Median Effective Dose of Intranasal Dexmedetomidine for Rescue Sedation in Pediatric Patients Undergoing Magnetic Resonance Imaging

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ABSTRACT

Background: The median effective dose (ED_{50}) of intranasal dexmedetomidine after failed chloral hydrate sedation has not been described for children. This study aims to determine the ED_{50} of intranasal dexmedetomidine for rescue sedation in children aged 1 to 36 months, who were inadequately sedated by chloral hydrate administration during magnetic resonance imaging (MRI).

Methods: This study was performed on 120 children, who were 1 to 36 months old and underwent MRI scanning. Intranasal dexmedetomidine was administered as a rescue sedative to children not adequately sedated after the initial oral dose of chloral hydrate (50 mg/kg). Children were stratified into four age groups. ED_{50} values were estimated from the up-and-down method of Dixon and Massey and probit regression. Other variables included induction time, time to wake up, vital signs, oxygen saturation, MRI scanning time, and recovery characteristics.

Results: ED_{50} of intranasal dexmedetomidine for rescue sedation was 0.4 μg/kg (95% CI, 0.34 to 0.50) in children aged 1 to 6 months, 0.5 μg/kg (95% CI, 0.48 to 0.56) in children aged 7 to 12 months, 0.9 μg/kg (95% CI, 0.83 to 0.89) in children aged 13 to 24 months, and 1.0 μg/kg (95% CI, 0.94 to 1.07) in children aged 25 to 36 months. There were no significant differences in sedation induction time or time to wake up between the different age groups. Additionally, no significant adverse hemodynamic or hypoxemic effects were noted.

Conclusions: The authors determined the ED_{50} for rescue sedation using intranasal dexmedetomidine after failed chloral hydrate sedation in children. It was found that ED_{50} increases with advancing age during the first 3 yr of life.
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MAGNETIC resonance imaging (MRI) in children is usually performed under sedation to render children immobile and cooperative.[1–3] Several sedative medications including chloral hydrates and midazolam are used for pediatric sedation during MRI.[4,5] However, these agents often fail to maintain the necessary depth of sedation to complete the procedure.[6–8] Sedation failure causes a delay in diagnosis, increases the cost of the procedure, and is inconvenient to the child and family.

Intravenous dexmedetomidine has been successfully used as a rescue sedative for children who fail to be sedated during MRI using chloral hydrate and/or midazolam.[8] On the other hand, intranasal dexmedetomidine has been found to be a safe and effective option for patients who require sedation during nonpainful procedures due to its limited cardiovascular and respiratory effects.[5,9–12]

To the best of our knowledge, the effective rescue dose of intranasal dexmedetomidine after failed sedation during MRI remains undetermined. Moreover, the effects of age on rescue sedation with intranasal dexmedetomidine remain controversial because some studies revealed a smaller volume of distribution and a higher clearance of dexmedetomidine with advancing age.[13–15]

The aim of this study was to determine the median effective dose (ED_{50}) values of intranasal dexmedetomidine for rescue sedation after failed chloral hydrate sedation and to determine the effect of age on the dose required for rescue sedation.

What We Already Know about This Topic

- Chloral hydrate is a common sedative for nonpainful procedures such as magnetic resonance imaging
- When chloral hydrate alone proves insufficient, sedation can be supplemented with intranasal dexmedetomidine

What This Article Tells Us That Is New

- The median effective dose of intranasal dexmedetomidine for rescue sedation after failed chloral hydrate was determined and found to increase with age during the initial 3 yr of life

Materials and Methods

The registry URL of this study is https://clinicaltrials.gov/Identifier (NCT02253199). Institutional review board is Medical Ethic Committee of Guangzhou Women and Children's Medical Center (Guangzhou, Guangdong Province, China).

Subjects and Study Protocol

This study protocol was approved by the local institutional review board (GCP/IEC2014010), and written informed

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consent was obtained from the parents or legal guardians of the patients. All children who presented for an MRI study from October 2014 to February 2016 and were sedated by the authors were enrolled in this study. Diagnostic brain MRI accounted for a majority of the scans, and other imaging sites included a small number of joints or tumor scans, with or without enhancement. Furthermore, patients enrolled into this study were between 1 and 36 months old and were classified as American Society of Anesthesiologists physical status I or II. These patients failed sedation within 30 min after the administration of chloral hydrate (50 mg/kg) during clinical routine diagnostic MRI scanning. Sedation was assessed using the modified Observer Assessment of Alertness and Sedation Scale (MOAA/S)[8,16,17] (table 1).

Sedation status was evaluated in the supine position by a blinded observer every 5 min before and after the MRI study. Successful sedation was defined as an MOAA/S score between 0 and 3 and allowed the acquisition of clinically adequate diagnostic-quality images, while failure was defined as an MOAA/S score of more than 3 or clinically adequate diagnostic-quality images could not be acquired. Exclusion criteria included known allergy to study drugs, recent or current treatment with α-2 adrenergic receptor agonist or antagonist, organ dysfunction, pneumonia, acute upper respiratory airway inflammation, history of preterm birth, cardiac arrhythmia, and known congenital heart disease.

A total of 120 children were included in this study. These children were stratified into four age groups of 1 to 6, 7 to 12, 13 to 24, and 25 to 36 months. Oral chloral hydrate (50 mg/kg) was administered after at least 1 h of fasting for liquids, as per the protocol followed in our unit. In case of failed sedation, undiluted preservative-free dexmedetomidine (Aibeining; Jiangsu Hengrui Medicine Co., Ltd., China) was prepared at a concentration of 100 μg/ml and dripped into both nostrils using a 1-ml syringe (precision graduated) with the children lying in the supine position. This position was maintained for 5 min in order to maximize drug absorption.

All study drugs were prepared by an independent investigator, who was not involved in the collection of data, and the study drugs were administered by two investigators, who were not involved in the observation of the children. Furthermore, observers and attending anesthesiologists were blinded to the study drug administration, according to previous studies.[14,15]

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

0	Does not respond to a noxious stimulus
1	Does not respond to mild prodding or shaking
2	Responds only after mild prodding or shaking
3	Responds only after name is called loudly and repeatedly
4	Lethargic response to name spoken in normal tone
5	Appears asleep but responds readily to name spoken in normal tone
6	Appears alert and awake and responds readily to name spoken in normal tone

Considering the pharmacokinetic difference in children aged between 1 and 36 months and our previous investigation,[6] the starting rescue dose of dexmedetomidine was 0.8 μg/kg. These doses varied by 0.1 μg/kg, according to the up-and-down method.[18] The endpoint was determined according to MOAA/S scores after rescue sedation and the acquisition of clinically adequate diagnostic-quality images. If the detected MOAA/S score was more than 3 within 30 min after intranasal administration of the rescue dexmedetomidine dose or clinically adequate diagnostic-quality images could not be acquired, rescue sedation was considered a failure, and the dexmedetomidine dose was increased by 0.1 μg/kg in the next patient of the same age group. In contrast, if the detected MOAA/S score was less than or equal to 3 and the acquisition of clinically adequate diagnostic-quality images was possible, the rescue sedation was considered successful, and the dexmedetomidine dose was decreased by 0.1 μg/kg in the next patient of the same age group.

Noninvasive discontinuous monitoring of systolic blood pressure (SBP), heart rate (HR), and oxygen saturation were collected in the ward at presedation assessment (T0), as well as before (T1) and at 15 (T2), 60 (T3), 75 (T4), and 90 min (T5) after dexmedetomidine administration. Sedation induction time was defined as the time from rescue drug administration to the onset of satisfactory sedation. The failure of sedation was defined as inadequate sedation observed within 30 min of rescue sedation. Children were classified as awake if the MOAA/S score was between 4 and 6, while wake-up time was defined as the time from successful sedation to the time the child woke up. Children were discharged upon attaining an Aldrete score[9] of 9. Hypotension or bradycardia was defined as a reduction in SBP or HR of more than 20% from baseline values. Significant oxyhemoglobin desaturation was defined as oxygen saturation less than 90%.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 for windows (SPSS Inc., USA). Data are expressed as mean (± SD) or count, as appropriate. Continuous normally distributed data were analyzed using one-way ANOVA, and the least significant difference method was used for multiple comparison tests between groups. Nonnormally distributed or skewed data were compared using Dunnett T3 one-way ANOVA. Counts were analyzed using Fisher exact test. ED_{50} was estimated from the up-and-down sequences, using the method of Dixon and Massey[18] and probit regression. The dosage of ED_{50} was determined from the midpoints of all independent pairs of patients who involve a crossover from failure to success. According to the study conducted by Paul and Fisher,[19] patients were enrolled until six pairs were obtained. The criterion for rejection of the null hypothesis was $P < 0.05$ for all tests.

Results

As shown in table 2, there were no differences in demographic data or the baseline sedation score before the administration of dexmedetomidine among the four age groups. Furthermore,

there was no difference in the cause for MRI scans among the groups. In addition, there were no differences in the duration of MRI examinations. All routine MRI examinations were completed within 35 min, which is significantly shorter than the average duration for rescue sedation time. Three patients (5%), who had MOAA/S scores less than 3, failed MRI, even with comfort maneuvers (repositioning and swaddle). Two patients were in the age group of 1 to 6 months, and one patient was in the age group of 25 to 36 months. One patient failed MRI due to uncomfortable contrast agent injection, while the other two failed MRI due to varying levels of sedation during MRI scanning.

The sequences of success and failure outcomes are shown in figure 1. Using the formula of Dixon and Massey, ED_{50} (95% CI) for the rescue sedation of intranasal dexmedetomidine was 0.4 (0.34 to 0.50) μg/kg for the age group of 1 to 6 months, 0.5 (0.48 to 0.56) μg/kg for that of 7 to 12 months, 0.9 (0.83 to 0.89) μg/kg for that of 13 to 24 months, and 1.0 (0.94 to 1.07) μg/kg for that of 25 to 36 months (table 3).

EC_{50} and EC_{95} (95% CI) values of the rescue sedation of intranasal dexmedetomidine obtained from probit regression analysis are also presented in table 3.

There were no differences in sedation induction time and wake-up time among the four groups ($P > 0.05$; table 4). None of the children had oxyhemoglobin desaturation less than 94% during the observation period. Hemodynamic variables were stable (within 20% of the presedation values) during the procedure, and there were no instances of clinically significant hemodynamic changes that required intervention.

Discussion

In the current study, we used Dixon and Massey's "up-and-down" methodology to extrapolate the ED_{50} of intranasal dexmedetomidine, in which dexmedetomidine was administered in different age strata during the first 3 yr of life after failed chloral hydrate sedation during diagnostic MRI. We also found that ED_{50} increases as the ages of children increases.

The optimal dose of intranasal dexmedetomidine for rescue sedation must take into consideration the residual effects of chloral hydrate. Our previous study[6] showed that increasing the dose of intranasal dexmedetomidine administration leads to a longer time to recovery to the baseline status. Therefore, a higher dosage of intranasal dexmedetomidine with the increasing success rate of sedation may result in delayed recovery, parental anxiety, hypotension, or sinus bradycardia,

Table 2. Demographic Data and Baseline Sedation Scores after Failed Chloral Hydrate Sedation

	1–6 mo (n = 30)	7–12 mo (n = 30)	13–24 mo (n = 30)	25–36 mo (n = 30)
Age, mo	3 ± 1.7	9 ± 1.7	19 ± 3.5	29 ± 3.5
Weight, kg	6.4 ± 1.9	8.1 ± 1.5	10.4 ± 1.4	12.6 ± 1.8
Male/female	16/14	21/9	17/13	18/12
MOAA/S	5 (4–6)	5 (4–6)	5 (5–6)	5 (5–6)

Data are presented as mean ± SD, except for gender, which is expressed as frequency.
MOAA/S = Modified Observer's Assessment of Alertness and Sedation Scale.

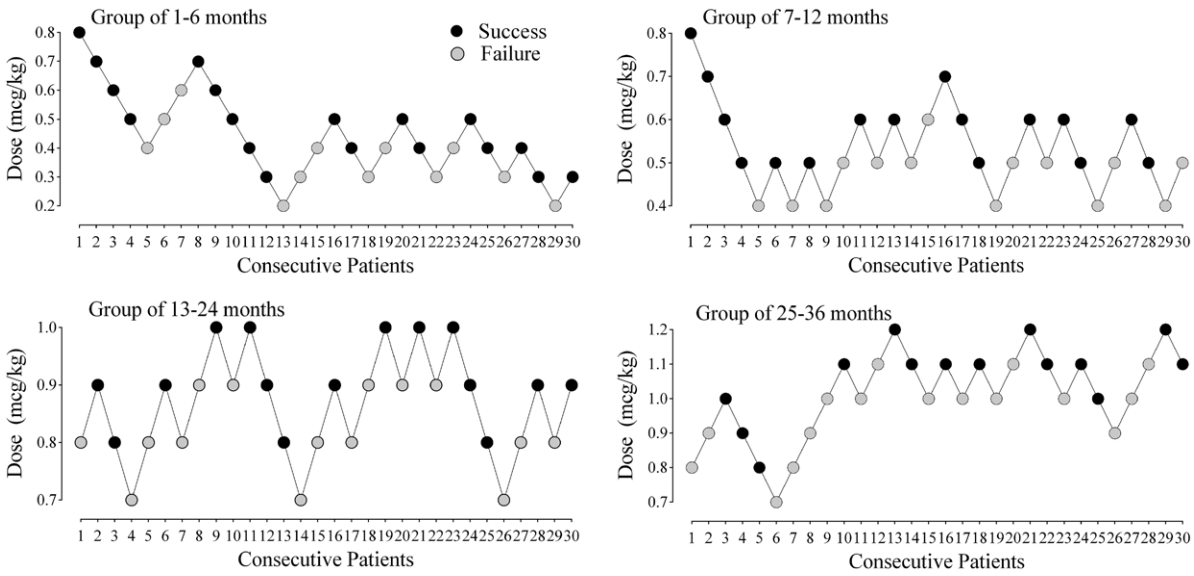

Fig. 1. Up-and-down sequential allocation study of intranasal dexmedetomidine for rescue sedation in the study groups. The testing interval was 0.1 μg/kg. The calculated median effective doses are 0.4, 0.5, 0.9, and 1.0 μg/kg for age groups of 1 to 6, 7 to 12, 13 to 24, and 25 to 36 months, respectively.

Table 3. Dose–Response Data for Intranasal Dexmedetomidine Administration for Rescue Sedation in the Study Groups Derived by the Dixon–Massey Up-and-Down Sequential Allocation Method and Probit Regression

	1–6 mo (n = 30)	7–12 mo (n = 30)	13–24 mo (n = 30)	25–36 mo (n = 30)
Dixon–Massey ED_{50}, μg/kg	0.4 (0.34–0.50)	0.5 (0.48–0.56)	0.9 (0.83–0.89)	1.0 (0.94–1.07)
Probit regression				
ED_{50}, μg/kg	0.4 (0.05–0.49)	0.5 (0.46–0.56)	0.9 (0.80–0.93)	1.0 (0.94–1.07)
ED_{95}, μg/kg	0.7 (0.55–2.33)	0.6 (0.57–0.84)	1.0 (0.94–1.34)	1.3 (1.17–2.60)

Data are ED_{50} or ED_{95} with 95% CI.
ED_{50} = 50% effective dose; ED_{95} = 95% effective dose.

Table 4. Sedation Induction Time and Wake-up Time for Children Who Were Successfully Sedated According to the Rescue Sedation Protocol

	1–6 mo (n = 18)	7–12 mo (n = 16)	13–24 mo (n = 15)	25–36 mo (n = 14)
MRI examination time, min	21 ± 5	21 ± 5	21 ± 5	21 ± 5
Induction time, min	15 ± 5	13 ± 5	17 ± 4	15 ± 6
Wake-up time, min	56 ± 16	46 ± 11	56 ± 12	51 ± 14

Data are presented as mean ± SD.
MRI = magnetic resonance imaging.

as well as potential hypoglycemia and dehydration due to prolonged fasting (especially in younger children).[3,8]

The use of intranasal dexmedetomidine for pediatric sedation has been previously described; however, the success rate of sedation was not uniform.[6,9,11,20] This may be partly due to age variability, the degree of sleep deprivation before sedation, and the type and duration of the noninvasive procedure performed. This study was performed on a narrow age range of children, which was within 3 yr (stratified into four groups), presenting for MRI study. In our opinion, this provides an ideal model for comparing rescue sedative potencies of intranasal dexmedetomidine due to a relatively homogenous population, the clearly defined endpoint of sedation, and the absence of other pharmacologic (sedative) confounding factors.

A previous study[9] revealed that intranasal dexmedetomidine could be successfully used as a rescue sedation after failed chloral hydrate sedation for nonpainful diagnostic procedures. The success rate was 83.6%, 89.2%, and 96.2% for 1, 1.5, and 2 μg/kg intranasal dexmedetomidine administered to children aged 1 to 120 months, respectively. This success rate was lower than that reported in our previous study,[6] which was 94% and 98% for 1 and 2 μg/kg intranasal dexmedetomidine administered to children aged 1 to 6 months.

Because it is interesting to examine the pharmacokinetic profiles as a function of age, our study revealed that the dose of dexmedetomidine to achieve the same level of rescue sedation was increased in younger children. Furthermore, in our study, ED_{50} of intranasal dexmedetomidine almost doubled in older children, in which ED_{50} was 0.4 μg in the age group of 1 to 6 months and 1 μg in those 25 to 36 months. Several possible explanations may account for our findings. First, the volume of distribution of the drug progressively decreases with age,[14] leading to a greater amount of tissue distribution in younger children. This may contribute to the faster onset of sedation after intranasal or intravenous administration of dexmedetomidine. Second, there were considerable clearance changes with age and weight, dictating different infusion regimens at different ages to achieve the same steady-state target concentration.[14,15,21] Dexmedetomidine clearance is significantly diminished in full-term newborns and increases rapidly in the first few weeks of life. The dependence of clearance on age during the first few weeks of life reflects the relative immaturity of the metabolic processes during the newborn period.[21] Clearance in term neonates is 42.2% of adult values, which reaches 84.5% by 1 yr of age.[15] Maintenance dosing, as a function of clearance, should be reduced in neonates and infants when using a target concentration approach.[13] Third, the development of the brain and blood-brain barrier may cause it to be sensitive to the sedative, in which some children of different ages have different sedation success rates with chloral hydrate.[1,7] In this way, it seems that the intranasal administration of dexmedetomidine was more sedative in younger children than in older children.[6,9]

Wake-up time was related to intranasally administered doses. Li *et al.*[9] reported a mean time to recovery to the baseline status of 70 min (25 to 160 min), after 1 μg/kg intranasal dexmedetomidine administration for rescue sedation in failed chloral hydrate sedation for noninvasive diagnostic procedures. Another study reported a mean recovery time of 61 min (range, 44 to 90 min).[6] In the current study, the mean average time to wake up was much shorter than that in previous reports,[6,9] which is probably due to the different ages of the study population in different studies.

α-2 agonists produce a modest reduction in SBP and HR. In a previous study[6] conducted on infants aged between 1 and 6 months, intranasal dexmedetomidine at a dose of 1 μg/kg caused a maximum dose-dependent decrease in HR of 15.9% and an SBP of 21.1%. In this study, due to lower doses used for rescue sedation, none of our patients

developed clinically significant hemodynamic or respiratory disturbance that required intervention.

Limitations of This Study

Some factors might have interfered with the dose selection in the current study. These include the variability of the disease, which MRI was requested, and the quality of sleep the night before sedation.

Since all routine MRI examinations in our center were completed within 35 min (range, 15 to 35 min), the extrapolated ED_{50} of intranasal dexmedetomidine for rescue sedation could not be generalized to other procedures or when MRI is performed for longer durations.

The up-and-down method was used to determine the ED_{50} in the current study, which often depended on a small sample size, but this did not provide reliable insight into the upper tail of the distribution. Many studies used probit or logistic regression to determine the ED_{50} and ED_{95} of drugs.[22,23] Probit analysis requires that the data be independent; in the current study, although probit analysis was performed to verify ED_{50} and determine ED_{95}, the study was not powered for probit regression for dependent data. We also did not make analysis of interrater reliability of multiple observers.

The absolute adult bioavailability of dexmedetomidine *via* the intranasal route is 65% (35 to 93%), medians (and ranges).[24] This may be different in a pediatric population since the biochemical characteristics and anatomical structure of the nose develop with advancing age.

Sedation in the current study was measured subjectively using MOAA/S. However, this score was found efficient in several studies.[5,6,9] In addition, a study[16] about intranasal dexmedetomidine found that the trend and variation of MOAA/S were clearly consistent with those of the visual analog scale of sedation, bispectral index.

In conclusion, ED_{50} of the intranasal dexmedetomidine used for rescue sedation after failed chloral hydrate sedation in children increased with advancing age, indicating that age had an influence on the potency of intranasal dexmedetomidine.

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Competing Interests

The authors declare no competing interests.

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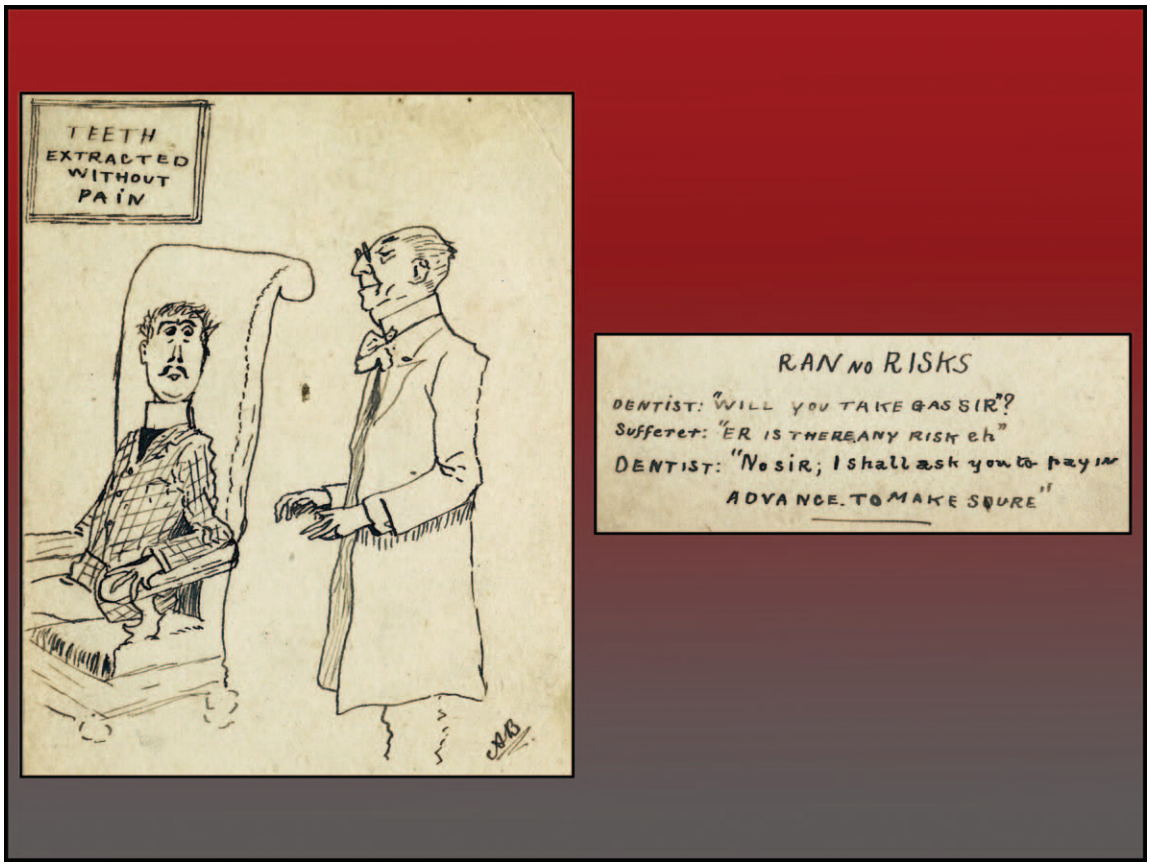
Cartoon by "AB" of a Dentist Anesthetist Who "Ran No Risks"



With his patient seated under a sign reading "TEETH EXTRACTED WITHOUT PAIN," a dentist asks, "Will you take gas, Sir?" The patient replies, "ER is there any risk eh" [sic]. "No sir," answers the dentist. "I shall ask you to pay in ADVANCE, TO MAKE SURE." Titled "Ran No Risks," this undated illustration reflected the discomfort of a public that by the late 1930s was reading that many dental patients were receiving no oxygen at the start of their nitrous oxide anesthetics. Hand drawn by a cartoonist who signed his work as "AB," this card is another delightful item in the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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