THE EFFECTS OF SUBANAESTHETIC DOSES OF ISOFLURANE AND ENFLURANE ON THE AUDITORY EVOKED RESPONSE AND TWO TESTS OF PSYCHOMETRIC PERFORMANCE.

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SUMMARY

We investigated the effects of subanaesthetic doses of isoflurane and enflurane on the auditory evoked response. and two tests of psychomotor performance, the choice reaction time and tracking task. The use of subanaesthetic doses of isoflurane has been used for dental sedation.

Thirty fasting volunteers (mean age 24y) had scalp electrodes placed at vertex and both mastoids. Fifteen were randomly allocated to receive doses of isoflurane of inspired concentrations (0, 0.31, 0.5, 0.75%), placebo or enflurane (0, 0.17, 0.42, 0.6%) and 15 received isoflurane (0, 0.2, 0.31, 0.4%) or placebo. At each step change in volatile agent concentration 20min were allowed for equilibration. The reclining volunteers received the gases through a Hudson mask connected to a Bain circuit (flow > $10lmin^{-1}$), delivering 30% oxygen in air. Basic physiological variables, heart rate, arterial pressure, axillary temperature, and oxygen saturation were monitored throughout each 2.5h experiment. End-tidal concentrations of carbon dioxide could not be practically measured in these conscious volunteers. Control baseline brainstem, and long latency recordings were made before introducing the volatile agents or placebo. A probability of $p \leq 0.05$ was considered significant.

The basic physiological variables remained within normal ranges throughout each experiment. The brainstem auditory

evoked responses (BSAER) latencies and amplitudes did not change significantly for either drug compared with the placebo, except for the wave V latency which increased significantly at 0.5% isoflurane and 0.42% enflurane.

The N100 latency of the long-latency auditory evoked responses (LLAER) increased significantly from the placebo at 0.3, 0.4, 0.5% isoflurane and enflurane 0.42%. The N100 amplitude differed significantly from the placebo at 0.2, 0.3, 0.5% isoflurane and 0.6% enflurane. The N100 latency seems to produce a graded response to isoflurane which might be useful in automatic control of anaesthesia, providing the waveforms can be reliably identified automatically.

The two tests of psychometric function were affected by the drugs. Mean reaction times and tracking times increased. The variability of the above two measures increased as measured by the coefficients of variation.

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CHAPTER ONE

INTRODUCTION AND HYPOTHESIS

HYPOTHESIS

The hypothesis to be tested:-

Subanaesthetic doses of isoflurane and enflurane alter two tests of psychometric function, and the components of the auditory evoked response.

INTRODUCTION

The visit to the dentist is a disturbing event for most people. Unfortunately there are some who will not tolerate local anaesthesia and require some form of sedation. Local anaesthesia is safe and reliable, but the present forms of sedation i.e. iv benzodiazepines, midazolam and diazepam, are prone to problems. A slow onset makes dosing often difficult to judge and is time-consuming. Patients may be left with a hangover effect which may make them drowsy until the next day. This, as with day case surgery, may have implications on the ability of the patient to drive and work etc.

The use of inhalation agents for dental sedation has many attractions. The patient does not require an iv injection, and the anaesthetist is able to use a technique which is easy to control and safe. If the patient becomes too drowsy, the dose can be easily reduced. As there is rapid excretion of the agent from the lungs there is likely to be rapid recovery.

The traditional inhalation agent for dental sedation is nitrous oxide in subanaesthetic concentrations. Although a useful agent, more recently its toxic effects on vitamin B metabolism in patients, associated with its prolonged use and also on staff using it on a regular basis, have lead to

its poor acceptability in this field. Staff have been shown to have bone marrow changes and neurotoxicity associated with the use of nitrous oxide regularly in the surgery where room ventilation and scavenging methods are poor. In some individuals it is often difficult to achieve adequate sedation, and is therefore not the perfect agent.

McLeod and colleagues used isoflurane for analgesia in labour. They reported that subanaesthetic concentrations of isoflurane produce potent analgesia, [McLeod, Ramayya, Tunstall 1985]. They were followed by Parbrook and co-authors who assessed the efficacy of subananesthetic concentrations of isoflurane for inhalational sedation in 38 anxious patients undergoing oral surgery,[Parbrook, James, Braid 1987]. They concluded that isoflurane produced satisfactory sedation similar to that produced by nitrous-oxide. Concentrations of 0.15%, 0.25% and 0.35% were used. After, the induction the inspired concentration was increased or decreased by concentrations of 0.05%, according to the patient's responses to treatment.

McMenemin and colleagues (Table 2) compared the use of subanaesthetic doses of isoflurane 0.4% with 25% nitrous oxide, [McMenemin, Parbrook 1988]. They assessed performance using a choice reaction time, visual analogue score, tapping speed and some mathematical problems. The 0.4% isoflurane gave consistently greater effects than those from the 25% nitrous oxide. They also noted that the degree of sedation

with 0.4% isoflurane was greater than that needed for most clinical procedures. Once administration of the agent had been stopped the objective tests showed no impairment of function, but the subjective tests demonstrated impairment during the recovery period for up to 15 minutes. They concluded that isoflurane was an acceptable agent for dental sedation in doses less than 0.4%, with the dose being reduced towards the end of the procedure to avoid excess sedation and prolonged recovery.

One of the problems of this method of sedation in clinical practice is that the patient response is variable. Factors which cause this are

a) a patient is required to breath through his nose using a nasal mask, causing dilution of the inspired mixture

b) anxiety may make a patient less susceptible to the effects of sedation; premedication is not available to this group of individuals.

c) patient variability is wide - some become sleepy, others communicative, while some show no obvious effects.

The objective of this project was to produce dose response curves for the effects of enflurane and isoflurane at low doses and the subsequent recovery characteristics of this method of sedation and to assess the concentration of isoflurane at which consciousness is lost in the absence of

painful stimulation. The dose response data for these two agents is known at higher anaesthetic concentrations. The effects of the agents can be divided into separate areas

1. The effects on behaviour, impairment of function and performance.
2. The neurophysiological effects on the brain i.e. delay in neuronal conduction.
3. The effects on the respiratory, cardiovascular systems etc.

To assess the characteristics in 1), two tests of psychomotor function were used, a choice reaction time and tracking task. These were specially implemented for use on a computer by Dr W. Gray. The choice reaction time is commonly used in studies of recovery from anaesthesia. But the tracking task has been used more extensively in pharmacological studies and the selection of aircraft pilots than the assessment of recovery from anaesthesia.

To indicate the neurophysiological effects of the drugs on the brain we used the auditory evoked response.

Auditory Evoked Responses are being evaluated for use in the assessment of awareness. If these waveforms are to be useful they need to show gradual changes at low concentrations of anaesthetic agents. Ideally the signal would be easily

produced, show similar changes with all general anaesthetic agents, be unaffected by muscle relaxants and show changes with brain injury [Jones 1987].

Other authors have assessed the effects of higher doses of isoflurane and enflurane on the AER. A clinical state evolves from consciousness through to adequate anaesthesia to relative overdose. Before consciousness is lost a window exists where the state of attention may vary in the transition from awake to asleep. Initially subjects are asleep but easily rousable, then a stage is reached where they fail to respond to commands. This is followed by the loss of the eyelash reflex and finally no response occurs to surgical stimulation. At some point the state of attention and arousal is lost. Few of these authors have assessed the effects on subanaesthetic doses of isoflurane and enflurane on the AER in sedated rather than anaesthetised patients, where no other drugs have been used.

We therefore attempted to use the AER - brainstem, middle latency cortical and long-latency cortical waveforms, at various concentrations of both agents.

The effects in 3), were measured to ensure safety to the volunteer i.e. heart rate, blood pressure, respiratory rate and oxygen saturation.

This thesis describes studies of thirty healthy volunteers,

sedated with subanaesthetic concentrations of isoflurane and enflurane, the AER being measured as an indicator of neurophysiological changes in the brain and two psychometric computer tests being measured to ascertain performance and impairment of function.

CHAPTER TWO

THE AUDITORY EVOKED RESPONSE

AUDITORY EVOKED RESPONSES

GENERAL BACKGROUND

With the introduction of neuromuscular blocking agents, the assessment of depth of anaesthesia has become difficult, as the clinical signs of spontaneous respiration and muscular movement are obscured. The anaesthetist has to rely on autonomic signs to assess depth of anaesthesia, which are often not reliable indicators. The standard electroencephalogram (EEG) has been used to assess the effect of anaesthetic drugs on the brain. Unfortunately it has been found that although anaesthetic drugs produce predictable changes, they do not produce them in the same sequence. This limits the usefulness of the standard electroencephalogram as a monitor of anaesthetic depth.One modification that may prove useful in the future is the use of sensory evoked potentials. These seem to have the advantage over the EEG of constant changes with different anaesthetic drugs.

The sensory evoked response can be defined as a computer averaged electrical response of the nervous system to sensory stimulation, [Spehlmann 1985]. When scalp electrodes are applied to the subject a background recording can be displayed. This shows microvolt potentials whose frequencies depend on the state of the subject but are unsynchronised in time. By applying a sensory stimulation

repeatedly, a response that is time locked to the stimulation occurs which can be averaged on a computer, the background EEG activity being cancelled in the averaging process. This enhances the features of the response component that is time-locked to the sensory stimulus.

Evoked Potentials (EPs) can be elicited by auditory, visual or somatosensory stimuli. They are recorded from electrodes over the scalp or placed on the surface of the body. A series of waves is produced which have associated latency and amplitude.

CLASSIFICATION

GENERAL CLASSIFICATION

1. Auditory Evoked Potentials (AEPs) are subdivided by latency into short-latency AEPs (brainstem BAER), middle or early cortical AEPs (MLAEPs) and long-latency or late cortical AEPS.
2. Visual evoked potentials (VEPs) are divided by stimulus characteristics into VEPs to checkerboard patterns, diffuse light, and other types of stimuli.
3. Somatosensory evoked potentials (SEPs) are subdivided by the location of the stimulation i.e. arm or leg nerve stimulation.

Classification according to generator site

Waveforms of the various evoked responses are sometimes classified by the generator producing the potential. For instance:-

1. Cortical EPs:

Cortical EPS are generated by primary sensory and higher cortical areas. They have latencies of over 10-20 msec and amplitudes of up to 10 microvolts.Although cortical VEPs and SEPs are derived with electrodes placed near the primary receiving areas in the occipital and parietal areas, respectively, cortical AEPs are recorded with electrodes not directly overlying the auditory cortex. In all three modalities, cortical EP peaks may be preceded by peaks generated by subcortical structures.

2. Subcortical EPs:

Subcortical EPs are generated by the chains of neurons in a sensory pathway to the cortical receiving area. These EPs have latencies of less than 10-20 msec. Because the brain stem and spinal cord are relatively far away from recording electrodes on the head and neck, potentials generated in the auditory and somatosensory afferent pathways are much attenuated by the intervening tissues and have amplitudes of usually less than 1μV at surface recording electrodes.

<u>Classification according to recording method</u>

As described above, cortical and subcortical EPs are recorded by near-field and far-field methods respectively:-

1. Near-field recordings:

Near-field recording methods are used to record cortical EPs. One electrode is placed close to the area under study, and the other electrode is placed over an electrically quieter area several centimetres away. A recording between

these electrodes yields responses of 1-10μV and requires collection of only about 100 responses for a clear definition of the cortical EP. Repetition rates of 1-2/sec are usually used for transient cortical EPs because these EPs have relatively long latencies and durations and may interact with each other at higher rates.

2. Far-field recordings:

Far-field recording methods are used mainly for recording of potentials produced in the brain stem and spinal cord, i.e. far away from surface electrodes. The electric field generated deep in the brain has a wide distribution at the surface so that the exact location of recording electrodes is not critical although they must be fairly far apart to pick up the small voltage differences on the surface. The amplitude of the potentials is much attenuated at the surface and usually measures less than 1 microvolt, requiring averages of 1,000 or more responses for a clearly defined EP. Because subcortical EPs have short latency and duration and are resistant to fast repetition, stimulus rates of 5-10/sec or more may be used.

Classification according to stimulus characteristic

Stimulus rate

1. Transient EPs:

Separate responses are elicited by stimuli spaced so far apart in time that each response is completed before the

beginning of the next one. This requires stimulus rates no faster than 1-2/sec for the relatively long-lasting VEPs and long-latency cortical AEPs and SEPs. Short-latency cortical AEPs and SEPs and subcortical EPs have much shorter duration and can be elicited as transient EPs at rates of 10/sec or more. Transient EPs are the most commonly used clinical EPs.

2. Steady-state EPs:

If repetitive stimuli are spaced so closely that each response interacts with the next one, the EP becomes a rhythmical wave which has peaks at the same frequency as the stimuli and may contain harmonic and subharmonic components at multiples of that frequency; at higher stimulus rates, EPs to individual stimuli can no longer be distinguished. Stimulus rates producing steady-state EPs vary with the EP type. The brief short-latency AEP can be driven to become a steady-state EP, or frequency following potential, at rates of about 250-1000/sec. The middle latency AEP can be driven into steady state at rates of about 40/sec.

3. EPS to unilateral and bilateral stimuli:

Auditory and somatosensory stimuli are usually applied to one side of the body at a time. Bilateral stimulation produces EPs that differ from the sum of the EPs to unilateral stimulation to an extent depending on the cortical and subcortical level of recording and on the anatomy of the sensory system under study.

THE GENERATORS OF EPs.

The features of an EP only very grossly suggest its origin. In general, peaks of relatively high amplitude and restricted distribution on the scalp are likely to be generated in the cortex under one of the recording electrodes. Peaks of low amplitude and wide distribution are more likely to be generated in subcortical structures, especially if they have short latency.

The location of EP generators may be studied by mapping the distribution of the peaks in simultaneous recordings from many scalp electrode positions. The magnitude of an EP deflection at a certain latency is plotted for each recording point on a head diagram; points of equal potential are connected to give a map of concentric isopotential lines, which outline the maximum of the scalp potential and its gradient.

The general principles of the production of EPs by elements of the nervous system have been the subject of many experimental studies that suggest some conclusions [Spehlmann 1985]:

1. "Cortical EPs are due to the spatial and temporal summation of excitatory and inhibitory postsynaptic potentials generated at nerve membranes in response to the input produced by the stimulus. The potential differences produced generate currents which penetrate to the cortical surface and the scalp and produce electric fields, being

modified by the properties of the intervening structures.

2. Subcortical EPs are probably a mixture of two components: Postsynaptic potentials generated in groups of neurons of subcortical relay nuclei, and action potentials of the connecting axonal tracts.

3. EPs recorded from sensory nerves are due to the depolarization wave propagated along the membrane of the nerve fibres when the axon fires. When passing under a stationary recording electrode on the skin, the wave produces a major surface-negative deflection that may be preceded and followed by minor positive deflections due to the approaching and disappearing wave. The compound action potential may include later deflections generated by fibre groups of lower conduction velocity, but these deflections are of low amplitude due to the greater temporal dispersion of slowly conducted impulses".

He stated that for all three kinds of EPs, the shape, size, and timing of an EP recorded from the scalp or skin depend on many factors:-

1. The spatial orientation and size of the generator potential in relation to the recording electrodes.
2. The distance between the generator and the electrodes.
3. The duration of the generator potential.
4. The electrical conductivity of the intervening tissues.

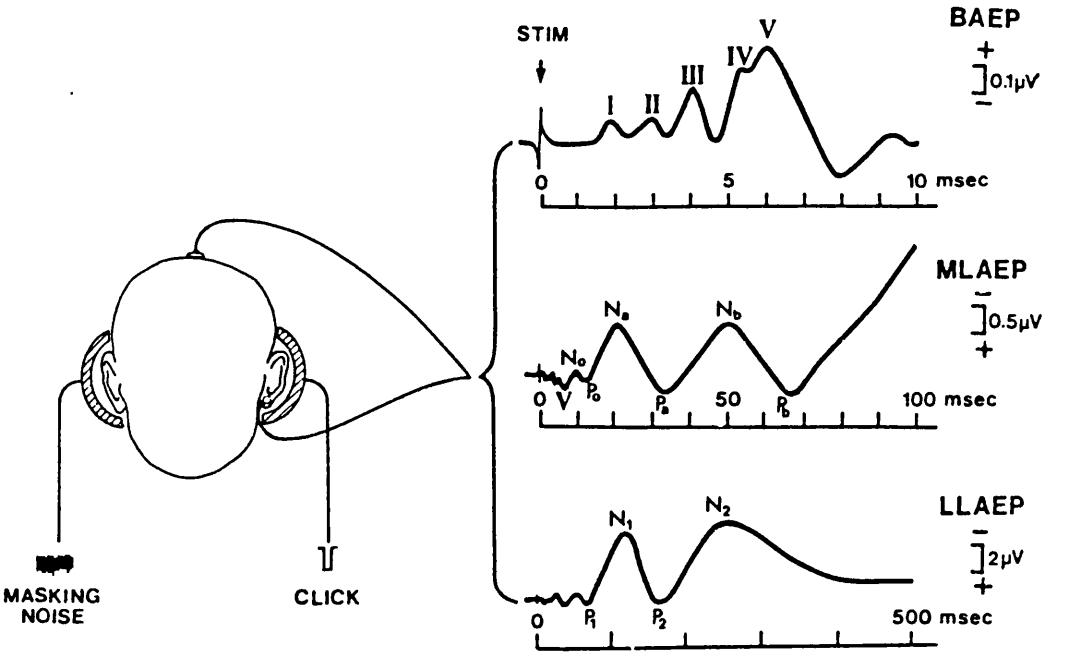


Figure 1 - Diagram of BAER, MLAER, and LLAER. Stimulation of one ear and recording between the ipsilateral earlobe and the vertex, different recording settings and gain settings used for each recording. Stimulation with rarefaction clicks at 60dB SL and continuous contralateral masking noise. MLAER and LLAER are displayed with a polarity opposite to that used for the BAER.

Reproduced from Spehlmann R, Evoked Potential Primer, Boston: Butterworths, 1985; Figure 11.1. 196.

AUDITORY EVOKED RESPONSES

Recordings between electrodes on the vertex and the earlobe or mastoid process yield AEPs of three latency and amplitude ranges.

1. The short-latency AEPs include peaks of up to 10 msec and 0.2 microvolts; they are generated in the brain stem.
2. The middle latency AEPs have several variable peaks with latencies of 10-50 msec and with amplitudes of about 1 microvolt; they probably reflect early cortical excitation.
3. The long-latency AEPs, beginning after 50msec and having peaks of 1-10 microvolts, represent later cortical excitation, [Figure 1].

In contrast to VEPs, AEPS are classified by recording methods, not by stimulus characteristics. Most AEPs are elicited with click stimuli.

DATA PROCESSING

Averaging

Averaging extracts the responses time-locked to a single stimulus from the background EEG and other electrical activity i.e. noise. The sensory stimuli are presented repeatedly, the responses collected and added to the preceding ones, the sum being divided by the number of responses. Averaging is carried out by a digital computer which records the electrical activity during the selected time interval , converts the voltage change of the analog recording into a series of numbers and adds the numbers from

each recording to the preceding recordings and averages them. Each period of analysis is called an epoch or sweep, which is divided into equal segments of time called points. The analysis dwells on each point for a dwell time or bin width, equivalent to a fraction of a second per point. This is equal to the reciprocal of the sampling rate (Sampling rate equals the number of points sampled each second).The analog to digital conversion allows the amplitude of the segment being recorded in each bin to be measured and converted into a binary number. This results in a series of binary numbers, which are added to the preceding ones and divided by the number of responses collected to give a running average.

Most averagers have 2,4, or 8 channels for recording. Multichannel recordings may be used to record EPs either simultaneously from different areas, or to study EPs to stimulation of either side of the body. Successive recordings allow the reproducibility of EPs to be examined successively.

Amplifiers

Electrical potential differences are recorded between the two electrodes which are connected to two inputs of an amplifier. A differential amplifier subtracts the voltage at one input from the voltage at the other, and amplifies this difference. Cerebral potentials usually have different voltages and timing at the two electrodes. The differential

amplifier discriminates between these and from the extracerebral potentials, or artifacts, which often have the same voltage and timing at the two electrodes and are therefore cancelled at the amplifier input.

Amplifiers used in Europe are wired to give a downward deflection at the output as a result of a relative positivity at input 1 and an upward deflection as a result of a relative positivity at input 2.

Simultaneous recordings of EPs in more than one channel are made by selecting different electrode pairs as inputs to each channel.

Differential amplification rejects only those artifacts that cause identical potential changes at both inputs; these are said to be in common mode. Artifacts greater at one electrode than the other are amplified like cerebral activity. Likewise, responses averaged in EPs are rejected if they have the same polarity etc at both inputs. The ability to reject common mode signals is expressed as the common mode rejection ratio. This is the ratio of the amplifier output produced by a signal applied differentially, i.e. between the two inputs, over the amplifier output produced by the same signal when it is applied in common mode, i.e. between both inputs tied together and the amplifier ground, [Spehlmann 1985]. The common mode rejection ratio of amplifiers used for EP recordings should be 10,000:1. Rejection of artifacts

depends on the following:-

a) discrimination at the inputs eg if mains power-line interference (50Hz) appears with similar amplitude at the inputs of a differential amplifier, it is rejected.

b) electrode impedance. If the electrode impedance becomes unequal, due to partial or complete loss of contact between one electrode and the scalp, or if a break in the continuity of the electrode occurs. Then the amplifier no longer operates differentially but increases signals between the remaining input and the ground electrode.

c) the ground electrode. If the ground is not connected to the volunteer, the amplifier inputs "float" without a reference to the potential level at the recording site, and the amplifier will use its own internal ground potential level to subtract signals at input 2 from those at input 1. Input potentials that are equal with respect to the subject's head and would normally be cancelled eg ECG interference may not now be rejected. Cerebral potentials are generally not distorted with floating inputs, but safety from electrical hazards is increased in the absence of a ground electrode. If only one input is connected to the subject then the resulting recording between the input and ground electrode may resemble a normal trace but is contaminated by artifacts.

Gain/Sensitivity - the increase of the voltage of a signal between the input and the output of an amplifier. Gain is

the ratio of signal voltage obtained at the amplifier output to the signal voltage applied at the input. Sensitivity is the ratio of input voltage to the size of the deflection it produces in the output.

Filters - exclude from the final recording those potential changes that have frequencies different from the frequencies represented in the response under study. They may reduce the number of responses required for a clear trace.

Filters may eliminate high or low frequencies outwith a middle range encompassing the frequencies of the EP under study. Analog filters reduce the amplitude of unwanted components before they are digitized, but may alter the time relationship between some of the desired signal components passing through the filter. This phase shift can be avoided by using digital filters. The middle range frequency between the low and high cutoff points, which is not affected by filter settings is called the bandpass or bandwidth.

The 50Hz notch filter reduces the signal amplitude in a very narrow band centering at 50Hz. The frequencies of the filtered band may be an important part of the EP, and the EP may be significantly distorted by the use of the filter, [Spehlmann 1985].

Digital filters are computer programmes that operate on the digitized responses before averaging or on the EP after

averaging. Smoothing is a simple form of a digital filter. Digital filters can eliminate components of low or high frequency with very sharp cut off and without phase shift.

Digital smoothing can reduce high frequency noise components superimposed on the EPs by replacing each point of a digital trace by a moving average of the 3, 5, or more neighbouring points. Smoothing does not distort the phase relationship between EP peaks, it may change the EP shape by reducing the amplitude of short waves more than that of long ones.

BRAINSTEM AUDITORY EVOKED RESPONSES

The brainstem auditory evoked response (BAER) recorded on the side of the stimulated ear contains five waves appearing in the first 10 msec after the stimulus and having peaks that are positive at the vertex with reference to the ear. These waves are usually labelled with Roman numerals I to V. The BAER recorded from the side opposite the stimulated ear shows no clearcut wave I; the negative peak preceding wave II is therefore sometimes used for measurements of interpeak latencies. Other peaks differ slightly but significantly on the two sides, [Figure 1].

Not all normal recordings contain all BAEP peaks. Wave V is present most often, waves I and III can usually also be identified. Wave II is often absent and wave IV may merge more or less completely with wave V. Wave V is sometimes followed by waves VI and VII. Peak and interpeak latencies of the BAEP waves are remarkably constant for a given set of subject, stimulus, and recording parameters. They vary little in repeated recordings in the same subject over many months; they vary only slightly more between recordings from the two sides of the same subject and between different subjects of the same age and sex. Latency is longer and more variable for condensation than for rarefaction clicks. Each laboratory must therefore establish its own normal values for these variables. Not all BAEP waves are present in every recording from a normal subject. A few practical manoeuvres are often helpful in enhancing and identifying

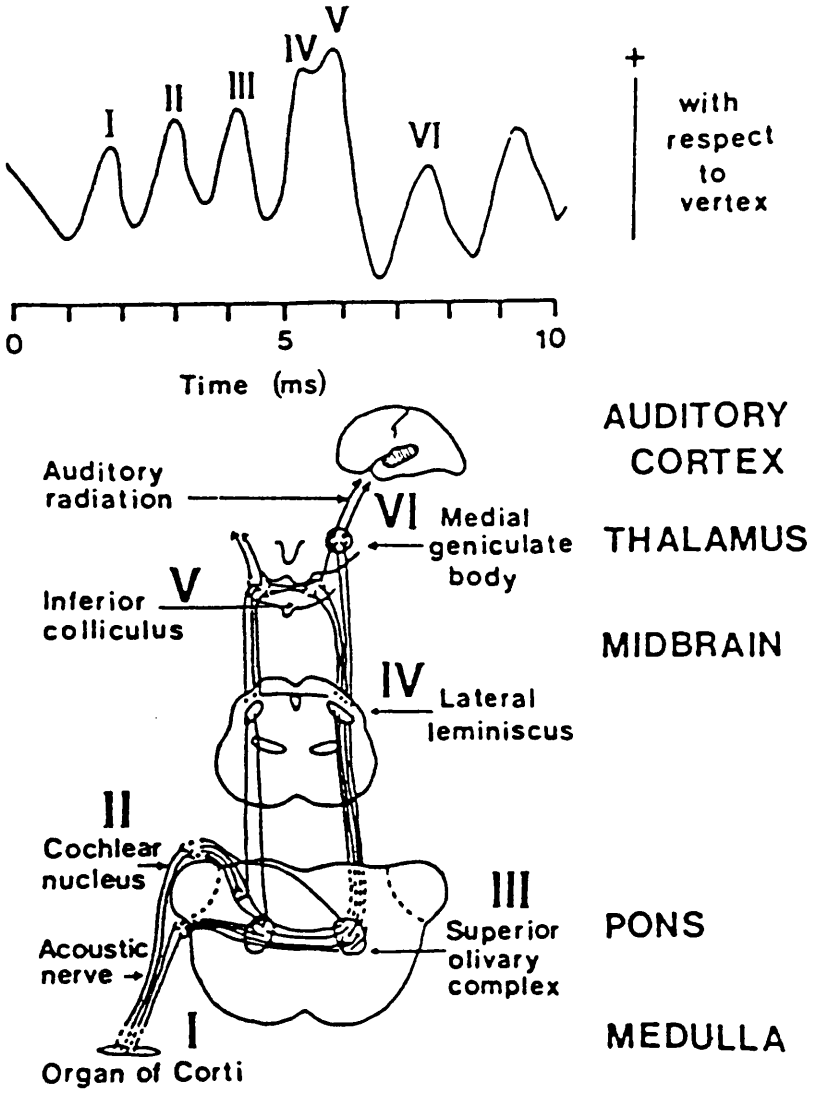


FIGURE 2. Brainstem auditory evoked response and the anatomical pathway, represented by the various waveforms. Reproduced from Maurer K, Leitner H, Schäfer E. 1980. Detection and localisation of brainstem lesions with auditory brainstem potentials; in Evoked Potentials (ed. C.Barber), p391. Lancaster: MTP Press.

BAEP waves, [Figure 1].

Wave II, is often absent in normal subjects.

Wave III may be normally split into two peaks; its latency is then measured to the first peak or to the middle point between the two peaks. A split, or bifid,wave III must be distinguished from a partial fusion of waves III and IV or of waves II and III.

Wave IV often normally fuses with wave V to form a complex with a peak latency equivalent to that of wave IV, wave V, or an intermediate value. Wave IV often varies in the same individual with time.

Wave V is the most reliable peak. It may be identified by its low threshold, its persistence during repetitive stimulation up to 100/sec, and by the large negative deflection that commonly follows it. Occasionally, wave V consists of only a small inflection on the downslope of wave IV.An unusually large negative deflection following wave IV may be a normal variant.

The seven peaks of the BAER have been ascribed to certain neurogenerators as follows:-

a) Wave I - the acoustic nerve

b) Wave II - the cochlear nucleus

c) Wave III - the superior olive

d) Wave IV - the lateral lemniscus

e) Wave V - the inferior colliculus

f) Wave VI - the medial geniculate body

g) Wave VII - the thalamocortical radiations.

Waves I and II originate from the peripheral portion of the auditory nerve, [Figure 2] wave III from the pons, wave IV and V from the midbrain, and waves VI and VII from cortical components, [Stockard, Stockard, Sharbrough 1978]. The latency between waves I and III represents conduction from the periphery to the brainstem. The interpeak latency III-V represents brainstem transmission.

During the recording of the AEP, the subject either reclines in a comfortable chair or lies on a bed in a quiet room. In most recordings, special care must be taken to relax neck muscles by placing pillows under the head and adjusting the position of the body. The subject wears earphones or listens to a loud speaker. The recording room should be so quiet that the subject cannot hear any sounds except for the stimulus and the masking noise. As sleep relaxes scalp muscles and reduces biological artifacts the subjects are encouraged to sleep during these recordings. The MLAEP may be recorded in light sleep, but its threshold increases in deep sleep. LLAEPs vary not only with sleep but even with changes of attention.

The stimulus is most commonly delivered through an earphone. Earphones are usually of the moving-coil, electrodynamic type which have low impedance and, especially at high

stimulus intensities, generate electromagnetic fields which induce stimulus artifacts that may require shielding of the earphone with mu metal. Electrostatic and piezoelectric earphones, having high impedance, require less current but higher signal voltage, and may not be able to generate sound levels as high as those produced by an electrodynamic earphone. These earphones produce mainly electrostatic stimulus artifacts that are more easily eliminated by shielding. In some laboratories, the stimulus artifact is reduced by separating the source of the sound from the ear by a piece of tubing that introduces a delay between the electric production of the sound and the AEP. Small earphones that fit into the external ear canal may be used for intraoperative monitoring of BAEPs.

STIMULUS CHARACTERISTICS

Stimulus type

Several types of stimuli may be used to elicit AEPS. Most AEPs are produced by clicks or tone pips. Click stimuli are very satisfactory for neurological studies because they produce sudden excitation resulting in a well-defined EP. However, clicks are not very suitable for audiological studies because they contain a wide range of tone frequencies, act mainly by virtue of their high frequency content, and do not test the lower frequency range which is important for speech. Stimulation with tones of lower frequency, although desirable for audiological purposes, creates several problems. Tones act as a stimulus mainly by virtue of their onset and should be short. However

expression of the tonal frequency of a stimulus requires a tone duration of at least a few cycles. Tones of low frequency have a wavelength too long for an effective stimulus, especially in cases of short-latency AEPs. Furthermore , although a stimulus of sudden onset is needed for a clearly defined EP, the sudden onset of a loud tone of any frequency introduces a high-frequency transient element i.e. it behaves like a click and thereby elicits an AEP that is not specific for the tone frequency. A compromise between the requirements of a specific tonal frequency and a well-defined onset is available in the form of the filtered click, the tone pip, or the logon, although low frequencies remain a poor stimulus for elicitation of AEPs. The receptors for low tones, located in the apical part of the cochlea, are not easily explored by AEP methods. The longer travel distance of sound waves to the apex of the cochlea, allows responses to low tones to be elicited later than responses to high frequencies, which excite the basal part of the cochlea. Also, because low frequency sound waves have a long duration, the responses are dispersed in time and have low amplitude. Response components to the low frequency contents of an auditory stimulus are therefore easily obscured by the earlier and larger response components generated by the more basal parts of the cochlea which respond to the high frequency content represented by the sudden onset of the stimulus. Attempts have been made to study BAEPs to low stimulus frequencies by masking high frequency components of the stimulus with continuous noise

or to record slow brain stem AERs to low frequency tone pips.

1. Broadband clicks:

Clicks may be produced by feeding electric monophasic square pulses into an earphone and thereby deflecting the earphone membrane. Even though the electric pulses are sharp and last only 100microsecs, the earphone membrane reacts imperfectly to the square pulse and generates pressure changes that are further modified by the material used for coupling the earphone to the head and by the intervening ear structures before they reach the sound receptors in the cochlea. These factors convert the original electric square pulse into a sequence of decaying pressure fluctuations with a peak acoustic power at 2-4 kHz. This sound stimulus still contains a fairly wide range of frequencies and is therefore called BROADBAND, or UNFILTERED click. A narrower band of stimulus frequencies can be obtained either by filtering the electric square pulse or by presenting broadband clicks on a background of a continuous masking noise that eliminates the effect of some of the frequencies in the click.

2. Filtered clicks and tone pips:

Filtered clicks are generated by simply passing a rectangular or sinusoidal wave through a filter with a narrow bandpass so as to produce a brief burst of waves

of a frequency centred at the filter bandpass. Tonepips have more symmetrical rising and falling phases and are produced either by passing one period of a sine wave through a bandpass filter of the same frequency or by modulating the amplitude of a pure tone electronically to give it the desired rise, fall and plateau times. Filtered clicks and tone pips are usually given rising and falling phases of two cycles and a plateau of one cycle. A logon is a tone with an amplitude modulated by the shape of a Gaussian distribution curve, said to give the best compromise between the definitions of stimulus onset and frequency. Filtered clicks, tone pips, and logons, must always start from the zero level and move in the same direction to give consistent AEPs.

3. Tone Bursts:

Tone Bursts with rise and fall times of at least 5msec and durations of at least 30 msec may be used for the LLAEP but are not suited for the MLAEP and BAEP.

Stimulus rate

The stimulus frequency varies for each AEP type. Transient short and medium latency AEPs such as the BAEP, slow brain stem AEP, ECochG, MLAEP are usually elicited at rates of 8-10/sec. The LLAEP requires stimulation at 1/sec or less. The steady-state 40Hz AEP is produced by tone bursts of various frequencies repeated at 40/sec; the fast frequency potential FFP can be obtained with tones of 100-1000Hz.

Avoidance of synchronisation with the power-line frequency should be avoided as this can lead to interference in the average. The stimulus frequency is usually not altered during a stimulation, a brief tone of changing frequency and a change of the frequency of a sustained tone are also capable of eliciting AEPs.

Stimulus Intensity

Although the stimulus intensity is usually not changed during the recording of an AEP, a change of the intensity of a continuous tone may also act as a stimulus and elicit an AEP.

Stimulus intensity is measured as a ratio of stimulus level to a reference level and is expressed in decibels. The number of decibels equals 20 times the logarithm_{10} of the ratio of amplitude or voltage when expressing amplitude, or 10 times the logarithm_{10} of that ratio when expressing power or the square root of voltage. The same type of measurement is used to indicate hearing loss: A subject hearing a tone only if it is increased by 40 dB above the normal hearing level is said to have a 40-dB hearing loss for that tone. Several different reference levels are used to describe stimulus intensity in AEP studies eg hearing level, normal hearing level, sensory level, sound pressure level, and peak equivalent sound pressure level.

Stimulus polarity

Click stimuli may be produced by electric pulses, which cause an initial deflection of the earphone membrane toward the eardrum, condensing or compressing the air in the ear canal and generating condensation, or compression, clicks. If the polarity of the electric pulse driving the earphone membrane is reversed, the pulse produces an initial deflection of the membrane away from the ear, rarefying the air in the ear canal and causing rarefaction clicks. The manufacturer or user must identify the electric polarity settings that produce rarefaction and compression clicks. Stimulus polarity is practically important for short-latency AEPs because condensation and rarefaction clicks produce slightly different BAEPs and ECochGs.

MASKING NOISE

When a sound stimulus is applied through an earphone to one ear, the sound is conducted by the skull and may reach the opposite ear. Although the stimulus is attenuated by about 50-60 dB on its travel across the head, it may excite the other ear. Such cross-stimulation is especially likely to occur when the ear to be tested has a higher threshold than the other ear and is exposed to strong stimuli. Cross-stimulation can be avoided by applying a constant masking noise through an earphone on the ear opposite the simulated one. The masking noise should have an intensity of about 40dB below the stimulus intensity. Masking intensities of

about 60dB SPL are sufficient for the stimulus intensities used in routine studies. Masking noise should contain either a wide range of frequencies at equal intensities (white noise) or include at least the frequencies of the stimulating sound. Masking is not necessary for the ECochG because the response is generated and recorded only at the stimulated ear. Masking noise may be used to mask unwanted frequencies of complex sound stimulus by mixing masking noise and stimulus sound at the same ear.

MONAURAL AND BINAURAL STIMULATION

Separate stimulation of each ear is needed for studies evaluating hearing, acoustic nerve, and brain stem function on each side. Simultaneous stimulation of both ears produces AEPs that differ from the sum of the AEPs to stimulation of each ear.

RECORDING ELECTRODES

For recordings of most AEPs, electrodes are placed on the vertex and on or near the ears. Ear electrodes may be placed on the lateral or medial surface of the left and right earlobe (A1, A2,) or on the scalp over the left and right mastoid bone (M1, M2). Placement on the medial surface of the earlobe can reduce the stimulus artifact of the click. If necessary, the definition of the first wave of the BAEP may be improved by recording the ECochG from an electrode inserted into the ear canal or through the tympanic membrane.

The same electrode combinations are used to record BAEPs, MLAEPs, and LLAEPs. For single-channel recordings, the vertex electrode and the electrode at the stimulated ear are connected to the two inputs of the amplifier and the third electrode connected to the amplifier ground. Dual-channel recordings are preferred for BAEPs, channel 1 recording between vertex and stimulated ear, channel 2 between vertex and nonstimulated ear. A ground electrode is placed anywhere on the head, e.g. at F_2, or elsewhere on the body and is connected to the amplifier ground.

The gain and filter settings, sweep length, and number of responses averaged vary with the AEP type. For every recording, at least two sets of averages must be superimposed to ascertain replication.
The polarity convention for AEPs is not uniform. Many laboratories record the BAEP so that an upward deflection at the output indicates increased positivity at the vertex. MLAEPs and LLAEPs are usually recorded with the opposite polarity convention: upward deflections indicate increased vertex negativity, [Figure 1].

REASONABLE NORMAL RANGES

Normal EPs vary between different subjects. Different laboratories must define their own set of "normal values", [Table 1]. These must represent the two sexes equally and generally the same age groups.

The normal range of EP characteristics is defined statistically for each subject group, EP type and EP characteristic. A group should comprise at least twenty individuals. Although in the work in this project, each volunteer acts as his own control.

EPs are highly dependent on stimulating and recording conditions. It is therefore of great importance that each laboratory determines control values for each response type and does not rely solely on the values from other labs. Guidelines from the American EEG Society state that on setting up a new lab, 2 requirements must be fulfilled:-

1. Stimulus and recording conditions must be the same in the new lab as those of the reference lab.
2. Control values of at least 20 individuals from a sample population eg 95% or 99% fall within the normal values studied from the reference lab.

The following are necessary requirements for control subjects:

a) health and fitness
b) No history of CNS disease
c) no influence of drugs or alcohol
d) no disorder of the sensory modality under study.

For AER, control subjects should have an audiometric examination.

The normal range of EP measurement is dependent on the distribution of the values in normal subjects i.e. an attempt should be made to determine whether control values fit a "normal distribution" curve from the mean, SD , or by determining the deviation from normal or skewness. To determine a normal range the mean should be within 2-3 SD. Each laboratory must set its limits for normal ranges, this must represent a compromise between false positive and false negative numbers that can be accepted.

Various authors have published data on the AER waveforms, [Table 1].

Table 1. - Normal values for components of the auditory evoked response.

Brainstem AER

Author	No	I	II	III	IV	V
Picton (1973)	20	1.5	2.6	3.8	5.0	5.8
Rosenblum (1982)	6	1.6		3.7		5.8
Thornton 1983 (SD)	6	1.6 0.17		3.7 0.22		5.8 0.5
Thornton 1984 (SD)	12	1.7 0.23		3.8 0.23		5.7 0.25
Schmidt 1986 (SEM)	18	1.9 0.46		4.3 0.38		6.6 0.26
Dubois 1982 (SEM)	10	1.58 0.02	2.69 0.05	3.65 0.08	4.65 0.08	5.57 0.07

Middle Latency AER.

Author	No	No	Po	Na	Pa	Nb
Picton (1973)	-	8.9	12	16	25	36
Thornton 1983 (SD)					28 2.9	39 3.1
Thornton 1984 (SD)					26 2.9	39 6.6

Long-latency AER.

Author	P1	N1	P2	N2
Picton (1973)	50	83	161	290

FACTORS WHICH AFFECT THE VALUES OF BAER

PHYSIOLOGICAL

1. Attention

The brainstem components have been found to be stable during changes in subjective arousal and environmental conditions.

Picton and Hillyard (1974) demonstrated that there was no significant change in the early and middle latency components of the AER when attention was directed towards auditory stimuli to perform loudness discrimination. They concluded that there was no evidence from this work to support the theory proposed by Hernandez-Peon (1966) that there was a gating system in the mechanism for auditory attention prior to sensory analysis.

Picton and Hillyard (1974) noted that the early and middle components of the AER were stable to any changes in the subject's level of arousal. Due to muscle artifact during awake states, they found that more defined recordings could be obtained during sleep when the scalp muscles are relaxed, [Picton, Hillyard, Krausz 1974].

2. Arterial Pressure

Various work has shown that VEP are altered by heart rate and blood pressure, [Callaway, Buchsbaum, 1965].

Grundy and co-workers (1982) used BAER to monitor neurosurgical operations in the cerebellopontine angle. These workers noted two patients displayed BAER changes

prior to incision which were temporarily related to a combination of hypocarbia and a degree of arterial hypotension.

In five cases, intervention with volume expansion with crystalloid or colloid, as a specific response to BAEP alteration was made, which improved the waveforms in some cases, [Grundy, Jannetta, Procopio, 1982].

In the majority of studies on the effects of anaesthetic drugs , an attempt is made to maintain systolic blood pressure > 80mmHg, so as to minimise changes in waveforms due to arterial hypotension.

3. Age

Due to conflicting reports of the effects of age on BAER, no age-specific standards have been established. Advancing age has often been reported to increase both peak and inter-peak latencies. Various authors reported that aging has no effect on peak latencies, [Beagley, Sheldrake, 1978].

Thornton (1987) investigated the data from five laboratories. Only some found a significant age effect and then only at certain levels. Even for the same age ranges and stimulus characteristics, two different laboratories showed conflicting results. She classed the effect of age as having a small effect on BAER waveforms. Below the age of two years, interpeak latencies (IPL) are prolonged relative to adult values and vary inversely with age,

[Thornton, 1987].

BAERs may be absent in normal premature infants under 30 weeks of conceptional age. BAER in full-term infants show an IPL I-V about 0.8-1msec longer than adults, mainly due to a longer latency of wave V. Latencies continue to decrease after term, [Stockard, Stockard, Westmoreland,1979].

The latency of wave I (peripheral conduction) reaches adult level at 6 weeks, and IPL I-V (central conduction) reaches that level at about 1.5 years. Age-specific normal values are required up to about 18 months of age.

4. Sex.

Females normally show shorter peak latencies and inter-peak latencies,III-V and I-V than do males, [Stockard, Stockard, Sharbrough, 1978].

The amplitudes of the waveforms tend to be higher and exhibit shorter stimulus to peak latencies; this may be related to smaller skull and brainstem anatomy.

PATHOLOGICAL

1. Temperature

Hypothermia may result in prolongation of both wave latency and IPL, [Stockard, Sharbrough, Tinker, 1978] . During hypothermic cardiopulmonary bypass, the upper limit of normal for the I-IV/V IPL at normothermia was exceeded at an oesophageal temperature of 32 ^{1} ^{o}C and that for the I-

III, III-V IPLs at 28°C. A temperature decrease from 37.1 to 34.5°C increases the latencies of wave I-V. Below 25°C waves totally disappear, [Kaga, Takiguchi, Myoka, 1979].

Hyperthermia has opposite effects on the BAER; slight IPL decreases are seen in humans and cats with mild hyperthermia, [Jones, Stockard, Weidner, 1980].

Variations of body temperature may explain circadian variations of these latencies, [Marshall & Donchin, 1981].

Changes in temperature of 0.5°C have negligible effects of latencies of BAER.

2. Ear Diseases.

BAER can be used to test hearing ability. The threshold stimulus intensity that produces a BAER is determined and the latencies of the various waveforms are tested. For instance, a click stimulus of 70dB is used to elicit a BAER, namely wave V which has the highest amplitude and lowest threshold. If wave V cannot be obtained, a click stimulus of 20dB is used and if wave V appears at this level, the test is terminated, as it is consistent with normal hearing. If wave V is not elicited, stimuli are increased by 10dB, until the threshold of wave V is found. Evoked response audiometry is a difficult technique.The most effective stimuli i.e. clicks and brief tones, test only the audible frequency ranges. Lower frequencies especially those around which speech occurs cannot be effectively tested. The presence of a BAER does not exclude a hearing deficit. Mild hearing

defects and defects in the low frequency ranges may not be identified.

Hearing loss will increase the threshold of a BAER, mostly that of wave V if the hearing loss involves the higher frequency range i.e. 1-4kHz. BAEPs to clicks are, at the moment, the best electrophysiological tests of hearing.

Hearing loss will increase the latency of wave V above the normal level. Central lesions may be excluded with a normal IPL I-V.

A conductive hearing loss interferes with conduction of sound waves to the cochlea i.e. effectively a reduction in stimulus intensity. This results in a BAEP of lower amplitude and longer latency of all waves i.e. wave I latency is increased more than that of other waves, therefore IPL I-III and I-V are shortened. Increasing the stimulus intensity may not overcome a conductive hearing loss.

With a sensorineural hearing loss the amplitude of BAER waveforms is reduced and the amplitude ratio V/I is increased. The latency of wave V will be increased, but wave I will also be increased in latency, resulting in a normal or even abnormally short IPL I-V.

Rosenblum and colleagues (1982) demonstrated that nitrous oxide may cause changes in the AER due to a conductive hearing deficit, being produced by the effect of N_2O on

middle ear pressure, [Rosenblum, Gal, Ruth 1982].

3. Brain Diseases

BAEP are most useful clinically in

1. The diagnosis and prognosis of coma
2. The diagnosis of demyelination
3. The detection and localisation of posterior fossa tumours.

Coma: BAEPs may be useful in the differentiation of metabolic from structural causes of brainstem dysfunction. BAER are resistant to the majority of nonspecific CNS depressants and metabolic insults, unlike the EEG which may show suppression of normal activity.

If brainstem death is diagnosed clinically, the BAER usually shows IPL abnormalities or the absence of waves III and IV/V, wave I remaining present. This suggests a structural cause for the brainstem dysfunction and corresponding poor prognosis.

If BAER are recorded, cautious interpretation is required due to technological or otological problems.

Absence of all waveforms or all except wave I are the most common patterns seen in brain death. Lesser degrees of abnormality or no abnormality are

seen in cases of cerebrocortical death in which there is no damage to brainstem auditory pathways.

Multiple Sclerosis: Patients with MS often have abnormal BAEPs. They occur most often in patients who have a diagnosis of MS and in those with brainstem involvement. Patients with likely MS but no brainstem clinical signs often have abnormal BAEPs.

There is no specific abnormality noted for MS, abnormalities depending on the site and location of disease.

BAER are less effective at detecting abnormalities in MS than VEPs to checkerboard stimulation and SEPs.

Posterior Fossa Tumours: Meningiomas and acoustic neuromas impinging on the brainstem, will produce BAER abnormalities. Acoustic neuromas are often diagnosed using BAER and CT scanning. Wave I is frequently absent, or of increased latency. The following waves are often grossly abnormal or absent. BAER recording has been used for intraoperative monitoring during surgical resection of acoustic neuromas, [Grundy, Jannetta, Procopio, 1982].

PHARMACOLOGICAL

Inhalation Agents

1. Nitrous Oxide

Rosenblum and co-workers (1982) reported no change in the latency of waves I, III, V of the BAER with addition of 70% nitrous oxide to enflurane anaesthesia in normal patients. However, in patients with certain forms of peripheral hearing impairment, the absolute latencies of BAER may be increased by the presence of nitrous oxide. This probably results from the diffusion of nitrous oxide, causing an increase in middle ear pressure and resultant conductive hearing deficit.

Thornton and colleagues (1983) showed that concentrations of up to 50% nitrous oxide did not alter BAER latencies, [Thornton et al, 1983].

Sebel and co-workers (1984) confirmed the earlier findings of Thornton and colleagues, that concentration of up to 50% nitrous oxide given to healthy volunteers did not alter BAER latencies. But SEP and VEP amplitudes were reduced in a graded manner following administration of nitrous oxide and this must be borne in mind when evaluating EP recordings during anaesthesia, [Sebel, Flynn, Ingram, 1984].

As the effects on latencies and amplitudes seen with increasing concentrations of enflurane were graded, these were not due to the constant concentration of nitrous oxide. Nitrous oxide equilibrates to 95% of inspired

concentration in the brain within 10 minutes of the start of inhalation and all the data collected in their analyses were collected after this time. The graded effects on wave latency and amplitude also reversed as enflurane was discontinued and the patient maintained in a constant environment of nitrous oxide.

Manninen and colleagues (1985) endorsed the work of the last two groups of investigators by showing that the addition of 50% nitrous oxide had no effect on BAER during isoflurane anaesthesia, [Manninen, Lam, Nicholas, 1985].

2. Halothane

Duncan and others (1979) investigated the effects of halothane on BAER in children. They reported that halothane did not influence BAER in children, [Duncan, Sanders, McCullough 1979]. This study has been criticised for the lack of a control group.

Thornton and co-workers (1984) observed a graded effect of halothane on BAER latencies, [Thornton, Heneghan, James, 1984]. Others have also reported a graded increase in latencies of BAER with halothane in adults. With increasing end-tidal concentration the latencies of waves I, III, V increased, as did the IPL I-V and III-V and I-III. The amplitude of wave V decreased significantly. They noticed a recovery in latencies of waves III and V in two of the four patients who received halothane during withdrawal of the agent, [James,Thornton,Jones, 1982].

3. Enflurane

Enflurane administrated at concentrations of 0.5-3%, significantly increased the latencies of peaks III, IV, V as well as the IPL I -V, [Dubois et al 1982].

Similar results have been reported by Thornton and co-workers suggesting that the latencies of wave I, III, and V and IPL I -V and III -V increased in a graded manner in the brainstem response with increasing concentrations of end-tidal CO_2. The graded fashion in which the latencies changed with increased end-tidal enflurane concentration suggested that these changes were due to the enflurane and not nitrous oxide, [Figure 3]. The changes also reversed with the removal of enflurane, although a constant environment of nitrous oxide was maintained, [Thornton et al, 1983].

Rosenblum and co-authors failed to show an effect of enflurane on BAER latencies. In this study the measurements were made while surgery was in progress, [Rosenblum, Gal, Ruth, 1982].]

Thornton and co-investigators investigated the effects of surgery on the early cortical AER and noticed that the amplitudes of waveforms were affected by anaesthetic concentration and surgical stimulation,[Thornton et al, 1988]. Although the effect of surgical stimulation on BAER is not known, during light anaesthesia at 1.5% enflurane, the AER may return to normal in response to surgical

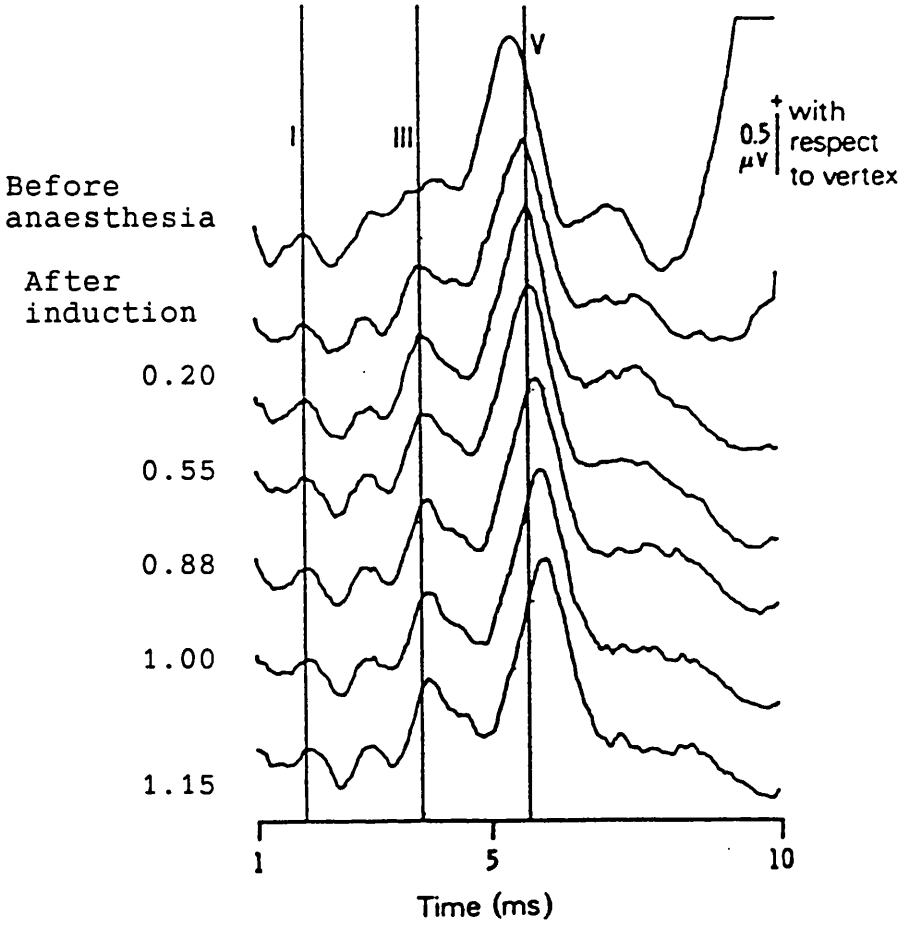


Figure 3. Average BAER for one subject, before anaesthesia, following induction and at different concentrations of end-tidal enflurane (vols %).The vertical line indicates the position of waves I,III and V at the lowest enflurane concentration.

Reproduced from Thornton C, Catley DM, Jordan C, Lehane JR, Royston D, and Jones JG. Enflurane anaesthesia causes graded changes in the brainstem and early cortical auditory evoked response in man. **British Journal of Anaesthesia 1983; 55:**479 - 485.

stimulation, [Thornton et al, 1984].

Burchiel and co-workers demonstrated that AER amplitudes increased 3-5 fold at normocapnia (P_aCO_2 = 40±5mmHg) with various enflurane concentrations. The introduction of hypocapnia(P_ACO_2=20±5mmHg)and enflurane, caused a 30-50 fold increase in amplitudes of AER over awake values. At relative hypercapnia (P_ACO_2=65±10mmHg) no spike-wave EEG discharges could be elicited unlike hypocapnia, and a progressive decrease in AER amplitudes was observed. These two reports give evidence of the generalised cerebral hyperexcitability reported with enflurane anaesthesia,[Burchiel et al, 1975].

4. Isoflurane

Manninen and colleagues (1985) investigated the effects of isoflurane on the BAER, so that intraoperative BAEP changes during neurosurgery could be interpreted. The BAER was examined in ten healthy volunteers during normothermic, normocapnic and normotensive conditions.

BAER were recorded at awake control, end-tidal isoflurane concentration of 1%; 1.5%; and 2%. Nitrous oxide was added at a concentration of 50% at each isoflurane concentration. Isoflurane increased the latencies of peaks III, IV, and V significantly above awake control levels. The addition of nitrous oxide did not influence these findings. The increase in latencies occurred at 1% end-tidal isoflurane and no further increase was noted after 1.5%. Similar changes were noted for the interpeak latencies, but nitrous oxide did not

influence these findings. No consistent change was observed in the amplitude. They concluded that any prolongation of peak V latency beyond 1msec from awake control would have to be explained by factors other than a direct effect of isoflurane eg effect of retractors, hypotension, or ischaemia, [Manninen, Lam, Nicholas, 1985].

Schmidt and co-workers (1986) looked at the effect of increasing end-tidal isoflurane concentration from 0.6%-2.4% on the BAER. The latencies of waves I, III, and V increased in a dose-related fashion. No indication of the actual concentration at which waveforms changed was given. The amplitude of wave V decreased with increasing isoflurane concentration. The authors commented on the increase in BAER latencies resulting from a non-specific influence of isoflurane on central conduction, through either enhancing inhibitory effects or depressing excitatory transmission in synaptic regions, [Schmidt, Chraemmer-Jorgensen, 1986].

Sebel and co-authors (1986) studied the effects of isoflurane on BAER in six patients. There was no consistent change in the latency of wave I, which was often difficult to identify. The latencies of waves III and V increased with increasing concentration of isoflurane. There was no change in the amplitudes of peaks III and V. The addition of nitrous oxide did not alter the BAER, [Sebel, Ingram, Flynn 1986].

Heneghan and colleagues (1987) examined the effects of isoflurane (0.6-2.9% end-tidal) on the auditory evoked

response. Confirming the work of other authors, they found that with increasing concentrations of isoflurane the latency of brainstem waves III and V increased, as did the interpeak latency of I -V, [Heneghan et al, 1987].

Both Thornton (1983),(1984) and Heneghan (1987) with their respective co-workers have shown that isoflurane , halothane and enflurane have similar effects on the brainstem AER in contrast to that of the intravenous induction agents etomidate [Thornton et al, 1985] and Althesin [Thornton et al, 1986], which have no effect on the BAER, but produce a profound effect on the early cortical waves. These two agents are noted for their minimal effect on respiratory and cardiovascular homeostasis. Thornton and co-authors suggested that this may be related to their minimal effects on the brainstem and thus brainstem auditory evoked potentials, [Thornton et al, 1985].

Other Drugs

Samra and co-workers, (1985) looked at the effect of scopolamine and morphine on the BAER in monkeys. Although the scopolamine produced clinical and cortical EEG effects on the CNS, it failed to have any effect on either the absolute or IPL latencies or the amplitudes of the BAER. The combination of morphine and scopolamine caused no change in absolute or IPL latencies or amplitude of the BAER. Others cited showed that cholinergic drugs had more effect on the late components of the AER, rather than the early

components,[Bhargara, Salamy, McKean, 1978] [Samra et al, 1985].

Samra and colleagues (1984) showed that large doses of fentanyl had no effect on the BAER, [Samra et al, 1984].

Various authors have shown that barbiturates have no effect on the BAER, even when obvious changes in the spontaneous electroencephalogram are recorded [Newton et al 1983]; [Stockard et al 1977]; [Duncan, Sanders, McCullough, 1979].

Drummond and co-authors (1985) examined the effect of high dose sodium thiopental on BAER in humans. They used an infusion in excess of the time needed for the EEG to become isoelectric and showed progressive and significant increases in latencies of Waves I,III V and in the IPL I-III, III-V, and the I-V. The amplitudes of the BAER were not significantly altered. The authors concluded that the administration of a dose of STP in excess of twice that required to produce an isoelectric EEG can be compatible with effective monitoring of BAER, [Drummond, Todd, Hoi Sang 1985].

CORTICAL AUDITORY EVOKED RESPONSES

I THE MIDDLE LATENCY AER

MLAEPs are very sensitive to sonomotor responses which obscure them, therefore it is important to have the patient's neck muscles relaxed. Recordings are usually made between electrodes on vertex and ear or mastoid. Only one channel is used since MLAEPs to monaural stimuli recorded from the two sides of the head do not differ from each other. The amplification requires a gain almost as high as that of BAEPs because MLAEPs are only slightly larger than BAEPs. The low frequency filter is usually set at about 10Hz to avoid distortion of slow components. High frequency filters settings of less than 150Hz may distort amplitude and latency of the MLAEP. Sweep length is usually about 100msec. This results in a dwell time of about 100microsec per point, or a sampling rate of about 10Hz, for the usual average having 1024 points per channel. Usually 1000-2000 responses are collected.

The MLAEP or early cortical AEP consists of several peaks of up to over one microvolt which occur 10-50msec after the stimulus, [Figure 1]. The MLAEP may show up to five peaks of negative and positive polarity at the vertex:

N_o at 8-10msec

P_o at 10-13msec

N_a at 16-30msec

P_a at 30-45msec usually the largest

N_b at 40-60msec.

A sixth peak P_b, at 50-90msec, is often found in recordings

including the first 100msec after the stimulus and represents the early peak (P1) of the late cortical AEP. A decrease of stimulus intensity reduces the amplitude and increases the latency of the MLAEP. The MLAEP has a wide distribution with a maximum over the frontocentral areas. A generator for the MLAEP near the auditory cortex has been postulated and is supported by direct recordings from the surgically exposed temporal cortex.

The active electrode is positioned on the mastoid and the reference on the vertex, the latter being the midpoint between inion and nasion.

Picton and colleagues (1974) noted that tension in scalp musculature profoundly alters MLAEP recordings, [Picton et al 1974]. Four separate muscle reflexes have been described : the posterior -auricular reflex, the frontalis reflex, temporalis, and the inion (neck muscle). Picton and colleagues (1974) attributed the middle latency components of the AER to be largely due to potentials originating in the auditory thalamus and cortex. The Pa response overlaps the inion sonomotor response.

STIMULUS CHARACTERISTICS

Although clicks and high frequency tone bursts are the most effective stimuli, tone pips and filtered clicks are often used. The response seems to depend as much on the sudden onset of the stimulus as on its frequency. Stimuli with a short rise time are more effective than stimuli with more

slowly increasing amplitude.

With decreasing stimulus intensity the components of the AER decrease in amplitude and increase in latency, amplitude changes being more apparent for the middle and long latency components. Higher rates of stimulation decrease the amplitude of the components.

FACTORS WHICH AFFECT THE MLAEP

PHYSIOLOGICAL

1. Sleep

The middle latency component is stable to changes in the subjects level of arousal. Due to attenuated reflex muscle tension, better recordings can be gained with the subject asleep rather than voluntary relaxing the muscles.

2. Attention

Picton and Hillyard (1974) showed that there was no significant change in the AER prior to the N1-P2 components, when attention is directed towards auditory stimuli in order to perform a difficult loudness discrimination.

3. Age

The latency of MLAEP peaks decreases only slightly between infancy and adulthood.

PATHOLOGICAL

1.Neurological

MLAEPs are used infrequently in the diagnosis of neurological disease. When used in combination with BAEPs, they have been reported to increase the incidence of abnormal findings in multiple sclerosis.

2.Ear Diseases

The usefulness of MLAEP has not yet been convincingly proved. The relationship between MLAEP and hearing threshold is very variable, and the frequent problem of muscle artifact in tracings makes this test less than ideal as a hearing test especially in young children.

PHARMACOLOGICAL

Mild sedation does not alter the MLAEP. [Mendel et al, 1975]; [Skinner, Shimotoa, 1975]

1.Nitrous oxide / Enflurane.

The latencies of Pa and Nb increase with increasing end-tidal enflurane concentrations in a mixture of oxygen and 70% nitrous oxide,[Figure 4]. Waves Pa and Nb show linear decreases in amplitude with increasing enflurane concentration. Although the nitrous oxide might exert an effect on latency and amplitude, the GRADED effects are unlikely to be caused by this agent. As the concentration in the brain of nitrous oxide equilibrates

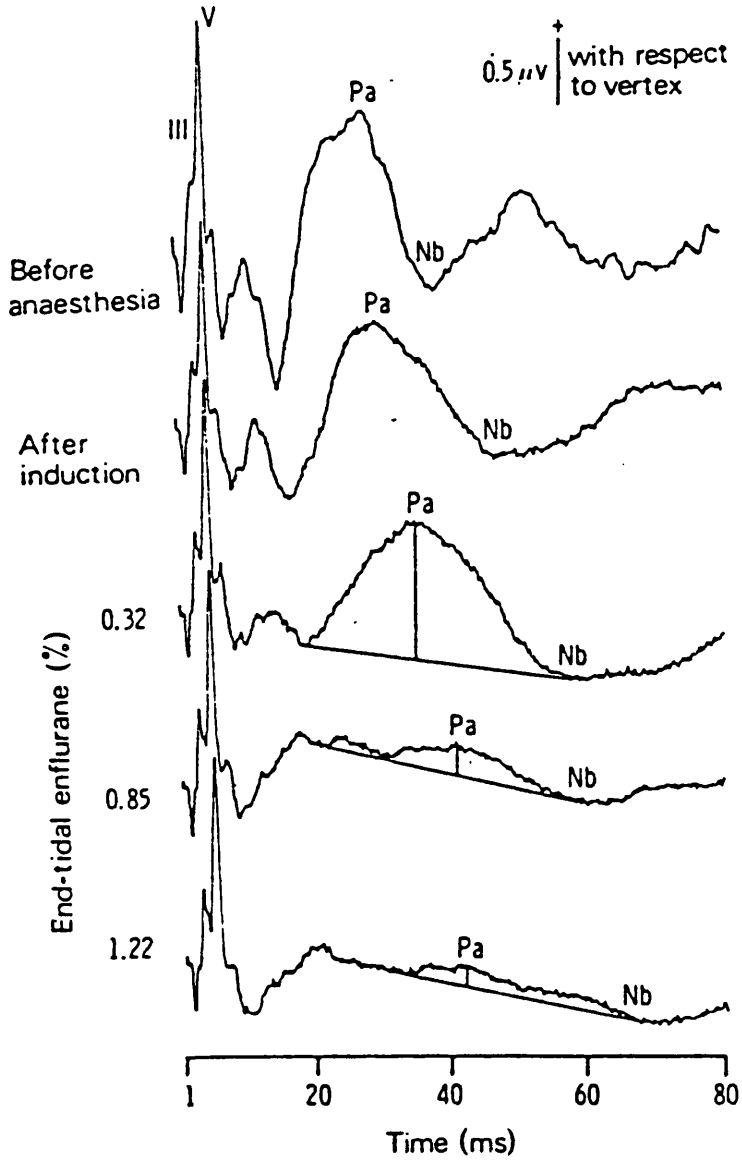


Figure 4. Averaged MLAER for one subject, before anaesthesia, following induction and at different concentrations of end-tidal enflurane (vols %).Amplitude measurements of Pa indicated by vertical line. Reproduced from Thornton C, Catley DM, Jordan C, Lehane JR, Royston D and Jones JG. Enflurane anaesthesia causes graded changes in the Brainstem and early cortical auditory evoked response in man. **British Journal of Anaesthesia 1983; 55:** 479-485.

by ten minutes after the start of inhalation, all Thornton's data were collected after this time. The amplitude of Pa and Nb decreases with increasing end-tidal concentration of enflurane to the point at 1.22% when they are nearly abolished,[Thornton et al, 1983]. These authors also concluded that after STP induction and the start of oxygen and nitrous oxide anaesthesia, there were no significant changes in the values of Pa and Nb from the awake values.

The effect of increases in carbon dioxide tension were associated with only small changes in the AER in this paper. The posterior-auricular response is a problem during consciousness, although it is less prominent at the inion than mastoid sites.

2.Halothane

The latency of waves Pa and Nb increases with increasing doses of both end-tidal halothane and enflurane. On withdrawal of these agents, waves Pa and Nb show partial recovery, [Thornton et al, 1984].

3.Isoflurane

Heneghan and colleagues (1987) examined the effect of isoflurane on the auditory evoked response in man. They looked at six patients before elective surgery. Isoflurane produced reductions in amplitude and increases in latency of the cortical waves Pa and Nb, and increases in the latency of brainstem waves III and

V. When isoflurane was compared with halothane and enflurane using a MAC-based comparison, they found no differences in the effect of the three agents on the amplitude of the early cortical waves, although the latencies showed significant differences. They concluded that all the anaesthetics studied by these workers so far have a dose-related effect on the cortical part of the AER, whereas some spare the brainstem. These observations, together with studies of regional brain metabolism, lead these authors to believe that loss of consciousness in anaesthesia may be more closely related to depression of cortical rather than brainstem function, [Heneghan et al, 1987]

Madler and co-workers (1991) showed a graded and statistically significant increase in both Pa and Na latencies with isoflurane. They detected an increase in the short latency brainstem potentials (wave V) only between the awake state and 0.3% isoflurane, [Madler et al, 1991].

Newton, Thornton and Konieczko (1992) assessed the AER (MLAER) and awareness using sub-MAC concentrations of isoflurane. Amplitudes decreased and latencies increased progressively with increasing anaesthetic concentration. Amplitudes were greatest and the latencies shortest when there was full response to command. These authors noted that the fine gradations in behavioural changes that

they expected were not shown, the loss of conscious awareness being an all-or-none phenomena rather than gradual. The 0.2MAC level produced the most interesting changes. The study group consisted of anaesthetists who may have been aware of the smell and likely effects of anaesthetic gases.

II THE LONG-LATENCY AUDITORY EVOKED RESPONSE

Recording of the long-latency AER requires the subject to be relaxed and alert. The LLAEP is reported to be changed by factors such as sleep, [Kevanishvili, Von Specht, 1979]; [Mendel, Hosick, and Windman 1975]; [Ornitz and Ritvo 1967]; [Rapin, Schimmel, 1972], sleep deprivation [Gauthier and Gottesmann, 1983]; [Pressman, Spielman, Pollak, 1982] and changes of attention [Goodin, Squires, Starr, 1983]; [Picton, Hillyard, 1974]; [Salamy, McKean, 1977]; [Schwent, Hillyard, 1975]; [Schwent, Hillyard, Galambos, 1976].

Myogenic components are unlikely to obscure LLAEPs therefore relaxation of scalp and neck muscles is not necessary.

Stimuli are usually tone bursts of 250-2000Hz, given with a gradual rise over a time of 25-50msec and a plateau of 30-50msec and repeated at a rate of 0.5-2/sec. Recordings are made in a single channel between vertex and mastoid. Displacement of the vertex electrode by up to 6cm does not change the response. Amplification is not as high as for BAEPs or MLAEPs because LLAEP amplitude is higher, ranging from 1-10microvolts. Filter settings that include a bandwidth of 0.2-100Hz are ample. The sweep length is usually about 500msec. Only about 30-100 responses need to be averaged for one LLAEP.

The LLAEP has an inconstant vertex-positive peak P1 at 50-70msec, a fairly large negative peak N1 at 100-150msec, and

a positive peak P2 at 170-200msec,[Figure 1].

The prominent N1-P2 complex is usually followed by a negative peak N2. A third positive peak P3 at about 300msec, depends on cognitive processes rather than the stimulus. Long tone stimuli cause a sustained negative potential shift with a delayed onset.

The amplitude of the LLAEP decreases and its latency increases with increasing stimulus rate, with increasing stimulus rise time, and with decreasing stimulus duration. Similar changes occur with decreasing stimulus intensity, especially near threshold, and more so for clicks than for tone stimuli. Tones of low frequency elicit larger LLAEPs than high tones of equal sensation level, and the amplitude of LLAEPs to low tones increases more with increasing stimulus intensity than does the amplitude of LLAEPs to high tones. With increasing stimulus intensity, the LLAEP reaches a maximum after which a further increase of intensity may cause a decrease of amplitude. Latency does not depend on the tonal frequency of the stimulus.

The LLAEP has a wide distribution with a maximum at the vertex.

The distribution varies with stimulus frequency. Responses recorded from the side opposite the stimulated ear are slightly larger.

1. Age

In neonates, the LLAEP is quite variable and depends on the

sleep stage. The variability decreases with age. the latency decreases and the amplitude increases, mainly during the first year of life. In adult and elderly subjects, LLAEP latency increases and amplitude decreases.

2. Neurological Disease

Multiple sclerosis produces abnormal LLAEPs. The following authors stated that the LLAEP could predict severity and outcome in head injuries [Greenberg, Newlon, Hyatt, 1981]; [Greenberg, Becker, Miller, 1977]; [Karnaze, Marshall, McCarthy, 1982]; [Lindsay, Karlin, Kennedy, 1981].

Spehlmann (1985) states that strokes and tumours in the frontoparietal region, but not in the frontal region, reduce the N100 waveform.
Both alcohol and diazepam alter the LLAEP [Wolpaw, Penry, 1978], [Herrmann, Hofmann, Kubicki, 1981].

COMPONENT STRUCTURE OF THE N100 WAVEFORM

Näätänen and Picton (1987) reviewed the literature on the component structure of the N100 wave. They stated that six different cerebral processes contributed to the N1 wave of the scalp-recorded AEP, [Näätänen, Picton, 1987].

The first three could be considered as true N100 components, the other three often exist in the latency region of the N1 wave but may occur independently.

Component 1 is generated in the cortex of the supratemporal

plane [Vaughan, Ritter, 1970]. This component which has a peak latency at 100msec, is maximally recorded from the frontocentral scalp and may be enhanced by attention through some thalamocortical gating mechanism, demonstrated by magnetic recordings.

Component 2 is a biphasic component with a positive wave at about 100msec and a negative wave at approximately 150msec [Wolpaw, Penry, 1975]. It is generated on the superior temporal gyrus and is recorded from the scalp with a maximum amplitude at the midtemporal electrodes. This component is not picked up magnetically and is probably generated in the auditory association areas, activated by connections from the primary auditory cortex and also possibly the thalamus.

Component 3 is a vertex negative wave with a peak latency of approximately 100msec. The generator of this component is not known but is possibly from the frontal motor and premotor cortex under the influence of the reticular formation and thalamus. It is recorded from the scalp with maximal amplitude at the vertex and the lateral central electrodes.

Component 4 is the negative deflection, generated in the same area of the brain as component 1.

Component 5 is the negative waveform which is specific to a sensory stimulus. This begins at approximately 50-100msec and lasts during the processing of an attended auditory stimulus, being generated in the auditory sensory and

association areas on the supratemporal plane and on the lateral aspects of the temporal lobe.

Component 6 is the "attentional supervisor" a second component of the processing negativity which is probably generated in the anterior frontal cortex since it receives information from the auditory association cortex.

Näätänen and Picton also attempted to consider the functional significance of the first three components of the N100 waveform. For component 1 they considered three possible functions for the neurons that are activated during the generation of component 1 of the N1 wave. The neurons may act to call attention to the availability of a stimulus, to read out sensory information from the auditory cortex, or to form a sensory memory of the stimulus within the auditory cortex. They could not describe any function of component 2, generated in the auditory association cortex on the lateral temporal lobe due to a lack of available data. Component 3 they stated probably evolved from an extensive cerebral mechanism that functions to produce a widespread transient arousal of the organism. This arousal response enhances sensory and motor responses to the eliciting stimulus, causing the organism to be in a more efficient functional state. Component 3 also serves some aspects of detection and perception by alerting sensory association and motor cortex when a stimulus occurs after a period of quiescence.

EFFECTS OF ATTENTION ON THE N100 WAVEFORM

The N100 wave is susceptible to three different modulations of the general state to the individual: [Näätänen, Picton, 1987]

1. arousal due to sleep-wakefulness state, drugs and alcohol, circadian rhythms, and involvement in task performance.

2. a sensory acceptance-rejection factor which may enhance responses to all sensory inputs during expectancy for important, interesting or pleasant stimuli, and attenuate responses elicited during expectancy for irrelevant, uninteresting or unpleasant stimuli

3. the degree of time uncertainty with regard to the next significant stimulus. These nonspecific influences probably have more effect on component 3 than on the first two components.

Näätänen and Picton (1987) stated that early experiments suggested that the N100 wave of the auditory EP was larger when the subject was attending to a stimuli than when ignoring them. They decided on two effects that may increase the N100 amplitude

a) prior uncertainty about stimulus timing

b) prior preparation for performing a demanding task.

They went on to suggest that in selective attention experiments, the timing of the attended and ignored stimuli

was made unpredictable (thereby eliminating the possibility of selective prior preparation), there were no attention-related changes in the N100 although there were problems in these experiments with the rate of delivery of stimuli. In summary, they concluded that auditory selective attention causes the superimposition on the N100 wave of a processing negativity, consisting of two components (5 and 6) that overlap the true N100 components. It is possible that under certain conditions attention may selectively enhance a true N100 component, as suggested by [Hillyard, Hink, Schwent 1973]. The enhanced component probably being the supratemporal component (component 1).

Attention is accompanied by a general and nonspecific increase in cerebral excitability which might increase the amplitude of the N100 wave. Hillyard and co-authors suggested that the effects of arousal are mediated in the brain by the same processes that underlie the enhancement of the N100 with selective attention. Picton and colleagues (1979) suggested that it is "probably impossible to change levels of arousal in the waking state independently of any attentional change." During increased states of arousal subjects usually increase their alertness or general attentiveness to the external world, [Picton, Ouellette, Hamel Smith, 1979].

Näätänen and Picton (1987) indicated that various authors had published conflicting results on the effects of sleep on the N100 waveform, some reported a decrease in amplitude

while others reported no change.

The late components of the AER are affected by sleep. The N100 component becomes attenuated during sleep and the addition of a large negative wave with a peak latency of 300msec, called the N2 or sleep N2 wave, is present during the non-REM stages of sleep early in the night. Nätäänen and Picton cited other authors who suggest that this wave is due to an excitatory phenomenon associated with unsuccessful attempts at arousal or an inhibitory wave preventing awareness.

They concluded that there is some evidence for task- or attention-induced stimulus-nonspecific increases in the excitability of some neurons which contribute to the N100 deflection, causing the N100 amplitude to be larger when the subject is occupied in some task, also the amplitude being larger in a demanding rather than less demanding task. While performing a continuous task, if the subject can predict the timing of delivery of the stimuli above the random chance level, these moments will be preceded by an excitability increase which causes the N100 amplitude to relevant stimuli to be bigger than that elicited by the irrelevant stimuli. This increase in excitability may be due to a general increase in sensory sensitivity which might be independent of arousal, the brain possessing a general gain control over its own sensory input.

CHAPTER THREE

ANAESTHESIA AND PSYCHOMETRIC TESTING

PSYCHOMETRIC TESTING AS USED IN ANAESTHESIA

Rapid and complete return of normal psychomotor and memory function are essential features of methods for dental sedation and anaesthesia for day case surgery. A review of the literature demonstrates that there are many methods for testing psychomotor recovery from anaesthesia. Unfortunately none of these tests are standardised and therefore it is difficult to evaluate one test and its ability to measure recovery, compared to another test.

Tests for recovery can be divided into various classes as described by Hindmarch and Bhatti, 1987. These are memory, intelligence, psychomotor function, attention and those that measure physiological characteristics.

1. Memory

Memory impairment may prevent the ability of patients to recall advice on ability to drive and drink alcohol and can be tested by asking patients about their spatial orientation and memory for recent events as used in normal neurological examination. The staff working with these patients may be able to assess their ability with regards to performance. Tasks to assess ability for the learning of new information and the retention of this information eg Wechsler's memory scale, are also available.

2. Intelligence tests

Tests such as the Wechsler adult intelligence scale are used

for the testing of intellectual function, [Blundel 1967, Riis, Lomholt, Haxholdt 1983].

3. Tests of attention

Alteration in attention can be measured using an uninteresting, lengthy, boring task eg the letter deletion task in which the patient is presented with a foolscap sheet containing closely spaced letters, the patient being required to delete the letter p in a specified time. The number of letters deleted being measured and the number of errors,[Dixon and Thornton 1973].

4.Psychophysiological measures of recovery

The electroencephalograph records electrical potentials from the scalp. However problems exist with interpretation.The Maddox Wing measures the balance of extraocular muscles and gives a sensitive indication of the rate of recovery from general anaesthesia. The natural position of rest for the eyes is in divergence with a slight upward displacement and the maintenance of normal vision is an active process, depending on the degree of tone in the medial rectus muscles. The reduction in general muscle tone with general anaesthesia causes divergence of the eyes which can be quantified by using the Maddox Wing.

5. Psychomotor function

Psychomotor tests used commonly in the assessment of performance are the post-box; the peg-board; simulated reaction time and critical flicker fusion.

In the post-box test patients are required to post as many shapes as possible through the lid of a child's post-box within a specified time limit.

The peg-board test contains a board with two sets of 48 holes, one set of which was filled with tight fitting pegs. The subject was required to transfer as many pegs as possible to the other set of holes. The score was recorded in 45 seconds.

Simulated driving tasks involve tracing shapes or drawing a pathway out of a maze without coming into contact with any of the edges. Computerised models also exist, reflecting hazards that are met when driving, measuring brake reaction time or number of accidents etc, [Hakkinen 1976].

The critical flicker fusion test (CFFT) involves the use of an intermittent light whose flicker rate is increased or decreased within specified limits. As the frequency of flicker increases, a point is reached when it is perceived as continuous, this point being termed the flicker fusion threshold. When the intermittent light is observed as the frequency of flicker decreases there will be a point when the light that initially appeared constant begins to flicker, the fusion flicker threshold. Usually the mean of three ascending and three descending trials is accepted. The test has been shown to give a sensitive measure of central processing of perceptual information in a study conducted by [Moss, Hindmarch, Pain et al 1987].

CFFT was shown to discriminate between different anaesthetic agents 19 hours after awakening. The scores on the two other tests; choice reaction time test (CRT) and Maddox Wing test both had returned to baseline earlier than those of the CFF test. Hindmarch (1980) concluded that critical flicker fusion threshold is the assessment of choice for investigation of change in the overall integrative activity of the CNS produced by psycho-active drugs, and that CRT is a very sensitive measure of drug-induced changes in sensori-motor performance, particularly if it is split into its motor and recognition components.

STREET-FITNESS

Due to economic considerations day-case surgery is being used more. Anaesthesia for day-case surgery requires the patient to be "street-fit" before discharge. This can be defined as a state in which cognitive and psychomotor skills are sufficient to permit the subject to indulge in everyday pursuits without hazard to themselves or others. Drowsiness may be associated with an impairment of attention and there is evidence that this occurs not as a stable phenomenon but in an episodic fashion. For most of the time a subject with lowered arousal will attend adequately to stimuli. But on occasion, performance will fall off markedly. The periods of inattention are associated with changes in the EEG, and are variously referred to as blocks, involuntary rest pauses of microsleeps [Bills 1931]. The frequency of such blocks, is increased by a number of

factors that impair arousal, in particular, sleep deprivation and during prolonged repetitive tasks.

STANDARDISATION OF TESTS.

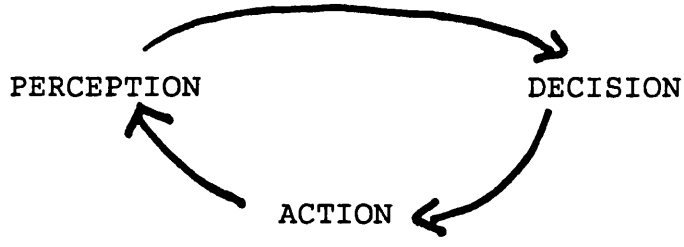
In 1989 NATO published a report describing the need for standardisation in the use of psychomotor tests, with the aim of introducing a more systematic approach to performance testing. The major applications of performance tests in military fields is for selection of personnel and research work into stress psychology. This working group produced a register of tests, and developed a protocol for the use of these tests with a proven record of success in stress research. In anaesthesia such tests are used to assess recovery profiles from drugs and to attempt to ascertain fitness for discharge of patients after surgery.

Human performance tasks can be used to evaluate the effects of environmental stressors, or to assess the information -processing abilities of individuals. Stressor effects are tested in comparison to control conditions eg the use of drugs, alcohol, illnesses, fatigue etc. The goal is to assess how the extent to which a particular stressor influences performance in real-life situations eg the effects of drugs used in day-case anaesthesia on the ability to drive a car.

In the use of performance tasks to assess information-processing abilities, the comparison is between individuals. Performance tests in laboratory conditions have to relate to

real-life situations, but it is of course difficult to assess whether they do or not. When examining the effects of stressors, performance should vary markedly when environmental conditions change, but the variation due to individual differences should ideally be small. To assess individual ability, tests should be insensitive to variations in environmental conditions but sensitive to individual differences.

A general idea underlying most models of information-processing in man is of a single information-processing system equipped with memory stores eg Perception - Decision - Action model shown below.



Various authors state that the primary failing in studies into recovery characteristics, is that the psychomotor tests used, have not been standardised. Furthermore they tend to measure several psychological functions simultaneously. When performance shows impairment it may be unclear which of these functions is affected, [Jones 1988] and [Zuurmond,Balk,van Dis, 1989].

Parrott attempted to establish a method of reliability, validity and standardisation of performance tasks for clinical use, [Parrott 1991,1991].

The establishment of the Recovery Interest Group may help to promote the use of sensitive and standardised tests.

BASELINE-PRACTICE EFFECTS

The reliability of a psychometric test is affected by practice. Performance improves until a "plateau" is reached ie the learning curve. Tests which are sufficiently sensitive to detect the presence of impairments, not clinically obvious, are often subject to practice effects. By giving patients a sufficient amount of practice they will overcome the steepest part of the learning curve.

At a later point a more refined learning may develop where there is a transition from "controlled" to "automatic" processing, during which time the amount of mental resources required to perform the task declines. If the test fails to provide consistent scores even after learning it may not measure adequately the attribute that it is designed to measure, [AGARD 1989].

Millar (1991) described that in the majority of papers written, the methodical details given, suggest that insufficient practice is usually provided. Figure 5 illustrates the concept of a practice effect. Lack of pre-training leads to the control group showing a distinct improvement in performance. The thiopentone and methohexitone groups will consequently be more grossly impaired than is evident in the graph.

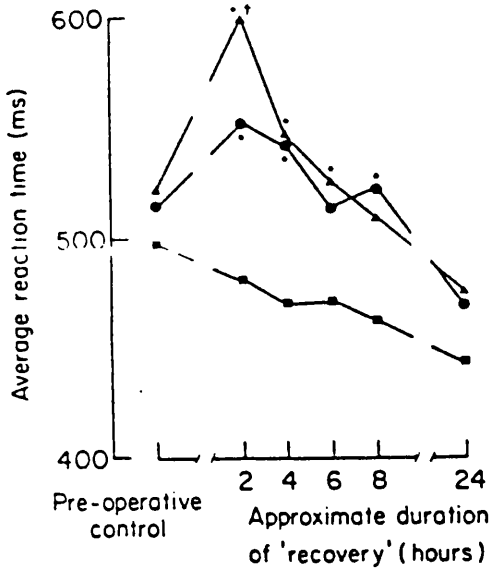


FIGURE 5. Mean reaction times of control subjects (squares), thiopentone subjects (circles) and methohexitone subjects (triangles) before, and at various times up to 24hrs after anaesthesia and surgery. Notice the decrease in reaction time with practice in the control group.

Reproduced from Scott WAC, Whitwam JG, and Wilkinson RT. Choice reaction time - a method of measuring postoperative psychomotor performance decrements. **Anaesthesia 1983; 38:** 1162-1168.

Herbert (1989) shows that in many studies recovery is assessed as a return to baseline (preanaesthetic) tests of psychomotor tests. This he suggests will bias the results if the effect of practice has not been adequately excluded.

Methods to overcome the effects of practice:-

1. Prepractice sessions
2. Tests which are not subject to practice effects, but they may be too insensitive to show changes.
3. Include an untreated control group to allow practice effects to be assessed.

Motivational factors can affect the results in performance studies. The intentions of volunteers, the level of payment and the expectations of the experimenter and subject can all have a profound influence on experimental results, [Ayd 1972].

WITHIN AND BETWEEN-SUBJECT DESIGN.

A major issue in the use of psychometric testing is whether a subject should perform in both conditions (within-subject design /crossover design) or whether separate groups of subjects should be tested in each condition (between-subject design).

The benefits of the within-subject design are;

1. Each subject acts as his own control, reducing the intersubject variation.
2. Fewer subjects are needed.

The between-group design gives better reliablity of data which is often worthwhile to use even considering the disadvantages.

Usually in within-subject designs half the subjects would undertake the condition under test initially and half would be assigned to the control group initially. This assumes that the effect of practice between the first and second conditions is identical regardless of which order the conditions are administered ie symmetrical transfer. However sometimes the initial performance under stress may lead to the adoption of inappropriate methods of completing the performance test, which may be carried over to the subsequent control conditions ie asymmetric transfer effects [Poulton and Freeman 1966, Millar 1983, Agard 1989].

Asymmetric transfer refers to the fact that reactions to different drugs may vary depending on which drug or condition was encountered first, and prior treatment with a drug may affect placebo conditions. Millar (1983) stated that adverse effects of a drug on the mental abilities of volunteers may be much greater in those who have already experienced a session under placebo than in those who have received the drug condition first and placebo second.

Asymmetrical transfer usually reduces the differences between test conditions and may therefore obscure potentially interesting findings.

INDIVIDUAL VARIATION IN RESPONSE.

Many studies of recovery from anaesthetic agents only include mean values, omitting standard deviations or error ie they show no inter-subject variation, [Grant and McKenzie 1985]. As some individuals will have been at the extremes of these groups, their recovery would probably be incomplete. Some authors showed that while most patients recover quickly from propofol, some do not recover normal psychomotor function until three hours after surgery, [Weightman and Zacharias 1987, Sanders 1989.

Others, have included information on variation,[Herbert et al 1983, Galletly 1988].

ENVIRONMENTAL CONDITIONS.

Expectations by a subject may affect their performance. Although ethically subjects need to be informed of the nature of drugs etc in use, the order should not be revealed to the subject, so as not to bias their performance, [Agard 1989].

The laboratory conditions used for psychometric testing are usually not available when these tests are used in conjunction with anaesthesia. Patients perform these tests in the least ideal conditions, initially a busy noisy ward just after admission, when they are anxious. They may awaken and do the tests in a noisy recovery room.

A learning curve if established is usually conducted with conditions of extreme anxiety, [Eysenck 1981]. Comparison is then made with recovery conditions when anxiety levels are much less, [Wallace 1987].

Anxiety can affect performance as Hindmarch described in his review 1980. He noted that all the following authors had shown that anxious patients had significantly lower CFF thresholds than age matched 'normals'. [Krugman 1947, Goldstone 1955, Jones 1958].

The effects of other drugs may confound studies eg antibiotics are known to have adverse effects on human learning, due to their effects on protein synthesis [Idzikowski and Oswald 1983] or premedicant drugs. Avoiding the use of premedication may help to eliminate this cause. Generally conditions should be controlled as possible. For instance lighting and heating should be controlled to a similar level on each day of the study, noise should be kept to a minimum. The position of the computer monitor relative to windows and light sources should be adjusted to avoid reflections on the screen and the distance of computer from subject should be constant (the Nato committee report, quote a distance of 60cm), [Agard 1989].

IMPAIRMENT.

Impaired performance is a term that is often used in the discussion of recovery from anaesthetic drugs. Millar (1992) described the problem with this term being a general

lack of definition when one takes into account the problems associated with baseline recording of performance tests eg the effects of practice.

Millar (1992) states that investigators have termed impairment as a mean difference between the treatment and control groups ie beyond the $P<0.05$ level of significance, although a statistically significant difference may be so small as to be of no clinical relevance. He continued to state that the effect of an anaesthetic may be to make performance more variable. This variability may be masked by expressing the data as mean values and not median.

He cited the work of [Gardner and Altman 1986] and [Matthews Altman, Campbell et al 1990] who suggested that individuals whose performance is similar, may be graphed within the same subpanel of a multi-panel figure in order to illustrate common trends with the group ie confidence intervals.

Matthews and colleagues (1990) suggested that conventional measures of performance mask individual variation. But also by conducting separate significance tests at each time point as is normally the case, and not correcting them for multiple comparisons, or timing the points close together thus allowing one point to influence other points, another source of error is introduced, [Matthews, Altman, Campbell, et al, 1990].

A summary measure of performance for each subject can be calculated from the area of the graph under the individual

subjects's performance curve [Matthews, Altman, Campbell, et al, 1990].

Hickey and colleagues were also quoted, they adopted the use of intervals in their study of semantic recognition memory performance after propofol anaesthesia. They only assumed impairment if the confidence interval did not encompass the baseline, [Hickey, Asbury, Millar 1991].

Millar (1991) pointed out that the summary measure method of analysis was superior when data was missing, and more accurate if time points vary to the nature of hospital life. Although time points of maximal impairment may be masked, so performance should also be mapped out over time.

Cooper (1984) suggested that 95% confidence intervals on either side of average data should be examined.

RECOVERY

The concept of recovery is a difficult to define.

Herbert (1991) described recovery as being a return to the baseline performance level. Millar (1992) described this as being dependent on a stable baseline performance with the effects of practice being overcome. Herbert has emphasised the importance of the control group. Only by looking at this group can it be shown that "recovery" values ie post anaesthetic are the same as baseline, indicating impairment, if the control group's performance improves throughout the period due to a practice effect.

TIME ON TASK

The time spent on a task may be one of the most important determinants of whether a stressor will show impairment in the performance of the individual.

Wilkinson (1969) has suggested that stress effects upon performance might be missed if the period was too short.If the test is short, a subject can arouse himself to maintain performance at a satisfactory level even when severely stressed. But if the test is prolonged, this ability cannot be sustained. Therefore very short tasks may miss the effect of the stress on performance. In the case of day-case surgery, subjects may be discharged when their performance returns to 'normal' although they are severely impaired.

Herbert (1987) showed that studies of immediate recovery from anaesthesia are based on the assumption that once performance has returned to pre-anaesthetic baseline levels, no further deterioration will occur, therefore tests are not extended for more than a few hours postoperatively. Folkard and colleagues suggested that if performance is 'naturally' poorer at some points of the day, the added effects of the drugs, may make patients more vulnerable or influence their normal circadian rhythms. Once baseline levels are achieved as a measure of recovery the patient may still be impaired, [Folkard,Simpson, Glynn 1979].

Zuurmond and co-authors used only three-minute letter

deletion task and twenty reaction time trials in assessment of recovery. Trials like this have to be questioned, when the length of the task is so short,[Zuurmond, Balk, van Dis et al 1989].

Millar and colleagues demonstrated this effect when they increased the time of a brief performance test to twenty minutes, demonstrating by doing this a significant impairment caused by the drug brompheniramine, [Millar and Standen 1982].

TIME OF DAY.

Hockey and co-authors showed that diurnal rhythm has an effect on psychological functioning as the day goes on,[Hockey and Colquhoun 1972].

Folkard (1975) stated that performance varies across the 24 hour period.

Prolonged bedrest may itself have adverse effects on performance, [Edwards 1981].

DOSE RELATED EFFECTS.

Millar (1991) states the effects of anaesthesia on cognitive and psychomotor performance are difficult to evaluate with reference to dose-related effects. Although all doses used are in the clinical range, it is difficult to compare dose-related effects because all the studies differ in their methods - for instance amount of practice, presence or absence of control group, time on task, surgical treatment ,

age of patients and other drugs administered. Nitrous oxide seems to show a curvilinear or threshold dose-response curve [Allison, Shirley, Smith 1979], [Wernberg, Nielson SF, Hommelgaand 1980].

Bruce (1976) demonstrated that small concentrations of nitrous oxide may produce significant performance decrements although other authors were unable to reproduce this,[Smith,Shirley 1978].

PATIENTS PERCEPTION OF THEIR OWN ABILITY.

Egber and colleagues noted that in several instances when subjects themselves felt completely recovered, a reaction time test showed that they were not back to normal, [Egber,Oech, Eckenhoff 1959]. Others have shown that those showing minimal performance effects continued to feel affected by the anaesthetic. This discrepancy may suggest that patients are not the best judges of their fitness for normal activity, [Herbert,Makin, Bourke et al 1985].

CHOOSING A PERFORMANCE TEST.

1. The longer a test lasts the more likely it is to reflect impairment.

2. The less challenging the test, the better it is in being able to detect performance changes.

3. The larger batteries of tests may be counterproductive ie they may raise motivation levels, [Wilkinson 1969].

FEATURES OF A PSYCHOMETRIC TEST.

Psychometric tests should exhibit the properties of

1. Validity ie measure what it is supposed to measure.

2. Reliability - it should measure it consistently eg on re-testing.

3. Sensitivity - the test should be able to detect environmental effects or individual effects to which it is sensitive, [Agard'89].

Herbert (1978) described tests as becoming more sensitive the more familiar they are, the longer they last, the more they demand sustained output or maintained concentration and the less if they are perceived as challenging or as novel and interesting.

PROBLEMS OF INTERPRETATION IN PSYCHOMOTOR TESTS.

1. Healthy volunteers versus mixed age.
2. Varying doses.
3. Intra-operative events for instance hypoxia.
4. Use of premedicant and other drugs.
5. The hospital environment.
6. Degree of cooperation of the individual concerned.

Many of the above problems are unresolvable.

PROBLEMS IN THE DESIGN OF EXPERIMENTAL STUDIES.

1. Within-subject group and the problems of asymmetric transfer (between group designs better reliability of data).

2. Mean values better replaced by 95% confidence intervals.

3. Return to pre-operative baseline as an adequate criterion of postanaesthetic recovery.

4. Once return to unimpaired levels, researchers assume no subsequent deterioration. Few studies extend performance to the few days after anaesthesia. The added effects of diurnal variation and drugs may make impairment reappear. Herbert and co-authors, looked at 55 patients for hernia repair who were divided into three groups in which the method of induction of anaesthesia was varied (iv/inhalation) and ventilation (spontaneous/controlled),[Herbert, Healy, Bourke et al 1983].

Performance in 5min serial reaction time and subjective estimates of coordination were assessed four times per day

for two postoperative days. After considerable impairment initially, reaction times in all groups gradually returned towards control values; however, in patients breathing spontaneously during anaesthesia, impairment recurred during the second postoperative day.

Herbert and colleagues in a second study using herniorraphy patients, tested over two complete postoperative days. Anaesthesia was induced with STP or propofol. Compared to the control group, thiopental continued to exert adverse effects on reaction time into the second postoperative day , where propofol had no statistically significant adverse consequences at any postoperative measurement point,[Herbert, Makin, Bourke et al 1985].

If a test of psychomotor performance is affected by anaesthetic agents, then everyday tasks which appear to depend upon those abilities are also likely to be affected. Millar (1986) states that the degree of familiarity of a test may determine how well patients perform after general anaesthesia. Everyday tasks with which patients are familiar with may be more resistant to the effects of general anaesthesia.

Zuurmond and colleagues comment "The choice of psychomotor and cognitive recovery tests after anaesthesia is an important but difficult issue. Recovery tests should be complete, reliable and valid, to permit conclusions to be drawn from their results, and cover all aspects,otherwise

patients may be sent home too soon. Different test situations measure different aspects of recovery, but in all cases basic cognitive and psychomotor functions must be assessed. Recovery tests should be as simple as possible, practical and cause the patient minimal strain. Measuring identical parameters should be avoided", [Zuurmond,Balk, van Dis, 1989].

Kortilla (1986) described the basic functions of psychomotor function - perception, coordination, motor function, and different aspects of cognition.

THE CHOICE REACTION TIME

The reaction time can be defined as the speed with which people are able to react to the onset of a stimulus.
There are two types of reaction time:-

1. The Simple reaction time in which a response to a single stimulus is required.

2. The Choice reaction time in which a response is made to varying stimuli CRT. The serial CRT provides no opportunity for the subject to rest. The discrete method allows the subject to self-pace each trial, as they are required to return their hand from the response key to a" home" key to indicate readiness for the next signal.

SERIAL CHOICE REACTION TIME

All the papers discussed in the following sections, have been summarised in Tables 2,3,4. Factors such as randomisation, presence of a control group, time spent on each task and the presence of any practice effects can be identified from the tables.

Wilkinson (1991) described work done in the mid-50s on individuals with sleep deprivation. He noted that highly demanding complex tasks were not the most vulnerable to sleep loss, but the simple, boring tasks. Complex tasks by providing a source of stimulation negated the effect of sleep deprivation returning the subject effectively to normal. Simple boring tasks which failed to act as a stimulus caused accuracy to diminish but speed to be

maintained.

The original five-choice serial reaction time was developed by Leonard (1959). Wilkinson continued this with the above factors in mind and it became the foundation of future research.

A subject was required to tap one of five discs when the corresponding light shone. Once this was completed another light would come on in a random fashion. Each test continued for twenty minutes with subjects responding as quickly as possible. Reaction time increased as the loss of sleep increased, as did the number of errors.

From his work on sleep deprivation, Wilkinson used his five-serial reaction time test, as a general test of assessing arousal experimentally or for use in other research projects, [Wilkinson 1975].

The essential features of the unit were a small light, portable apparatus to use in various settings. To enable it to be more portable, it was battery-powered. Ability to store data collected was a feature, as was ability to exchange software and compatibility with standard laboratory computers. After various redesigns the final product was a four-choice RT. The display consisted of four light bulbs (light-emitting diodes) producing the stimulus with four buttons for the response. The lights lit up in a random order, being extinguished when the response button was pressed, 120 seconds lapse until the next stimulus occurs.

Storage of data was on a cassette tape in the form of tones - 4kHz for an error, 2kHz or a correct response. Retrieval of data was from a standard laboratory computer in the form of average reaction time and the number of errors and standard deviation.

Kortilla and co-authors (1977), [Table 2, Page 1] assessed recovery from anaesthesia in 34 healthy student volunteers, using a psychomotor test battery 1 and 5 hours and a driving simulator 2, 4.5, and 7 hours after 3.5min of anaesthesia with halothane or enflurane combined with nitrous oxide and oxygen. Psychomotor performances remained significantly ($p<0.05$ to $P<0.001$) worse than in an unanaesthetised control group for 5 hours after both halothane and enflurane. Impairment of driving skills 4.5 hours after anaesthesia was measurable only after halothane ($P<0.05$). It was concluded by these authors that after brief periods of halothane or enflurane anaesthesia patients should not drive or operate machinery for at least 7 hours. The magnitudes and durations of the residual effects of both agents on psychomotor performance were, however, less than those previously found after thiopental, methohexital, or diazepam. Reaction skills were measured with two choice-reaction tests. The first programme involved subjects having to react to 25 consecutive light stimuli from two different lights. The second programme involved reaction times to 25 stimuli from two different lights or sounds. In both programmes there was a special light to which the subjects were told not to

react. The reaction times were recorded as cumulative totals, and the inaccuracy of responses were recorded as the incorrect responses.

The residual effects of the anaesthetics were seen more clearly in the choice-reaction test when two light and two sound stimuli with a disturbance stimulus (programme II) were used. The improvement in the control group was probably due to practice effects, and this implies that the deterioration in the enflurane / halothane group is of a greater magnitude than expressed. In comparison to other psychometric tests the CRT is an acceptable measure of impairment post-anaesthesia.

Local anaesthesia has been suggested for outpatient anaesthesia due to the lack of effect on psychomotor function. Kortilla (1974) assessed psychomotor skills related to driving after intramuscular lidocaine. They used serial choice reaction time and noted impairment in psychomotor skills after 200mg of plain lidocaine. Reaction skills and presumably driving ability were impaired for 0.5 - 1.5hrs after injection.

Kortilla and colleagues in a study of bupivicaine and etidocaine showed that despite practice, all improved performance with training in control group on the CRT and coordination tests, [Kortilla, Hakkinen, Linnoila 1975],[Table 2,Page 1].

CFFF was significantly impaired with both etidocaine and

bupivicaine compared with placebo. The tests used assess arousal, coordination and reaction times.

No mention is made of total time on each task, which may affect performance , if as stated the task was short enough to allow a subject to arouse themselves to perform the task but not long enough to elicit an element of boredom.

Kortilla (1977) repeated the above experiments; only using the local anaesthetic drugs prilocaine or mepivicaine, in place of etidocaine and bupivicaine. In contrast to the impairment in psychomotor performance caused by lidocaine, bupivicaine and etidocaine; mepivicaine and prilocaine were noted not to have any effects on the central nervous system, and were the preferred agents for out-patient practice. Again, despite an hour of training, there was still a practice effect on the saline control.

Hakkinen (1976) stated that CRT, coordination and attention tests have been shown to correlate with,the ability to encounter traffic accidents.

Bruce (1976) used a battery of psychomotor tests to assess the effect of trace concentration of anaesthetic gases on performance in volunteers. Subjects were allowed 15 minutes of practice although no control group was included to assess the effect of the practice session. As can be seen from the table, the AV reaction time was a sensitive test, and the authors suggest the test most closely allied to the anaesthetist's work. In view of the lack of control group

data available and the use of healthy volunteers, it is difficult to assess the accuracy of this study.

Smith and colleagues used progressive visual reaction times to assess exposure of anaesthetist subjects to either halothane 100 - 150ppm in air or air alone, and demonstrated no significant difference between control and test situations. They also studied 15 psychology students using an audiovisual reaction timer and noted no significant differences in the subjects responses in other control or test situations. Each group was given a practice session with the reaction timer, but neither group demonstrated a significant practice effect. Volunteers were given caffeine to drink, to emulate theatre conditions, and it is known that this has a variable effect, both on simple and complex reaction times. Two types of choice reaction time were used both the serial and discrete forms. The discrete form should theoretically be more highly sensitive than the serial. But it is possible that it may not be sensitive enough to reveal the possible small change in mean reaction time with such small trace concentrations of gas. Again in this paper, there are a large number of variables such as concentration of gases used, type of reaction timer, use of anaesthetic and non-anaesthetic staff. With so many variables it is difficult to assess one variable against another,[Smith, Shirley 1977].

Wernberg and co-authors used a serial visual reaction timer to both single and double-handed usage. They compared these

with a critical flicker fusion frequency test, using nitrous oxide in concentrations of 0, 10, 20, and 30%. With the double-handed method a shortening of reaction time was seen at 10% nitrous oxide, the authors described this as being due to nitrous oxide at low concentrations facilitating the reaction to a stimulus. At 30% nitrous oxide the reaction timer (double-handed) was significantly prolonged. The single-handed reaction time was prolonged at 30%, no change was noted in the reaction time at 10 or 20%,[Wernberg, Nielson, Hommelgaand 1980].

The flicker fusion frequency was significantly increased at 20% nitrous oxide and another increase noted at 30% nitrous oxide. The fusion flicker frequency did not alter until the concentration reached 30% nitrous oxide.

These authors concluded that critical flicker fusion frequency was a simpler, more time-saving and sensitive method for estimation of changes which nitrous oxide produced in healthy volunteers.

[Edwards, Rose, Schorow et al 1981], [Table 2 Page 2].

Millar and co-author (1982), [Table 2 Page 2], used the four-choice reaction time described by Wilkinson (1975) and a visual search task to assess the effect of a linear release system and non-linear release system of the antihistamine drug Brompheniramine Maleate 10mg,[Millar, Standen 1982]. They included not only a measurement of mean correct response latency but also of 'blocks'[Bills 1931].

These are response latencies that are 1.5 times longer than the overall mean latency. Such blocks or pauses in performances are thought to indicate states of fatigue or low arousal. The linear release system showed increased pausing in serial reaction time at 5.5 hours post-dosage.

Scott and colleagues [Table 2 Page 2], used the four-choice RT described by [Wilkinson 1975], to measure postoperative psychomotor performance decrements in three groups of 13 subjects, [Scott, Whitman, Wilkinson 1983]. Anaesthesia consisted of either thiopentone,nitrous oxide and halothane or methohexitone, fentanyl/nitrous oxide and incremental methohexitone. Tests were performed on the day before surgery and after at 2,4,6,8 and approximately 24hrs recovery, on both groups of patients and at approximately the same times on a nonoperated control group. The mean CRT of thiopentone and methohexitone subjects increased from 515 to 550ms and 552 to 600ms respectively after 2 hrs recovery. Subsequent CRT decreased in both groups although methohexitone subjects were still significantly slower than controls after 6hrs. Thiopentone subjects were slower than controls at 2,4,and 8 hrs after recovery. There was no significant difference between the three groups of subjects after 24hrs recovery. The data from this study showed a considerable practice effect in the control group [Figure 5]. The thiopentone and methohexitone group at 8 hrs had achieved the performance in reaction time equivalent to their baseline. By looking at the control group it is evident that a large practice effect has occurred. Therefore

at 24hrs the thiopentone and methohexitone groups were still impaired relative to control values. The authors concluded that CRT was a sensitive test for psychomotor performance.

Herbert and co-workers used the four-choice CRT to study the impairment of mental function in 55 patients undergoing hernia repair. Patients were divided into three groups in which the method of induction of anaesthesia (iv or inhal) and ventilation (spontaneous or controlled) were varied (thiopentone/halothane). The serial CRT was used in a five minute test four times a day for two days postoperatively. A control group also being included. After impairment initially, the reaction times in all groups returned towards control values, but in patients breathing spontaneously during anaesthesia, impairment recurred during the second postoperative day. Herbert and his co-authors indicated that "this re-emergence of impaired reaction times two days after the operation emphasises the importance of extending the testing beyond the point where patients have apparently recovered. Without such testing results of the present study would have concurred with those of earlier reports showing that psychomotor consequences of general anaesthesia are fairly short-lived. This present data, however, suggests that it would seem wise to extend the warning not to drive to at least 48 hrs postoperatively".When we look at graphs of MRT there is some evidence of practice effects with the control group, [Herbert, Healy, Bourke et al 1983].

Herbert and colleagues again used CRT to examine recovery of mental abilities following GA induced by propofol or thiopentone, using herniorraphy patents premedicated again with diazepam 10mg,[Herbert, Makin, Bourke et al 1985].

Five minute serial CRT were preformed before the premed, 90 min after regaining consciousness and at four constant times across the mornings and afternoons of the next two postoperative days. Visual analogue scales to describe perceived level of coordination were also measured. Reaction times of all groups were similar before surgery, but propofol group were significantly faster than STP at all postoperative points. The performance of the thiopentone group remained significantly slower than that of controls up to and including the morning of the second postoperative day. The propofol group did not differ from controls at any measurement point. Herbert indicates that evidence from Visual analogue scales implies that individuals assessments of their perceived level of coordination should not be relied upon.

Barker and colleagues [Table 2 Page 3] used a serial CRT as a measure of recovery on patients sedated with midazolam and the emulsion formulation of diazepam in a cross-over study for 50 patients undergoing out-patient conservative dentistry using a four-choice reaction time [described by Wilkinson 1975]. They failed to show any difference in psychometric performance between the treatments. One criticism is that they only gave a practice period of thirty

seconds with the CRT apparatus, [Barker,Butchart, Gibson et al 1986].

McMenemin and co-author used a serial choice reaction time test to assess the potency of 25% nitrous oxide compared to 0.4% isoflurane. The CRT used was similar to that used by Smith and Shirley (1977). Both nitrous oxide and isoflurane prolonged performance compared to control. The effect of the isoflurane was greater than the nitrous oxide, although the isoflurane did not reach its maximum effect until 15 mins. Within five minutes subjects gained values similar to those obtained while breathing oxygen. No practice effects were evident, [McMenemin, Parbrook 1988].

Baillie and co-workers used a battery of computerised psychomotor tests to assess the effects of temazepam premedication on cognitive recovery following alfentanil-propofol anaesthesia. They showed significant deficits in attention and memory following anaesthesia, which increased in range and magnitude with temazepam. These were obvious 30minutes after surgery but had largely but not completely recovered at four hours,[Baillie, Christmas, Price et al 1989].

Kortilla and colleagues used a task of serial multiple reaction time to a visual or auditory stimulus and their combination (computer-assisted). Psychomotor performance remained significantly worse compared to control for one hour after propofol and five hours after thiopental. They concluded that propofol is ideal for day-case surgery due to

its fast and complete recovery of psychomotor performance. Driving and psychomotor skills are impaired for as long as eight hours after brief thiopental and methohexital anaesthesia. This study was appropriate in that only thiopental and propofol were used and no other premedicant drugs or anaesthetic agents,[Kortilla,Nuotto, Lichtor et al 1992.

DISCRETE CHOICE REACTION TIME

The discrete CRT is effectively a subject-paced test, in that the subject has to return their finger to a 'home' key to await the next signal. The Leeds Psychomotor Performance Tester is a compact portable apparatus measuring critical flicker fusion threshold (CFFT) and Choice reaction time. In the CRT the subject scans an array of six small lights which are illuminated on a random basis. As soon as he detects a light he touches the appropriate button to extinguish it. The latency of this response is an assessment of the integrity of sensori-motor function and an accurate measure of psychomotor performance. The distance the subject has to move his hand to touch the response button is the same for each light, making it possible to measure motor time separately from recognition time. The CFFT is an sensitive index of CNS arousal and the ability to integrate discrete units of sensory data,[Hindmarch, Parrott 1977].

Landauer and colleagues examined the decision and movement time components of a visual discrete choice reaction time task, using healthy volunteers. The results of two separate studies showed that women have a faster decision time than men, and that men have a faster movement time. Since these two effects are in an opposite direction, no sex differences in the mean choice reaction times were found. It was concluded that on this particular task the cognitive performance of women was superior,[Landauer, Armstrong ,Digwood 1980].

MacKenzie and co-authors [Table3 Page1] assessed the recovery characteristics of anaesthesia induced with propofol, thiopentone and methohexitone. Propofol showed a superior recovery, with virtually no side-effects and little impairment of psychomotor function 30min after anaesthesia. No practice effects were evident, [MacKenzie and Grant 1985 a].

MacKenzie and colleagues compared propofol with methohexitone in patients undergoing light general anaesthesia [Table 3 Page1]. The choice reaction time and critical flicker fusion threshold were assessed as can be seen from the table. Both agents depressed the Critical Flicker Fusion Threshold in a similar manner. With propofol this was significant at all times, but with methohexitone it was no longer significant after four hours. Similar impairment of CRT was also seen with the two groups. Recovery after anaesthesia was rapid in both groups however the quality of recovery was superior following propofol, in that side effects such as headache, nausea and vomiting occurring much less commonly than after methohexitone,[MacKenzie and Grant 1985 b].

Sanders and co-authors [Table 3 Page 2] findings were in conflict with the previous authors. They found no significant difference between the unpremedicated propofol group and the unpremedicated thiopentone group, the only difference being halothane in the technique rather than

enflurane. It was apparent that the motor functions of the patients were significantly affected by the anaesthetic drugs up to 3 hours later. The authors noticed that "patients are still significantly impaired in psychomotor functions at the time when they are customarily discharged from hospital." As can be seen from the table no control was included and there is no indication of the number of practice sessions given to each patient initially, therefore there may be a large practice effect that is unaccounted for, with a larger degree of residual impairment being present, compared to baseline,[Sanders, Issac, Yeomans, et al 1989].

Hickey and co-investigators assessed recovery from outpatient anaesthesia with propofol in which 10 patients, were followed using a semantic recognition memory test (SemRT) ,choice reaction time and critical flicker fusion threshold (CFFT). Group analysis of results revealed an effect on psychomotor performance as measured by the Sematic recognition memory test (SemRT) and Critical flicker fusion test (CFFT) but not the CRT, 30 mins after the end of the procedure. Performance on all three tasks had returned to baseline values within 60min of completing the anaesthetic. Group analysis, however, masks individual impairment which may be clinically important as was discussed earlier. There was no statistically significant correlation between postanaesthetic task performance and age, sex, dose of propofol, anxiety or depression score,[Hickey,Asbury, Millar 1991]. The CRT was of the Leeds psychomotor testing system

as previously described. The return of patient performance to pre-anaesthetic levels occurred within 60mins of discontinuing the anaesthetic [cf MacKenzie and Grant 1985a].

Anderson and colleagues investigated the nature and duration of cognitive effects of atropine and hyoscine. The tests they used included orientation questions, memory tests, a CRT and two tests of visuo-motor coordination. The results showed that hyoscine had detrimental effects on memory and on motor tasks compared with placebo, while atropine did not. These effects on motor performance had not disappeared three hours after the operation,[Anderson, McGuire, McKeown 1985].

This study had shown that clinical doses of atropine have minimal effects on cognitive performance compared with placebo. Hyoscine showed a slowing of motor speed and visuo-motor coordination which lasted a sufficient length of time to allow such patients to be affected after discharge from day-case surgery.

Fagan and co-authors looked at the effects of three separate doses of alcohol (0.2,0.4,0.8g/kg) when given to eight volunteers compared with a placebo trial. They used a battery of psychometric tests including a CRT and CR latency repeatedly performed for 3.5hours. Alcohol, even in the highest dose, had little effects on psychomotor performance. All the psychometric tests used had previously been shown to

be sensitive to the effects of moderate doses of other CNS depressant drugs,[Fagan, Tiplady and Scott 1987].

Moss and colleagues, [Table 3 Page2] compared the results of a battery of psychometric tests using an alfentanil anaesthetic technique and inhalational halothane technique. Both groups showed an initial large impairment of psychomotor function, gradually increasing during the afternoon and returning to baseline next morning. Only the CFF test demonstrated a difference in the two anaesthetic techniques. The alfentanil group were found to be significantly less sedated than the halothane patients on the morning after anaesthesia,[Moss, Hindmarch,Pain 1987].

Zuurmond and co-investigators attempted to determine the minimum requirements for a battery of psychomotor tests to assess recovery from anaesthesia. They used six recovery tests, choice reaction time (CRT), CRT doubletask, finger tapping test (FTT), critical flicker fusion frequency (CFF),Maddox wing , and p-deletion test. These tests, cover basic cognitive, motor and perceptive functions as well as concentration , were analysed and compared with each other. Correlation between the tests after recovery from standardised general anaesthesia was calculated in 22 patients. Moderate to high correlation was found between CRT and CRT doubletask($r=0.62$ to $r=0.73$), when parameters of six different tests were compared. Finger tapping correlated moderately with the movement time of both the CRT and the CRT doubletask ($r=0.46$ and $r=0.47$ respectively). They

concluded that the CRT test, which measures initiation and movement time might replace the CRT doubletask and the FTT. The CFF correlated moderately with the initiation time of the CRT doubletask but because a slightly different function seems to be involved, further research is needed. Maddox wing and the p-deletion test correlated with no other test. Results indicated that recovery is differentiated in at least four distinct psychomotor functions which should be tested by CRT (to measure initiation and movement time), Maddox wing and p-deletion, [Zuurmond, Balk, van Dis et al 1989].

They used a discrete CRT, in which several processes can be differentiated within the reaction, of which the choice reaction time test subsequently estimates the initiation time (a cognitive component of the reaction time, measured by the release of the initially held button) and the movement time (a motor component of the reaction time, measured by the movement from the initially held button to the stimulus button). Initiation time and movement time together make up the total reaction time. The CRT doubletask measures the reaction time but the patient also has to count the appearing stimuli. One out of the five possible stimuli buttons must be excluded; at each subsequent presentation of the CRT doubletask, a different stimulus button must be excluded to prevent recognition. The patient's attention is divided, and the reaction time is slowed down as a result of the simultaneous counting and reacting. The order of the stimuli and the interstimulus

intervals are again randomly defined, as with the CRT test. These authors concluded that as recovery is not a unidimensional concept that several tests are necessary to measure street-fitness, home-readiness or full recovery. To include all aspects of recovery important in the decision to send patients home, motor ability and coordination as well as perception and cognitive recovery need to be tested. The choice reaction time, the Maddox wing and p-deletion tests were the tests recommended by these authors.

Sanders and co-authors assessed recovery over 48 hours after anaesthesia with propofol or thiopentone as sole anaesthetic agent in 36 unpremedicated gynaecological patients, [Table3 Page2]. There was a substantial practice effect with the choice reaction time, digit span and aiming task which may have obscured impairment. The authors concluded that better recovery profile after propofol was still evident at 24hours,[Sanders, Clyburn, Rosen, et al 1991].

The review of the literature on choice reaction time apparatus demonstrates that this test is a sensitive indicator of impairment after anaesthesia or from other CNS depressant drugs. However there are many problems when comparing one drug against another. There seems to be no set parameters for the CRT design. In effect authors are using CRT apparatus that is designed,operates differently and in many cases is measuring different parameters ie no of mistakes, mean RT etc. The general design of the studies indicates problems with [Table2 &3] lack of initial training

and the effect of practice , inadequate length of the CRT test to elicit boredom, and in some cases the lack of a control group to enable comparisons to be made.

From the papers reviewed it is apparent despite all these criticisms that the effect of anaesthetic drugs can last well in to the recovery period. Patients undergoing day-case anaesthesia should be warned of these effects and the importance of refraining from driving etc for 24hours and possibly even 36-48hours.

TRACKING TASKS

A tracking task can be defined as a task in which a volunteer is required to make a response to a visual cue provided by the relative positions and rates of travel of a target and cursor. Tracking tasks are also known as rotary pursuit tests or tests of visuo-motor coordination.

Visual tracking is used frequently in the study of general human behaviour.

Lincoln and colleagues looked at the transfer in training in tracking performance at different target speeds. They studied the effect of training in performance at one target speed upon later performance at different target speeds. The subjects' task was to track a small target rotating at varying speeds, using a mechanical tracking device that tested the specificity of tracking training in relation to target speeds. Thirty-six subjects were divided into three groups equated as to initial tracking ability. Each group was trained at a different target speed. After completion of this training, the groups were transferred to tests run at the three training speeds, so that all groups tracked for one day at each of the three speeds.

The data showed significant differences between performances at the three target speeds, and practice appeared to be relatively ineffective as a means of increasing accuracy scores. Subjects trained at medium target speed made scores significantly superior to those made by groups trained at low and high target speeds,when later tested on low and

medium target speeds. The same group, showed poorer scores when tested on high speeds. The authors concluded that training at certain target speeds leads to better performance when particular speeds are introduced at a later time,[Lincoln, Smith 1951a].

In another paper written by these authors, they established that accuracy of performance is greater and the degree of learning is less in direct tracking than in types of tracking in which some aid is provided to the operator. These differences they thought were due to the tracking device modifying the movements of the observed cursor, [Lincoln and Smith 1952b].

Lincoln and co-authors again looked at visual tracking but this time as a response pattern composed of simultaneous adaptive reactions of position, rate and acceleration control, rather than as a direct response to sensory cues. These authors set out to determine how tracking accuracy varied with the brightness of the target area, width of the target and with changes in the pattern of the target and cursor. Their experiments were designed to determine the nature of target-width effect relative to variation in target brightness and target-cursor pattern. They found that the pattern relations of target and cursor were indeed related to the accuracy of visual tracking. A discrete relation of target and cursor generally produced more accurate performance than an overlapping pattern of target and cursor when the colour of both was the same. The

illumination level of the target and cursor also reflected in the accuracy of tracking. Accuracy was poor at low levels of illumination but this involved complex interactions,[Lincoln ,Smith 1952c].

The most important result of the study was the observation that an increase in the width of the target produced no marked change in the level of tracking accuracy.

From these results the authors concluded that "tracking behaviour was due mainly to the phenomenon of organisation of visual pattern rather than tolerances of alignment and misalignment of visual contours. The tracker's accuracy is determined by precision in scaling or bisection of the visual pattern rather than in terms of the optical resolution of limiting contours that define the visual presentation. The above interpretation of the psychophysical organisation of tracking implies that any aspect of the tracking situation which does not alter the critical oscillatory features of response will not change materially the level of accuracy in the situation."

Lincoln in 1953 described three types of instrumental alteration of motion in remote-control tracking devices:

1. TRANSLATIONS- the motion of the cursor directly reflect the characteristics of the motion made by the operator, these translated motions being either amplifications or reductions of the operators' motions.

Instrumental Alterations of the Operator Motions Required to Achieve Control of the Position and Rate of Travel of the Cursor

Type of Tracking	Positioning Motion	Rate Motion
Direct	Translated into cursor positioning	Translated into rate of cursor travel
Velocity	Transformed into direction of cursor travel Transformed into rate of cursor travel	—
Aided	Translated into cursor positioning Transformed into rate of cursor travel—the translation and transformation are integrated.	—

FIGURE 6. Instrumental alterations of the operator motions required to achieve control of the position and rate of travel of the cursor.

Lincoln RS. Visual Tracking: III. The Instrumental Dimension of Motion in Relation to Tracking Accuracy. **The Journal of Applied Psychology 1953; 37**:489-493.

2. TRANSFORMED MOTIONS- reflect the operator's movements only in a special way, since the system output is not a direct counterpart of the motion input.

3. INTEGRATIONS of motion involve the combination of one output of a simultaneous translation and transformation of the same movement of the operator.

Three instrumental alterations of motion have been described

a) Direct tracking system

b) Velocity tracking system

c) Aided tracking system, [Table 6].

Direct tracking involves two translations of motion, velocity tracking produces two transformation of motion. Aided tracking system involves the integration of the simultaneous translation and transformation of the same positioning motion.

Lincoln's study was designed to show acquisition and transfer of skill in the operation of remote control tracking devices.

Eighteen subjects were divided into three groups each of which received training on either direct, velocity or aided tracking for a period extending through six successive days. On the seventh day, twelve subjects form each training group transferred to different types of tracking while the remaining six subjects in each group continued on the device on which they had been trained. The authors described that

the instrumental characteristics of control devices are prime determinants of the accuracy with which those devices may be operated. The accuracy of direct tracking was consistently superior to both aided tracking and velocity tracking. Aided tracking was superior to velocity tracking. The effects of training are highly specific in nature, the best performance in transfer to any type of tracking is achieved by subjects who are trained on that specific type. Negative transfer effects appear when subjects transfer from aided or velocity tracking to direct control tracking. While on transfer from direct control to aided or velocity, positive transfer effects appear.

Borland and colleagues have done extensive work using an ADAPTIVE TRACKING TASK .In this version of the tracking task the subject is required to position a spot inside a randomly moving circle displayed on an oscilloscope. The movement of the spot is controlled by a hand-held stick, and an error signal, proportional to the distance between the spot and the centre of the circle, controls the difficulty of the task by modulating the mean amplitude of the movement of the circle. The apparatus provides the adaptive component which maintains optimum performance of the operator. Experiments were carried out in sound-attenuated rooms. Subjects were required to reach a steady level of performance on the task before the studies commenced. Each assessment of performance lasted ten minutes, with only the mean amplitude of the task over the final 500sec being computed. Healthy male subjects

were used. Avoidance of alcohol was ensured. These authors described decrements in performance 10hours after 200mg heptabaritone ,at 10 and 13hours after 300mg and 10h,13h,16h and 19hrs after 400mg of heptabarbitone,[Borland, Nicholson 1974].

Borland and colleagues using pentobarbitone sodium showed the residual decrement in performance after overnight ingestion of 200mg was very similar to those observed after heptabarbitone 400mg. Residual effects on visuo-motor coordination were related to dose both in their persistence and in the decrement at a given time interval ie impaired performance persisted longer with higher doses (although still within the therapeutic range).The above studies using the tracking task, established it as a sensitive tool in the investigation of performance related effects. It was therefore used to investigate the residual effects of benzodiazepines - diazepam, flurazepam HCl, nitrazepam . Performance was impaired for 16hrs after flurazepam HCl 30mg and to, 19hrs after nitrazepam 10mg, the effects with diazepam 10mg were more limited,[Borland, Nicholson 1975].

Kortilla and colleagues,[Table 4 Page1] in a study comparing etidocaine and bupivicaine demonstrated that despite practice, all subjects improved performance with training in the control group on the CRT and coordination tests,[Kortilla, Hakkinen, Linnoila 1975].

Two different tracking tasks were used to measure coordination. Subjects attempted to keep a black ball on an

illuminated track by turning a steering wheel. Tracking test I was driven at a fixed speed, while tracking task II was driven at a free speed, and the driving time recorded. Measurements made were

a) the number of mistakes ie no of times the subjects went off the track)

b) mistake percentage ie the percentage of the total length of the track the subjects were off).

Neither bupivicaine or etidocaine impaired CRT compared to placebo. Bupivicaine impaired the parameters measured in the coordination tracking tasks. The mistake percent in tracking task II was significantly ($P<0.05$) higher after bupivicaine than after the saline placebo, whereas a significantly ($P<0.05$) lower percentage was observed with etidocaine than after saline. Driving times were unaltered during the entire experiment. CFFF was significantly impaired with both etidocaine and bupivicaine compared with placebo. The above tests give a suitable battery of tests to assess arousal, coordination and reaction times.

No mention is made of total time on each task, which may affect performance , if as stated the task was short enough to allow a subject to arouse themselves to do the task and not long enough to elicit an element of boredom.

Nicholson (1979) concluded that studies on the immediate and residual effects of benzodiazepines, showed impaired performance after diazepam 10mg, which was limited to a few

hours after ingestion and there was little likelihood of residual impairment with overnight ingestion, as long as the dose did not exceed 10mg.

Kleinknecht and colleagues reviewed the effects of diazepam on a variety of psychomotor and cognitive tasks. The 40-50 different tests used in the studies reviewed were grouped by the authors into six classes according to similarity of functions tested. As with other reviews the number of variables eg dosage level, route of administration, type of subject etc render the results difficult to compare,[Kleinknecht,Donaldson 1975]. They reviewed the pursuit rotor test - which is similar to a tracking task. They included details on Milner and Laudauer (1973) who administered 10mg of diazepam over a 14hour period and found the pursuit rotor test to be unaffected. Also included was work by Hughes and colleagues who devised a "pursuit meter" to measure attentive motor performance - which Kleinknecht et al described as having similarities to both driving simulators and the pursuit rotor task. They found no effect on this test from 6mg of diazepam for 48hrs prior to testing,[Hughes, Forney, Richards 1965].

Clarke and Nicholson (1978) studied the effects of diazepam and its metabolites 3-hydroxydiazepam (temazepam) and 3 hydroxy, N-desmethyldiazepam (oxazepam) on performance using a tracking task. Performance was observed from 10-16hours after overnight ingestation of diazepam 5 & 10mg, temazepam 10,20 and 30mg and oxazepam 15,30 and 45mg and from 0.5 -

6.5hrs after morning ingestion of diazepam 10mg,temazepam 20mg, oxazepam 30mg. Visuo-motor coordination (VM coordination) was not impaired by overnight ingestion of diazepam 5& 10mg, temazepam 10,20 and30mg or oxazepam 15&30mg.But with temazepam 30mg there was a residual effect on performance, (oxazepam, performance 10hrs after ingestation).

With morning ingestion VM coordination was impaired at 0.5 and 2.5hrs after diazepam,10mg, at 0.5h temazepam 20mg, and at 2.5 and 4.5hrs after oxazepam 30mg.

These results of impaired performance a few hours after ingestion of diazepam are in keeping with results by other authors using other performance tests (eg auditory vigilance, reaction time, digit symbol substitution), showing that the adaptive tracking task is an accurate test for the detection of impaired performance. No control groups were included in this review.

Various authors have questioned the reliability of psychomotor performance tests with reference to general everyday activities that patients are involved in, on discharge from hospital. Are the psychomotor tests really a good reflection of driving ability? Hindmarch and co-authors, compared three commonly used psychomotor tests with an objective measure of car driving performance, brake reaction time which they developed. These tests were used to evaluate a new antidepressant ZIMELDINE in comparison to placebo and amitriptyline,[Hindmarch, Subhan, Stoker 1983].

The tracking task that was used was computer-controlled similar to those of an adaptive tracking procedure using parallel information processing. A joystick control was used to keep a cursor in alignment with a moving target. A visual stimulus was also presented in the peripheral field of vision. Two measures of performance were

1. 'Tracking accuracy' - the root mean square deviation of movements of the cursor from the 'track' programme.
2. Reaction time to peripheral stimuli.

Other laboratory tests included CRT, CFFT.
Brake reaction time was carried out in a SAAB 900 TURBO. A VDU fixed to the windscreen presented visual stimuli, to which the subject was required to respond by depressing the brake pedal as quickly as possible. One hour after treatment with both drugs, no significant differences in tracking accuracy were found. Significant differences were seen four hours after treatment - amitriptyline produced a significant reduction in tracking accuracy compared to placebo and zimeldine. There was no significant difference between zimeldine and placebo at this time.

The peripheral awareness component produced no significant differences either at one hour or four hours post treatment.

The brake reaction time was significantly prolonged for measurements taken two hours after treatment, but no statistically significant difference after five hours. As

the authors stated, there seems to be a significant practice effect in this test, which has not been adequately resolved by the learning period.

This paper has attempted to compare a tracking task with a more realistic form of driving. The major problem from the point of comparison being the different times at which measurements were made due to practical problems - the laboratory tasks preceding the BRT by one hour. The maximum effect of amitriptyline was seen at two hours for BRT but at 4 hours for tracking task - suggests a peak effect between 2-4 hours. The effect of practice also has to be taken into account for the BRT falling between 1 & 5 hours for all treatments.

No significant treatment differences were found for the reaction time obtained from the peripheral awareness component of the tracking task either at one or four hours post-treatment.

Borland and Nicholson (1984) attempt to define the basic forms of visuo-motor coordination tasks - compensatory and pursuit. In a compensatory tracking task the display presents a stimulus which shows only the difference between the forcing function and the system output. In a pursuit tracking task there is a visual presentation of both the forcing function and the system output. They both require the operator to maintain a minimum error score; in the pursuit task the operator can use an element of anticipation based on the knowledge of the parameters of the forcing

function.

The tracking task they used was a micro-processor based pursuit tracking task, in which the mean amplitude is automatically adjusted to match the subject's skill.The target circle (1.5cm diameter) was driven in X & Y planes across a screen of a Cathode Ray Oscilloscope (CRO) (25cm x 25cm). The subject was seated 40cm from the display and used a two axis joystick to maintain the marker dot within the moving circle. A gradual increase in the mean amplitude of the target movement occurs if trials are successful and a decrease occurs if failures occur. Each test run lasts 600sec and the last 500sec is scored.

Borland and Nicholson included two criteria into their tracking task - ensuring that the overall difficulty of the tasks should remain constant from run-to-run, but also the movements must change enough to prevent subjects remembering parts of the task. They achieved these objectives by selecting a random starting point within X and Y for each trial, digitally low-pass filtering a random sequence to produce a task with the required amplitude and frequency, but lasting 1/8th of the total time required, they also selected two subsequences (x & y) of different length, within the main sequence, enabling no discontinuity of movement to be detected. And finally by playing out x in the forward direction and looping these back at the appropriate points to produce a continuous task of the desired length. The circle and dot positions were updated by the computer 40

times per sec and a radial error signal calculated and compared to the circle radius. For precise mathematics see original paper [Borland, Nicholson 1984]

VMC was used by Nicholson and Stone to assess the central effects of H_1 and H_2 antagonists. The H_1 antagonist triprolidine(10mg) being used as an active control.

Nicholson and co-authors assessed the effects of single oral doses of mequitazine (5and 10mg), terfenadine (60mg) and triprolidine (10mg) as active controls using a tracking task, digit symbol substitution, CFF test and dynamic visual acuity. Mequitazine (5mg) impaired visuo-motor control 7.5hr after ingestion, the authors attributing this to a chance result, as there was no effect on other tests, [Nicholson and Stone 1983].

Nicholson and colleagues also used a tracking task to assess the effects of single oral doses of cimetidine (200 and 400mg) and rantidine (150 and 300mg). There were no adverse changes in performance. The triprolidine being used as an active control and impairing visuo-motor coordination,[Nicholson,Stone 1984].

They concluded that use of a VMC task (tracking) in drug studies was a very sensitive task providing useful information on the persistence of a drug effect, but the interpretation of the impairment as that of the obvious skill implied by the task may not be entirely correct.

Denis and co-authors [Table4 Page 2], attempted to assess the reliability and validity of three psychomotor tests of recovery from anaesthesia; rotary pursuit, pegboard, or track tracer. The used a Lafayette polar pursuit apparatus (No 30013) - an illuminated stimulus 1.9cm long and 1.85 cm wide moved in a clockwise direction in a circle with an outside diameter of 15.9cm and at a constant speed of 20rpm,[Denis,Letourneau,Londorf 1984]. The subject required to keep a photoelectric wand inside the target in motion as long as possible. A counter-clock connected to the apparatus was inhibited each time the wand was off the target. Each run lasted 30 sec. This test was compared with a pegboard and trace tracker. They concluded that both the rotary pursuit test and pegboard had significant practice effects and the experimental groups ie those anaesthetised did not reach the baseline at the end of the trial. Only the patients on the trace tracker returned to baseline testing levels, but the authors themselves point out that this may be in part due to the short period of time the task is in use, which may have an arousal effect on higher cortical functions.

Miles and colleagues used a tracking task as the primary task and a secondary (signal detection) task to assess the interactive effects of mood induction and alcohol consumption. Although tracking ability was independently sensitive to both time on task and alcohol, no interaction between alcohol and mood was observed, [Miles, Porter, Jones

1986].

Moss and co-investigators [Table 4 Page 2] assessed recovery after anaesthesia using the Maddox Wing test(MW), Critical flicker fusion test (CFFT),Choice reaction time (CRT), Line analogue rating scales (LARS), a tracking test and a test of semantic memory in 44 patients who had undergone minor gynaecological surgery,[Moss,Hindmarch, Pain et al 1987]. The patients were allocated randomly to one of two groups and received either methohexitone, nitrous oxide, oxygen and halothane or methohexitone, alfentanil, nitrous oxide and oxygen. Except for the CFF test, which showed the alfentanil patents to be less sedated than the halothane patients on the morning after anaesthesia ($P<0.05$), the results of the tests were similar in both groups and showed, initially, substantial impairment of psychomotor functions which gradually returned to baseline values. The CFFT test was found to be the most sensitive test of cognitive function following anaesthesia. This comparison with halothane anaesthesia indicated that a technique using methohexitone and alfentanil is suitable for day-case surgery. The study suffered from inadequate time for training, as tests on the morning after anaesthesia indicated that performance in both treatment groups had improved on baseline as a result of practice. The authors point out that it is essential to provide adequate practice when using tasks with a pronounced learning effect. This paper again emphasises that psychomotor function may not have returned to normal for

some hours after either anaesthetic technique, confirming the need to warn patients not to drive for at least 24hrs after day-case anaesthesia.

Maylor and colleagues looked at the effects of alcohol and extended practice on divided-attention performance using a tracking task and auditory detection task,[Maylor,Rabbitt, James et al 1990]. Previous work has suggested that practice has an effect on performance as practice leads to the development of automatic, processes,(Schneider and Shiffrin 1977). Craik (1977) suggested that alcohol is thought to reduce attentional capacity or cognitive processing resources. Therefore alcohol will show a greater decrease in performance on tasks requiring effortful processing (early in practice) than on tasks requiring less effortful and more automatic processing (late in practice). Maylor 1990 used a computerised visual tracking task incorporating a joystick. This controlled the movement of a cross on the screen measuring 11mm x11mm. The joystick allowed the cross to move in one of eight directions (N,NE,E,SE,S,SW,W,NW). The target was a regular octagon (12mm diameter) that moved randomly around the screen (but never beyond it), also in eight directions. It changed direction every 1.33sec. Both target and cross moved at constant speeds. When a finger controlled trigger button on the joystick was held down, the cross doubled its speed, and when the trigger was released, the cross returned to its original speed.

Performance in the tracking task was not significantly

affected by alcohol, but it did improve with practice. The effect of a dual-task condition with tracking was to impair performance.

From the above, it can be seen that tracking times have been used extensively in pharmacological research. Again few are standardised in time, apparatus and drugs used and environmental conditions. But generally it is regarded as a sensitive tool in the assessment of psychomotor impairment (coordination).

ABBREVIATIONS FOR TABLES 2,3,4.

AC - active controls

AN - anaesthetists

atps - attempts

ATT - adaptive tracking task

attent test - attentional test

BC - baseline

CFFT - critical flicker fusion frequency

DP - dental patients

Enf - enflurane

GP - gynaecology patients

Hal - halothane

HV - healthy volunteers

OC - own controls

OP - orthopaedic patients

PM - premedication

Prg - programme

PS - psychology students

SP - surgical patients

STP - sodium thiopentone

T - trials

TT - tracking task

↑ ↓ - increase/decrease

Table 2. PSYCHOLOGICAL TESTING

A REVIEW OF THE SERIAL REACTION TIME TEST

Kortilla et al 1975	11	HV	Bupivicaine 0.5% 1.3mg/kg Etidocaine 1% 2.6mg/kg Saline	Y	?	Y	Y	SCRT TT	CRT not impaired by any of the drugs.
Bruce & Bach	100	HV	N_2O 500ppm + hal 10ppm N_2O 500ppm N_2O 50ppm + hal 1ppm N_2O 50ppm N_2O 25ppm + hal 0.5ppm.	N	3&7 min	N	N	SCRT	Very sensitive decrement in perf as small as 50ppm. Very sensitive test.
Kortilla et al 1977	34	HV	Premed-Atropine0.5mg Hal/N_2O/O_2 0.75%-1.5% Enf/N_2O/O_2 1.5%-3%	?	25stim	Y	Y	SCRT Prg I Prg II	Hal+Enf ↑CRT Residual effects seen more clearly with Prg II.
Kortilla et al 1977	10	HV	Prilocaine 2% 3mg/kg Mepivicaine 2% 3mg/kg Saline	Y	?	Y	Y	SCRT TT	No change in any test (CFFT, TT,ATT)

Smith & Shirley 1977	10	AN	Air Air/Hal 100-150ppm	N	-	Y	N	DCRT	No change post air & post-hal.
	15	PS	Air Air/N_2O 500ppm /hal 15ppm	N	9min	Y	-	SCRT	No sign diff pre or post air or air/hal N_2O.
Wernberg et al 1980	10	HV	NO 0% 10% 20% 30%	N	-	N OC	N	SCRT	30% NO prolonged CRT. (single & double-handed)
Edwards 1981	40	HV SP	Not standardised	Y	6T	Y	N	SCRT	CRT ↑ days 2-6 Max impairment at 4-5days postop 14days, 27 SP recovered, 3 impaired for 3 weeks.
Millar & Standen 1982	40		Brompheniramine 12mg Linear release (LR) Non-LR	-	30min	Y	Y	SCRT	Impaired at 2.75 & 5.5hrs for NLR, CRT↑ 5.5hrs for LR.
Scott et al 1983	39	GP	Thiopental(4.5mg/kg) N_2O,O_2/hal Fentanyl + Methohex N_2O,O_2 + Methohexitone.	Y	5min	Y	N	SCRT	MRT ↑ 2hrs, 6hrs methohex grp slower than others.

Herbert et al 1983	55	SP	Premed-diazepam 10mg Thiopental (250mg) N_2O,O_2,hal IPPV in 22SP SR in 21SP	Y	5min	Y	-	-	Mrt ↑ 90min. ↑MRT 1st day those induced wih halothane. Impaired MRT 2nd day post-op SR grp.
Herbert, Makin,1985	54	SP OP	Premed-diazepam10mg Propofol 2.5mg/kg STP 5mg/kg N_2O,O_2,hal	-	5min	Y	Y	SCRT	STP grp slower at all points on MRT.Propofol grp did not differ from controls.
Barker et al 1986	50	DP	No premed Midazolam 2.5mg→ 1.25mg/30mins Diazepam 5mg → 2.5mg/30mins.	-	2min	N	Y	SCRT	No sign diff between grps.
Baillie et al 1989.	65	GP	Premed-temazepam placebo Alfent 10µg Propofol 2mg/kg (infusions of both)	N	75sec	Y	-	SCRT	Sign diff CRT 30min after anaes cf BL of placebo grp. Temazepam grp highly sign diff cf BL.

Kortilla, Nuotto, Lichtor 1992.	12	HV	No premed Propofol 2.5mg/kg→ 1mg/kg. STP 5mg/kg → 2mg/kg.	N	40stim	Y	Y	SCRT	Sign ↑ MRT in STP grp up to 5hrs post-injection.
McMenemin et al 1988	12	HV	100% O_2 0.4%isof 25% N_2O	N	15 trials	Y	Y	SCRT	N_2O & isof ↑MRT. Isof ↑ cf N_2O.Isof reached effect at 15min.

Table 3. PSYCHOLOGICAL TESTING

A REVIEW OF THE DISCRETE CHOICE REACTION TIME TEST.

MacKenzie& Grant 1985	80	SP	No premed Propofol 2.5mg/kg Methohex 1.5mg/kg STP 5mg/kg ↓ 66% N_2O/O_2+ enf	N	25atps	Y	Y	DCRT	STP ↑ CRT 30, 60,90,120min. Methohex ↑MRT 30min,normal 60,90mins. Propofol,↑ motor component of CRT, normal by 60min.
MacKenzie & Grant 1985	60	SP	No premed Spinal anaes Propofol 2.5mg/kg Methohex 1.5mg/kg	N	25atps	Y	Y	DCRT	Propofol ↑CRT both elements 30min, only motorcomponent at 60min. Meth both components ↑ 30 & 60mins. No sign effects at 2 & 4hrs.
Anderson et al 1985	30	GP	Hyoscine 0.4mg Atropine 0.6mg Placebo ↓ STP→N_2O,O_2, hal		15 trials	Y	Y	DCRT	Hyoscine grp slower total CRT. Hyoscine grp slower to initiate motor movement.

Fagan et al 1987	8	HV	Ethanol 0, 0.2g/kg, 0.4g/kg,0.8g/kg.	No PT	-	Y	Y	DCRT	CRT not sign prolonged until 2.5hrs after 0.8g/kg dose.
Moss et al 1987	44	GP UP	No premed Alfent, methohex → N_2O,O_2,Hal	N	5 trials	-	Y	DCRT	↑ CRT after surgery, 19hrs approx at baseline levels
Zuurmond et al 1989.	22	OP	No premed Methohex 1mg/kg Atracurium 0.5mg/kg N_2O,O_2,isof	N	-	-	-	DCRT	↑ CRT up to & including 120 min.
Sanders et al 1989	40	SP	No premed Propofol STP N_2O,O_2,hal	?	?	N	Y	DCRT	↑ CRT at 1hr cf baseline 3hrs CRT ↑ above baseline
Sanders et al 1991.	36	GP	No premed Propofol →boluses STP → boluses	Y	?	N	Y	DCRT	↑ CRT for grps at 1hr. 2nd day improvement in in CRT of both grps from baseline.
Hickey et al 1991.	10	SP	No premed Propofol N_2O,O_2,enf/ hal	-	20 resps	N	N	DCRT	↑ median RT in 30-60min post-anaes period was not sign.

Table 4.

PSYCHOLOGICAL TESTING

A REVIEW OF THE TRACKING TASK

Authors Date	Num in Grp	Popln Grp	Drugs Dose	Pract Effect occurs	Time on Task	Cont Grp	Rand	Variables Studied	Effect on each Task
Borland Nicholson 1974	7	♂HV	Heptabarb 2,3,400mg	N	10m	Y	Y	Adapt Track	Decr in perf persists longer after higher doses
Kortilla et al 1975	11	HV	Bupivicaine 0.5% 1.3mg/kg Etidocaine 1% 2.6mg/kg Saline	Y	?	Y	Y	Track I-fixed speed driver II-free speed driver.	Bupiv higher % of mistakes than placebo. Etid lower % of mistakes than placebo.
Hindmarch et al 1983	9	HV ♀	Amitriptyline 50mg Zimeldine	N	?	Y	Y	Adapt TT	No sign diff between zimeld & placebo.

Nicholson Stone 1983	6	HV	Mequitazine 5mg Triprolidine 10mg Terfenadine 60mg	?	10min	Y	Y	VM coord AC	Impaired 7.5hr with meq 5mg. Triprol impair VMC. No other impairment.
Nicholson Stone 1984	7	HV	Cimetidine 200mg 400mg Ranitidine 150mg 300mg Triprolidine 10mg	?	10min	Y AC	Y	VM coord	Cimet/Rantid no perf decre. Triprol impair VMC at 1.5-5.5 hrs.
Denis et al 1984	60	SP	PM-Meperidine 1mg/kg Atropine 0.4mg Thiopental, sux, nitrous oxide,oxygen isof/enf.	Y	30sec	Y	N	Rotary Pursuit	Sign diff between SP & control. Baseline not achieved at final trial.
Moss et al 1987	44	SP	No premed. Alfent 250µg Methohexitone Nitrous oxide,oxygen Alfent 250µg/5mins	Y	1min	N	Y	TT	Alfent grp impaired at 2hrs.
			Methohexitone Nitrous oxide,oxygen halothane					TT + distract test	Impaired at 2h Alfent grp poorer scores at 3hr than pre-test. Halothane grp better at 19hr than baseline.

CHAPTER FOUR

METHOD

METHOD

Ethical committee approval was obtained.

DESIGN

Volunteers were randomly sedated with subanaesthetic doses of isoflurane (0.2 - 0.75%) and enflurane (0.2-0.6%). During each sedation session the components of the auditory evoked response (AER) were measured at each concentration step, along with two measurements of performance, the choice reaction time and a tracking task, both presented to the volunteer on a computer.

RECRUITMENT OF VOLUNTEERS.

For the initial part of the study 10-15 volunteers were required. They were required to be within the age range of 16-65 and to be healthy. Volunteers were recruited in three ways.

1. Three advertisements were placed in the Glasgow Herald in three successive weeks. Volunteers were asked to apply to the stated address, as can be seen below.

2. Notices were placed in the unions of Glasgow University, asking for volunteers to apply (with the exception of medical and nursing students, who were excluded by the protocol).

3. Notices were also placed in Glasgow hospitals, other than

the Western Infirmary.

The responses from the three areas were good, and about 50 names were collected initially.

Once volunteers applied to the advertisements, they were sent a questionnaire on their general medical health. These were returned to the department and analysed for selection. The following were criteria for exclusion:-

1. Age other than from 16-65.
2. General ill health
3. People with chronic pain.
4. Neurological disease
5. Females likely to be pregnant.
6. Alcohol abuse.
7. Those on sedative drugs.
8. Solvent abusers or drug addicts.

Selected volunteers were then asked to visit the hospital, for their initial session to assess fitness.

SESSION ONE

Volunteers were questioned if there were any queries on the initial questionnaire. A full physical examination was undertaken to exclude cardiovascular, respiratory and neurological disease and to assess hearing ability. The ears were examined with an auriscope to check for the presence of wax or any disease. Volunteers then undertook an audiometric test using a screening audiometer, [Figure 7 and 8]. Clinical assessment of the airway was also performed.

Ability to obtain adequate AERs was an essential part of the study. This was assessed at the initial visit when the volunteers would lie on a bed, and have three electrodes placed on their head, after thorough cleaning of the skin with Omniprep (SLE) and alcohol. The active electrode was placed on the right mastoid, the reference electrode at the vertex and the ground electrode at the left mastoid. Headphones were applied to stimulate the right ear.

The long-latency and brainstem AERs were measured. Parameters for AER are given under the section on equipment. The two performance tests used for this project were:-

1. A choice reaction time task (CRT)
2. A tracking task (TT).

Volunteers needed a period of time to learn the two tasks, they were therefore allowed to perform the tests five times each. The first group of volunteers (Group A containing 15 volunteers) performed these tests while sitting at a desk

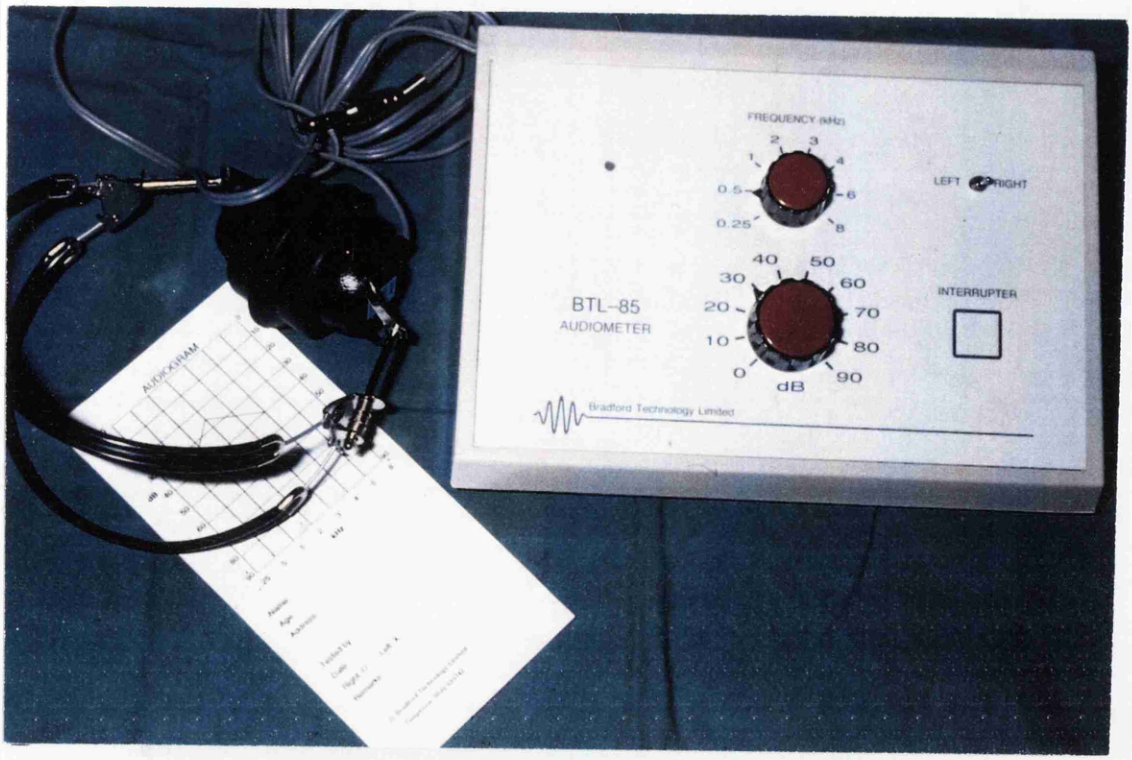


FIGURE 7. Photograph showing audiometric equipment.

FIGURE 8 The photograph shows a volunteer having his hearing tested.

with the computer in front of them. It subsequently became clear that they could attain faster mean reaction times (MRT) and tracking times (TT) in this position, than while sitting in a bed with the computer in front of them.
Finally 20mls of blood were obtained for the following tests.

1. Full Blood Count and Platelets
2. Urea and electrolytes
3. Liver function tests

Several volunteers were excluded for the following reasons:-

1. Hypertension
2. Previous myocardial infarction (noted from questionnaire)
3. Inability to perform performance tests adequently on a computer
4. Minor biochemical upsets eg Gilbert's syndrome.

Thirty volunteers were assessed. They were divided into two groups A & B. Group A each attended three sedation sessions, and were given isoflurane 0, 0.31, 0.5, 0.75%(actual concentration),enflurane 0, 0.17, 0.42, 0.6%(actual concentration); the layout of the placebo session was the same as that for the isoflurane and enflurane. Group B attended for two sedation sessions and were given a placebo run and isoflurane 0, 0.2, 0.31, 0.4% (actual concentration). Actual mean concentrations are given as the vaporisers were calibrated using an accurate gas chromatography technique, [Gray ,1986].

SEDATION SESSION - PREPARATORY RUN

A preparatory run of the sedation session was performed to ensure that small practicalities were correct before the procedure took place.

The following points were obvious problems:-

1. A tilting bed was necessary in the event of regurgitation and vomiting of a sedated volunteer. The bed was positioned and experience gained of the tilting mechanism.

2. The gas delivery system needed to be positioned to allow access to the patient with the Bain circuit connecting and access to the four size G air and oxygen cylinders, [Figure 9].

3. The computer and apparatus necessary to measure AER was positioned on the right side of the bed.

4. A table was obtained to place the computer on, over the bed, allowing the volunteer to see the screen easily. A small portable lap tray was obtained to accommodate the keyboard and mouse, allowing the volunteer to manipulate them.

5. Monitors to measure heart rate, blood pressure, axillary temperature and oxygen saturation were positioned and attached to the patient. All the above measurements were made with one system, a Criticare

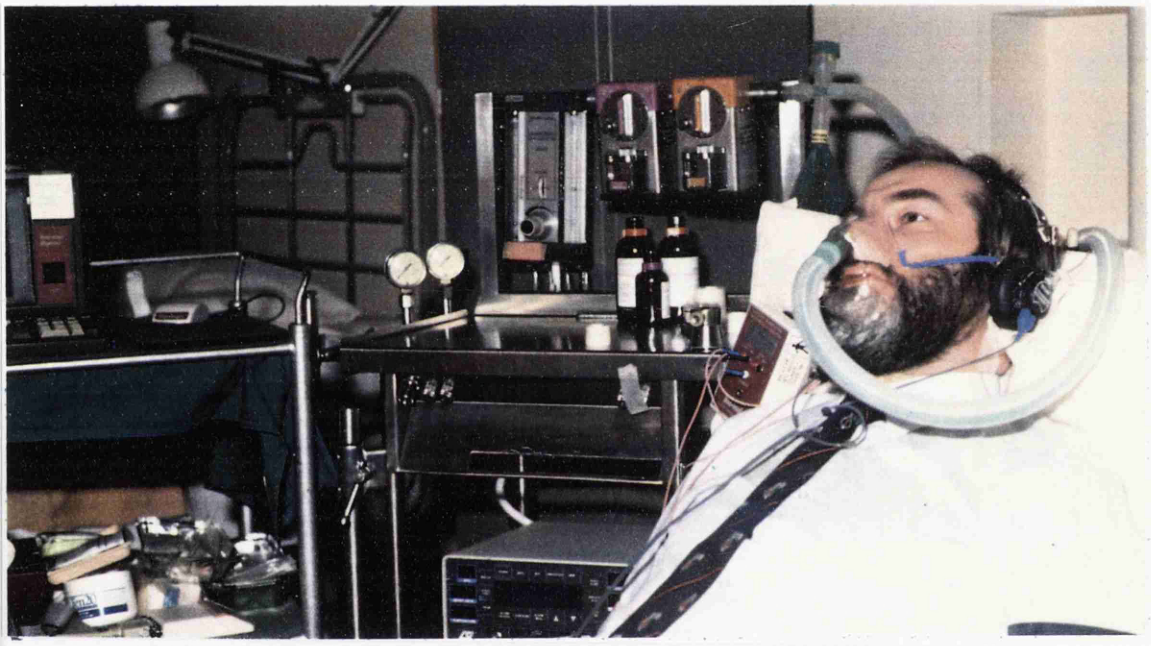


FIGURE 9. Photograph illustrating the arrangement of equipment on the volunteer, and the anaesthetic machine and auditory evoked equipment in the background.

monitor.

6. As volunteers were required to wear a large amount of apparatus around the head and neck, a system for placing this on with the least inconvenience was devised. Initially the Hudson mask was fitted in a comfortable position for the volunteer. The AER electrodes were placed behind the two mastoids and on the vertex, after preparation of the skin. These were secured with a swab and micropore tape. Finally the headphones were adjusted for size and placed on the ears.

7. The brainstem AER, early and late cortical AERs were measured.

8. The Normac monitor to measure end-tidal CO2 was calibrated using calibration gas.

The Normac was not quite in calibration but compensation was possible. Reading on normac was 1% higher than actual enflurane concentration.

Normac reads	Actual enflurane
0.15	0
3.8	2.8

Monitor was reset and recalibrated (subtracting 1% from each reading). The Normac was not used throughout the study because the information in gave was unreliable.

BASIC FORMAT FOR SEDATION SESSION

For each visit ie placebo, enflurane, isoflurane, volunteers underwent a common sequence of events.

Initially they signed a consent form and agreed to be accompanied home or to go home by taxis. They then reclined on a bed , their neck muscles were supported with pillows. Monitoring equipment for non-invasive blood pressure, heart rate, saturation and temperature were attached to the volunteer. A Hudson oxygen mask was applied (the side ports being occluded), and the electrodes for the AERs were applied behind both mastoids and on the vertex, [Figure 10]. These were secured with tape and the headphones applied. The volunteer was asked if the computer for the psychometric tests was easily visible, and if the keyboard and mouse were in a comfortable position.

Baseline results were then collected in the following order

1. Long latency AER (LLAER)
2. Brainstem AER (BSAER)
3. Middle latency AER (MLAER)
4. Tracking task (TT)
5. Choice reaction time (CRT)
6. Heart rate (HR)
7. Blood pressure (BP)
8. Saturation (SaO_2)
9. Respiratory rate (RR)
10. Volunteers are were asked about smell, taste, diplopia, dizziness.

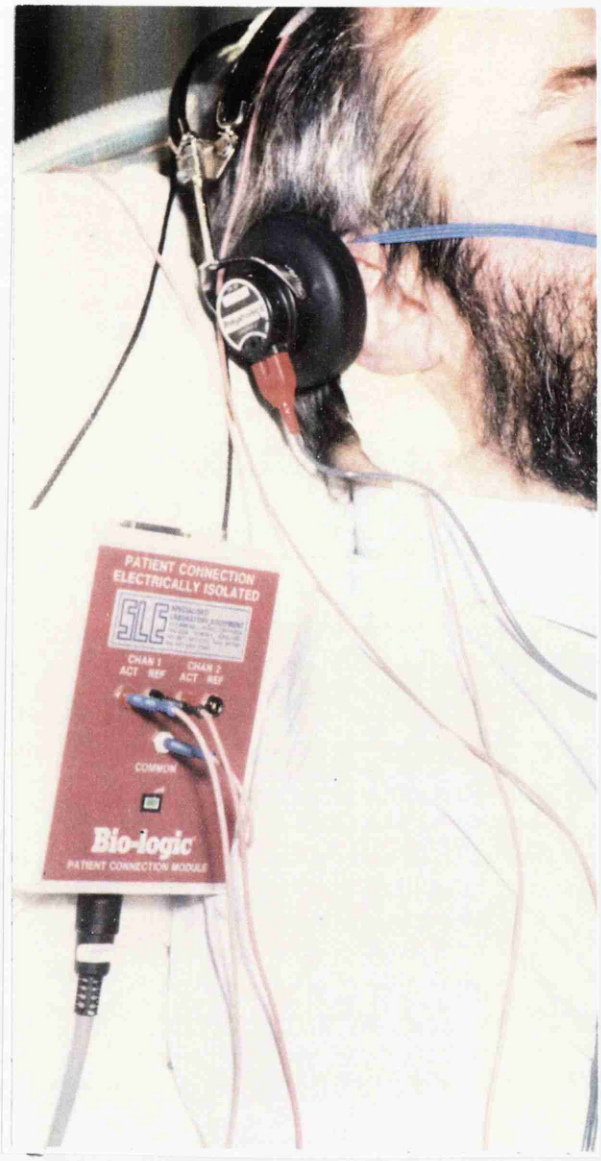


FIGURE 10. The arrangement of electrodes and headphones on the volunteer.

Both 4 & 5 are repeated until the volunteer attains a stable result or achieves the results that he/she attained at the previous visits. During each session twenty minutes was given for each concentration of gas to equilibrate before any measurements were made.

At each concentration of volatile agent and equivalent placebo level, the volunteer underwent the above tasks and was also assessed as to their ability to cooperate with the tasks, verbal contact, patency of the airway or snoring, and general state of consciousness from fully conscious, conscious but uncooperative, to unconsciousness.

Recovery was assessed at ten minutes and twenty minutes after the gas was switched off. Psychometric tests were assessed at ten minutes along with cardiovascular parameters, the AERs are measured after this, and finally the cardiovascular parameters and psychometric tests were again assessed.

The placebo session was conducted similarly, the time scale being the same ie at each " level" twenty minutes was given to allow "equilibration" as for the isoflurane and enflurane sessions.

INITIAL SEDATION SESSION WITH VOLUNTEER

On 22/10/91 the first sedation session, using a volunteer was performed.The volunteer was a 28 year old male, previously in good health

1. An audiogram was initially performed, which was normal. The volunteer rested on the bed in a sitting position to enable him to see the computer.

2. The gas measuring probe was taped to his cheek to measure end-tidal carbon dioxide and end-tidal enflurane and isoflurane at 1457hrs. The Hudson mask, AEP electrodes and headphones were all applied. A control brainstem and late cortical AEP was performed. The volunteer was then asked to perform baseline performances tests.

3. The gas cylinders at the start of the session showed the following pressures:-

   Air cylinder 13700kPa
   Oxygen cylinder 15000kPa.

   A flow of 10l/min of gas was supplied, with an FiO_2 of 0.3 through an Quantiflex mixer.

4. The first trials of AERs showed marked interference - a regular sine wave, due to the AC current from the computer and fluorescent lights. The plug arrangements were adjusted and the computer (Amstrad PC1512) was switched off. The interference on the trace was no longer present. If ambient lighting decreased, tungsten bedside lamps were used instead.

The session continued in the following way:-

1510hrs the first BSAER was completed.

1516hrs the first LLAEP was completed.

1518hrs enflurane was switched on at 0.2%. The volunteer noticed this immediately, at this point he seemed very relaxed.

1520hrs volunteer feeling fine, not sleepy as yet. NORMAC shows a respiratory swing.

1525hrs volunteer comfortable, all well.

1526hrs computer on for loading programs.

1528hrs no feelings of sleepiness.

1533hrs respiratory swings on NORMAC obviously less, but still showing very small movement - not sleepy, but feels relaxed.

1538hrs reaction time completed

Mean Reaction time (MRT) 1.05s

Reaction time Coefficient of Variation (RCV) 12.5s

Reaction success (RS) 97%

1544hrs

Mean Tracking time (MTT) 0.709sec

Tracking time Coefficient of Variation (TCV) 40.67

Both tracking time and reaction time showed a small but probably non-significant decrement in both.

1544hrs computer off to facilitate AERs, good BSAER.

1557hrs enflurane increased to 0.4%.

1603hrs all well

1604hrs volunteer feeling drowsy (equivalent to about half a pint of beer).

1618hrs CVS observations made, reaction time started, significantly more mistakes made.

MRT 1.15

RCV 13.15

RS 93.3

MTT 0.72

TCV 44.83

1623hrs AERS measured, computer off.

Marking of AERs during next run, saves time.

1631hrs AERs going well, time overrunning, from estimated time, volunteer informed of this, and agreed to stay.

1635hrs enflurane increased to 0.6%, need to keep flow of Bain circuit at 100mls/kg.

1642hrs all well, may need to start earlier, as recovery room closes at 5pm.

1644hrs volunteer describing ' feeling of floating', probably equivalent to 4-5 pints.

1655hrs

MRT 1.32

RCV 2.52

RS 86%

MTT 0.915s

TCV 42.43s

(subjects approach to target different - target is circled).

1657hrs AERs

1705hrs no problems

1707hrs slight snoring, saturation 98%.

1708hrs volunteer very sleepy, no spontaneous movement, enflurane to zero %.

1712hrs sleeping comfortably, no airway problems.

1714hrs awakened by gently shaking and saying of name.

MRT 1.353

RCV 15.06

RS 100%

MTT 0.738

TCV 34.07

1719hrs volunteer still feels sleepy, equivalent to 4-5 pints of beer.

1722hrs volunteer now feeling less sleepy,but aware that he 'dozed off'.

1728hrs Final performance tasks

MRT 1.12

RCV 10.32

RS 100%

MTT 0.711

TCV 40.89

1731hrs final AER

1744hrs mask off, volunteer feeling well.

This initial run of the experiment allowed us to predict any problems, for instance the interference on the AER computer from other ac mains sources such and the Amstrad computer and fluorescent lightening. The normac vapour analyser, demonstrated respiratory swings, but gave no useful readings, as the scale was too small.

PSYCHOMOTOR TASKS

CHOICE REACTION TIME

A choice reaction task is a task which requires the volunteer to react to the onset of a discrete random stimuli. The magnitude of this reaction time is measured.

In this project we used a computerised CRT task developed by Dr W. Gray. The volunteer views the monitor, by keeping his finger on the letter "B" key, a random number will then appear on the screen; the numbers used are 4,5,6,7,8,9. The volunteer presses the appropriate number key in response. The sequence involves 30 trials ie 30 numbers each requiring a response. The computer programme checks that the starting key has been pressed initially, and checks that it remains pressed after one second and subsequently after every 0.1 second. These times correspond to the times the computer waits before the first (1s) and subsequent (0.1s) auto-repeats of a pressed key.

The programme allows a minimum delay, between pressing the letter B and a number appearing on the screen, is one second, although this delay period varies between one and three seconds, [Figure 11].

At the end of each sequence the computer displays the number of trials, number of successes, success rate, mean reaction time(sec), standard deviation, coefficient of variation.

FIGURE 11. Volunteer attempting the tracking task.

TRACKING TASK

In a typical tracking task a volunteer is required to make a response to a visual cue provided by the relative positions and rates of travel of a target and a cursor.

We have used a computerised tracking task developed by Dr W. Gray. On the monitor a small circle appears along with a cursor in the form of a cross. The movement of the cursor is controlled with a mouse by the volunteer. The small circle moves randomly. The volunteer attempts to place the cursor in the circle, at which point the circle changes colour to white.

The circle starts in the middle of the screen and moves with a fixed step length in a random direction. Obviously if the circle moves to the edge of the screen, as will have eventually happen with a randomly moving object, the task will become easier as it will allow the cursor to be placed in the circle more easily. To avoid this, there is a large invisible "boundary" circle within which the small circle is restricted, preventing the small circle approaching the edge of the screen.

The large boundary circle has a diameter of 90% of the screen height. The target circle diameter has diameter of 4% of the screen height. The fixed step length by which the small circle moves is twice the diameter of the small circle.

The default values for the mouse cursor were changed in the

computer programme to allow the cursor to have the same sensitivity to mouse movement in the x and y directions.

In the original version of the programme, once the circle was moved to a new position a fixed time would elapse before a trial was considered a success or failure, and this would then be expressed as a percentage success. This was altered in the version used in this study. Once the circle has moved to a new position, the cursor catches up and the time is measured. This alteration was made to prevent the volunteer with practice achieving 100% success with practice. Each sequence involves 100 trials.

Previous tracking tasks have measured at the end of a fixed time the distance of the cursor from the circle, [Hindmarch, 1980].The cursor on a computer used with the mouse is usually an arrow, this has been changed to a cross for ease of use. To prevent the subject moving the cursor straight through the circle but not halting inside it, the programme ensures that the cursor is inside the circle for 0.25sec before it is registered as a success. This 0.25 sec is not taken into account when the time is calculated. If the cursor does not remain in the circle for 0.25sec, the programme continues and keeps on adding to the time for that trial.

The final display shows

Number of trials

Mean tracking time (sec)

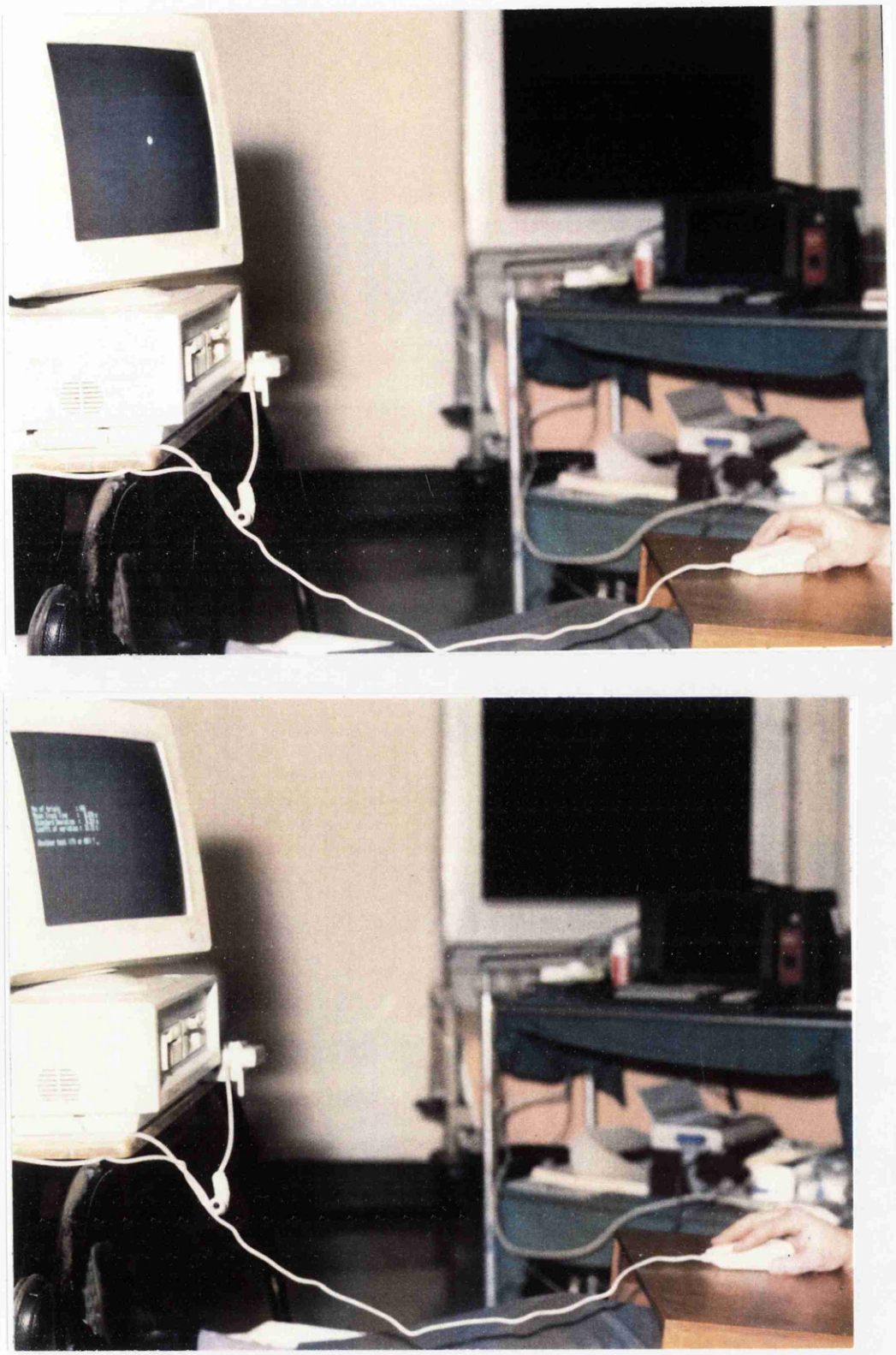


FIGURE 12. The photographs show the volunteer attempting the tracking task, and the display of results once it had been completed.

Standard deviation

Coefficient of variation, [Figure 12].

The computer programme for both the choice reaction time and tracking task were written in Borland Turbo Pascal Version.

Calculation of Results

Significance values of the means were calculated using a Mann-Whitney test.

The following comments apply to both the table of values for each variable and the accompanying graph. Significance values have been calculated for the means at each specified gas concentration and its corresponding lower concentration, and also the means at each specified concentration of isoflurane and enflurane compared to the corresponding placebo values.

STATISTICAL ANALYSIS

PROBLEMS

The data presents several analytical problems:-
First, within the data there are two studies A and B, and some concentrations of the same volatile agent occur in both groups; can the groups be combined?

Second, the numbers in some subgroups are dissimilar because excessively sedated volunteers, were been taken out of the study for safety reasons. For example in some cases there are 15 placebo results and 3 results at the high volatile agent concentrations.

Third, every hypothesis testing method makes assumptions about the data, and a common assumption is that the results in the subgroups (eg the CRT at 0.3% isoflurane) are technically independent of each other. The independence of the measurements made in the same patients at on week intervals (ie the exposures to the placebo, isoflurane and enflurane) occurred is obvious.

When comparing the effects of different concentrations of any agent (placebo. isoflurane or enflurane) during one exposure session in the same patient, the assumption of independence becomes more difficult to sustain.

Fourth, there is always a danger when undertaking multiple comparisons that by chance alone significant results might arise.

Method

Before combining data from the same concentration of volatile agents in volunteers from groups A and B, the data was tested to determine whether it could be considered to be

part of one population, by comparing both parts (ie A and B) using the Mann Whitney test. The data was only combined if the probability was less than 0.01. This testing of the Group A placebo against the Group B placebo, and the Group A concentration (eg 0.3% isoflurane) against the Group B concentration data for 0.3 isoflurane. In no case was there a significant difference between the groups, and therefore the groups were combined.

To analyse the differences between the placebo data and the data at each individual concentration a Mann Whitney test as implemented in Minitab 7 was used with a probability less than 0.01 being considered significant. The Mann Whitney test readily copes with the problems of different numbers in the groups.

To analyse the data between different concentrations the Wilcoxon Signed Ranks test was used; this was achieved in Minitab 7 by simple differencing between the relevant columns and then performing a one sample rank sum test (WTEST) on the difference results, a probability less than 0.01 being considered significant. Note that the differencing using the 'LET" Minitab command puts a missing data '*' in the column, and WTEST ignores these. This effectively means that this Wilcoxon Signed Ranks test copes with the problem of imperfect data pairing by ignoring data that is not paired.

The problem of the multiple comparisons was dealt with by choosing a more conservative level at which to assign

significance, ie a probability less than 0.01, rather than the conventional 0.05.

CHAPTER FIVE

EQUIPMENT

EQUIPMENT

1. THE GAS DELIVERY SYSTEM

The apparatus required for the delivery of the gas mixture was assembled specifically for this project. The following requirements had to be fulfilled:-

a) The apparatus required to deliver a high flow of gas, sufficient to adequately supply a Bain circuit.

b) A Bain circuit was chosen as it connects easily to a lightweight Hudson mask (the air vents at the side were taped over, to prevent dilution by air).

c) A mixture of air and oxygen was chosen to prevent any possible side-effects from the delivery of 100% oxygen, or from the supply of an inadequate amount of oxygen present in air, in a sedated patient.

d) Two specially calibrated vaporisers were obtained from Penlon to deliver low concentrations of volatile agent. As these were not of the Selectatec variety, they had to be mounted on the back bar of an anaesthetic machine.

2. COMPONENTS OF GAS DELIVERY SYSTEM

a) Four size G cylinders of each of oxygen or air.

b) A reducing valve and pressure indicator for the cylinders in use (one cylinder oxygen and one cylinder air were kept as back up cylinders).

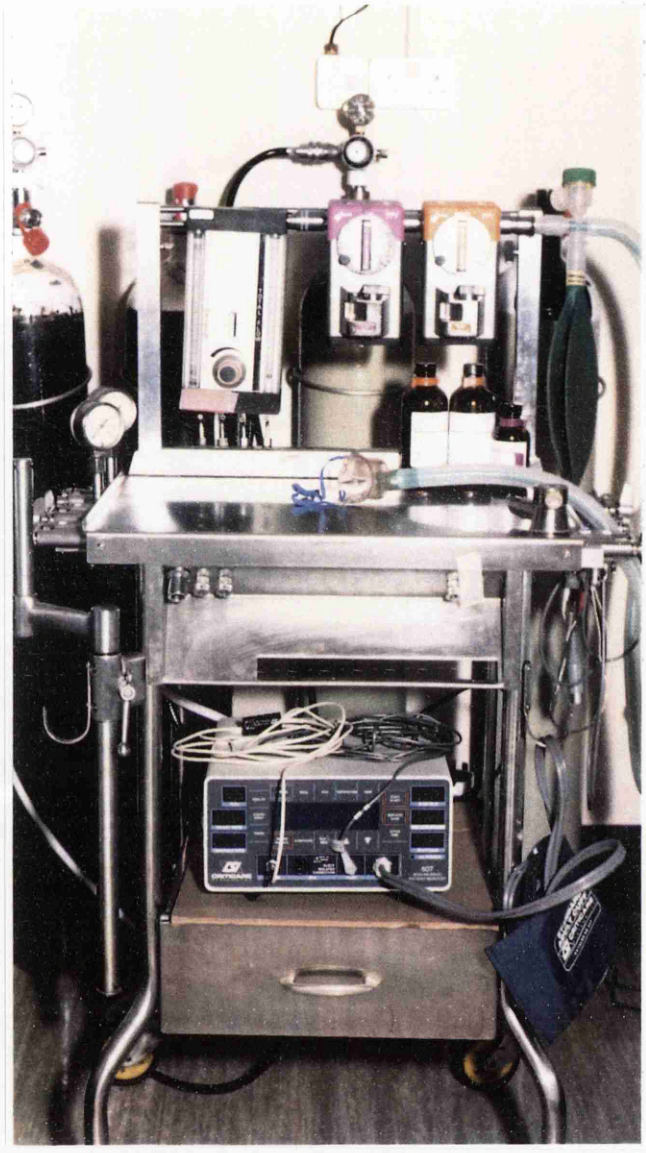


FIGURE 13. The photograph shows the equipment used to deliver the anaesthetic gases. The Quantiflex mixer is on the left of the machine, the two vapourisers on the right and a Bain circuit on the extreme right. Oxygen cylinders can be seen in the background. On the lower shelf the Criticare monitor for measuring blood pressure, heart rate oxygen saturation and temperature can be seen.

c) On the Boyles machine a Quantiflex oxygen/air mixer was mounted, along with the two Penlon vaporisers for enflurane and isoflurane.

d) The Bain circuit, [Figure 13].

3. CALIBRATION

Flow through the Quantiflex vaporiser was calibrated using a pneumotachograph, the following results were obtained.

Flow through Quantiflex	Reading on Pneumotachograph
5l/min	5.1l/min
7l/min	7.1l/min
10l/min	10l/min

The vaporisers were calibrated using a gas chromatography technique. The definitive calibration using the above technique gave the following calibrations.

Using concentration of 30% oxygen in air. Air flow being 10l/min, therefore a total flow of about 11l/min.

Isoflurane

Dial Setting	Actual conc
1st mark	0.1
2nd mark	0.2
3rd mark	0.25
0.2 click stop	0.31
5th mark	0.4
0.4 click stop	0.57

Enflurane

Dial Setting	Actual Conc
0.2 click stop	0.17
0.4 click stop	0.42
0.6 click stop	0.6

EQUIPMENT USED TO MEASURE AUDITORY EVOKED RESPONSES.

The equipment used to measure the AER was a Bio-logic Traveller Express portable computer. This computer is an IBM/AT compatible 80286 machine with 1MB RAM and two 5.25" 360K floppy disk drives, [Figure 14].

This computer is equipped with a supertwist electro-luminescent backlit LCD, 10.5in diagonal size, 640x400 resolution. There is a detachable keyboard and a mouse is present.

Hardware/software interface.

The apparatus comes complete with single or dual channel, optically-isolated preamplifiers which have the following features:-

Gain - 10-300,000
Noise level - 0.6microvolts RMS
Input impedance - >100Mohm
Common Mode rejection ratio - > 110dB at 50/60Hz
Built in impedance test - 20Hz sinewave
Active filters - 2-pole Butterworth - (12dB/octave)

High pass - (low cut) DC to 300Hz
Low pass - (high cut) 30Hz to 10kHz
50/60 Hz notch filter

Filter cutoffs, gains, and notch filter under software/operator control.

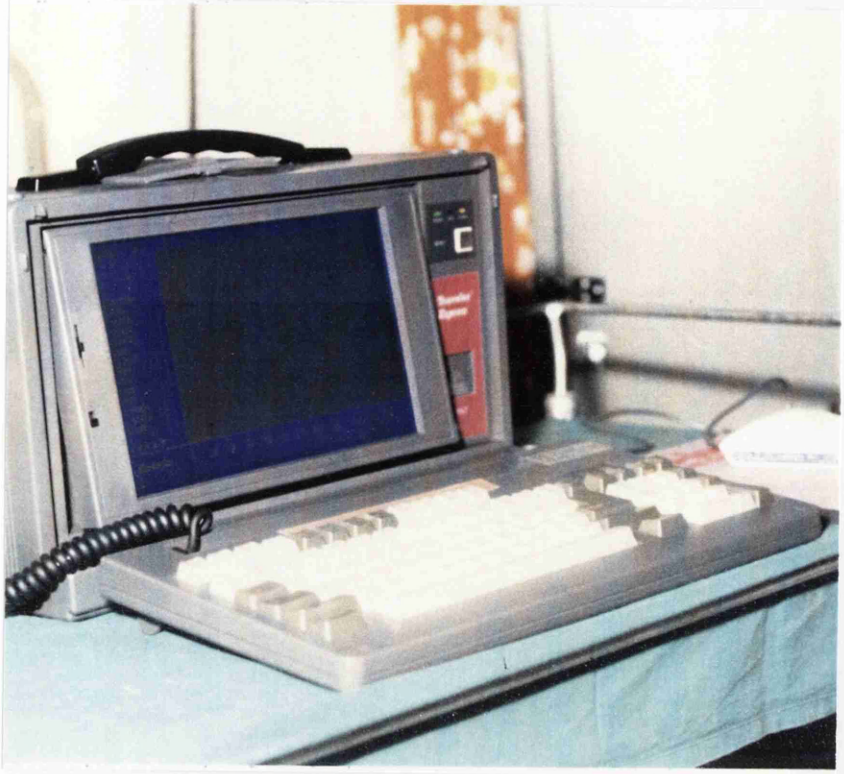


FIGURE 14. Photograph showing the computer used to measure auditory evoked responses. The screen displays the BAER and LLAER waveforms.

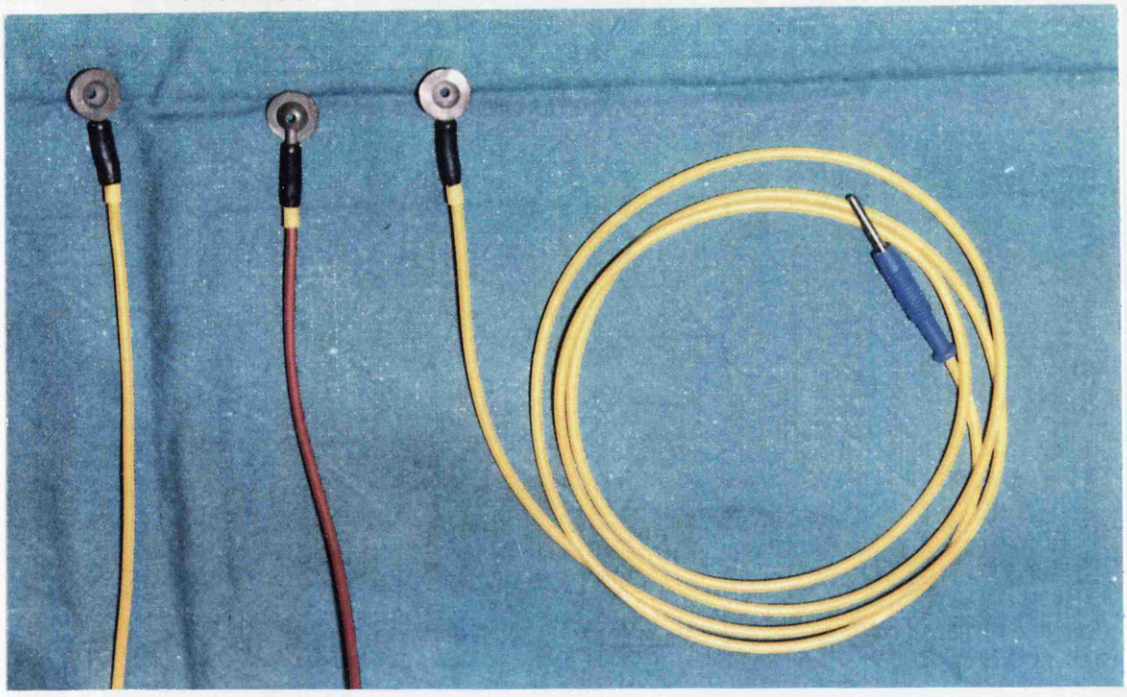


FIGURE 15. Photograph showing the electrodes used to measure the auditory evoked response.

Software and transducer

The computer is capable of measuring auditory, visual, somatosensory and electroneurography evoked responses. The operating system is Microsoft MS-DOS.

The auditory software enables the operator to programme stimulus type:- click, filtered click, single sine wave,and tone bursts.

The transducer used for this project was a TDH-39 earphones.

The frequencies, intensities, durations, rise/fall times are all programmable.

Stimulus rates: 0.1 to 200/sec in 0.1 per sec steps are available.

Stimulus intensity : 0-125 dB peak-equivalent SPL(sound pressure level) or user specified nHL (normal hearing level).

Masking is available with white noise, the intensity of which is programmable.

Analysis time: 2.56 to 9,999msec.

Analog/Digital converter: 8-bit resolution, 2 channels, 1.2 microsec conversion time per channel.

The use of keyboard or mouse controlled cursors, allows interactive positioning on waveforms during data analysis,

and calculation of absolute and interpeak latencies, amplitudes, and amplitude ratios.

A choice of 256 or 512 points per trace

The impedance of the electrodes was kept below five kohms.

This was achieved by careful preparation of the skin with Omniprep, a ground glass abrasive fluid and further cleaning of the skin with alcohol swabs. As the surface often came off the silver chloride electrodes with use, it was very important to maintain the electrodes adequently by placing them in Milton 0.01% hypochlorite solution for 24hrs. When the coating disintegrated it became very difficult to obtain low impedances, [Figure 15].

PARAMETERS USED FOR RECORDING OF AUDITORY EVOKED POTENTIALS.

BRAINSTEM

Channel 1. Window 10.24

Points 512/trace. Gain 150,000

High filter 3000Hz. Low filter 100Hz.

Notch filter in. Artifact rejection enabled.

Electrodes Cz/mastoid

Stimulus-alternating click 75dB

Max no stimulations 2048.

Stimulus rate 11.1/sec.

Stimulated ear right.

Masking white noise to left ear 45dB.

Stimulator headphones.

LONG-LATENCY CORTICAL AER.

Channel 1. Window 250

Points 512/trace. Gain 24000

High filter 150Hz. Low filter 1Hz.

Notch filter in. Artifact rejection enabled.

Electrodes Cz/mastoid.

Stimulus-alternating tone burst 75dB

Frequency 1000Hz. Plateau 180

Stimulated ear - right Rise 10

Ramp linear

Masking white noise left ear.

Max no stimulations 50. Stimulus rate 0.5/sec.

Stimulator headphones.

MIDDLE LATENCY CORTICAL EVOKED RESPONSE.

Channel 1.	Window 100.
Points 512/trace.	Gain 150,000.
High filter 300Hz.	Low filter 10Hz.
Notch filter in.	Artifact rejection enabled.
Electrodes Cz/mastoid.	
Stimulus-alternating click 75dB.	
Max no stimulations 2048.	Stimulus rate 10/sec.
Stimulated ear right.	Stimulator headphones.
Masking white noise left ear.	

The middle latency AER proved to be very difficult to measure due to artifact, most probably from muscle activity. This did not seem to be abolished with sedation until the volunteer was unconscious, although in many cases even this did not abolish the interference. Other causes of interference were excluded, such as electricity sources. When these caused interference the pattern was not the same, and much more obvious.

OTHER EQUIPMENT INVOLVED

1. Criticare combined non-invasive blood pressure, temperature, ECG, and pulse oximeter.

2. Amstrad 512 IBM compatible personal computer for performance tasks. This computer has two 5.25" floppy disk drives and 512kB of RAM, [Figure 12 & 13].

CHAPTER SIX

RESULTS.

RESULTS

Thirty volunteers were assessed, of those 19 were males (63.3%) and 11 were females (36.6%). The median age of the group was 22.5 years and the median weight was 67.5 kg.

Axillary temperature was measured and all values were within normal limits. Blood pressure, temperature and carbon dioxide levels which are all reputed to alter the AERs were measured and all those values that were measured were within normal limits. Oxygen saturation was measured for safety and no volunteer had a value below 96%.

Otherwise no major side-effects were noted. Volunteers noticed the smell of the two gases when the concentration was altered. But by the time it came to measuring the variables after 20min the majority could not detect the smell.

For each of the variables examined, there is a table showing numbers in each group, the mean, median, standard deviation and interquartile range at each concentration of volatile agent and corresponding placebo.

P100 Latency - Table 5. Isoflurane and enflurane increased the latency of the waveforms compared with placebo but not significantly, with the exception of one value 0.75% isoflurane and the recovery period at 10 minutes. When the P100 at each concentration of gas is compared with the corresponding placebo value they are all non-significant

with the exception of the 0.4% isoflurane concentration. The values for standard deviation and IQR also increase with increasing concentration of enflurane and isoflurane, while those for placebo remain stable.

P100 Amplitude - Table 6. Again the majority of P100A values are non-significant with the exception of the difference of the means between 0.3% and 0.4% isoflurane, and 0.75% isoflurane compared with placebo.

N100 Latency- Table 7. No significant differences were found between the isoflurane concentration steps and placebo values. Mean values of N100L at concentrations of isoflurane 0.3% and 0.5% compared with the corresponding placebo levels were highly significant as was the enflurane 0.4% level compared with its corresponding placebo value. 0.4% isoflurane was significantly different from the corresponding placebo value. The placebo level compared with isoflurane 0.75% was non-significant, but this may have been due to the low numbers in the group (2). Standard deviations and IQR increased for both isoflurane and enflurane,while those for placebo also increased.

N100 Amplitude- Table 8. Again significant differences between mean N100A's were found at 0.2% isoflurane and 0.6% enflurane in comparison to placebo. The mean N100A's at 0.3% and 0.5% isoflurane were highly significantly different when compared with equivalent placebo means.

P200 Latency- Table 9. Significant differences in mean P200L were found at 0.4% and 0.5% isoflurane and 0.4% enflurane when compared with placebo.

P200 Amplitude - Table 10. A highly significant difference in means was noted between 0.3% isoflurane and 0.6% enflurane and the corresponding placebo levels. The mean P200A at 0.5% isoflurane compared with placebo was significantly different, as was the comparison between 0.4% and 0.6% enflurane and placebo. A significant difference was noted between 0.6% enflurane and recovery at 10min.

Brainstem Waveforms - Table 11-20.The means of the latencies and amplitudes of the brainstem waveforms did not change with increasing concentrations of enflurane or isoflurane. The mean of waveform V latency at 0.5% isoflurane was significantly different from the corresponding placebo level. Although there were significant differences with 0.5% isoflurane and 0.42% enflurane compared with their respective placebo means. No significant differences were noted for the mean of BSVlat at 0.75% isoflurane and the corresponding placebo mean, but as there were only three volunteers in the group who were still rousable, the data can not easily be interpreted.

The means for brainstem waveform V amplitude showed no significant differences except for the placebo mean between baseline, the placebo equivalent of 0.2% and 0.3%, and a

highly significant difference between means of placebo 0.3% and 0.4%.

Mean Tracking Time - Table 21.

Mean tracking time is the mean of the mean of 100 attempts on the tracking task which constitutes one trial.

1.Isoflurane affects the mean MTT significantly at 0.3% compared with placebo values. The IQR (a measure of dispersion based on the median, the 50th percentile, i.e. the distance between the 25th and 75th percentiles) becomes larger, as does the standard deviation. By the recovery period all these values have returned to pre-anaesthetic levels or below.

The standard deviation and IQR of the placebo group, remain essentially the same. The median values for baseline placebo and recovery do not change significantly.

2. Enflurane sedation changes the mean MTT at about 0.42% when compared with placebo and at higher values. Again the standard deviation and the IQR are altered with increasing concentration of volatile agent, but return to baseline with recovery. Recovery values are not significantly altered from placebo values.

Tracking Coefficient of Variation - Table 22.

The tracking coefficient of variation is the standard deviation divided by the mean expressed as a percentage.

The median can be seen to be rising with a maximum at 167%

at (0.75% isoflurane), the standard deviation and IQR rising as well. The placebo means do not significantly differ from baseline.

Again enflurane has altered the mean TCV significantly, initially at 0.4% when compared with placebo. The IQR and standard deviation also increased. Notice that although the median value at recovery 10mins has attained baseline levels, the mean value was significantly lower than baseline.

Recovery for isoflurane and enflurane are not significantly different from placebo.

Mean Reaction Time - Table 23.

The mean reaction time is the mean of the mean of 30 attempts of the reaction time task which constitute one trial.

Mean Reaction times became highly significantly different at 0.3% isoflurane when compared with placebo. Standard deviations and IQR again increase with increasing concentrations of isoflurane up to 0.75%. Placebo median values do not change significantly, and standard deviations and IQR do not alter.

Enflurane causes significant changes in MRT at 0.17% and 0.42%, the standard deviations and IQR values increasing as well. At recovery 20 mins ,these values have all returned to baseline.

Mean Reaction Time-Coefficient of Variation - Table 24.
The mean reaction time coefficient of variation is the standard deviation divided by the mean expressed as a percentage.

The mean MCV becomes significantly different at 0.3% isoflurane compared with placebo. By recovery 10min the median values are equivalent to baseline levels.

The placebo mean values remain non-significantly different with the exception of 0.75% isoflurane and recovery 10 mins. Enflurane causes no significant change in the MCV compared with placebo although the median values do change.

Reaction Success - Table 25.
The reaction success became significantly different at 0.3% isoflurane compared with placebo, the recovery values approaching baseline.

Again the IQR and standard deviations increase with increasing concentration.
The placebo values again being not significantly different.
Enflurane cause a significant difference at 0.4% compared with placebo; The IQR and standard deviations increasing.

TABLE 5. Long-latency cortical AER P100 latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0.0	29	42.7	7.4	43.0	12.7	-	NS
0.2	12	47.4	7.8	46.6	13.7	NS	NS
0.3	28	44.8	8.8	43.5	9.6	NS	NS
0.4	14	51.3	13.4	46.4	26.0	NS	S
0.5	14	46.2	14.1	46.2	23.7	-	NS
0.75	2	58.6	11.1	58.6	-	NS	NS
R10	28	39.2	7.5	38.8	10.0	NS	NS
Placebo							
0.0	28	42.3	8.3	41.5	11.8	-	-
0.2	15	41.2	9.5	39.6	19.0	NS	
0.3	27	40.8	6.9	41.5	10.2	NS	-
0.4	12	39.4	7.9	39.6	12.0	NS	-
0.5	14	39.1	7.1	41.0	8.9	NS	-
0.75	13	41.8	10.4	40.5	5.4	NS	-
R10	27	41.9	8.5	42.5	10.3	NS	-
Enflurane							
0	15	41.6	5.9	42.0	8.8	-	NS
0.17	15	39.4	10.6	42.5	14.1	NS	NS
0.42	14	43.4	8.5	44.4	12.8	NS	NS
0.6	12	49.1	12.7	44.2	22.2	NS	NS
R10	28	39.2	7.45	38.8	10.0	NS	NS

TABLE 6. Long-latency cortical AER P100 amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	-1.8	2.0	-1.5	2.7	-	NS
0.2	12	-1.8	1.7	-1.8	3.2	NS	NS
0.3	28	-2.3	1.7	-2.2	2.5	NS	NS
0.4	14	-1.1	1.4	-1.2	2.4	S	NS
0.5	14	-2.2	1.9	-1.9	1.6	-	NS
0.75	2	-4.2	0.1	-4.2	-	NS	S
R10	28	-2.0	2.0	-1.7	2.6	NS	NS
Placebo							
0	28	-1.8	1.5	-2.2	2.5	-	-
0.2	15	-1.1	2.6	-0.3	3.2	NS	-
0.3	27	-1.8	1.7	-2.1	1.7	NS	-
0.4	12	-1.4	2.1	-1.4	3.5	NS	-
0.5	14	-1.7	1.4	-1.8	2.0	NS	-
0.75	13	-1.0	1.8	-0.6	2.7	NS	-
R10	27	-1.6	1.7	-1.8	2.1	NS	-
Enflurane							
0	14	-2.0	1.7	-2.1	1.6	-	NS
0.17	15	-1.2	2.4	-1.0	3.6	NS	NS
0.42	14	-1.9	1.7	-1.7	2.8	NS	NS
0.6	12	-2.4	2.0	-2.4	3.6	NS	NS
R10	14	-1.9	1.5	-2.5	2.7	NS	NS

TABLE 7. Long-latency cortical AER N100 latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	MEAN	SD	MEDIAN	IQR	A	B
Isoflurane							
0	30	94.9	6.1	96.2	7.68	-	NS
0.2	15	100	11.81	97.7	15.6	NS	NS
0.3	30	102.6	10.5	100.8	8.6	NS	HS
0.4	13	105.1	13.3	106.4	25.2	NS	S
0.5	14	105.4	11.1	103.8	13.4	-	HS
0.75	2	95.5	4.5	95.5	-	NS	NS
R10	30	94.4	8.7	95.7	10.7	NS	NS
Placebo							
0	30	95.2	7.0	94.2	7.4	-	-
0.2	15	95.3	7.4	96.2	8.8	NS	-
0.3	29	93.0	7.6	91.8	9.5	NS	-
0.4	15	92.6	7.95	91.8	10.3	NS	-
0.5	15	86.2	17.2	91.3	15.6	NS	-
0.75	13	96.7	13.8	91.3	20	NS	-
R10	28	94.2	8.3	95.0	10.1	NS	-
Enflurane							
0	15	94.8	7.4	92.8	7.81	-	NS
0.17	15	94.3	11.9	90.8	16.1	NS	NS
0.42	15	102.2	11.7	101.6	14.6	NS	HS
0.6	13	104.9	16.3	100.6	24.9	NS	NS
R10	15	92.7	11.6	95.2	17.1	NS	NS

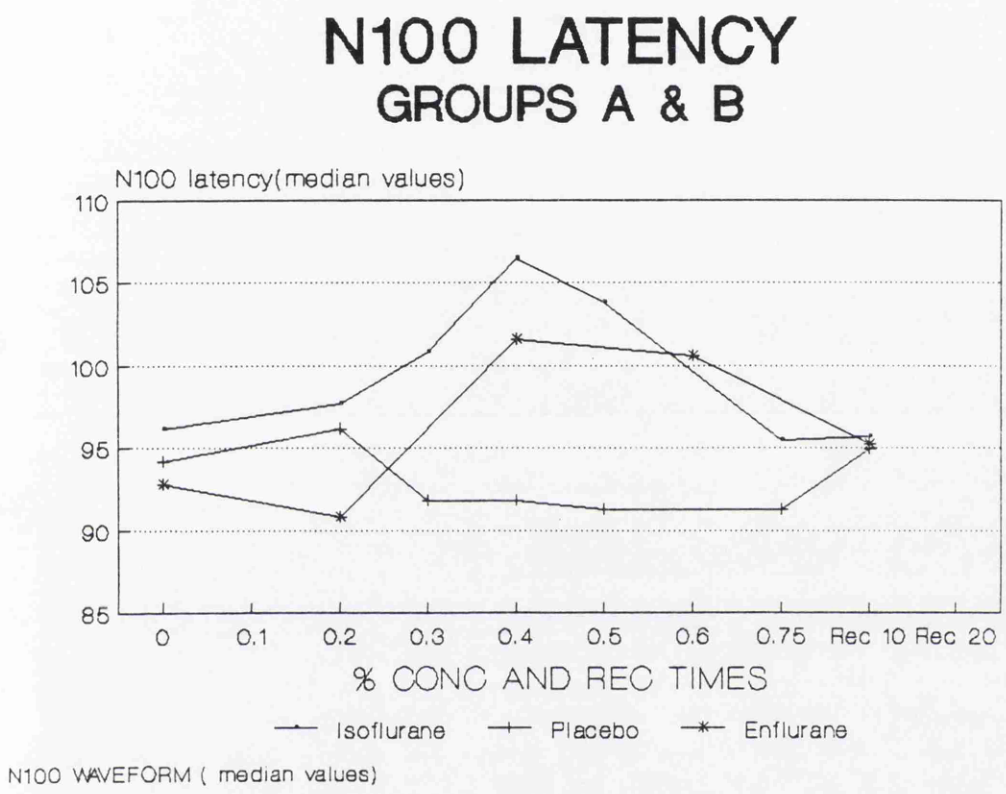


FIGURE 16. Graph showing the N100 latency (median values). Values for enflurane and isoflurane show a significant difference from placebo values. Values have achieved baseline at the recovery period.

Table 8. Long-latency cortical AER N100 amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	7.0	2.0	7.0	2.6	-	NS
0.2	15	5.9	1.4	6.1	1.9	NS	S
0.3	30	5.6	2.1	5.6	3.1	NS	HS
0.4	13	4.9	2.4	4.8	3.5	NS	NS
0.5	14	4.5	2.6	4.4	3.7	-	HS
0.75	2	6.6	1.6	6.6	-	NS	NS
R10	30	6.5	2.5	6.4	4.0	NS	NS
Placebo							
0	30	7.0	2.0	6.9	3.2	-	-
0.2	15	7.2	1.6	7.4	2.8	NS	-
0.3	29	7.5	2.3	7.5	3.1	NS	-
0.4	15	6.5	2.1	6.9	3.8	NS	-
0.5	15	7.6	2.3	7.6	3.3	NS	-
0.75	13	7.7	3.1	7.2	4.7	NS	-
R10	29	7.0	2.7	7.1	4.2	NS	-
Enflurane							
0	15	6.6	2.3	6.9	4.3	-	NS
0.17	15	6.3	2.7	5.3	4.9	NS	NS
0.42	15	6.2	2.3	5.8	3.6	NS	NS
0.6	13	5.0	1.9	5.0	3.1	NS	S
R10	15	6.5	2.1	6.1	2.8	NS	NS

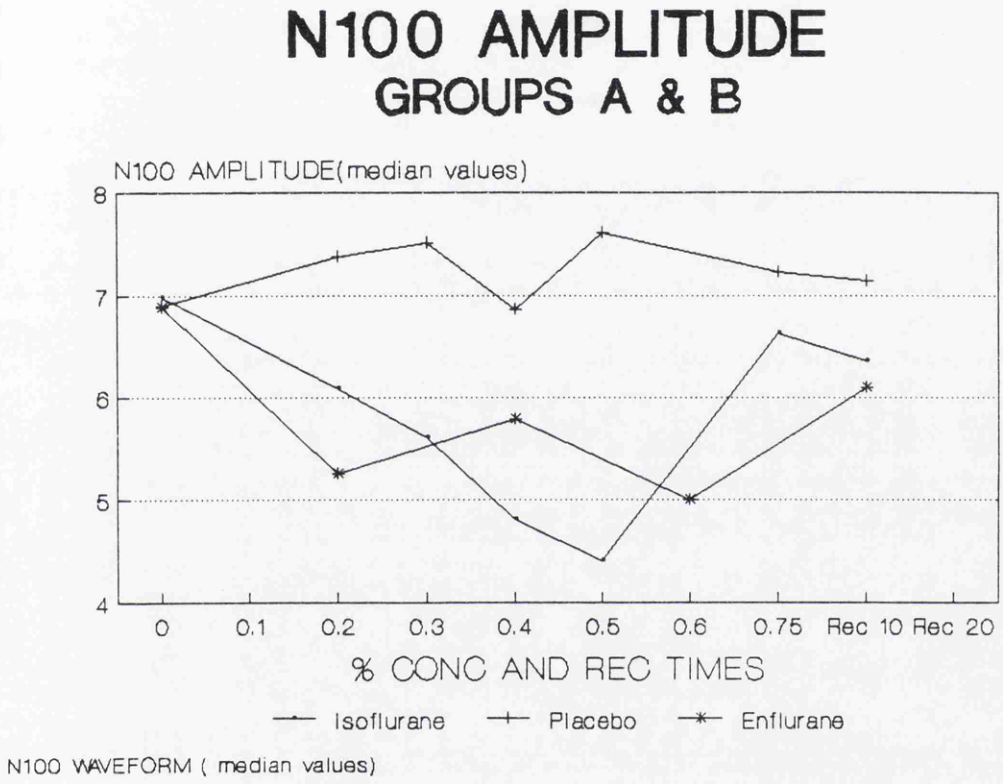


FIGURE 17. The graph illustrates values for N100 amplitude (median values). Values for enflurane and isoflurane show significant reductions in amplitude, compared with placebo.

Table 9. Long-latency cortical AER P200 latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	166.2	11.35	164.8	16.5	-	NS
0.2	15	174.1	16.03	170.9	27.8	NS	NS
0.3	30	177.1	21.5	171.9	34.8	NS	NS
0.4	14	183.2	20.3	185.1	21.5	NS	S
0.5	14	184.0	27.7	176.9	50.5	-	S
0.75	2	161.4	9.32	161.4	-	NS	NS
R10	30	170.3	13.4	169.2	19.8	NS	NS
Placebo							
0	29	169.5	13.3	167.5	20.3	-	-
0.2	15	167.1	14.7	165.0	16.1	NS	-
0.3	30	168.2	17.4	166.0	23.8	NS	-
0.4	15	165.8	19.7	157.7	24.2	NS	-
0.5	15	161.0	10.5	161.1	14.6	NS	-
0.75	13	171.6	16.6	163.6	25.6	NS	-
R10	29	164.2	11.3	163.6	18.1	NS	-
Enflurane							
0	15	166.5	12.5	167.5	18.1	-	NS
0.17	15	170.5	20.9	166.5	21.0	NS	NS
0.4	15	176.5	22.3	169.4	22.0	NS	S
0.6	13	176.9	19.7	180.7	27.1	NS	NS
R10	14	158.1	14.2	153.7	23.3	NS	NS

Table 10. Long-latency cortical AER P200 amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	-7.0	2.5	-6.8	2.71	-	NS
0.2	15	-6.0	1.4	-5.6	2.1	NS	NS
0.3	30	-5.8	1.9	-5.4	2.3	NS	HS
0.4	14	-5.0	2.0	-4.9	3.6	NS	NS
0.5	14	-5.1	2.2	-5.0	3.3	-	S
0.75	2	-7.4	0.5	-7.4	-	NS	NS
R10	30	-6.7	2.5	-5.8	3.7	NS	NS
Placebo							
0	29	-6.7	3.0	-6-7.0	3.3	-	-
0.2	15	-6.7	1.3	-6.8	2.1	NS	-
0.3	30	-7.2	2.2	-7.3	2.9	NS	-
0.4	15	-6.5	2.1	-6.3	3.4	NS	-
0.5	15	-7.2	2.4	-7.5	3.5	NS	-
0.75	13	-7.6	2.7	-7.0	3.8	NS	-
R10	29	-7.3	2.1	-7.0	3.4	NS	-
Enflurane							
0	15	-6.5	2.1	-6.4	2.8	-	NS
0.2	15	-6.5	2.1	-6.1	3.8	NS	NS
0.4	15	-6.2	2.0	-5.9	3.3	NS	NS
0.6	13	-4.1	2.1	-4.2	3.1	S	HS
R10	15	-6.2	1.8	-6.5	2.3	S	NS

Table 11. Brainstem AER Wave I latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	26	1.6	0.1	1.6	0.1	-	NS
0.2	15	1.6	0.1	1.6	0.1	NS	NS
0.3	28	1.6	0.1	1.6	0.1	NS	NS
0.4	13	1.7	0.1	1.6	0.2	NS	NS
0.5	15	1.6	0.1	1.6	0.1	-	NS
0.75	3	1.6	0.1	1.6	0.1	NS	NS
R10	13	1.6	0.12	1.6	0.2	NS	NS
Placebo							
0	27	1.7	0.2	1.6	0.2	-	-
0.2	12	1.6	0.1	1.6	0.2	NS	-
0.3	25	1.7	0.1	1.7	0.2	NS	-
0.4	12	1.8	0.5	1.6	0.2	NS	-
0.5	15	1.7	0.1	1.7	0.2	NS	-
0.75	13	1.7	0.1	1.6	0.3	NS	-
R10	24	1.6	0.1	1.6	0.2	NS	-
Enflurane							
0	14	1.6	0.1	1.6	0.1	-	NS
0.17	15	1.6	0.1	1.7	0.1	NS	NS
0.4	15	1.7	0.1	1.7	0.2	NS	NS
0.6	13	1.7	0.2	1.7	0.2	NS	NS
R10	14	1.5	0.3	1.6	0.3	NS	NS

Table 12. Brainstem AER wave I amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	26	0.1	0.2	0.2	0.3	-	NS
0.2	15	0.1	0.1	0.1	0.2	NS	NS
0.3	28	0.1	0.1	0.1	0.1	NS	NS
0.4	13	0.2	0.1	0.2	0.2	NS	NS
0.5	15	0.1	0.1	0.2	0.1	-	NS
0.75	3	0.2	0.1	0.2	0.2	NS	NS
R10	27	0.1	0.1	0.1	0.2	NS	NS
Placebo							
0	27	0.1	0.1	0.1	0.2	-	-
0.2	12	0.1	0.2	0.1	0.2	NS	-
0.3	25	0.2	0.1	0.2	0.1	NS	-
0.4	12	0.1	0.2	0.1	0.2	NS	-
0.5	15	0.1	0.3	0.1	0.1	NS	-
0.75	13	0.1	0.1	0.1	0.1	NS	-
R10	23	0.1	0.2	0.1	0.2	NS	-
Enflurane							
0	14	0.1	0.2	0.1	0.2	-	NS
0.17	15	0.2	0.3	0.1	0.1	NS	NS
0.42	15	0.2	0.1	0.2	0.1	NS	NS
0.6	13	0.1	0.1	0.1	0.1	NS	NS
R10	14	0.1	0.2	0.1	0.2	NS	NS

Table 13. Brainstem AER wave II latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	2.7		0.2	2.70.2	-	NS
0.2	14	2.7	0.2	2.7	0.3	NS	NS
0.3	26	2.8	0.2	2.8	0.2	NS	NS
0.4	13	2.8	0.2	2.8	0.3	NS	NS
0.5	14	2.7	0.2	2.8	0.2	-	NS
0.75	2	2.8	0.0	2.8	-	NS	NS
R10	26	2.8	0.1	2.8	0.2	NS	NS
Placebo							
0	29	2.8	0.2	2.7	0.2	-	-
0.2	14	2.9	0.2	2.8	0.2	NS	-
0.3	26	2.8	0.1	2.8	0.2	NS	-
0.4	13	2.9	0.3	2.8	0.3	NS	-
0.5	13	2.8	0.1	2.8	0.2	NS	-
0.75	12	2.9	0.1	2.9	0.2	NS	-
R10	23	2.8	0.1	2.8	0.2	NS	-
Enflurane							
0	13	2.8	0.2	2.8	0.2	-	NS
0.17	12	2.8	0.1	2.8	0.1	NS	NS
0.42	14	2.8	0.1	2.8	0.1	NS	NS
0.6	11	2.8	0.1	2.8	0.1	NS	NS
R10	13	2.6	0.4	2.8	0.5	NS	NS

Table 14. Brainstem AER wave II amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	0.1	0.1	0.1	0.1	-	NS
0.2	14	0.1	0.1	0.1	0.2	NS	NS
0.3	26	0.1	0.1	0.1	0.1	NS	NS
0.4	13	0.1	0.1	0.1	0.1	NS	NS
0.5	14	0.1	0.1	0.1	0.1	-	NS
0.75	2	0.1	0.0	0.1	-	NS	NS
R10	26	0.1	0.1	0.1	0.2	NS	NS
Placebo							
0	29	0.1	0.1	0.1	0.1	-	-
0.2	14	0.1	0.2	0.1	0.2	NS	-
0.3	26	0.1	0.1	0.1	0.1	NS	-
0.4	13	0.1	0.2	0.1	0.2	NS	-
0.5	13	0.0	0.2	0.1	0.1	NS	-
0.75	12	0.1	0.1	0.1	0.2	NS	-
R10	23	0.1	0.2	0.1	0.2	NS	-
Enflurane							
0	13	0.0	0.2	0.1	0.1	-	NS
0.2	12	0.1	0.3	0.1	0.1	NS	NS
0.4	14	0.1	0.1	0.1	0.1	NS	NS
0.6	11	0.1	0.1	0.1	0.1	NS	NS
R10	13	0.0	0.3	0.1	0.2	NS	NS

Table 15. Brainstem AER wave III latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	3.7	0.1	3.7	0.2	-	NS
0.2	15	3.7	0.2	3.7	0.3	NS	NS
0.3	28	3.7	0.2	3.8	0.2	NS	NS
0.4	13	3.8	0.2	3.8	0.3	NS	NS
0.5	15	3.8	0.1	3.8	0.1	-	NS
0.75	3	3.9	0.0	3.9	0.1	NS	NS
R10	27	3.8	0.2	3.8	0.2	NS	NS
Placebo							
0	30	3.8	0.1	3.8	0.2	-	-
0.2	15	3.8	0.2	3.7	0.3	NS	-
0.3	29	3.8	0.2	3.8	0.3	NS	-
0.4	14	3.9	0.3	3.8	0.3	NS	-
0.5	15	3.8	0.1	3.8	0.3	NS	-
0.75	13	3.9	0.1	3.8	0.2	NS	-
R10	28	3.8	0.2	3.8	0.2	NS	-
Enflurane							
0	15	3.8	0.1	3.8	0.2	-	NS
0.17	15	3.8	0.1	3.8	0.3	NS	NS
0.42	15	3.8	0.1	3.8	0.2	NS	NS
0.6	13	3.9	0.1	3.9	0.2	NS	NS
R10	15	3.7	0.4	3.8	0.3	NS	NS

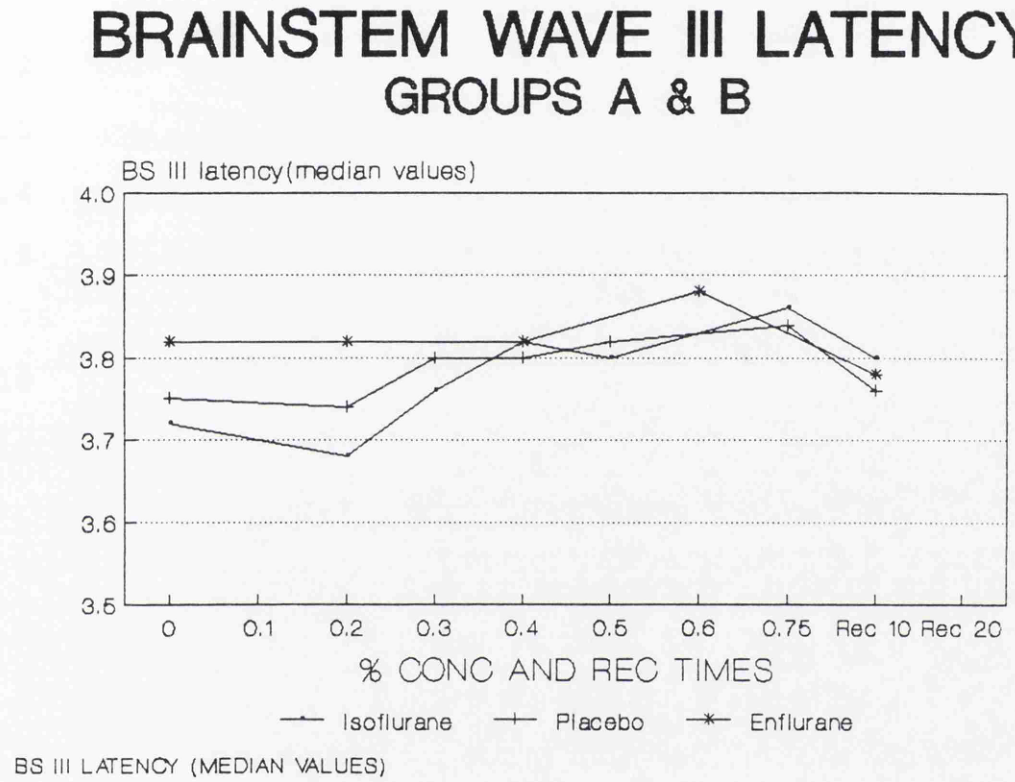


FIGURE 18. The graph illustrates the values for brainstem wave III latency (median values). No significant difference can be noted for any of the values for placebo, enflurane and isoflurane.

Table 16. Brainstem AER wave III amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	3.7	0.1	3.7	0.2	-	NS
0.2	15	3.7	0.2	3.7	0.3	NS	NS
0.3	28	3.7	0.2	3.8	0.2	NS	NS
0.4	13	3.8	0.2	3.8	0.3	NS	NS
0.5	15	3.8	0.1	3.8	0.1	-	NS
0.75	3	3.9	0.0	3.9	0.1	NS	NS
R10	27	3.8	0.2	3.8	0.2	NS	NS
Placebo							
0	30	3.8	0.1	3.8	0.2	-	-
0.2	15	3.8	0.2	3.7	0.3	NS	-
0.3	29	3.8	0.2	3.8	0.3	NS	-
0.4	14	3.9	0.3	3.8	0.3	NS	-
0.5	15	3.8	0.1	3.8	0.3	NS	-
0.75	13	3.9	0.1	3.8	0.2	NS	-
R10	28	3.8	0.2	3.8	0.2	NS	-
Enflurane							
0	15	3.8	0.1	3.8	0.2	-	NS
0.17	15	3.8	0.1	3.8	0.3	NS	NS
0.42	15	3.9	0.1	3.8	0.2	NS	NS
0.6	13	3.9	0.1	3.9	0.2	NS	NS
R10	15	3.7	0.3	3.8	0.3	NS	NS

Table 17. Brainstem AER wave IV latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	27	4.9	0.3	5.0	0.4	-	NS
0.2	11	5.1	0.2	5.1	0.4	NS	NS
0.3	24	5.1	0.2	5.1	0.2	NS	NS
0.4	11	5.1	0.2	5.1	0.5	NS	NS
0.5	14	5.3	0.2	5.3	0.3	-	NS
0.75	3	5.2	0.0	5.2	0.0	NS	NS
R10	24	5.1	0.2	5.1	0.3	NS	NS
Placebo							
0	21	5.0	0.3	5.0	0.2	-	-
0.2	11	5.0	0.2	5.1	0.4	NS	-
0.3	24	5.1	0.2	5.1	0.4	NS	-
0.4	10	5.1	0.3	5.1	0.4	NS	-
0.5	14	5.2	0.2	5.1	0.2	NS	-
0.75	11	5.2	0.1	5.1	0.2	NS	-
R10	21	5.1	0.3	5.1	0.4	NS	-
Enflurane							
0	14	5.2	0.2	5.1	0.3	-	NS
0.17	13	5.2	0.2	5.1	0.3	NS	NS
0.42	12	5.2	0.1	5.2	0.2	NS	NS
0.6	11	5.2	0.1	5.2	0.2	NS	NS
R10	14	5.2	0.3	5.1	0.2	NS	NS

Table 18. Brainstem AER wave IV amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	27	0.2	0.1	0.2	0.2	-	NS
0.2	11	0.2	0.1	0.3	0.2	NS	NS
0.3	24	0.3	0.1	0.3	0.1	NS	NS
0.4	11	0.2	0.1	0.2	0.2	NS	NS
0.5	14	0.2	0.1	0.2	0.1	-	NS
0.75	3	0.2	0.0	0.2	0.1	NS	NS
R10	23	0.2	0.1	0.2	0.2	NS	NS
Placebo							
0	21	0.1	0.1	0.2	0.2	-	-
0.2	11	0.2	0.1	0.2	0.3	NS	-
0.3	25	0.2	0.1	0.2	0.1	NS	-
0.4	10	0.2	0.1	0.2	0.2	NS	-
0.5	14	0.2	0.1	0.2	0.1	NS	-
0.75	11	0.2	0.1	0.2	0.1	NS	-
R10	21	0.2	0.1	0.3	0.2	NS	-
Enflurane							
0	13	0.2	0.1	0.2	0.2	NS	NS
0.17	13	0.2	0.1	0.2	0.2	NS	NS
0.42	12	0.2	0.1	0.2	0.2	NS	NS
0.6	11	0.2	0.1	0.2	0.1	NS	NS
R10	14	0.2	0.1	0.2	0.2	NS	NS

Table 19. Brainstem AER wave V latency. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	5.7	0.2	5.7	0.3	-	NS
0.2	15	5.7	0.3	5.7	0.3	NS	NS
0.3	29	5.7	0.2	5.8	0.3	NS	NS
0.4	14	5.8	0.2	5.7	0.5	NS	NS
0.5	15	5.9	0.2	5.9	0.2	-	S
0.75	3	5.8	0.2	5.8	0.4	NS	NS
R10	27	5.8	0.2	5.8	0.2	NS	NS
Placebo							
0	30	5.6	0.2	5.6	0.2	-	-
0.2	15	5.7	0.3	5.6	0.4	NS	-
0.3	29	5.7	0.2	5.7	0.2	NS	-
0.4	15	5.8	0.4	5.7	0.3	NS	-
0.5	15	5.7	0.2	5.7	0.2	NS	-
0.75	13	5.7	0.2	5.7	0.3	NS	-
R10	28	5.8	0.2	5.7	0.2	NS	-
Enflurane							
0	15	5.7	0.2	5.8	0.3	-	NS
0.17	15	5.8	0.2	5.8	0.2	NS	NS
0.42	15	5.8	0.2	5.8	0.1	NS	S
0.6	13	5.9	0.2	5.8	0.2	NS	NS
R10	15	5.8	0.2	5.8	0.2	NS	NS

Table 20. Brainstem AER wave V amplitude. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	29	0.2	0.1	0.3	0.1	-	NS
0.2	15	0.2	0.1	0.2	0.1	NS	NS
0.3	29	0.3	0.1	0.3	0.1	NS	NS
0.4	14	0.2	0.1	0.2	0.1	NS	NS
0.5	15	0.2	0.1	0.2	0.1	-	NS
0.75	3	0.2	0.1	0.2	0.1	NS	NS
R10	27	0.2	0.1	0.2	0.2	NS	NS
Placebo							
0	30	0.3	0.1	0.3	0.1	-	-
0.2	15	0.2	0.2	0.2	0.2	S	-
0.3	29	0.3	0.1	0.3	0.2	S	-
0.4	14	0.1	0.2	0.2	0.3	HS	-
0.5	15	0.2	0.1	0.2	0.1	NS	-
0.75	13	0.3	0.1	0.3	0.2	NS	-
R10	28	0.2	0.2	0.2	0.2	NS	-
Enflurane							
0	15	0.2	0.2	0.3	0.1	-	NS
0.17	15	0.3	0.2	0.3	0.1	NS	NS
0.42	15	0.3	0.1	0.3	0.2	NS	NS
0.6	13	0.3	0.1	0.2	0.1	NS	NS
R10	15	0.2	0.3	0.3	0.12	NS	NS

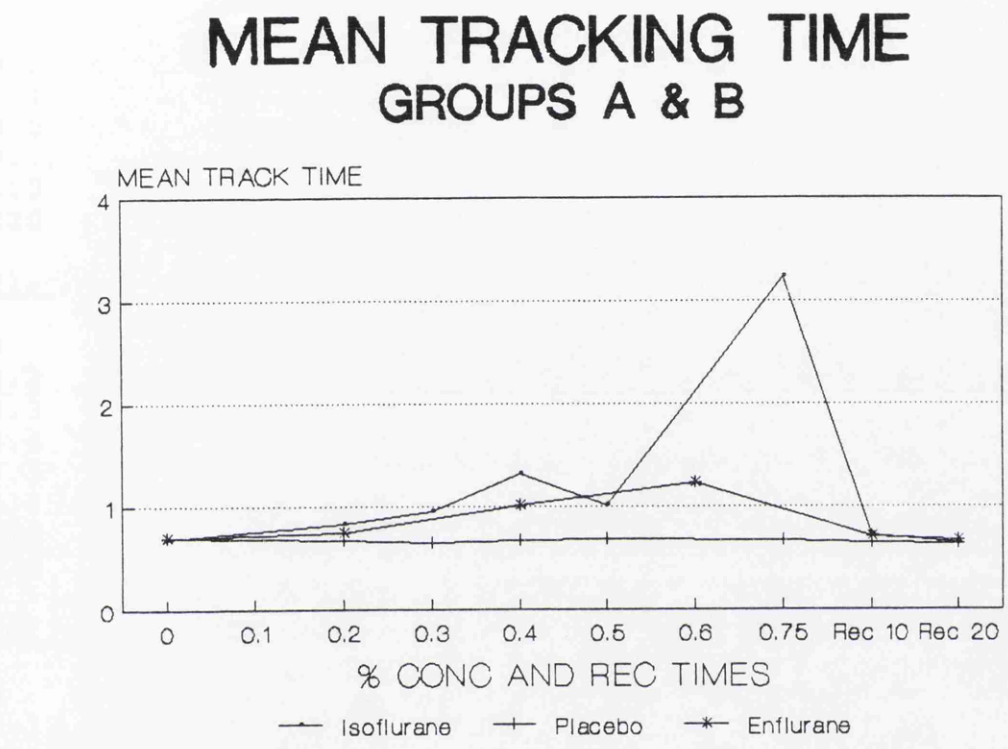


FIGURE 19. Graph illustrating median values for mean tracking time. Significant differences can be seen for values for enflurane and isoflurane compared with placebo. The maximum impairment in MTT occuring at 0.6% enflurane and 0.75% isoflurane. Values have returned to baseline at the 10min recovery time.

Table 21. Values for Mean Tracking Time. A, indicates significance with respect to the previous concentration. B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	0.7	0.2	0.7	0.2	-	NS
0.2	15	1.0	0.6	0.8	0.6	S	NS
0.3	30	1.4	1.0	1.0	0.9	S	HS
0.4	14	1.7	1.2	1.3	1.1	NS	HS
0.5	15	2.0	1.9	1.0	1.7	-	HS
0.75	3	2.9	1.0	3.2	1.9	NS	HS
R10	30	0.8	0.2	0.7	0.2	NS	NS
R20	30	0.7	0.2	0.7	0.1	NS	NS
Placebo							
0	30	0.7	0.2	0.7	0.2	-	-
0.2	14	0.7	0.2	0.7	0.3	NS	-
0.3	30	0.7	0.2	0.7	0.2	NS	-
0.4	15	0.8	0.2	0.7	0.4	NS	-
0.5	15	0.7	0.1	0.7	0.2	NS	-
0.75	14	0.7	0.1	0.7	0.1	NS	-
R10	30	0.7	0.2	0.7	0.1	NS	-
R20	30	0.7	0.1	0.6	0.2	NS	-
Enflurane							
0	15	0.7	0.1	0.7	0.1	-	NS
0.17	15	0.8	0.1	0.8	0.1	NS	NS
0.42	15	1.23	0.9	1.0	0.3	S	HS
0.6	13	1.6	1.1	1.2	1.0	NS	HS
R10	15	0.7	0.1	0.7	0.2	S	NS
R20	15	0.7	0.1	0.7	0.1	NS	NS

Table 22. Values for Tracking coefficient of variation. A, indicates significance with respect to the previous concentration.B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	44.8	13	41.6	12.4	-	NS
0.2	15	67.4	33.5	52.3	61.8	NS	HS
0.3	30	68.6	43.8	47.2	37.0	NS	HS
0.4	14	79.0	41.0	64.4	64.7	NS	S
0.5	15	75.9	39.9	57.7	74.9	-	HS
0.75	3	316.0	340.0	167.0	629	NS	S
R10	30	43.6	18.5	38.9	12.5	NS	NS
R20	30	42.5	27.5	37.1	10.5	NS	NS
Placebo							
0	30	41.8	8.65	41.0	10.2	-	-
0.2	15	41.8	7.6	40.0	11.8	NS	-
0.3	30	43.2	10.8	43.0	11.4	NS	-
0.4	15	59.7	51.1	47.7	9.9	NS	-
0.5	15	45.6	20.7	39.2	11	NS	-
0.75	14	48.5	17.2	43.7	14.2	NS	-
R10	30	41.1	9.0	39.2	9.5	NS	-
R20	30	41.8	10.6	39.0	10.5	NS	-
Enflurane							
0	15	66.4	77.6	40.6	9.1	-	NS
0.17	15	46.1	11.5	42.6	16.5	NS	NS
0.42	15	94.4	146.6	56.3	19.1	S	HS
0.6	13	83.3	54.9	74.8	60.2	NS	S
R10	15	44.1	11.6	40.5	14.7	S	NS
R20	15	47.2	11.9	44.6	17.8	NS	NS

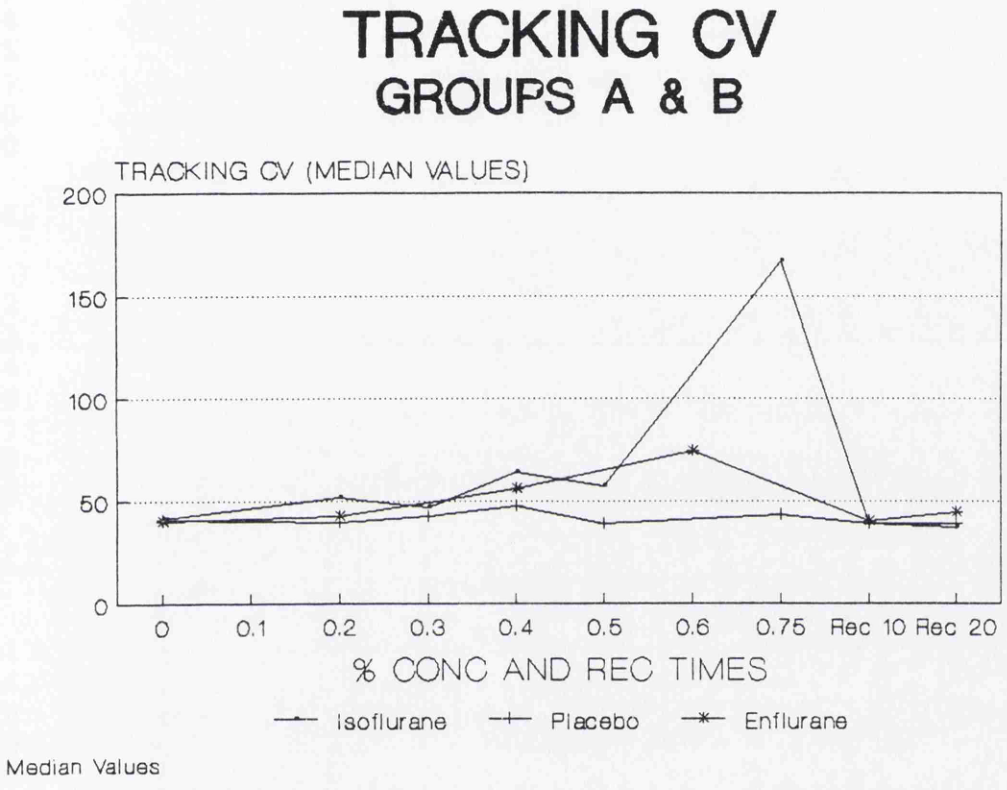


FIGURE 20. Graph illustrating median values for tracking time coefficient of variation. Variation increases for volunteers inhaling isoflurane and enflurane compared with control values. Values have returned to baseline at the 10min recovery time.

Table 23. Values for Mean Reaction Time.
A, indicates significance with respect to the previous concentration.B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	0.9	0.1	0.9	0.2	-	NS
0.2	15	1.1	0.2	1.0	0.3	S	NS
0.3	30	1.3	0.3	1.2	0.4	-	HS
0.4	14	1.5	0.5	1.3	0.7	NS	HS
0.5	15	1.7	0.8	1.4	0.7	-	HS
0.75	3	1.6	0.5	1.5	0.9	NS	HS
R10	30	1.0	0.1	0.1	0.2	NS	S
R20	30	1.0	0.1	1.0	0.2	S	NS
Placebo							
0	30	0.9	0.1	0.9	0.2	-	-
0.2	15	0.9	0.2	0.9	0.2	NS	-
0.3	30	0.9	0.2	0.9	0.2	NS	-
0.4	15	0.9	0.2	0.9	0.2	NS	-
0.5	15	1.0	0.1	1.0	0.2	NS	-
0.75	14	1.0	0.1	0.9	0.2	NS	-
R10	30	0.9	0.1	0.9	0.2	NS	-
R20	30	0.9	0.1	0.9	0.2	NS	-
Enflurane							
0	15	0.9	0.1	0.9	0.2	-	NS
0.17	15	1.0	0.2	1.0	0.2	S	NS
0.42	15	1.4	0.6	1.2	0.3	S	HS
0.6	13	1.5	0.6	1.3	0.9	-	HS
R10	15	1.0	0.2	1.0	0.3	-	S
R20	15	1.0	0.2	0.9	0.3	NS	NS

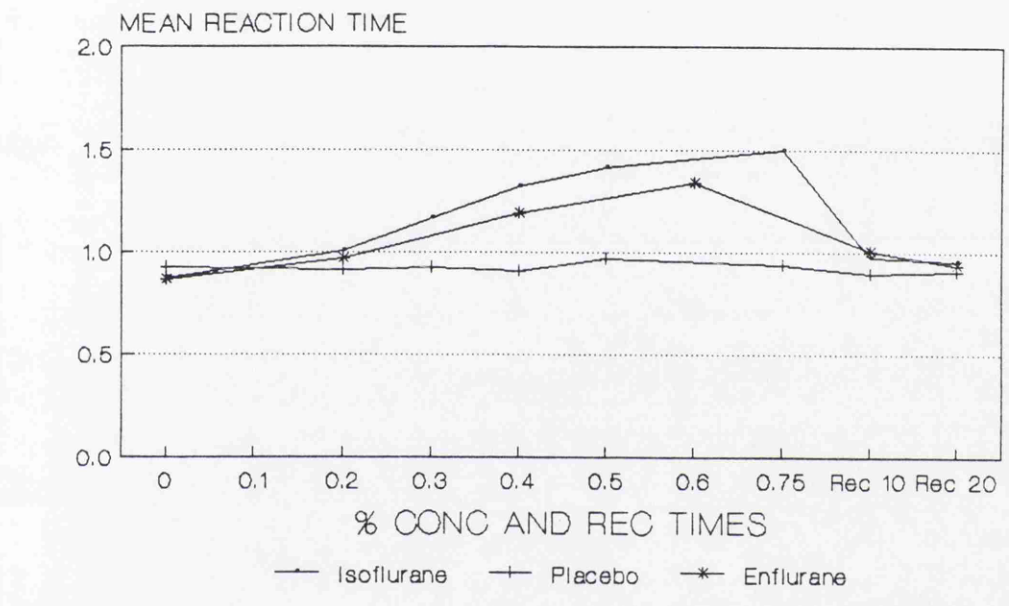


FIGURE 21. Graph showing median values for mean reaction time. Mean values for enflurane and isoflurane show a significant difference from those for the control. At the 10min recovery period the MRT has not attained baseline values, but at 20min the values have reached baseline levels.

Table 24. Values for MRT - Coefficient of Variation. A, indicates significance with respect to the previous concentration.B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	13.5	5.4	12.2	4.7	-	NS
0.2	15	17.0	8.7	14.5	7.3	S	NS
0.3	30	25.6	22.6	19.4	13.4	NS	HS
0.4	14	32.6	26.7	21.5	41.9	NS	NS
0.5	15	40	50.8	30.6	21.3	-	HS
0.75	3	14.4	0.7	14.3	1.4	NS	NS
R10	30	13.2	3.9	12.6	4.5	NS	NS
R20	30	13.1	3.5	11.9	3.1	NS	NS
Placebo							
0	30	13.0	4.2	11.7	4.1	-	-
0.2	15	13.1	2.7	12.8	2.4	NS	-
0.3	30	14.2	9.9	11.9	2.4	NS	-
0.4	15	15.2	7.8	12.6	5.1	NS	-
0.5	15	15.2	6.4	14.4	3.3	NS	-
0.75	14	27.4	45.4	13.1	7.9	NS	-
R10	30	12.8	3.8	11.8	4.0	S	-
R20	30	13.0	2.9	12.7	3.7	NS	-
Enflurane							
0	15	15.7	7.6	13.2	4.3	-	NS
0.17	15	15.9	7.0	12.8	9.1	NS	NS
0.42	15	20.0	11.4	18.6	7.2	NS	NS
0.6	13	32.6	39.5	18.9	12.4	NS	NS
R10	15	12.2	3.0	11.8	4.1	S	NS
R20	15	12.4	3.5	11.6	4.1	NS	NS

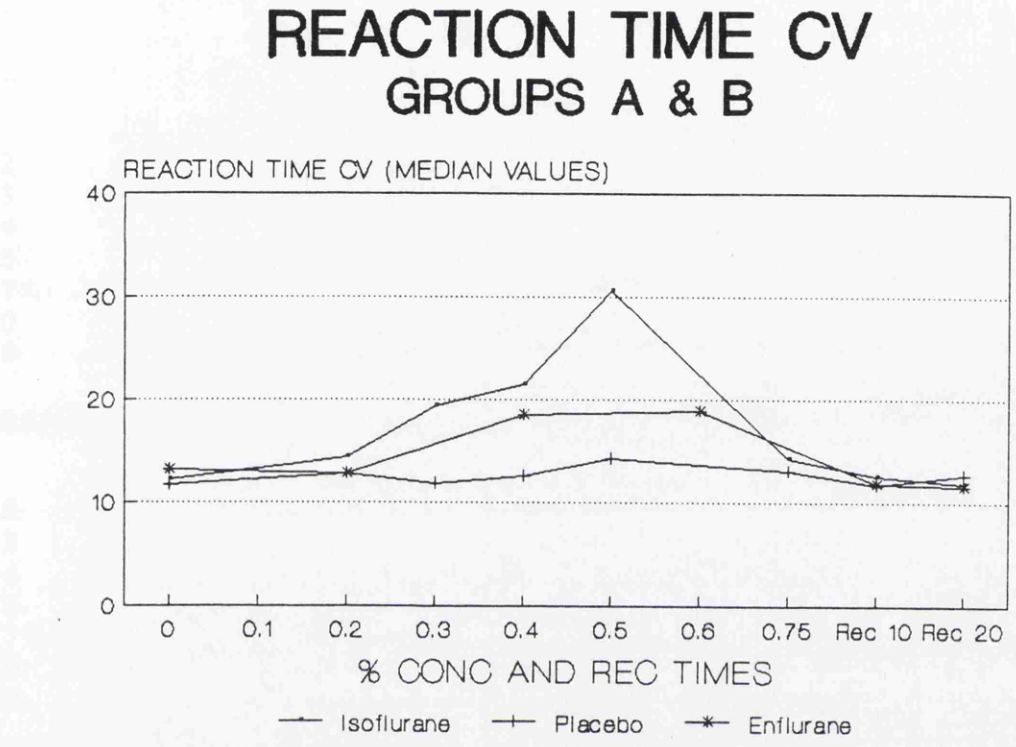


FIGURE 22. Graph illustrating the median values for the reaction time coefficient of variation. Values for enflurane and isoflurane show significant differences compared with the control. The maximum change in variation occurs at 0.6% enfluane and 0.5% isoflurane, but decreases at 0.75% isoflurane, only 3 volunteers were left in the 0.75% group. This may explain the unusual result.

Table 25. Values for Reaction Success.
A, indicates significance with respect to the previous concentration.B, indicates significance with respect to the placebo concentration at each level.

Conc	No	Mean	SD	Median	IQR	A	B
Isoflurane							
0	30	98.2	3.0	100	3.3	-	NS
0.2	15	97.1	2.5	97.0	3.3	S	NS
0.3	30	94.9	5.2	96.7	10	NS	S
0.4	14	95.0	3.9	96.7	7.5	NS	HS
0.5	15	82.9	17.6	90.0	26.7	-	HS
0.75	3	94.4	2.0	93.3	3.4	NS	NS
R10	30	99.0	2.2	100	0	NS	NS
R20	30	98.1	4.8	100	4.2	NS	NS
Placebo							
0	30	98.2	2.7	100	3.3	-	-
0.2	15	98.7	2.1	100	3.3	NS	-
0.3	30	98.0	3.1	100	3.3	NS	-
0.4	15	98.9	3.0	100	0	NS	-
0.5	15	98.5	2.5	100	3.3	NS	-
0.75	14	96.9	6.7	100	1.7	NS	-
R10	30	98.3	2.8	100	3.3	NS	-
R20	30	97.8	3.6	100	3.3	NS	-
Enflurane							
0	15	97.1	5.8	100	6.7	-	NS
0.17	15	99.0	1.5	100	3.3	NS	NS
0.42	15	93.1	6.24	93.3	6.7	NS	HS
0.6	13	92.3	7.0	93.3	13.4	NS	S
R10	15	97.3	4.0	100	6.7	S	NS
R20	15	97.6	3.7	100	3.3	NS	NS

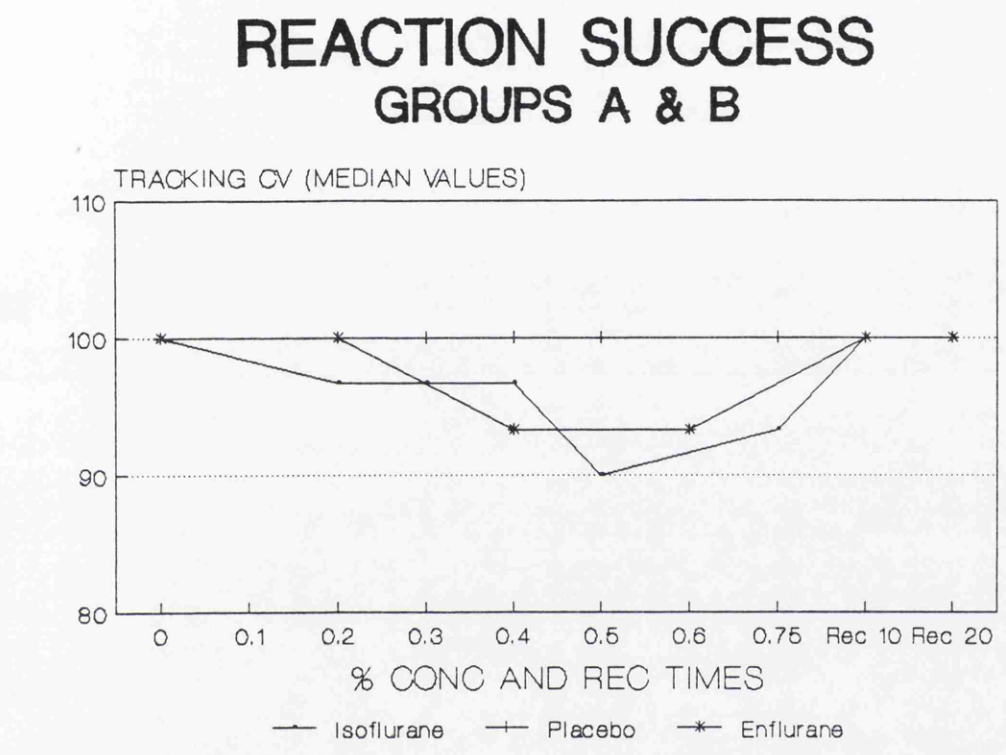


FIGURE 23. Values for reaction success are illustrated. The enflurane and isoflurane cause a significant decrement in RS compared with placebo.

TABLE 26. LEVEL OF CONSCIOUSNESS AT VARIOUS CONCENTRATIONS OF VOLATILE AGENTS. Grade 1-Conscious, Grade 2-Unconscious i.e. loss of verbal contact, Grade 3-Poorly coordinated, but not unconscious, Grade 4-not attempted.

Conc	Grade 1	Grade 2	Grade3	Grade 4
ISOFLURANE				
0	30	-	-	-
0.2	15	-	-	-
0.31	29	-	-	-
0.4	7	3	4	-
0.5	4	9	2	-
0.75	1	2	-	12
R10	30	-	-	-
R20	30	-	-	-
PLACEBO				
0	30	-	-	-
0.2	15	-	-	-
0.31	30	-	-	-
0.4	15	-	-	-
0.5	15	-	-	-
0.75	14	-	-	1
R10	30	-	-	-
R20	30	-	-	-
ENFLURANE				
0	15	-	-	-
0.17	15	-	-	-
0.42	12	2	-	2
0.6	6	7	-	2
R10	15	-	-	-
R20	15	-	-	-

CHAPTER SEVEN

DISCUSSION AND SUMMARY

DISCUSSION

RESULTS

Auditory Evoked Responses

The principle findings of this study in relation to auditory evoked responses were that the long-latency cortical N100 showed the most significant changes at 0.3%, 0.4%, 0.5% isoflurane compared with placebo, and 0.42% enflurane compared with placebo. No significant change was noted at 0.75% isoflurane compared with placebo but only two individuals were left in this category. 0.6% enflurane compared with placebo showed no significant change. The N100 amplitude showed significant changes at 0.2%, 0.3%, and 0.5%,isoflurane and enflurane 0.6% compared with placebo.

The P100 waveform showed only a significant change in amplitude at 0.75% isoflurane compared with placebo and no other significant changes in either latency or amplitude.

The P200 latency showed significant changes at 0.4% and 0.5% isoflurane compared with placebo, but no significant change at 0.75% isoflurane compared with placebo although there were only two in the group. Enflurane 0.4% showed a significant change compared with placebo. P200 amplitude showed significant changes at 0.3%, 0.5% isoflurane and 0.6% enflurane compared with placebo.

The brainstem waveforms did not change significantly with the exception of the V waveform. This showed a significant change at 0.5% isoflurane and 0.42% enflurane compared with

placebo. V amplitude showed significant changes between 0, 0.2%, 0.3% placebo levels.

In general the long-latency cortical waveform N100 was the most sensitive to the volatile agents, for both latency and amplitude. The brainstem waves were unaffected by the effects of volatile agents at these low concentrations.

Performance Tests

The tracking task showed highly significant changes from 0.3-0.75% isoflurane and 0.42-0.6% enflurane compared with placebo.

The coefficient of variation showing significant changes at 0.2-0.75% isoflurane and 0.42-0.6% enflurane compared with placebo, indicating that not only does the tracking time increase, but also the variability increased.

Mean reaction time shows the same pattern with significant changes in the range of isoflurane 0.3-0.75% and enflurane 0.42-0.6% and recovery at 10min indicating that a significant decrement in performance occurs again at 0.3% isoflurane and 0.42% enflurane, although non-significant changes do occur below this.

Again the variability increases with 0.3% and 0.5% isoflurane (MCV), the reaction success changing with both isoflurane (0.3-0.5%) and enflurane (0.4% and 0.6%), the volunteers ability to accurately perform the test decreased.

All the psychomotor test parameters MTT, TCV, RS,MCV returned to non-significant levels compared with placebo by recovery at 10 mins. Only MRT for both isoflurane and enflurane showed significant differences compared with placebo.

Millar (1992) states that the effect of an anaesthetic may be to make performance more variable, an effect which is often masked by expressing the data as mean values and not median, our data confirm this finding.

SOURCES OF ERROR

There were various problems that arose throughout the course of the study:-

Initially we attempted to measure the end-tidal concentration of volatile agent by placing a narrow catheter, between the nose and the mouth, which was connected to a Normac vapour analyser. Unfortunately this provided no useful measurements.

The alternative methods, had to be simple to use, accurate, non-invasive, as we were using volunteers. The main alternative was to place a nasopharyngeal catheter into the pharynx, place a nose clip on the nose and measure the end-tidal concentration of volatile agent. This scheme was impractical for two reasons. The volunteer would have had to undergo an unpleasant procedure, and the tests lasted for 2½- 3hours, thus a nose clip would have been extremely unpleasant for such a time.

The only other alternative was an anaesthetic face-mask, attached firmly onto the face with a Clausen harness to enable a small connector to be attached to the circuit, to allow a continuous measure of inspired and expired gases, which would have been the ideal method. In view of the above problems we decided that by accurately calibrating the vaporisers at the required gas flows, we could use inspired concentrations instead of end-tidal concentrations.

We felt there was no need to measure end-tidal carbon dioxide concentrations in view of the above problems and also because the volunteers were sedated as opposed to anaesthetised, were therefore at a lighter plane and more responsive, controlling their airway, and if consciousness was lost (under the protocol for the ethics committee) the volatile agent was discontinued.

We attempted to measure the middle latency auditory evoked response, as this in previous studies had been shown to be the most useful waveform. We were unable to obtain reasonable waveforms due to the presence of interference. We excluded the interference from the mains AC current, by switching off equipment that was unnecessary. We obtained good brainstem and long-latency cortical waveforms with these measures. We felt the source was probably muscle artifact. The previous authors who used this waveform have either used anaesthetised or paralysed patients.

The problem of asymmetric transfer is one which affects all

authors in this field. The use of a separate-groups design to avoid the within- subject design and to reduce intersubject variability by expressing performance as a change score from pretreatment baseline was advocated by Miller 1991. He cited other authors who suggest that benzodiazepine experience should be given to volunteers before they participate in crossover studies of such drugs because the major change in impairment tends to occur differentially between the first and second exposure to the drug [File, Lister, 1983].

We attempted to maintain a constant environment. The variation that occurred with natural light, when decreased, was supplemented with tungsten lamps, to increase the ambient light to allow the keyboard to be seen.

We reduced the effects of practice by ensuring an adequate level of practice prior to the commencement of the study.

McMenemin and Parbrook in 1988 assessed the effect of 0.4% isoflurane in healthy volunteers from an anaesthetic department. In our study at 0.4% isoflurane 3 volunteers had lost verbal contact, four volunteers were poorly coordinated and the remaining seven were conscious. The above authors make no reference to loss of verbal contact, which presumably means all 12 volunteers remained conscious. The reason for this could be that McMenemin used volunteers who were familiar in some way with the effects of anaesthesia and were therefore biased. We used volunteers who had no connection with anaesthesia. McMenemin and coworkers

described that objective tests of recovery demonstrated no marked impairment of function once the administration of the gas had been discontinued, at 5min,15min, 25min,35min. The subjective tests on the other hand showed impairment in the recovery period.

The values for mean reaction time in our study showed a significant impairment at five mins compared with placebo for both enflurane and isoflurane. The other parameters ie mean tracking time, tracking coefficient of variation, reaction success, and reaction coefficient of variation were all non-significantly changed at 5 and 10min when compared with placebo for both enflurane and isoflurane. McMenemin used the mean of 15 responses for the mean reaction time, whereas we used 30 trails. Wilkinson 1969 suggested that if a test is too short, a subject can arouse himself to maintain performance at a satisfactory level even when severely stressed. Short tasks may miss the effect of the stress on performance and a subject may return to normal although they are severely impaired. These authors noted that two subjects were nauseated, while one vomited. Likewise in our study two vomited at the higher doses.

GENERAL CONSIDERATIONS

The group of volunteers selected were all reasonably young (mean age 24y). This raises the problem of how relevant are these results to geriatric patients. Although the population of dental patients tend to be younger at the present, in

future years this may alter with improved dental care in the community.

We exclude the possibility of hearing defects by examination of the ears and the use of an audiometric test. Therefore our population had normal hearing, but if the AERs were to be used as tool in the investigation of awareness, one might ask whether the likelihood of impaired hearing in the subjects used, particularly an older population, might impair the usefulness of the measure.

The time of each task was just long enough to ensure that volunteers became "bored" and did not just arouse themselves long enough to complete the task. In 1969 Wilkinson suggested that stress effects upon performance might be missed if the test period was too short. A short test allowing a subject to arouse himself to maintain performance at a satisfactory level even when severely stressed. But if the test is prolonged, this ability cannot be sustained. Therefore very short tasks may miss the effect of the stress on performance. In the case of day-case surgery, subjects may be discharged when their performance returns to 'normal' although they are severely impaired.

We initially sought advice on the likelihood of the changes in AER expected with low concentrations of volatile agent. We knew from previous work about changes associated with the MLAEP and selected waves of the brainstem response. After a through literature review no work at that time appeared to have been completed using low concentrations of volatile

agent and the AER.

We therefore decided to examine the MLAEP and BSAEP. This was expanded to include the long-latency AEP after a personal communication from Dr Weir (Consultant Neurophysiologist, SGH, Glasgow). He indicated to us that the waveform which was most sensitive to anaesthetic agents was the LLAEP N100 waveform, and was therefore of no use in monitoring the effects of neurosugical procedures on the brain.

The N100 wave was demonstrated by Picton and Hillyard in 1974 to increase in amplitude in the conscious subject when attention was aroused. Näätänen and Picton in 1987 reviewed the literature on the N100 component. They concluded that in most conditions auditory selective attention causes the superimposition on the N100 wave of a negative deflection consisting of two components (5&6) that overlap the true N100 components. It is possible that under certain conditions attention may selectively enhance a true N100 component, as suggested by Hillyard and coworkers in 1973. In that case, the enhanced component would be the supratemporal component.

Plourde and Picton in 1991 stated that simple auditory attention does not usually affect the N100, provided the level of arousal remains the same. The N100 amplitude is larger for attended than for nonattended stimuli when near-threshold intensities are used, when difficult

discriminations are required or when selective attention is necessary.

Various authors have assessed the effect of isoflurane and enflurane on the AER, few up to the last year have attempted to do so in low doses with no other drugs involved, [Newton, Thornton,Konieczko, 1992].

The effect of enflurane and isoflurane has been assessed on the BAER by various authors. Dubois and co authors found that enflurane administrated at concentrations of 0.5-3% significantly increases the latencies of peaks III,IV,V [Dubois, Satto, Chassy, et al,1982]. Similar results were reported by others.

Manninen and co-investigators stated isoflurane increased the latencies of peaks III,IV,and V occuring at an end-tidal concentration of 1%. Other authors have also shown these changes. Few actually state at which concentrations these changes begin to occur.

The marking of waveforms can often lead to a source of error, Figure 24 illustrates how specific rules are needed to mark the waves in a concise fashion on each occasion.In Figure 25 the long-latency cortical waveform can be seen with changing isoflurane concentrations. At 0.2% isoflurane the waveform developed two negative peaks. This occurred frequently at the higher concentrations and lead to a problem with defining the N100 peak. We defined the N100 in these situations as being at the mid-point of the waveform,

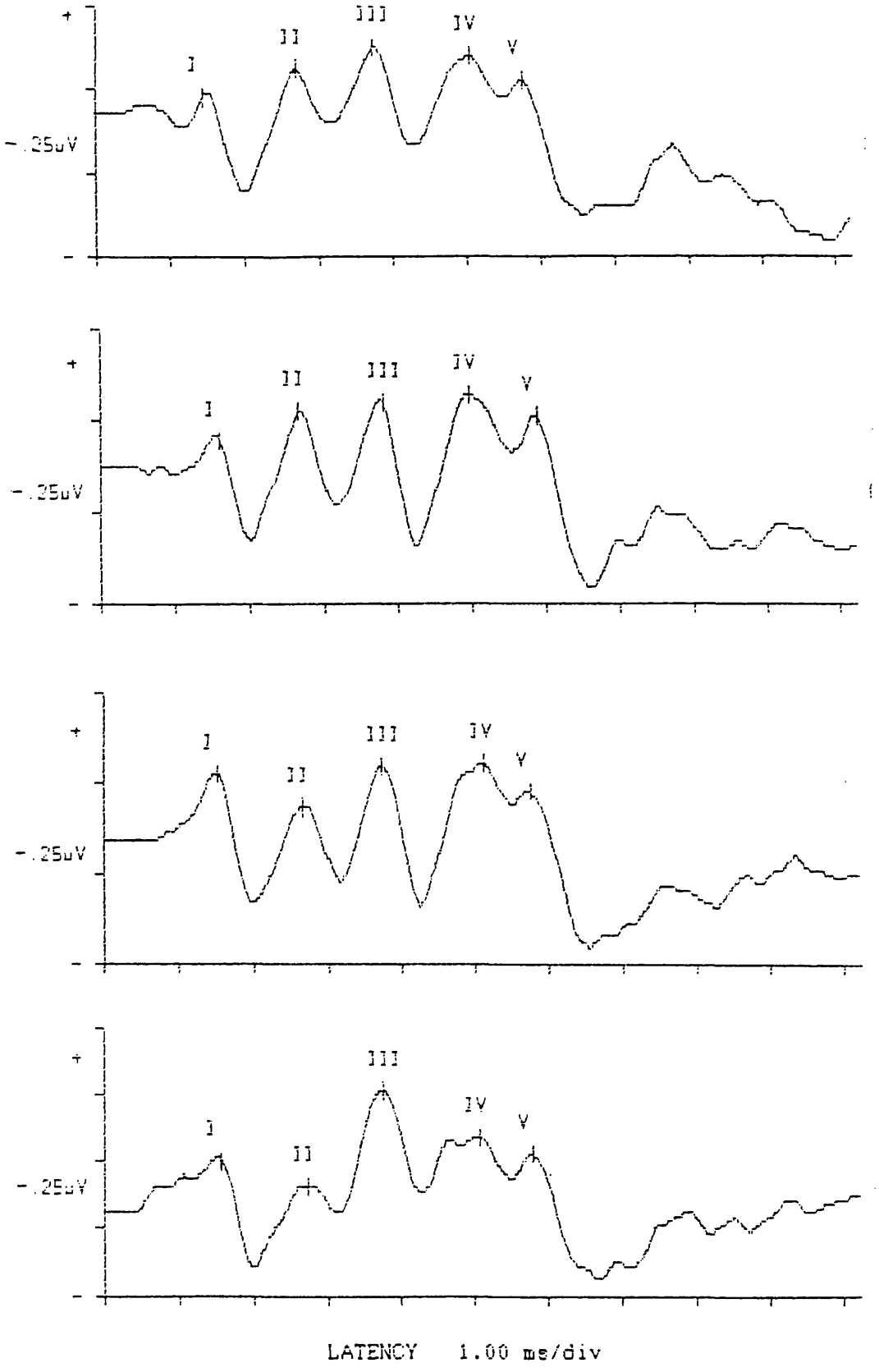


FIGURE 24. Example of the brainstem auditory evoked responses, from above down, concentrations of isoflurane 0, 0.1%, 0.2% and recovery.

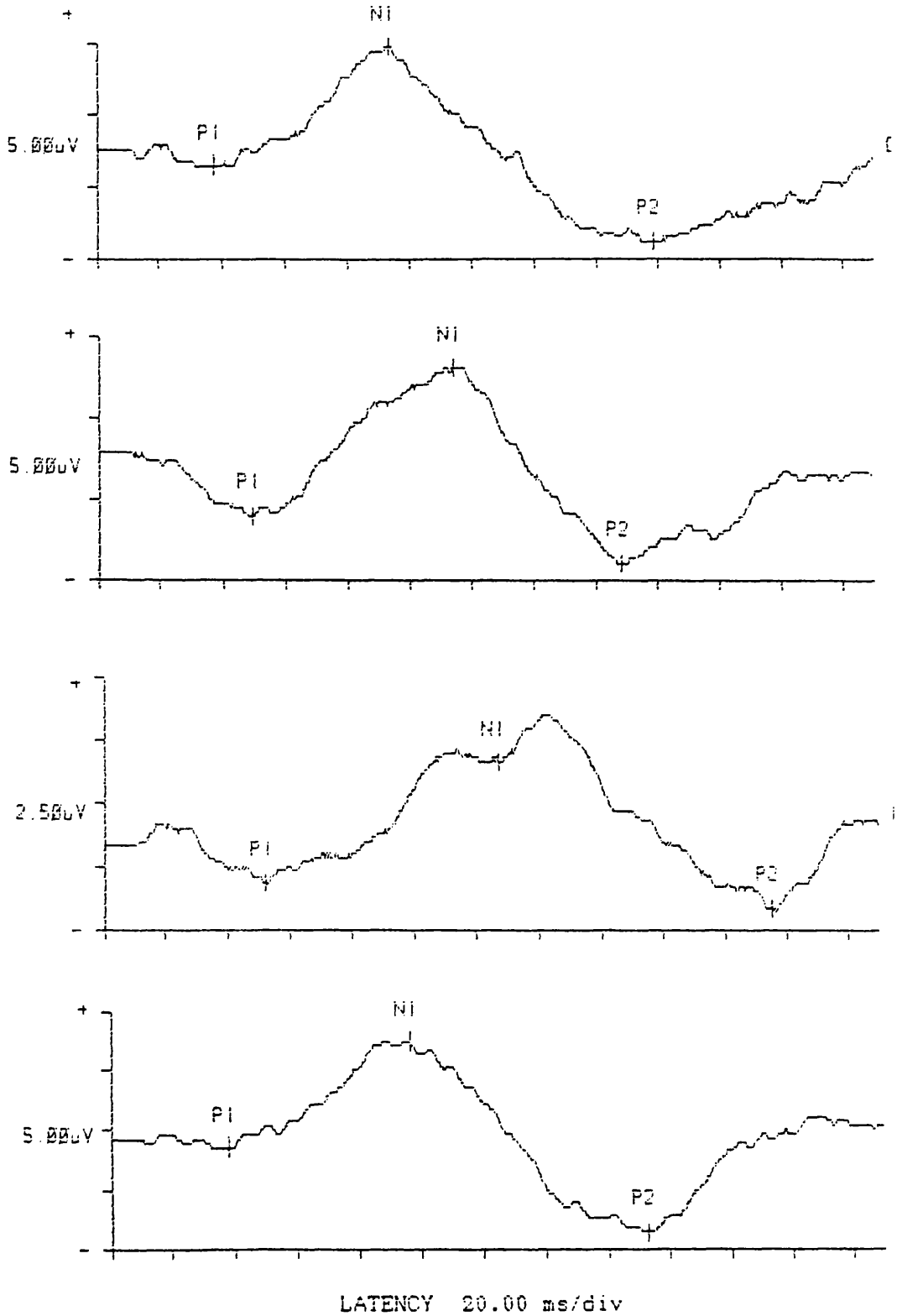


FIGURE 25. Example of the long-latency cortical waveform (N100), from above down, at concentrations of isoflurane 0, 0.1%, 0.2%, and recovery. Note presence of double peak of wave, N100 taken as mid-point.

usually between the two outlying peaks. We concluded that this "double peak" could be explained by a differential slowing of the components that comprise the N100 waveform, with the volatile agents.

Newton and colleagues assessed consciousness in volunteers breathing sub-MAC concentrations of isoflurane. Eight volunteers from the anaesthetic department inhaled isoflurane in concentrations of 0.1, 0.2 and 0.4MAC and a control of 100% oxygen (MAC of isoflurane 1.15%). Their findings were more in keeping with those of ours. At 0.4MAC isoflurane all subjects failed to respond to commands, five had no eyelash reflex. Seven were obviously sleeping, snoring or requiring airway support, and the eighth was making uncoordinated movements similar to the excitatory movements seen at Guedel's stage two of anaesthesia. At 0.2MAC seven of the eight subjects opened eyes on command. At 0.1MAC isoflurane the response to commands was impaired in three subjects and lost at 0.2MAC. One has to remember that these authors were measuring end-tidal concentration rather than inspired as in our study. No mention was made of randomisation in this study, [Newton, Thornton, Konieczko 1990]. Conscious level can be seen in Table 26.

DEDUCTIONS

The technique would be useful for dental sedation, in that all volunteers had returned to pre-anaesthetic levels of performance by twenty minutes after the termination of the volatile agent.

Originally the study was designed to assess the effect of these sub-anaesthetic concentrations of volatile agents on the psychomotor tests. The AER was included to give a neurophysiological parameter against which the psychomotor tests could be compared. When the BSAER are related to the psychomotor tests it becomes apparent that they are very much less sensitive than the psychomotor tests. But when the N100 waveform is compared we can see that highly significant changes occur at 0.3% isoflurane and 0.42% enflurane for latency, and significant changes at 0.2% isoflurane and 0.6% enflurane for amplitude, these changes in latency mirror the changes in the psychomotor test quite closely.

Finally the AER has been used as an assessment of awareness under anaesthesia. Working with this measure over the last year, I feel that in its present form it would be a less than ideal way of assessing awareness under GA due to the practicalities of the equipment. In theatre it may be difficult to exclude the interference from other power sources. The subjective nature for marking the waveforms may lead to problems, experience has to be gained before one can confidently mark the waves. Often interference is present which can markedly alter the appearance of the wave, which may lead to mis-interpretation in inexperienced hands. About 2000 stimuli are required for the BSAER and MLAER, which may take 2-3mins to measure. The LLAER requires 50 stimuli and may take less time to measure. This would prove difficult in theatre when one would want to use such a measure for many

cases on a busy list. Therefore the concept would require some refinement for use in theatre.

The hypothesis is true for the effect of subanaesthetic doses of isoflurane and enflurane on the two tests of psychometric function and long-latency cortical AER, but is untrue for its effect on the brainstem AER.

IN SUMMARY

We have found that subanaesthetic doses of enflurane and isoflurane have no effect on the BSAER, but alter the N100 component of the LLAER. The two computerised psychometric tests, choice reaction time and tracking time are affected by the two agents in low concentrations. There is a correlation between the point at which the psychometric tests start to alter and the point at which the N100 latency and amplitude alters i.e. 0.3% isoflurane and 0.42% enflurane.

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