Dose response relationships in clinical pharmacology
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THE DOSE RESPONSE RELATIONSHIP IN ANESTHESIOLOGY

WALTER S NIMMO

Department of Anaesthesia, University of Sheffield, Sheffield S10 2RX, (UK).

INTRODUCTION

Anaesthesia is a state of drug induced unconsciousness in which a patient neither perceives nor recalls a noxious stimulus such as a surgical incision[1]. It is a threshold event and therefore there cannot be degrees or depths of anaesthesia. Thus, the most obvious and reliably measured effect of an anaesthetic drug is a lack of movement in a cohort of patients or in animals exposed to noxious stimuli but other responses have been measured in attempts to relate drug concentration with effect (Table 1).

TABLE 1

Measured responses to anaesthetic drugs

Immobility to noxious stimuli
Autonomic signs
Oesophageal contractions
Electroencephalogram
Surface electromyogram
Recovery tests
Metabolic response

IMMOBILITY TO NOXIOUS STIMULI

The motor response to somatic noxious stimulation is seen as a reflex withdrawal of the stimulated part or movement of the body in general. Suppression of this reflex by a certain dose of a drug is used as one of the main indicators of anaesthetic potency for inhaled anaesthetic drugs[2].

Minimum alveolar concentration (MAC)

MAC is the minimum alveolar concentration of anaesthetic at 1 atmosphere that produces immobility in 50% of patients or animals exposed to a noxious stimulus. It is assumed that the alveolar

partial pressure is transmitted without change to the arterial blood and that, given time for equilibration, the partial pressure of gas at the site of drug action equals that of arterial blood. Under normal circumstances, these are reasonable assumptions. Neither the inspired gas concentration nor the drug concentration in blood bears such a constant relationship to the concentration or partial pressure at the anaesthetic site of action. Examples of MAC values in man are given in Table 2.

TABLE 2

MAC values in man[2] (%)

halothane	0.75
enflurane	1.68
isoflurane	1.15
ether	1.92
cyclopropane	9.2
nitrous oxide	105

One of the most surprising properties of MAC is its constancy within and between different species (Table 3)

TABLE 3

MAC values for halothane in different species[2] (%)

man	dog	cat	rat	goldfish	toad
0.75	0.87	0.82	0.95	0.76	0.67

The value of MAC is not dependent on the intensity of stimulus, duration of drug administration, sex, acid-base status, carbon dioxide or oxygen tensions in arterial blood (within certain limitations). Values are altered by circadian rhythms, body temperature, diseases such as thyrotoxicosis and other drugs. Age has a marked effect and halothane MAC falls from 1.1% in the neonate to 0.63% in the 70 year old

Minimum infusion rate

For intravenous anaesthetic drugs the concept of minimum infusion rate (MIR) was proposed as an attempt to compare potencies[3]. This is the infusion rate that will prevent movement in response to surgical incision in 50% of patients. However, the

relationship between infusion rate and plasma concentrations is governed by many factors even after the 25 minute period that is allowed in the calculation of MIR. There is not always a linear relationship between infusion rate and blood concentrations using this method. The MIR for methohexitone after a loading dose of 1.5 mg/kg is described as 50 mcg/kg/min in patients premedicated with morphine 0.15mg/kg and receiving nitrous oxide 67%.

Dose or concentration response relationships

Simple dose response studies of intravenous anaesthetic drugs have revealed useful information. The normal dose of thiopentone given to abolish the eyelash reflex and prevent movement in response to surgery in young adults is 3-5 mg/kg [4]. In 23 of 24 geriatric patients studied, 1.8-2.5 mg/kg resulted in loss of the reflex[5]. This alteration of dose-response in the elderly was confirmed and shown to be caused by an alteration in the initial distribution of thiopentone[6]. Similar effects were demonstrated for propofol[7]. In children aged 5 to 15 years, 5 mg/kg of thiopentone abolished the eyelid reflex in 90% but lack of response to surgical stimuli was achieved in only 70% of children given 6mg/kg. Thus children required a larger dose for a given response and the exact reason for this increased dose requirement is unknown.

When anaesthesia was induced with thiopentone 2-4 mg/kg and maintained by repeated small injections or infusion, a mean plasma concentration of 42.2 mcg/ml was associated with lack of response to surgery[8] (free drug concentration 6.3 mcg/ml). Premedication with hydroxyzine or pethidine reduced requirements by 50% while nitrous oxide 67% by inhalation reduced thiopentone anaesthetic concentrations by 67-71%. Others have found that 55% of patients who breathed 60 % nitrous oxide and had a serum thiopentone concentration of 37.4 mcg/ml moved at the time of skin incision[9].

In children who received rectal methohexitone, sleep, (defined as loss of consciousness and unresponsiveness to vocal stimuli) occurred in all patients with plasma concentrations greater than 2 mcg/ml[10]. Others have shown that loss of corneal reflex occurs when methohexitone concentrations are 5-6 mcg/ml[11].

Propofol blood concentrations of 3-5 mcg/ml are associated with lack of response to surgical stimuli[12]. Ausems and others analysed alfentanil plasma concentration data from 37 patients in the presence of 66% nitrous oxide. They calculated dose response curves for different surgical stimuli. Response was defined as movement or a rise in arterial pressure or pulse rate or an increase in sweating[13]. Plasma concentrations associated with a 50% probability of no response are shown in table 4.

TABLE 4

Plasma alfentanil concentrations resulting in a 50% probability of no response[13]

Event	mean conc (ng/ml)	95% confidence limits (ng/ml)
intubation	475	418-532
skin incision	279	238-320
skin closure	150	103-196
ventilation	223	197-249

In studies of MAC and MIR, it was noted that patients who moved in response to a surgical stimulus did not recall any of the surgery or anaesthesia. Thus it appears that the blood concentration necessary to suppress the somatic motor response is higher than that required to induce amnesia and perhaps unconsciousness.

In patients who are paralysed to facilitate surgery, lack of movement in response to a stimulus is not a good indicator of anaesthesia. Tunstall[14] used a sphygmomanometer cuff to isolate one forearm from the effects of neuromuscular blocking drugs administered to the other arm. He showed that all patients moved the arm at the time of skin incision, patients breathing only low concentrations of nitrous oxide responded to verbal command but no patient had postoperative recall. In paralysed patients, other signs of anaesthesia must be observed.

AUTONOMIC SIGNS

Noxious stimuli can produce reflex activation of the autonomic nervous system and observation of pulse rate, arterial pressure, sweating or tears have been the mainstay of the clinical assessment of adequacy of anaesthesia for many years since the

use of neuromuscular blocking drugs became common. In 1981, the concept or MAC-BAR was described[15]. This is the alveolar concentration of an inhaled anaesthetic which will suppress haemodynamic and adrenergic response in 50% of patients. The ratio of MAC-BAR to MAC is 1.45 for halothane and 1.6 for enflurane.

However, in general, autonomic signs bear no relationship to conscious awareness or semi-purposeful movements seen with the isolated arm technique. No constant or close relationship between autonomic signs and cortical activity has been demonstrated and autonomic signs may be modified by drugs independently of the anaesthetic effect.

In a study in which diazepam or midazolam was given intravenously to volunteers, there was a correlation between the plasma drug concentrations and arterial pressure reduction and arterial carbon dioxide tension (P_{CO2}) increase[16]. A maximum increase in P_{CO2} and decrease in arterial pressure was detected after sedative doses of both drugs. The influence on respiration and arterial pressure occurred at lower concentrations than sedation. The threshold concentration for impairment of reaction time by midazolam is 30 - 100 ng/ml. On average, mean arterial pressure started to fall at plasma concentrations of 25 ng/ml with a maximum fall of 17 mm Hg occurring at concentrations of 100 ng/ml. Arterial carbon dioxide tension began to rise at 25 ng/ml with a peak rise of 0.8 kPa (6 mm Hg) at concentrations greater than 150 ng/ml[16].

OESOPHAGEAL CONTRACTIONS

It has been proposed that lower oesophageal contractions (LOC), both spontaneous and induced by transient oesophageal distension, may be a useful guide to graded effects of anaesthetic drugs[17]. Normally, contractions occur several times each minute and last up to 5 seconds. During inhalation anaesthesia, when the inspired concentration of anaesthetic drug is increased, the rate and amplitude of contractions are decreased. In a study of 46 patients undergoing halothane anaesthesia, two x MAC halothane abolished contractions[17]. In addition,there was a correlation between LOC, clinical signs of anaesthesia (judged by changes of arterial pressure, heart rate, sweating and tears) and dose of

halothane. Some relationship has been demonstrated for propofol infusion[18] but changes on LOC did not occur in every patient and many changes were minor. No particular frequency or amplitude of LOC signified a particular level of awareness and this obseervation may be little different from the traditional autonomic signs of anaesthesia[19].

ELECTROENCEPHALOGRAM.

There have been various attempts to quantitate the effect of anaesthetic drugs using the electroencephalogram (EEG)[19] (Table 5).

TABLE 5

Electrophysiological measurement of effect of anaesthetic drugs

* EEG analysis
zero crossing
fourier transform
compressed spectral array (CSA)
aperiodic analysis
spectral edge frequency (SEF)
median frequency
cerebral function analysing monitor
* Evoked responses
auditory evoked potentials
somatosensory evoked potentials
visual evoked potentials

General anaesthetic drugs have profound effects on the EEG and produce a dose-related slowing of the dominant EEG frequency. For example, thiopentone produces characteristic changes. During the early period of anaesthesia when loss of consciousness occurs, there is an increase in frequency and a slight increase in amplitude. Later there is marked slowing of the frequency and during surgical anaesthesia (lack of response to surgical stimuli), there are bursts of electrical activity interspersed with relatively isoelectric periods[20]. However, equipotent anaesthetic concentrations produce very different EEG frequencies (Table 6)

TABLE 6

EEG frequencies produced by different anaesthetic drugs at equipotent concentrations

Anaesthetic drug	EEG frequency when no response to surgery (Hz)
halothane	6
enflurane	7-12
isoflurane	4-8
thiopentone	1-3

Spectral edge frequency (SEF)

This analysis is an attempt to circumvent the problem of different EEG frequencies at similar anaesthetic concentrations. The SEF is the frequency below which 95% of the EEG power is present; in awake man it is 25-30 Hz. It falls rapidly in response to increases in concentrations of enflurane, halothane or thiopentone. Enflurane anaesthesia reduces the SEF by 20 Hz/MAC while halothane decreases it by 8 Hz/MAC[19]. Thiopentone administration shifts the SEF down to 4 to 8 Hz. There is a classic sigmoid relationship between the venous serum concentrations and the SEF[21]. A value for IC_{50} (the serum concentration needed to cause one half of the maximal slowing) can be calculated. From these data it is possible to determine brain responsiveness to thiopentone and to demonstrate that repeat administration, a history of alcohol intake or old age have no effect on brain sensitivity. In addition, if the SEF is reduced below 15 Hz during induction of anaesthesia, there is unlikely to be a marked rise in arterial pressure in response to laryngoscopy and tracheal intubation[22].

Although the change in SEF mirrors increasing anaesthetic concentrations during induction of anaesthesia, there is a considerable lag in recovery of SEF when anaesthetic concentrations are falling.

Median frequency (MF)

The median frequency of the EEG power spectrum may be a better index of anaesthetic drug activity[23]. It is 9 Hz in fully conscious subjects and must fall to below 5 Hz for subjects to become unresponsive to verbal commands. It shows dose related changes with anaesthetic drugs and, compared with SEF, there is

less lag during recovery. However there is still some lag and MF is not ideal to monitor anaesthesia itself.

Etomidate, like thiopentone, produces slowing of the EEG but it maintains a degree of high frequency (beta) activity. Therefore, MF has been used as a measure of drug effect instead of SEF. In 3 infusions in 6 volunteers, MF changed with clinical effects and drug plasma concentrations (Table 7)[24]. Autonomic changes were minimal at all concentrations. The IC_{50} for etomidate was 0.32 mcg/ml. In studies in the elderly, this was not changed although dosage requirements were reduced because of altered initial distribution of etomidate[25].

TABLE 7

Median frequency and etomidate concentrations during infusion of etomidate to 6 volunteers[24]

clinical state	etomidate concentration (mcg/ml)	median frequency (Hz)
falling asleep	0.21	4.7
no response	0.31	2.9
loss of eyelid reflex	0.46	2.3
loss of corneal reflex	0.65	1.9

The effect of propofol on MF has been studied and the relative hypnotic potency has been determined. Based on IC_{50} values, the relative potencies of thiopentone, propofol and etomidate are 1:6.7:50. The ratios of the doses recommended to induce anaesthesia are 1:2:15.

Evoked responses in the EEG

Auditory evoked potentials. A series of clicks at 70 db above hearing threshold are presented at a rate of 6 Hz through headphones. The EEG over the 80msec period following the stimulus is monitored and the 'response' is obtained by averaging 2048 consecutive click stimuli. Thiopentone, methohexitone, enflurane, halothane and isoflurane produce dose related changes in the latency of brain stem waves III and IV without any change in amplitude. No effect is seen with nitrous oxide, etomidate, propofol or fentanyl. Thus the brain stem latencies cannot be used to demonstrate the effects of all anaesthetic drugs in man.

Early cortical (middle latency) responses are more promising. Halothane, enflurane, isoflurane, etomidate and propofol all produce dose related changes in the amplitude of the early cortical waves. Using propofol infusion and nitrous oxide 67% by inhalation to maintain anaesthesia, the amplitude and latency of the early cortical waves correlated significantly with blood propofol concentrations[19].

Somatosensory (SEP) and Visual (VEP) evoked potentials Studies of the effects of anaesthetic drugs on SEP and VEP also show a predominant effect on cortical activity which is dose related.

SURFACE ELECTROMYOGRAM (EMG)

The EMG obtained from the frontalis muscle demonstrates a reduction in tonic activity with loss of consciousness and an increase in activity when the subject awakens. The signal increases during some forms of surgical stimulation. Information is limited on the relationship to drug dose or concentration.

RECOVERY TESTS

A variety of observations have been made to assess recovery from anaesthesia and to relate this effect with drug concentrations (Table 8). These include simple observations of eye opening memory for date of birth as well as more complex psychometric testing.

Simple observations of spontaneous eyeopening after anaesthesia have identified that adults awaken from ketamine anaesthesia at plasma concentrations of 650 ng/ml[25] while children awaken at concentrations which are, on average, twice as great[26]. This may be related to higher concentrations of the metabolite norketamine in children. Norketamine is known to be less potent than the parent drug.

TABLE 8

Tests of recovery from anaesthesia

spontaneous eyeopening
recall of date of birth or perioperative events
critical flicker fusion
post box
letter deletion
picture recall/recognition
peg board
simple or choice reaction time
simulated driving
attention tasks
Maddox Wing

In a study of 50 patients undergoing surgery with general anaesthesia produced by pethidine premedication, nitrous oxide 67% by inhalation and propofol infusion, various psychometric tests were carried out for 150 minutes after the end of anaesthesia and results were related to blood propofol concentrations[27]. The blood propofol concentration at which patients awoke was of the order of 1 mcg/ml. The majority of patients returned to their preoperative values for psychometric testing within 60 minutes of surgery. At blood concentrations at which the Treiger dot joining test and a letter deletion test were normal, 50% of the patients tested still rated themselves on a visual analogue sedation scale as partially sedated.

METABOLIC RESPONSE

Metabolic responses to the injury of surgery can be measured well into the postoperative period. They are not suppressed by anaesthesia produced by halothane, isoflurane or enflurane but are suppressed partially by very high doses of opioids and by regional anaesthesia. They are suppressed only partially by beta-adrenoreceptor blockade[1].

NEUROMUSCULAR BLOCKADE

Measurement of the degree of myoneural blockade is straightforward using a peripheral nerve stimulator and electromyography, accelerography or measuring force of contraction of a muscle. Single twitch, train of four (2Hz) or

tetanic stimulation make it possible to detect degree and duration of paralysis after administration of competitive neuromuscular blocking drugs. Because the measurement of the pharmacodynamic properties is so precise, there is little to be gained from extensive investigation of the pharmacokinetics of these drugs.

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Discussion - The dose response relationship in anaesthesiology

L. Lemberger

In the case of intravenous barbiturates, are the plasma concentrations at which the eyelash reflex is lost quite similar to those observed when the reflex returns?

W.S. Nimmo

In some instances, as in the study with methohexitone, the blood concentrations at on-set of effect are remarkably similar to those at off-set, but that is not always the case.

P. Simon

Are there studies showing shift of dose-response curves for general anaesthetics induced by pretreatment with benzodiazepines?

W.S. Nimmo

There is not a single study that shows the effects of benzodiazepine or opiate premedication on these relationships, but if one takes several studies together, one gets the impression that such shift exists.

L. Lasagna

Does the shape of the MAC curve have no relevance to the clinical use of the drug? I mean, is this 50% point all you need to know as you move into the clinic?

W.S. Nimmo

The shapes all seem to be remarkably similar. All these drugs exhibit very steep dose-response curves and the slope may change a little bit, but not markedly. Basically the shape doesn't seem to have made much difference to the use of these drugs. It's the position, the relative potency that influences how we use the drugs. Other properties of the drug are most important, eg. the volatility of the drug and how quickly it is taken up. It will change the rate of on-set of effect and the rate at which one reaches steady state.

J. Bigorra

Since all the anaesthetics have a high liposolubility, could the MAC be altered by obesity or other pathological conditions?

W.S. Nimmo

No, the MAC is influenced by age, (it falls throughout life) but it doesn't seem to be influenced by obesity. The rate of the uptake of the drug will be influenced by obesity. MAC is a percentage of the drug in the alveolar gas, so the relationship between the effect and that concentration is not influenced by obesity.

R.L. Galeazzi

Anaesthesiology is a good field to do dose-response curves as you have demonstrated. You have shown that age and interaction with other drugs influence dose-response curves. Are there studies about diseases, for instance heart failure, influencing these dose-response curves?

W.S. Nimmo

Yes, and one of the best examples is provided by alcoholism, where higher doses are required. Interestingly we cannot detect changes in the concentration-response in alcoholics. I know of no studies in cardiac failure as such, but after cardiac surgery the changes all seem to be pharmacokinetic and not pharmacodynamic. You can explain all changes on the basis of changes in the distribution of the drugs.

P.L. Morselli

Does emphysema modify the dose-response curve of an inhalatory anaesthetic?

W.S. Nimmo

No. It changes the pharmacokinetics of inhaled drugs, but to the best of my knowledge there is no alteration in the concentration response relationship.

L.F. Prescott

The relationship of clinical anaesthesia to the MAC looks very

nice and tidy and well defined, and as you said, constant over species and under different circumstances. What about the relationships at the deeper end of anaesthesia? If one gets to the point of suppression of respiration, for example, how does that compare with different agents and different circumstances in relation to the MAC?

W.S. Nimmo

They are relatively different because the drugs have different therapeutic indices. Some are more respiratory depressant than others, while some are more cardiovascular depressant than others. Safety varies from one agent to another and that is a property of the drug which is important in the selection of a drug. Relatively dangerous drugs are all right during anaesthesia because they are always given by an anaesthetist and not usually used in overdosage. So the problems of overdosage are not as marked during use of an anaesthetic drug than they are for other drugs.