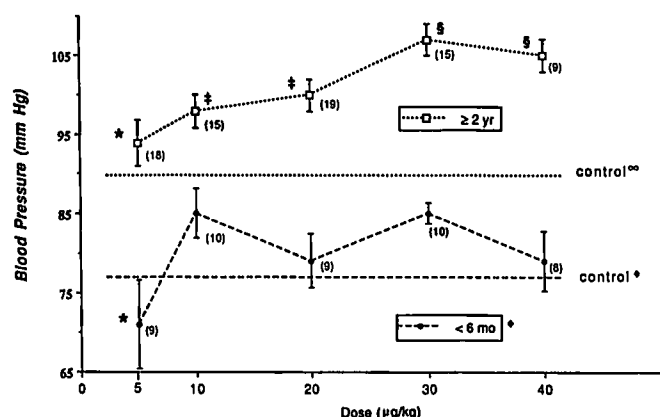


FIG. 4. Dose-response curves for atropine and systolic blood pressure for infants < 6 months and ≥ 2 yr old. Values are means \pm SEM. Numbers in parenthesis are number of subjects in each group. Infinity symbol: for children ≥ 2 yr old, systolic blood pressures after atropine are different from control for all doses ($P < 0.01$), but for subjects < 6 months none is different from control. For subjects ≥ 2 yr old, blood pressures after 30 and $40 \mu\text{g} \cdot \text{kg}^{-1}$ are greater than after 10 and $20 \mu\text{g} \cdot \text{kg}^{-1}$, which are greater than after $5 \mu\text{g} \cdot \text{kg}^{-1}$ ($P < 0.05$). For subjects < 6 months old, systolic blood pressure after $5 \mu\text{g} \cdot \text{kg}^{-1}$ is significantly less than after all other doses ($P < 0.05$), but blood pressures after higher doses are not different from each other. Control and response blood pressures after all doses are lower for infants < 6 months old than for children ≥ 2 yr old (indicated by diamonds; $P < 0.01$). (Control blood pressure SEM = 2 and 1, respectively, for < 6 months and ≥ 2 yr old.)

increased blood pressure ($P < 0.05$). The smallest dose, $5 \mu\text{g} \cdot \text{kg}^{-1}$, did not increase blood pressure, and the number of subjects in the $40 \mu\text{g} \cdot \text{kg}^{-1}$ group was insufficient for statistical analysis for this intermediate age.

Discussion

Atropine in doses of 5 – $40 \mu\text{g} \cdot \text{kg}^{-1}$ increased heart rate in a dose-related manner in children anesthetized with halothane and nitrous oxide. Half-maximal response corresponded to a dose of $9 \mu\text{g} \cdot \text{kg}^{-1}$, and 90% maximal response corresponded to a dose of $26 \mu\text{g} \cdot \text{kg}^{-1}$. Infants < 6 months of age had higher control and peak heart rates than did children ≥ 2 yr old but had less change in heart rate after most doses of atropine. The heart rate of infants also did not increase after the smallest dose, $5 \mu\text{g} \cdot \text{kg}^{-1}$. Our results are similar to those in unanesthetized children, in whom control heart rate is inversely related to age and in whom change in heart rate after atropine is inversely related to control heart rate.¹⁵ In our study, varying depths of anesthesia may also have contributed to differences between younger and older subjects in control heart rates. In our study, assessment of depth of anesthesia was made by clinical judgment. End-tidal concentrations of gases were not recorded because all subjects were breathing through pneumatic-cushioned face masks with a relatively large dead space.¹⁶ In this circumstance,

end-tidal readings do not accurately reflect alveolar gas concentrations.¹⁷

In six subjects, heart rate decreased slightly after $5 \mu\text{g} \cdot \text{kg}^{-1}$ atropine by amounts that were not clinically significant (7 beats per min maximum). These decreases may have been due to the anesthetic agents or the small dose of atropine or both.^{12,18} All subjects had sinus rhythm after doses of atropine $\geq 10 \mu\text{g} \cdot \text{kg}^{-1}$ whether the control rhythm was sinus or nonsinus. Both sinus and nonsinus rhythms occurred after $5 \mu\text{g} \cdot \text{kg}^{-1}$. Nonsinus rhythms before atropine can be attributed to interactions among halothane, the autonomic nervous system, and the conducting system of the heart.¹⁹ Small doses of atropine also have been associated with these rhythms.¹²

Systolic blood pressure increased after doses of atropine $\geq 10 \mu\text{g} \cdot \text{kg}^{-1}$ for children anesthetized with halothane and nitrous oxide. For infants < 6 months old, atropine did not significantly change blood pressure, although blood pressure was lower after $5 \mu\text{g} \cdot \text{kg}^{-1}$ than after larger doses. With a larger number of subjects < 6 months old, response blood pressure may become statistically greater than control for some doses of atropine. The change in blood pressure produced by atropine, however, still is generally greater for older than for younger subjects. Atropine increases blood pressure by increasing heart rate.²⁰ The greater change in systolic blood pressure in older than in younger subjects is consistent with the greater change in heart rate in older subjects.

Others have reported heart rate changes after one or two doses of intravenous atropine in anesthetized children, but we can find no other report of the dose-response relationship.^{1,5,7–9,21,22} Comparisons among studies are hindered by variations and combinations of anesthetic agents that may have dissimilar effects on the heart and autonomic nervous system. Our results are similar to those of Samra and Cohen, who noted a heart rate increase of 35 beats per min after $10 \mu\text{g} \cdot \text{kg}^{-1}$ of atropine in children anesthetized with halothane and nitrous oxide.⁹ However, they noted the presence of junctional rhythm in some subjects after $10 \mu\text{g} \cdot \text{kg}^{-1}$ of atropine, and we did not. Mirakhur and Jones also noted junctional rhythm in anesthetized children after $10 \mu\text{g} \cdot \text{kg}^{-1}$ of atropine but not after $15 \mu\text{g} \cdot \text{kg}^{-1}$.⁷ In conscious children, atrial and high nodal rhythms were noted after 1.8 and $3.6 \mu\text{g} \cdot \text{kg}^{-1}$ of atropine but not after doses $\geq 7.2 \mu\text{g} \cdot \text{kg}^{-1}$.¹² Ventricular extrasystoles were absent in our study, in contrast to that of Thurlow,²³ perhaps because we frequently assisted or controlled ventilation so that hypercapnia probably was avoided. Very slow injection of atropine may be associated with bradycardia, but in our study injections were made rapidly, and there were no occurrences of clinically significant bradycardia.²⁴ Although maximum heart rate is reached approximately 15 min after injection of 1 mg atropine in adults, of more interest to the clinician is the

rapid increase in heart rate that occurs immediately after injection.²⁵

Based on these data we conclude that atropine in a minimum dose of $10 \mu\text{g} \cdot \text{kg}^{-1}$ is required to increase heart rate by 50% and promote sinus rhythm in infants and children anesthetized with halothane and nitrous oxide. This dose also increases systolic blood pressure in children 6 months of age and older.

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