General Anesthetics

Mary Jeanne Kallman

Contents

M.J. Kallman (✉)
Kallman Preclinical Consulting, Greenfield, IN, USA
e-mail: maykall76@gmail.com

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Intravenous Anesthesia

General Considerations

Purpose and Rationale

The first agents which could be used as intravenous anesthetics were **barbiturates**. Barbiturates with a duration of action appropriate to the requirements of surgery became available with the introduction of hexobarbital and thiopental (Volwiler and Tabern 1930; Miller et al. 1936). The studies with barbiturates were extended (Butler and Bush 1942; Christensen and Lee 1973). Intravenous anesthetics from other chemical groups were developed, such as **acetamidoeugenol** (Estil, Domenjoz 1959), steroid derivatives (Presuren = **hydroxydione sodium**, Laubach et al. 1955; **alfaxolone**, CT1341, Child et al. 1971), **propanidid** (Goidenthai 1971), **ketamine** (CI-581, Chen et al. 1966; Reich and Silvay 1989), **etomidate** (Janssen et al. 1975), **propofol** (ICI 35868, Glen 1980), and **midazolam** (Pieri 1983; Reilly and Nimmo 1987).

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Screening of Intravenous Anesthetics

Purpose and Rationale

Screening of intravenous anesthetics or hypnotics is performed mostly in mice or rats. Doses for loss of righting reflex and lethal doses are determined. Onset of action and duration of action are the secondary parameters.

Procedure

Male mice weighing 18–22 g are injected intravenously via the tail vein. The anesthetic activity is estimated from the number of animals that lose their righting reflex. The righting reflex is considered lost when the mouse, placed on its back, fails to recover from this position within 1 min. The acute toxicity is based on lethality within a 24-h observation period.

To determine onset and duration of action, groups of 20 mice are used. They are placed in individual observation cages maintained at room temperature (24 ± 1 °C). They are not stimulated during the interval between loss and recovery of the righting reflex. The onset is defined as the complete loss of the righting reflex, i.e., no attempt to move the head or body. Recovery is considered to have occurred when the animal after spontaneous righting would reright itself within 15 s when placed on its back.

Evaluation

The median anesthetic dose (AD_{50}) and the median lethal dose (LD_{50}) are determined from dose–response curves with at least four doses by the method of Litchfield and Wilcoxon (1949).

The data for onset and duration of action are analyzed statistically by Student's *t*-test.

Modifications of the Method

Volwiler and Tabern (1930) determined the minimum effective dose in rats after subcutaneous injection of various barbiturates not being awakened when outer ear passage was tickled with a straw.

Büch et al. (1968) studied the distribution, anesthetic potency, and metabolic elimination of the optical isomers of methylphenobarbital in rats.

Glen (1977) described a method for the laboratory evaluation of the speed of onset of i.v. anesthesia in **mice**. Various clinically used intravenous anesthetics were compared. The technique involves (a) determination of the medium hypnotic dose (HD_{50}) by plotting the probit value of the mice sleeping against dose on a logarithmic scale, (b) plotting mean induction time over a range of doses against the logarithm of the dose, and (c) comparison of induction times at 1.25 HD_{50}. All doses were given over 1 s or 10 s. A 1-s injection was thought to be of most value in the of structure activity effects.

Chen et al. (1966) tested the anesthetic activity and the neuropharmacological spectrum of ketamine (CI-581) in mice, pigeons, and monkeys.

Child et al. (1971) tested the anesthetic activity of alfaxolone (CT1341) in **mice**, **rats**, **rabbits**, **cats**, **dogs**, and **monkeys**.

Janssen et al. (1975) tested onset and duration of anesthesia after etomidate in mice, rats, guinea pigs, and dogs.

New intravenous anesthetics were reviewed by Reilly and Nimmo (1987).

The anesthetic potency of remifentanil in dogs in terms of reduction of enflurane *MAC* was tested by Michelsen et al. (1996).

Dingwall et al. (1993) described the tolerometer as a fast, automated method for the measurement of righting reflex latency.

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EEG Threshold Test in Rats

Purpose and Rationale

The electroencephalographic (EEG) threshold test has been used to determine and compare the potency of several CNS depressant agents (Boiander et al. 1984; Koskela and Wahlstrom 1989; Norberg and Wahlstrom 1988; Norberg et al. 1987). Korkmaz and Wahlstrom (1997) described in detail the protocol of the EEG burst suppression threshold test for the determination of CNS sensitivity to intravenous anesthetics in rats.

Procedure

Adult Sprague–Dawley rats are housed at a reversed light/dark cycle and an ambient temperature of 23 ± 1 °C. Twenty-four hours prior to the EEG threshold test, the rats are placed in a tube restrainer. Twisted stainless steel wire and suitable surgical needles are used to sew the electrodes to the scalp above the frontal cortex. Since generalized changes in EEG recordings are used, this stainless steel material is adequate for recording purposes. Care is taken to prevent irritation of periosteal tissue. Since this procedure causes little discomfort, the use of local anesthetics and general anesthesia can be avoided.

For EEG threshold testing, the rat is placed on a warm cloth and held gently by the assistant. A needle is placed on one lateral tail vein and connected with an infusion pump. Crocodile clips are used to connect the electrodes to the EEG recorder, and a crocodile clip is attached to one of the ears of the rats as a signal ground.

The EEG recording is closely observed by the technician. The changes in the EEG induced by the anesthetic agent are used to measure drug effects on the CNS. The normal EEG in an awake rat has low amplitude and a frequency of approximately 30 cycles/s. During the first part of infusion, an increase in amplitude and a slight decrease in frequency are observed. At this stage of infusion, dependent on the anesthetic agent, jerks or sometimes convulsive episodes may occur. As the infusion continues, the frequency decreases, and burst suppression periods appear. The loss of righting reflex occurs at this stage. When burst suppression lasts 1 second, the threshold criterion which is called "silent second" is reached and the time is recorded. After the threshold determination, the rats are placed in the recovery room.

Evaluation

The threshold dose is calculated by multiplying the time required to reach the threshold criterion with the dose administration rate. Threshold doses are determined for each anesthetic at various dose administration rates indicating the optimal dose administration rate.

Modifications of the Method

Wauquier et al. (1988) studied relationships between quantitative EEG measures and pharmacodynamics of alfentanil in dogs. Before, during, and up to 3 h after infusion, the effects of three doses on six quantitative EEG measures (zero-crossing frequency, root mean square amplitude, spectral edge, relative delta, alpha, and beta power) were assessed.

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Efficacy and Safety of Intravenous Anesthetics

Purpose and Rationale

Besides determination of the ratio between anesthetic and lethal dose, intravenous anesthetics have to be tested for their influence on the cardiovascular and pulmonary system. Borkowski et al. (1990) described a method to compare intravenous anesthetics in rabbits.

Procedure

Adult New Zealand White rabbits with a mean weight of 4.5 kg are used. To provide access for direct blood pressure measurement and arterial blood samples, an 18-gauge catheter is implanted into the left carotid artery under halothane anesthesia. Following a minimum 24-h recovery period, the rabbit is placed in a sling and a pneumograph fitted around the rabbit's caudal thorax at the level of 10th to 12th ribs to monitor respiratory rate and pattern. From the arterial catheter blood is withdrawn for blood gas analysis. Then the catheter is connected to a blood pressure transducer. A 10-min acclimatization period is allowed before control measurements are recorded. Each rabbit serves as its own control in that cardiopulmonary parameters and responses to noxious stimuli are determined before anesthesia is induced. The right marginal ear vein is catheterized with a 22-gauge catheter, which is secured with adhesive tape, flushed with physiological sterile saline, and used for the administration of the anesthetic agents.

One-third of the dose of the anesthetic to be tested is injected manually over a 1-min period. When the rabbit is relaxed it is removed from the sling and placed in left lateral recumbence on a heating blanket. The degree of muscle tension and reaction to noxious stimuli are determined while the rabbit is in the sling and at 15 min intervals following anesthesia. The assessments performed include those of jaw tone, leg muscle tone, palpebral reflex, corneal reflex, ear pinch reflex, and pedal withdrawal reflex. Jaw tone is evaluated subjectively by pulling the lower jaw open by an index finger. Leg muscle tone is evaluated by flexion and extension of the right rear leg according to subjective scores. The corneal reflex is tested by placing a moistened cotton swab on the cornea. The palpebral reflex is tested by touching the medial canthus with a dry cotton swab. Assessment of the ear pinch reflex is performed by applying a compression force with an alligator clip. The pedal withdrawal reflex is determined by applying the same clip on the right rear fifth digit at the distal phalanx.

Cardiopulmonary parameters and rectal body temperature are determined while the rabbit is in the sling and also at 15 min intervals following induction of anesthesia with the rabbit in lateral recumbency. Heart rate, mean arterial blood pressure, respiratory rate, and respiratory pattern are calculated from tracings from the physiological recorder. Arterial blood pH, partial pressure of oxygen (PaO_2), and partial pressure of carbon dioxide ($PaCO_2$) are determined from arterial blood samples.

Evaluation

The heart rate, mean arterial blood pressure, respiratory rate, pH, PaO_2, and $PaCO_2$ are analyzed using a two-factor analysis on repeated measures. The control values are treated as covariate to allow standardization of the inherent variation between rabbits. The single *t*-test for paired differences is used to compare control values to data obtained during the later testing intervals. The standard error of the mean (SEM) is calculated for each variable at each time interval. Data for muscle tone and responses to noxious stimuli are calculated as frequency percentages. The Fisher's exact test is used to compare between treatments. For all of the statistical analyses, a p-value of less than 0.05 is considered significant.

Modifications of the Method

Details of anesthesia in the rabbit were also described by Murdock (1969).

Peeters et al. (1988) performed a comparative study of four methods for general anesthesia in rabbits.

Glenn (1980) examined the anesthetic activity of propofol (ICI 35868) in mice, rats, rabbits, cats, pigs, and monkeys including cardiovascular and respiratory parameters and EEG studies.

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Inhalation Anesthesia

General Considerations

Purpose and Rationale

The efficacy and safety of new inhalation anesthetics has to be evaluated in pharmacological experiments. Robbins (1946) defined the anesthetic AD_{50} as the concentration of anesthetic at which 50 % of mice failed to right themselves for 15 s when placed in a rotating bottle with a known concentration of anesthetic. The concentration of the anesthetic that caused apnea in 50 % of the mice in 10 min was defined as the LD_{50} and the ratio LD_{50}/AD_{50} as index of safety.

Wolfson et al. (1972) recommended brain anesthetic concentration for construction of anesthetic indices.

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Screening of Volatile Anesthetics

Purpose and Rationale

A simple technique for preliminary testing of anesthetic agents is the introduction of a measured amount of volatile liquid into a covered glass container of known volume. If the density and molecular weight of the liquid are known, the volume % concentration of the anesthetic mixture can be calculated (assuming 1 mol of vapor = 22.4 l). Mice or rats are introduced into the chamber, and the quality of anesthesia is noted. Conditions are then adjusted until the anesthetic concentration has been established.

Procedure

Male NMRI mice weighing 20–25 g or male Wistar rats weighing 250–300 g are used. A wide-mouth, screw-cap glass jar of 3 l volume is flushed with oxygen for 1 min and a measured amount of the volatile substance placed on the bottom through a suitable syringe. The amount is calculated to give 1.25 vol.% concentration of vapor in the jar (or a logarithmic multiple of 1.25 %, i.e., 0.63, 2.5, 5.0, 10.0). The jar is closed and evaporation of the substance facilitated by gentle rotation of the jar. One rat or five mice are quickly placed from a beaker into the jar, and the jar is immediately closed. Every 15 s the jar is gently rotated and the time noted for each animal to become anesthetized (loss of righting reflexes). The procedure is repeated until all animals are anesthetized. Induction should occur not sooner than 30 s and not later than 5 min. The animals are allowed to remain in the anesthesia jar for 10 min, with testing of righting reflexes until they are quickly removed into room air. The time of recovery to righting or walking is recorded for each animal. Postanesthetic analgesia is tested by

gently pressing the base of the tail every min until recovery has occurred. Recovery time is defined as the time in min until the mouse spontaneously moves in upright position. If induction time is shorter than 30 s or longer than 10 min, the concentration of anesthetic is decreased or increased until the proper concentration is found.

Evaluation

The results are reported as mean induction time and mean recovery time. Twenty-four-hour survival rate is recorded for latent toxicity.

Modifications of the Method

Burns et al. (1961) used a simplified mouse test apparatus with a small container and an open-circuit technique.

Raventós (1956) used cats, dogs, and monkeys to evaluate the cardiovascular effects of fluothane.

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Determination of Minimal Alveolar Anesthetic Concentration (MAC)

Purpose and Rationale

The term "**minimum alveolar anesthetic concentration**" (**MAC**) was coined by Merkel and Eger (1963) as an index to compare various anesthetic agents.

The use of *MAC* which represents the partial anesthetic pressure in the brain has gained wide acceptance (Eger et al. 1965; Quasha et al. 1980).

For **man**, Saidman and Eger (1964) defined *MAC* as the point at which 50 % of the patients moved in response to a surgical incision.

A method for determining minimum alveolar concentration of anesthetic in the **rat** was published by Waizer et al. (1973). Kashimoto et al. (1997) determined the minimum alveolar concentration of sevoflurane in rats. Eger et al. (1999) studied maximum alveolar anesthetic concentration of fluorinated alkanols in rats and discussed the relevance to theories of narcosis. Eger et al. (2003) studied additive minimum alveolar concentration (MAC) effects of halothane and isofluroane in rats.

Issues in the design and interpretation of minimum alveolar anesthetic concentration (MAC) studies were discussed by Sonner (2002).

Procedure

Minimum alveolar anesthetic concentrations (MAC) are determined in Sprague Dawley rats weighing 300–450 g. Each rat is placed in an individual gas-tight plastic cylinder closed at both ends by rubber stoppers. The stoppers are pierced with holes for various purposes. A rectal temperature probe (temperature maintained between 36 °C and 38.5 °C) and the rat's tail are drawn separately through holes in the rubber stopper closing the distal end of the cylinder. Delivered gases at an average inflow rate of 1 L/min to each rat enter through ports at the head (proximal) end of the cylinder and exit at the tail (distal end), a flow to minimize rebreathing (inspired $CO_2 < 10$ mmHg). Exiting gases are scavenged.

The anesthetics are introduced from conventional vaporizers. For the determination of MAC, an initial concentration is used that permits movement of the rats in response to noxious stimulation. A tail clamp is applied for one minor until the animal moves, and the anesthetic partial pressure is measured by gas chromatography. If the animal moves, the partial pressure is increased by 0.2 % or 0.3 % atmospheres. After equilibration for

30 min, the tail clamp is applied again and the anesthetic partial pressure measured by gas chromatography. This procedure is repeated until the partial pressures bracketing movement-nonmovement are determined for each rat.

Evaluation

MAC is defined as the average of the partial pressures that just prevented movement in response to clamping of the tail. Differences between anesthetics are accepted at $P < 0.05$.

Modifications of the Method

Fang et al. (1997) found that maturation decreases ethanol minimum alveolar anesthetic concentration (*MAC*) more than desflurane *MAC* in **rats**.

Gong et al. (1998) assessed the effect of rat strain on susceptibility to anesthesia and convulsions produced by inhaled compounds.in five different rat strains. Strain minimally influenced anesthetic and convulsant requirements of inhaled compounds in rats.

Doquier et al. (2003) studied the minimum alveolar anesthetic concentration of volatile anesthetics in rats as tools to assess antinociception in animals.

Determination of the minimal alveolar concentration (*MAC*) of halothane in the New Zealand white **rabbit** was published by Davis et al. (1975).

Determination of an anesthetic index (Apnea/MAC) in experiments in **dogs** has been proposed by Regan and Eger (1967).

Murphy and Hug (1982)and Hall et al. (1987) used the reduction of enflurane *MAC* values in **dogs** as parameter for the anesthetic potency of fentanyl or sufentanyl, respectively.

Seifen et al. (1987) used *MAC* values for comparison of cardiac effects of enflurane, isoflurane, and halothane in the **dog heart-lung preparation**.

Ide et al. (1998) used airway occlusion in **cats** as a noxious respiratory stimulus that induces a visceral sensation of choking for determination of minimum alveolar anesthetic concentrations during halothane, isoflurane, and sevoflurane anesthesia. These values were compared with *MAC* values for somatic noxious stimuli such as toe pinch or tetanic stimulus. The authors recommended this method as a new concept for *MAC* determination.

Eger et al. (1988) determined minimum alveolar concentration of fluorinated anesthetics in **pigs**.

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Efficacy and Safety of Inhalation Anesthetics

Purpose and Rationale

To assess the safety margin of an inhalation anesthetic not only the ED_{50} values but also the maximally effective dose and the dose with a minimal danger of fatal outcome should be determined. In particular, *cardiovascular parameters* are observed (Kissin et al. 1983).

Procedure

Male Sprague Dawley rats weighing 300–350 g are placed into a clear chamber with the tail protruding from a special opening. An anesthetic-oxygen nonhumidified mixture is directed into the chamber at a rate of 4 l/min. The inhalation anesthetics, e.g., halothane or isoflurane, are vaporized in Draeger vaporizers, and the level in the chamber is monitored with a gas analyzer which is calibrated with a mass spectrometer. Rectal temperature is monitored and maintained at 37 °C with a heating pad. Each rat is exposed to only one predetermined concentration of anesthetic for 30 min, at which time the presence or absence of the end point of anesthesia is determined. For the lethal end point, rats are tracheotomized and ventilated at 60 strokes/min through an endotracheal catheter. Tidal volume is adjusted to maintain $PaCO_2$ at 40 ± 5 mmHg.

As end points of anesthesia are used

- Loss of righting reflex. The test is regarded as positive if the animal fails to right itself with all four feet on the floor within 15 s after being placed in a side position.
- Prevention of purposeful movement response to a noxious stimulus. The animals are stimulated for 60 s by placement of a 1-kg weight on the middle of the tail. Only the purposeful movement of the head or legs is considered to be a response.
- Prevention of the heart rate increase to a noxious stimulus (ECG signals). An increase in heart rate of greater than 1 % is regarded as a positive response.
- The end point for the lethal effect is 7 mmHg in the femoral artery with artificial respiration.

With each of the anesthetics, four series of experiments are performed: determining the righting reflex, purposeful movement response, heart rate response, and lethal effect. The concentrations of the test compounds and the standard are spaced equally between the abovementioned doses.

After determination of the heart rate effect and the lethal effect, the rats are sacrificed for

determinations of brain tissue concentrations. The whole brain is removed and tissue anesthetic concentration determined by gas chromatography.

Evaluation

For calculation of the dose-effect curves, the probit method of statistical analysis is used.

For the assessment of anesthetic safety, not only the therapeutic ratio (LD_{50}/ED_{50}) but also the standard safety margin

$$SSM = (LD_5 - ED_{95})/ED_{95} \times 100$$

is used. This represents the percentage by which the ED_{95} has to be increased before LD_5 is reached.

Critical Assessment of the Method

The standard safety margin has definitive advantages over therapeutic ratio. In contrast to the LD_{50}/ED_{50} index, the standard safety margin is influenced not only by the distance between central points of the anesthetic and lethal dose-effect curves but also by the slope of these curves.

Modifications of the Method

A similar concept based on response to tail clamping, respiratory arrest, and cardiovascular failure in the **rat** was published as anesthetic index by Wolfson et al. (1973).

Another attempt to determine anesthetic requirements in rats was published by White et al. (1974).

Kissin et al. (1984) studied the morphine-halothane interaction in rats.

Fukuda et al. (1996) investigated the effects of sevoflurane and isoflurane on bupivacaine-induced arrhythmias and seizures in rats.

Kanaya et al. (1998) compared myocardial depression by sevoflurane, isofluorane, or halothane in **cultured neonatal rat ventricular myocytes**. Changes in beating rate and amplitude during exposure to the anesthetics were measured.

Chaves et al. (2003) used noninvasive electrocardiography in **mice** to study the effects of intravenous and inhalation anesthetics and of age.

Krantz et al. (1941, 1953) described an anesthetic index between surgical anesthesia (cornea and wink reflexes abolished) and respiratory failure in **dogs**.

Van Poznak and Artusio (1960a, b) determined the anesthetic properties of fluorinated compounds in dogs using a face mask for the induction of anesthesia and a cuffed endotracheal tube later on. ECG (lead II) and EEG were monitored.

Steffey and Howland (1978) determined the potency of enflurane in dogs in comparison with halothane and isoflurane.

Johnson et al. (1998) compared isoflurane with sevoflurane for anesthesia induction and recovery in adult dogs.

Salmempera et al. (1992) studied in dogs the potency of remifentanil, a short-acting opioid analgesic, which is used as anesthetic adjunct by variable-rate infusion. Enfluorane minimal alveolar concentration was measured by the tail-clamp method in dogs before and after sequential infusion of various doses of remifentanil. The plasma concentration causing a 50 % reduction of enfluorane minimal alveolar concentration was determined.

Kataoka et al. (1994) studied the negative inotropic effects of sevoflurane, isoflurane, enflurane, and halothane in canine blood-perfused papillary muscles.

Hirano et al. (1995) compared the coronary hemodynamics during isoflurane and sevoflurane anesthesia in dogs.

Mutoh et al. (1997) compared the cardiopulmonary effects of sevoflurane with those of halothane, enflurane, and isoflurane, in dogs.

Hashimoto et al. (1994) examined the effects of sevoflurane and halothane on the effective refractory period and ventricular activation in a canine myocardial infarction model.

The effects of desflurane, sevoflurane, and halothane on postinfarction spontaneous dysrhythmias in dogs were examined by Novalija et al. (1998).

Cardiopulmonary effects in **cats** were studied for desflurane by McMurphy and Hodgson (1996) and for sevoflurane by Hisaka et al. (1997).

Saeki et al. (1996) determined the effects of sevoflurane, enflurane, and isoflurane on baroreceptor-sympathetic reflex in **rabbits**.

Hanagata et al. (1995) found that isoflurane and sevoflurane produce a dose-dependent reduction in the shivering threshold in rabbits.

Antognini and Eisele (1993) determined anesthetic potency and cardiopulmonary effects of enfluorane, halothane, and isofluorane in **goats**.

The effects of multiple administrations of sevoflurane to cynomolgus **monkeys** were evaluated by Soma et al. (1995).

The effect of inhalation anesthetics on the **respiratory system** was investigated in several studies:

Mazzeo et al. (1996) compared the relaxing effects of desflurane and halothane at various MACs on isolated proximal and distal airways of dogs precontracted with acetylcholine.

Hashimoto et al. (1996) compared the bronchodilating effect of sevoflurane, enflurane, and halothane in dogs using a superfine fiberoptic bronchoscope. The dogs were anesthetized with pentobarbital, paralyzed with pancuronium, and the lungs were mechanically ventilated. The endotracheal tube had an additional lumen to insert the superfine fiberoptic bronchoscope (outer diameter 2.2 mm) which was located between a second and third bronchial bifurcation to continuously monitor the bronchial cross-sectional area of third- or fourth-generation bronchi. Bronchoconstriction was produced by histamine injection and infusion. The bronchial cross-sectional area was printed out by a video printer at the end of expiration and was calculated on a computer using an image program after various *MAC*s of the different inhalation anesthetics.

Mitsuhata et al. (1994) induced systemic anaphylaxis in dogs sensitized to Ascaris suum by intravenous injection of the antigen and measured pulmonary resistance and dynamic pulmonary compliance. Sevoflurane was as effective as isoflurane in attenuating bronchoconstriction associated with anaphylaxis in dogs.

Cervin and Lindberg (1998) examined the short-term effects of halothane, isoflurane, and desflurane on mucociliary activity in the rabbit maxillary sinus in vivo.

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