A COMPARISON OF TWO CONVENTIONAL SEDATIVES-DIAZEPAM AND DROPERIDOL IN COMBINATION WITH FENTANYL IN SURGICAL PATIENTS

by

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ABSTRACT

One hundred patients who were to have cataract extraction and intraocular lens replacement carried out were randomly assigned to one of two drug groups. The purpose was to compare droperidol/fentanyl and diazepam/fentanyl for the following effects: central nervous system depression, cardiovascular depression and ability to alleviate anxiety. Patients, psychology observes, and surgeons were not cognizant of others' opionons, nor of assignment of drug treatment group. Experimental design was a between group single treatment design. Psychological testing consisted of State-Trait Anxiety Inventory of Spielberger, Gorsuch and Lushene, and the Sensory/Affect ratio pain descriptors of Gracely, Dubner and McGrath. Opinion of ease of carrying out the surgical procedure was obtained from the surgeon, and opinion of the anaesthetic outcome was obtained from the anaesthetist.

While both drug combinations proved to be successful for use as a sedative adjunct to local anaesthetic for this type of surgical procedure some differences were found. Patients found the diazepam/fentanyl combination provided for a less intense overall procedure, and had little if any recall of the procedure. The surgeons also found the patients less restless in the diazepam/fentanyl group. Anaesthetists rated the level of sedation as equivalent for both groups and found there was not a significant difference between the amount of sedation they observed.

TABLE OF ABBREVIATIONS

p.o.	per os
min.	minutes
mg.	milligrams
C.N.S.	central nervous system
GABA	gamma amino butyric acid
i.v.	intravenous
i.m.	intramuscular
G.I.S.	gastro intestinal system
PAR	post anaesthetic recovery
E.E.G.	electro-encephalograph
R.E.M.	random eye movement

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INTRODUCTION

Like other forms of behavior, dental fear develops through the interaction of three phenomena - those which are inate, those dependant on maturation processes, and those developed through learning processes from individual and social experiences. Learning may result directly, through aversive conditioning, or indirectly, through modeling (1).

When voluntary efforts cannot reason away dental phobias, avoidance of dental treatment ultimately results. In 1958, Janis (2) pointed out that the fear of patients prior to dental procedures exceeded the fear of general surgical patients prior to general surgery. Hayden pointed out that more than 50% of the population surveyed did not attend dental appointments because of fear, rather than for financial reasons (50).

Non pharmacological methods of obtaining a reduction in patient anxiety and an increase in patient cooperation are presently available for some patients. Hypnosis, bio-feedback and guided imagery methods have been used by psychologists for a considerable period of time, for the treatment of other phobias with considerable success. As with learning intravenous sedation techniques, the operator requires a considerable amount of training in hypnosis and bio-feedback techniques to become successful in treating the phobic patient. Also, not every patient can be helped with hypnosis. However if the time is afforded, certanly this is a viable alternative to the use of intravenous sedation.

The aim of pharmacological adjuncts, when used to help the anxiety prone dental patient is to produce a state of conscious sedation attained via depression of the central nervous system (CNS), enabling treatment to be carried out, yet maintaining the protective reflexes normally obtunded with the use of such procedures as general anaesthesia.

Prior to the introduction of chlordiazepoxide (LIBRIUM) in 1960, the first clinically used benzodiazepine, numerous drugs had been used as hypnotics and sedatives. A number of definitions for these terms exist, however a sedative may be considered to be a compound which has a calming effect on the patient and which produces a reduction in activity. The conscious patient is rendered free of fear and anxiety and depression while remaining comfortably relaxed. It is not a method of pain control. A hypnotic may be the same compound, but is used in a greater dose, in order to reduce sleep latency (46).

Anxiolytic drugs which are not used for the treatment of psychogenic disorders are often used as sedatives and hypnotics, except that efforts are made not to interfere with daytime productivity. Obviously the nature of the drugs themselves and the variability encountered in the physiological processes of the human leads to the necessity of these definitions being somewhat liberally interpreted.

Since chlordiazepoxide, there has been a major decrease in the use of previously employed drugs for attaining sedation and hypnosis. There has been a general shift in presciption writing to

other members of the benzodiazepine group. In addition to producing a reduction in activity, benzodiazepines have the capacity to produce widespread CNS depression, yet do so more selectively than the barbiturates. Due to the high numbers of dental patients avoiding dental treatment due to high anxiety levels, prior to and during dental appointments (15%-20% of the population (3)), numerous drugs have been employed to allay patients' fear and make the dental appointment more acceptable to the patient, and thus the dentist.

Clinical examples of sudden and unexpected death due to stress have been reported, even where patients have been generally in good health (4). Obviously a reduction in this risk would be a considerable benefit. As well, the dentist could only benefit by having a calm, cooperative and relaxed patient whose protective reflexes are maintained. The most precise method of obtaining sedation in patients is by intravenous sedation technique. The majority of dentists use oral sedation techniques, either for reasons of insecurity with intravenous techniques, or if not having offices capable of handling possible complications efficiently.

However, orally administered drugs are not as predictable nor as consistant in onset and intensity of effects as intravenously administered drugs as there are numerous factors which influence blood plasma levels. By use of the intravenous route the drugs may be titrated to meet the individual needs of the patients.

At present the most commonly used drugs for intravenous sedation are benzodiazepines, butyrophenones or barbiturates. There is a need to compare these different drug regimes for variations in pharmacological and psychological effects on the patients, and from this to make recommendations as to the appropriate use of the particular drug regimen for dental patients.

Since barbiturates are most commonly used as induction agents for general anaesthesia, and have been studied at length with their shortcomings and advantages known to those involved in their use it would be interesting to study the other two groups; benzodiazepines and butyrophenones.

For the purposes of this study it was decided to compare two conventional drug treatment regimens presently in use at the Centre for Health Sciences at the University of British Columbia, for pharmacological and psychological variation amongst patients, and to formulate guidelines for their use in dentistry.

A REVIEW OF LITERATURE REGARDING SEDATIVE DRUGS PERTINANT TO DENTISTRY

II - DENTAL SEDATIVES-PRIOR TO THE INTRODUCTION OF BENZODIAZEPINES

Prior to the introduction of the benzodiazepines, the barbiturates were the most commonly used drugs for purposes of sedation and alleviation of anxiety. Certain other non-barbiturates had some popularity, e.g. ethchlorvynol, glutethimide, paraldehyde, ethinamid, meprobamate, chloral hydrate and some antihistaminic drugs with sedative effects.

Chronologically, the bromides and chloral hydrate "replaced" opium, alcohol, and the belladonna alkaloids toward the end of the 19th century. Chloral hydrate (NOCTEC) and chloral betaine are inexpensive and orally effective sedatives with a fast onset of action (20-30) minutes and duration of four hours. Chloral hydrate has many disadvantages; it is highly irritating to the skin and mucous membranes and gastric irritation often results if taken without food. Administration is absolutely contraindicated to those patients with gastric or duodenal ulcers. It has been helpful in the treatment of status epilepticus and eclamptic seizures. As the margin between therapeutic and toxic dose is narrow it should be avoided in patients where general anaesthesia is planned. Even small doses of chloral hydrate may result in peripheral vasodilation and hypotension, and some degree of myocardial depression. Internally it is rapidly converted to trichlorethanol which is believed to cause the central depressant effects.

In spite of the bad taste there is an abuse potential, and sudden withdrawal after chronic use results in a similar syndrome to that caused by alcohol withdrawal (8). Considering these problems it is difficult to understand why it is still used in dental sedation. While benzodiazepines have largely taken over, there is still some use of this drug in rest homes, chronic care centres and some peadodontic practices.

Paraldehyde, a polymer of acetaldehyde has been available for sedative use for over a century. It is inexpensive and orally effective with a rapid onset and a longer duration than chloral hydrate. It has a disagreeable taste and more than 25% is exhaled. The balance undergoes liver metabolism. In spite of the bad taste it has some abuse potential, but dental patient acceptance is poor and the drug has little to offer (8).

Ethinamate (VALMID), a urethane, was introduced to the market in 1954. Taken orally it has a fast onset and short duration of action. Because of the short duration it has had limited popularity as a preoperative sedative in dentistry. Paradoxical excitement has been reported in children andrashes and gastric upset are relatively common in both adults and children (8).

Ethchlorvynol (PLACIDYL), appeared on the market in 1954. Because of its relatively fast onset and duration (approximately 30 minutes and 4-6 hours respectively), it has had some popularity as an oral sedative in dentistry. It has a wide margin of safety and has anticonvulsant and muscle relaxant properties. However,

being a condensation product of chloral hydrate, it therefore exhibits similar advantages and disadvantages. The most common side effects are: after-teste, dizziness, nausea and vomiting, hypokinesia and facial numbness. Mild hangover and ataxia also occur relatively commonly. Rarely, there are allergic reactions. Cases of suppressed anticipated anticoagulant response to dicoumerol in patients have been reported, and ethchlorvynol is absolutely contraindicated in patients with intermittent porphyria. Taken orally, approximately 770 milligrams (mg) ethchlorvynol is considered to give an equivalent sedative response to that of 100 mg secobarbital (6).

Glutethimide (DORIDEN) was introduced in 1955. It is a piperadinedione similar in structure to methyprylon. It has been associated with acute allergic reactions, porphyria and blood dyscrasias. With prolonged use, physical and psychic dependence may follow. Withdrawal symptoms are equivalent to those of the barbiturates. Gastric absorption is somewhat erratic. Intravenously its absorption pattern resembles that of thiopental. Acute intoxication may result from overdose or from a combination with other central nervous system (CNS) depressants. Respiratory depression occurs less frequently than with the barbiturates but circulatory depression may be more severe in overdose situations and the anti-muscarinic effects persist for hours. There is no longer any reason to recommend its use in dentistry (8).

Meprobamate (MILTOWN) introduced in 1955, received both rapid medical and lay popularity. Its first use was as a muscle relaxing agent and later as an anxiolytic. Clinical testing has shown

it to be little better than a placebo at suggested therapeutic doses, and less effective than an intermediate acting barbiturate regarding sedative effects. It may cause widespread C.N.S. depression, yet does so unevenly, and it is not a general anaesthetic. It is more selective than the barbiturates in the depression of spinal chord reflexes, being selective only for polysynaptic, not monosynaptic reflexes. Although it is reported to be hyperalgesic, when it is combined with analgesic compounds, it enhances the analgesic effect. Well absorbed orally, its plasma concentration peaks in 1-3 hours. Most of the drug is excreted in the urine unchanged. Little is plasma protein bound. Plasma T 1/2 is 6-17 hours. Major problems which could arise with a sedative dose are drowsiness and ataxia. In multiple doses there is considerable impairment of learning and motor coordination. Hypotonia also may occur in response to clinical doses. C.N.S. depressant drugs will have enhanced effects when used in combination with meprobamate.

The abuse potential is high, and within a year of marketing major problems had been reported. Abrupt discontinuation after chronic use results in a withdrawal syndrome which includes anxiety, insomnia, tremors, gastric disturbances and hallucinations. Though popularity has dropped considerably in recent years, overdose reports in hospitals are still not uncommon, and there is a relatively high suicide risk in patients taking the drug on a chronic basis. Since the introduction of the benzodiazepines in the 60's, there is little indication for its continued use in dentistry (8).

Methaqualone (QUALUDE) a quinazoline, possesses hypnotic, anticonvulsant, antispasmotic, local anaesthetic and weak antihistaminic properties. Antitussive properties are equivalent to those of codeine. Tolerance develops to its depressant, anticonvulsant and behaviorial effects. In large doses it causes myocardial depression. Orally, it is absorbed in 2 hours, and becomes 70-90% plasma protein bound. In sedative doses it causes fatigue and occasionally dizziness, and in hypnotic doses it may cause transient paresthesias. Residual peripheral neuropathies have been reported to last months or years. Excessive dreaming, somnambulism, and drug hangover are common occurrences. CNS depression is potentiated when it is combined with alcohol or other depressant drugs. Its drug abuse seems to stem from the belief that methaqualone is an aphrodisiac which also provides a 'high' without the usual barbiturate-like drowsiness. Some feel it gives effects similar to heroin. In light of its abuse potential, it would be unwise to use this in dentistry, though it is marketed for use as such (5).

Prior to the marketing of the benzodiazepines, the barbiturates were the most popular dental sedatives. Formed by a condensation of urea and malonic acid, on its own barbituric acid has no sedative effect. Substitution of different length alkyl chains, and the presence or absence of a sulpher atom determines, to a great extent, the onset and duration of the particular drug (6).

Onset of barbiturate effects is also determined by its solubility in fat. Thiopental, which is highly lipid soluble, enters the brain rapidly causing C.N.S. depression and then is quickly

distributed to the other tissues. The redistribution results in only a short duration of action. In contrast, secobarbarbital is distributed to other body tissues before peak concentrations in the brain have been reached. Recovery is longer with secobarbital since metabolism is responsible for the duration of action to a greater degree than with thiopental. The degree of ionization also has a bearing on the duration of effects. In low pH conditions, the unionized form of the drug is predominant, while in high pH conditions the ionized forms predominate. Therefore it is reasonable that the alkalinization of urine would result in the excretion of the inactive ionized form. Metabolism is also enhanced by the replacement of sulpher with oxygen, the oxidation of side chains at C-5 and the removal of methyl groups at N-3.

In low doses barbiturates act by selective removal of inhibitory influence of reticular structures, resulting in uncontrolled cortical activity. Clinically, the picture is similar to early alcohol intoxication. An increased dose will result in depression of the hypothalamus and medullary centres which are responsible for cardio-vascular and respiratory control. In overdose situations, respiration is slowed, reflexes are absent and death results ultimately from respiratory failure.

These drugs have a high abuse potential and chronic use has lead to both metabolic and adaptive tolerance, and addiction. Barbiturates will cause the induction of hepatic microsomal enzymes

responsible for barbiturate metabolism. However the drug must be present for a sufficient time to cause induction. Tolerance also develops to the adaptive changes in the nervous system. These changes compensate for the drug effects by causing an increase in neuronal exciteability. Upon withdrawal of barbituates an abstinance syndrome develops which is similar to that occurring with alcohol withdrawal. In addition, barbiturates aggravate acute attacks in individuals suffering from congenital porphyria.

Therapeutically there are still several indications for the use of barbiturates, although their indications for use as day time sedatives and night time sleep-inducing agents have decreased. They are still used in hospitals for premedication prior to anaesthesia, as an anticonvulsant in the treatment of grand mal epilepsy, and as a diagnostic aid in the practice of psychiatry.

Certain sedatives with antihistaminic effects have also been used with some success. Hydroxyzine (ATARAX), is available for oral and intramuscular administration. It also has antiemetic and muscle relaxant properties. Due to its wide margin of safety it has become popular with dentists with paedodontic practices. The most common adverse effect is drowsiness, and peak plasma concentrations are not reached for three or four hours, so administration must be carried out by the parent well in advance.

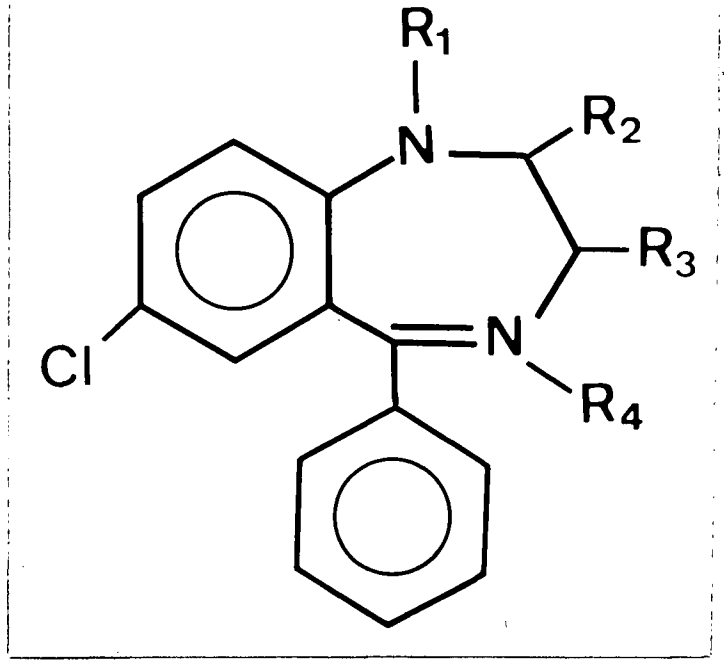
Promethazine (PHENERGAN) is a powerful antihistamine with prominant sedative effects. It is available in over the counter

preparations, and parents often use this drug to induce sleep in their children. As it is a member of the phenothiazine group, it is liable to produce serious reactions when taken with other psychotherapeutic agents. In dentistry it gained some popularity when marketed as (MEPERGAN), a combination of promethazine and meperidine. Since potentiation is a problem with this combination, it is wise to use a reduced dosage with this preparation. In addition, when used with children, since drug metabolism mechanisms are not fully developed, drug overdose may occur unexpectedly.

III BENZODIAZEPINES-GENERAL PHARMACOLOGY

Since the clinical introduction of chlordiazepoxide as LIBRIUM, over 2000 benzodiazepines have been produced, and about 50 have been marketed. The term benzodiazepine refers to the 5, aryl 1-4 benzodiazepine, as all C.N.S. depressant types have the 5 aryl group. In particular, for those in clinical use, low electron density exists about R-4. Generally all benzodiazepines have the same qualitative and mechanisms of action, but differ in duration and quantitative effects. "Little evidance that the pharmacological profile of any single compound among the many now available to the clinician, is significantly different from any other : i.e. all produce sedation/ anxiolysis in approximately the same proportions" (7). However, it is possible to accentuate certain effects by analyzing the pharmacokinetics of the group. e.g. those with a long T 1/2 could be used where prolonged effects such as daytime anxiolysis are desirable, and those

with a short T 1/2 used where short term sedation, or hypnosis are desired.



GENERAL BENZODIAZEPINE STRUCTURE

Theories for binding sites for the benzodiazepines have been suggested by several people. One current theory is that receptors have stereospecific binding sites, and an excellent correlation has been shown between binding affinities and average therapeutic doses. The existance of a post-synaptic triad of a gamma amino butyric acid (GABA) receptor-benzodiazepine receptor - and chloride ionophore complex has been suggested (7). The activation of the benzodiazepine receptor would produce a conformational change in the GABA receptor (from low to high affinity) by blocking the actions of GABA modulin; a protein which lowers receptor affinity. Thus, benzodiazepines and their receptors are viewed as an amplifying system which potentiates GABA's inhibitory effects (8).

The work of Squires et al. (1979) showed that triazalopyradazine displaced benzodiazepines from two binding sites, whereas diazepam was unable to distinguish between these same two sites. Their theory suggested one binding site existed for anxiolytic and anticonvulsant effects, and another for sedative effects. The Roche Company developed a compound which is structurally related to the benzodiazepines with high receptor affinity, for use as an antagonist. Ciba-Geigy has also developed an antagonist, but with little structural resemblance to benzodiazepines yet with high receptor affinity. These observations may be explained by the existance of different conformations or states of the same receptor.

The theory of different receptors for different effects seems a reasonable one, since tolerance develops to the ataxic, muscle relaxant and anti-convulsant properties more quickly than does tolerance to the sedative and hypnotic effects. Generally the benzodiazepines are capable of the following central effects: sedation, hypnosis, anxiolysis, muscle relaxation, and anticonvulsant activity in the treatment of epilespsy. In the case of alprazolam, a possible anti-depressant action exists. When given intravenously (i.v.) in low doses there may be mild coronary vasodilation, while in high doses neuromuscular blockade may result.

Unlike the barbiturates, alcohol, other sedatives and general anaesthetics, the benzodiazepines are not general neuronal depressants. The benzodiazepines act at all levels of the neuraxis, however at a given level some members of the group produce more

effects than others. The general pharmacological profile is similar for all members although some variation in selectivity at a particular level of the neuraxis will result in variations for the clinical indications of the different benzodiazepines, e.g. alprazolam as an anti-depressant (13).

In the healthy patient sedative/hypnotic doses have little if any effect on both the cardiovascular and respiratory systems. In the debilitated patient or in a healthy patient subjected to intoxicating doses, effects on these systems will vary. These effects will be discussed with the individual drugs.

Indirect actions on the gastrointestinal tract may occur, since it has been shown that in antianxiety doses benzodiazepines have been shown to decrease some gastrointestinal disorders in nervous patients.

PHARMACOKINETICS-ONSET AND DURATION

The pharmacokinetics of the benzodiazepines are determined by numerous variables. Administered per os (p.o.),the rate of absorption from the gastrointestinal system (G.I.S.) is a major determinant of rate of onset of activity. Absorption of some may be as rapid as 20 min. as in the case of diazepam, and as slow as six hours as in the case of bromazepam. Effects may be delayed by slow disintigration of tablets, or the presence of food in the stomach. In addition, the presence of aluminum containing compounds in the stomach reduces the rate of absorption.

Given intramuscularly (i.m.), the water soluble benzodiazepines are more predictably absorbed than non-water soluble benzodiazepines. For example, lorazepam, a water soluble benzodiazepine is predictably absorbed i.m., and is used for the treatment of anxiety prior to surgical procedures.

Given intravenously (i.v.), the onset is most predictable, both for water and non-water soluble members, and variations in onset are within minutes from one drug to another. All benzodiazepines bind to human plasma albumin. The degree of binding varies directly with the lipid solubility of the particular drug. For the most lipid soluble drugs, a three compartment model is proposed, but for the majority a two compartment model is considered to resemble observed drug patterns. Generally, the suggested model is: a fast uptake to the grey matter, followed by a slower redistribution to the white matter, vessel rich organs, plasma proteins, muscle, bone and fat. To a great extent, distribution determines single dose duration of action.

Apparently there is a considerable effect on diazepam, bromazepam and nitrazepam by enterohepatic circulation. Early on, there is considerable biliary secretion, followed hours later by reabsorption, with a subsequent surge in plasma concentration and pharmacological effects (6).

METABOLISM AND ELIMINATION

Unlike most other phenyl or benzo group containing drugs, the benzodiazepines are resistant to hydroxylation at the benzo ring. Biotransformation takes place by nitro-reduction of the benzo ring and acetylation of the resulting amines. Otherwise metabolism takes place at the 1,4-diazepine moiety, with glucuronide being the major resulting conjugate. Acetamides are the chief conjugates of the 7-nitro compounds, and some types have trace amounts of sulfates. Many non-conjugated metabolites are active in themselves, e.g. medazepam --→ diazepam+oxazepam+temazepam. Biotransformation for most members takes place in the liver, except for flurazepam where the drug disappears rapidly from the small intestine to the circulation and only the metabolite appears in the urine.

Elderly patients metabolize and eliminate the drgus more slowly, therefore the drug dose should be adjusted downwards accordingly.

As a group the benzodiazepines do not induce microsomal enzyme synthesis significantly. Chlordiazepoxide, diazepam and fluorazepam are exceptions however and these three are capable of inducing their own metabolism. Others in the group are not (6).

ADVERSE EFFECTS

At peak plasma concentrations, the most commonly occuring adverse effects are: variations in lightheadedness, lassitude

increased reaction time to stimuli, ataxia, and impaired mental and psychomotor functions. Confusion, amnesia, xerostomia, and dysarthria are also common. Alcohol or other CNS depressents will prolong and intensify these effects. Although uncommon, a paradoxical adverse psychological reaction may occur, the mechanism of which is unknown.

TOLERANCE

Tolerance to benzodiazepines results in cross-tolerance to methaqualone and the barbiturates, and to a lesser extent to alcohol. It is reasonable clinical therapeutic practice to withdraw the drug, in some cases, at the first sign of a need for increased dose for maintenance of effect.

As with the barbiturates, tolerance develops to electroencephalographic (EEG) effects. Withdrawal of benzodiazepines after chronic use has been shown to result in possible depression, anxiety and agitation, with the accompaniment of abnormal sleep and dreams. Less often, cases of acute psychoses, delerium, and the return of convulsions have been reported.

EFFECTS ON SLEEP

In therapeutic hypnotic doses there is a decrease in sleep latency and an increase in wakening threshold. Not all stages of sleep are uniformly effected by all benzodiazepines. Oxazepam, diazepam, and chlordiazepoxide have been shown to increase stage 1 sleep while flurazepam, lorazepam, nitrazepam and temazepam will

decrease this interval. Stage 2 is uniformly increased, while stages 3 and 4 are decreased. All types increase random eye movement (REM) latency.

USE IN PREGNANCY

Because of the risk of teratogenesis, the use of benzodiazepines is not recommended in the first trimester of pregnancy. Benzodiazepines have been used during labour, with the warnings that hypothermia, hypotonia, and mild respiratory depression may occur. Reportedly, cases of chronic abuse by the mother has resulted in a withdrawal syndrome in the infant.

DRUG INTERACTIONS

Major problems with drug interactions may occur when benzodiazepines are combined with alcohol and other CNS depressants since drug potentiation may occur. In normal therapeutic doses in healthy individuals benzodiazepines have little respiratory effect, but when combined with the aforementioned drugs, respiratory depression is a probability. Also, it is possible for combinations of valproate and the benzodiazepines to cause psychotic episodes. Valproate is normally used for treatment of petit mal epilepsy. When taken in combination with a histamine H_2 receptor antagonist such as cimetidine (TAGAMET), there is a delay in hepatic metabolism and thus elimination of benzodiazepines, resulting in an enhanced effect. Where benzodiazepines are metabolized other than by the hepatic system, this elimination problem is not exhibited.

IV SPECIFIC BENZODIAZEPINES AND THEIR SEDATIVE USE IN DENTISTRY

Diazepam (VALIUM) was introduced by the Roche company shortly after it introduced chlordiazepoxide (LIBRIUM). Diazepam was marketed mainly for its anti-anxiety effects. The aim was to produce a calming effect with minimal hypnosis and minimal reduction of the 'fight/flight' mechanism. The patient would still be aware of day to day dangers, and be able to make the decision to avoid them (9). Later, diazepam was also used for its anti-convulsant and muscle relaxant effects. The anti-convulsant effects have been shown to be superior to those of phenobarbital in the reduction of generalized seizures, in that diazepam will reduce seizures without the significant CNS depression caused by equivalent anti-seizure doses of phenobarbital. In clinical doses, muscle relaxant properties of diazepam are superior to those of meprobamate (6).

Roche claims single oral doses will peak in plasma within one hour and rapidly decline over 2-3 hours. In practice, the many variables previously mentioned will effect onset and half life. A recognized rebound effect occurs at about 8-10 hours after intravenous administration due to drug redistribution and/or the presence of active metabolites.

With intravenous use in repetative doses, minor depressive effects on blood pressure have been noted. With therapeutic doses of diazepam there are insignificant changes in blood pressure and normal responses to adrenaline, acetylcholine, serotonin, carotid occlusion and central vagal stimulation occur.

CLINICAL INDICATIONS

Being the first non-general anaesthetic administered intravenously in dentistry for anti-anxiety purposes, diazepam gained rapid popularity with dentists since in sedative doses protective reflexes are not obtunded. For many patients, the realization that they will not be "put to sleep", will in itself allay much anxiety. The duration of action in the average adult patient after intravenous administration is 15-45 minutes, with a mean of about 30 minutes. Most patients will exhibit a certain degree of amnesia regarding the procedure. Usually they recall only the latter parts of the procedure.

This amnesic effect could be particularly useful in patients requiring quadrant dentistry, surgical removal of impacted teeth, apical or periodontal surgery and lengthy crown and bridge procedures. The less traumatic procedures could be left for the end of the appointment when sedative effects are diminishing.

Clinically, the dosage used for the patient is that required to produce marked ptosis (the Verrill sign), and a slurring of speech. The exact amount will vary from patient to patient, but in most healthy adult patients 12.5 mg administered intravenously is sufficient.

LOCAL COMPLICATIONS

Considerable research has been devoted to the incidence of thrombophlebitis. It has been found that when the drug is injected slowly into the veins of the ante-cubital fossa there is a decreased

risk of thrombophlebitis when compared to injection into the dorsum of the hand. In addition, use of the i.v.drip technique when injecting the veins of the dorsum of the hand has proven effective in avoiding thrombophlebitis over direct injection of diazepam.

Other local complications include: hematoma, phlebitis, and inadvertant brachial artery injection (at the ante-cubital fossa) (48). Proper i.v.technique and knowledge of local anatomy is important in avoiding these sequelae.

SYSTEMIC COMPLICATIONS

In order to avoid systemic complications, patient selection is important. Suitable patients generally fit into the American Society of Anaesthesiology (ASA I), and certain (ASA II) categories. When treating patients taking other CNS acting drugs, or those with cardiovascular abnormalities and those with mental abberations, alternative methods of sedation should be sought (24,38).

A suggested intravenous dose for children over two years is 2-10 mg depending on weight and degree of excitement. Alternatively, the manufacturer suggests giving 2-5 mg p.o. before retiring the night prior to the appointment and 5-10 mg, taken on an empty stomach, 45 minutes before the appointment.

Shortly after diazepam became available for use in dentistry, numerous papers appeared discussing the advantages and disadvantages

of its intravenous use. It has been shown that "preoperative anxiety, by itself and in healthy patients, is not the only major indication for conscious sedation (10)." The occurrence of cardiac arrhythmias during oral surgical procedures has been demonstrated by conducting studies on cardiac function. In their study, Hillman and McFall showed "no incidence of vasovagal or frank syncopal reaction, with sedation, whereas two subjects during the control experience displayed transient bradycardia and hypotension in the first 10 minutes after intravenous placebo injection and during local anaesthesia administration (10)". They also demonstrated consistantly lower serum 17-hydrocorticosteroid levels, in sedated versus placebo treated patients; consistantly lower systolic and diastolic blood pressures and a stabilization of respiration in sedated patients over placebo patients.

The authors explain the significance of the drop in steroid level with the following reasoning. A patient about to undergo a surgical procedure is bound to experience some psychological manifestions of stress. The autonomic nervous system comes into play with the activation of the sympathetic nervous system, i.e. the 'fight or flight' response. Assuming the patient is going to stay for the procedure, the parasympathetic nervous system will continue to strive to retrieve the loss of equilibrium with the sympathetic nervous system, which has since gained dominance. If vasovagal syncope occurs, then the parasympathetic nervous system has suddenly achieved dominance. This, in the extreme circumstance may cause death (11). Since patients who had been sedated displayed consistantly lower corticosteroid levels and

lower systolic and diastolic blood pressures than did unsedated patients, Taggard and Hedworthy-Whitely propose that the loss of equilibrium between the two nervous systems is less likely to occur in the sedated patient. They proposed the ideal state as one in which the patient is sedated, almost to the point of sleeping, yet is easily aroused, remains cooperative, and has an anterograde amnesic experience.

In another study Goldstein, Dionne et al., observed the effects of intravenous diazepam and the inclusion of epinephrine with the local anaesthetic in patients undergoing third molar extraction. Specifically they were interested in the circulatory, psychological, plasma catecholamine, cortisol and lipid changes in response to third molar extractions. Whereas plasma norepinephrine increased 60% during surgery in the non-sedated patients, diazepam abolished the norepinephrine response in sedated patients without significant change in the heart rate or systolic pressure. However the inclusion of epinephrine was shown to result in a significant increase in plasma epinephrine and cardiac output within minutes of the injection. The direct effect of epinephrine would account for the increase noted. The participation of the sympathetic nervous system is suggested in producing the response noted. They concluded that the elimination of the sympathetic nervous system response by diazepam without accompanying reductions in systolic pressure and heart rate, indicate that, more than just the sympathetic nervous system is responsible for the circulatory changes which occur during stress

situations (12). This is in agreement with the aforementioned study. Regarding the psychological responses of the patients, "the pre-medicated patients reported significantly less anxiety during surgery. This would suggest that the elevated norepinephrine responses in the nonsedated patients resulted from an anxiety-produced increase in sympathetic neural activity (12)." For ethical reasons, since the effects of local anaesthetic without epinephrine are of considerably shorter duration than the effects of local anaesthetic with spinephrine, and since evaluation was made at three hours postoperatively, the authors, not wishing to leave their patients in pain decided to omit the group which would have been treated without sedation and with an epinephrine free local anaesthetic. Therefore conclusions regarding epinephrine effects were based on sedated patients only.

SHORT ACTING VERSUS LONG ACTING BENZODIAZEPINES

Whereas diazepam has held a prominant position for many years as the sedative agent of choice, further research has lead to the development of numerous competitors. Several guidelines have appeared for the indications and uses of drugs in the group. In a systematic review of the benzodiazepines, the British Medical Journal in 1980 suggested that seven factors in should be considered before use in therapy (13).

This Committee on the Review of Medicines drew attention to the following factors:

1. anxiety and insomnia
2. long term efficacy in all indications
3. residual effects of therapy (particularly daytime sedation)
4. possible dependence syndrome
5. withdrawal symptoms
6. evaluation of the pharmacological implications on general practice and
7. use in the elderly

The committee drew a distinction between 'long-acting agents', (where plasma T 1/2 exceeds 10 hours) e.g. diazepam, chlorazepate, chlordiazepoxide and medazepam and 'short-acting agents' e.g. triazolam, lorazepam, and temazepam.

Particularly in the elderly and in those with impaired renal or hepatic function, the rapid excretion and lack of accumulation properties of the short-acting group would be advantageous over the properties of the long-acting group.

Regarding efficacy of the individual drugs, the committee found that any of the drugs in the short-acting group would be effective in the short term treatment of anxiety and insomnia. A rigid division of the drugs as anxiolytics and hypnotics is not based on sound pharmacological principles (14). It was not recommended that these drugs be used in treatment of dysmennorrhoea, depression, tension

headaches, psychotic illness, or in the use of anxiety or insomnia in children. Indications for the long-acting agents were for muscular spasm, symptomatic treatment of alcohol withdrawal, night terrors, and somnambulism.

Considerable discussion has been raised on the effectiveness of the benzodiazepines when used over a period of a few months in the treatment of insomnia. The Food and Drug Administration (FDA-USA) hold the view that there is little to support the long term use of hypnotics, (including benzodiazepines) since most sleep laboratory studies show loss of efficacy in the reduction of sleep latency, over a few weeks/ months of use. A loss of efficacy in anti-anxiety treatment was also demonstrated when these drugs were used chronically; yet there are continued repeat prescriptions for patients with these problems (15).

The conclusion of the British Medical Journal study (13) stated that despite media reports there is little addiction potential to benzodiazepines. This is not to say that symptoms after abrupt withdrawal will not occur. Indeed symptoms including anxiety, apprehension, tremor, ataxia, nausea and vomiting reportedly do occur. Depending on the half life of the particular drug involved, latency could be as short as 24 hours, as is the case with short-acting drugs, and as long as three days, as is the case with long-acting benzodiazepines. In light of these symptoms, it is possible to see why a physician would represcribe the drug, as it would appear the previous drug regimen had been appropriate and should therefore be continued in order to avoid the 'return' of anxiety and its manifestations.

LONG-ACTING BENZODIAZEPINES

Chlordiazepoxide (LIBRIUM) is presently used for antianxiety treatment and alcohol withdrawal and is considered to be approximately half as potent a sedative as diazepam. While chlordiazepoxide itself has a half life of 12-28 hours, the possibility of accumulation in the patient with liver disease is relevant because of its numerous active metabolites: desmethylchlordiazepoxide, demoxepam, desmethyldiazepam and oxazepam. The latter is marketed as (SERAX) and has a half life of 5-15 hours. Desmethyldiazepam reportedly has a half life of elimination of up to 120 hours. While absorption is good orally, it is not well absorbed intramuscularly and chlordiazepoxide should not be given by that route.

Oxazepam (SERAX) is also used for antianxiety and alcohol withdrawal treatment. It does not have active metabolites and does not accumulate in patients with liver disease. About 1/3 as potent as diazepam, it is usually given in doses of 30-60 mg for anti-anxiety. Unlike diazepam, it has not been shown to react with the drug cimetidine, nor with disulfiram. Its usefulness as an anaesthetic adjunct has not been demonstrated since it is only available for oral administration (17).

Another long-acting agent, chlorazepate (TRANXENE) is indicated in the treatment of anxiety and alcohol withdrawal. Due to rapid decarboxylation of the compound in the stomach, the drug

is absorbed as desmethyldiazepam. Because chlorazepate levels peak in 30-60 minutes, the effects are likely due instead to this active metabolite which has a plasma half life of about 50-120 hours since effects increase over two to three days of continued use. The potentiation reaction with alcohol appears to be considerable. The effects of motor impairment seem particularly severe and last for days. It is therefore of little use in dentistry.

SHORT-ACTING AGENTS

Some of the more common short-acting agents in use are lorazepam, temazepam, triazolam, and halazepam. Marketing strategies by the drug companies have emphasized only some effects of these agents. However research continues to show them to be more widely applicable than was originally thought.

Lorazepam (ATIVAN), was initially introduced for the treatment of anxiety only. In recent years it has risen in popularity as an adjunct to general anaesthesia. Considered to be about five times as potent a sedative as diazepam, it has no active metabolities, and has demonstrated no accumulation in patients with liver disease. The Wyeth Co. presently markets the drug in three forms for administration:

1. tablets for oral administration
2. tablets for sublingual administration and
3. in suspension for intramuscular or intravenous administration.

When administered sublingually, the peak plasma concentration achieved is claimed to be equivalent to that achieved via intramuscular administration. The peak concentration occurs in about an hour. Orally, it takes about an hour and a half to reach the peak (18). For lorazepam, absorption intramuscularly is far more rapid and predictable than for diazepam and chlordiazepoxide. However since the introduction of sublingual tablets, the availability of the i.m. preparation would seem redundant, as administering lorazepam sublingually provides equivalent effects, without the pain of an injection.

Lorazepam has been shown to be compatable with general anaesthetic agents, muscle relaxants, atropine sulphate, narcotic analgesies, and antiemetics.

Due to its insolubility in water, lorazepam irritates the walls of blood vessels. Properly diluted, the incidence of pain on injection, thrombophlebitis and phlebitis, has been shown to be consistantly less than with diazepam (19). Clinical onset of antianxiety effects when administered intravenously and intramuscularly is considerably longer than with diazepam. Because of this, administration must be 12-15 minutes prior to the anticipated surgical/dental procedure. This contrasts with diazepam, which provides peak effects within 2-3 minutes when given intravenously. The relatively long onset of lorazepam somewhat limits its practical intravenous use in dentistry since waiting 15 minutes prior to administering the local anaesthetic is usually not feasible in most general dental office situations. In

teaching situations, or in some surgical situations such as multiple third molar extractions, the use of lorazepam is more feasible.

Interestingly, most research with intravenous lorazepam has used large doses. Due to prolonged recovery time, Wyeth has suggested that administration be up to two hours prior to surgery, to minimize recovery time. This also would present a problem in dentistry as it is difficult to hold a patient for two hours recovery time. The manufacturer admits that only upper ends of recommended doses have been consistantly studied, and they believe that recovery time could be considerably reduced if the dose was also reduced, e.g. instead of 2-4 mg iv, 0.5mg should be tested.

A danger exists with the administration of the drug in this form since operators accustomed to the fast onset of diazepam could fail to wait sufficient time to assess the effects of lorazepam and administer additional drug. Since the lack of immediate clinical response could mask itself as lack of efficacy the operator may be tempted to administer additional drug resulting in an overdose.

Regarding the amnesic effects of lorazepam, especially at the higher therapeutic doses, it has been found that patients do not recall entering the surgical theatre, the entire procedure itself or entering the recovery area. Compared with diazepam i.v.,patient amnesia peaks about two minutes after administration and steadily declines for about 30 minutes. This has been shown to be the case in about 20% of patients treated with diazepam versus 80-90% of

patients treated with lorazepam (20). The additional lack of recall could be a considerable benefit if it could be confined to the recall of the dental procedure alone.

Lorazepam, like diazepam in therapeutic doses in healthy patients, has little appreciable effect on the cardiovascular or the respiratory system. While oral doses reach peak plasma concentrations in one and a half to two hours and sublingual doses in one hour, the sublingual route may have considerable use in dentistry since at least 50% is absorbed within the first 20 minutes. While 85% is plasma protein bound, lorazepam does not appreciably displace most other plasma protein bound drugs. Its main metabolite, a glucuronide has no demonstrable central or accumulation effect.

Due to its potentiation with narcotic analgesics it is advisable to reduce drug doses when narcotics are used in combination with lorazepam. The only absolute contraindications for lorazepam, other than in combination with scopolamine, are in patients with known hypersensitivities to other benzodiazepines, in patients with acute narrow angle glaucoma, and in patients with a primary depressive disorder or psychosis, and in those with myasthenia gravis.

Adverse effects are similar to those occuring with diazepam. Because of the long onset time when taken orally, the abuse potential seems to be somewhat less pronounced than with diazepam.

TABLE 1 (17)

GENERIC NAME	DIAZEPAM	FLURAZEPAM	LORAZEPAM	OXAZEPAM	TRIAZOLAM
TRADE NAME	VALIUM	DALMANE	ATIVAN	SERAX	HALCION
PRESENT USES	-anticonvulsant -muscle relaxant -anaesthetic adjunct -antianxiety	-hypnotic	-antianxiety -alcohol withdrawal	-antianxiety -alcohol withdrawal	-hypnotic
PATHWAY OF METABOLISM	-oxidation	oxidation	conjugation	conjugation	oxidation
CATEGORY OF ELIMINATION HALF-LIFE	-long	-long	-short	-short	-ultra-short
T 1/2 PARENT & METABOLITES (HOURS)	-diazepam (24-28) -desmethyldiazepam (50-120) -temazepam (9.5-12.5) -oxazepam (5-15)	-desalkylflurazepam (47-100)	-lorazepam(9-25)	-oxazepam (5-15)	-triazolam (2-3)

V APPLICATION OF NEWER BENZODIAZEPINES FOR DENTAL USE

The recent introduction of lorazepam tablets for sublingual administration has been shown to "produce a clinically useful lack of recall for those patients who might otherwise have unpleasant memories of the period before the operation (21)". Gale, Galloon and Porter demonstrated that lorazepam impairs retrieval of information in contrast to diazepam which has been shown instead to affect recall by causing impairment of memory input on the consolidation process by affecting both recall and recognition equally. This amnesic effect was also demonstrated to be more profound when lorazepam was administered sublingually than intramuscularly although absorption by both routes follows similar patterns. A suitable explanation for this phenomena is not available. Since absorption is slightly more rapid by sublingual than intramuscular route, the added advantage of not administering a painful injection would seem to indicate little if any indication for intramuscular use in dentistry, except on a hospital out-patient basis.

Another benzodiazepine which has demonstrated predictable absorption when administered intramuscularly is flunitrazepam (ROHYPNOL). It may also be administered i.v. or p.o. Nevertheless, when compared with other more commonly used members of the group, oral flunitrazepam was found to be superior in several aspects. It was associated with less post-operative vomiting than diazepam. In children flunitrazepam has been shown to prevent fasciculations

caused by suxamethonium more effectively than diazepam (22). With regard to sedation in equipotent oral doses, flunitrazepam was found to be superior to diazepam and flurazepam in patients prior to anaesthetic induction. Regarding anxiolysis, diazepam was shown to be superior, using higher doses in a similar situation. Regarding adverse effects, a reduction in the incidence of headache was demonstrated with flunitrazepam over lorazepam and diazepam.

A water soluble benzodiazepine, flunitrazepam was compared with diazepam, a non-water soluble drug, via intravenous administration, in equipotent does (23). Forty minutes after the start of the procedure about 85% of the patients could not remember the local anaesthetic injection for either drug. Thirty mintues after, 25% had recovered in each group, and one week later most patients could not remember the procedures at all. Ataxia immediately after the procedure was somewhat more pronounced with flunitrazepam.

The incidence of arm pain and thrombophlebitis was less frequent with flunitrazepam (23). This is considered to be due to the water solubility of flunitrazepam and its less irritating effect on vessel walls. It would appear flunitrazepam is a viable alternative to diazepam for intravenous sedation purposes in dentistry. The patient will still need an escort in either case.

Regarding the high incidence of thrombotic phenomena with the intravenous use of diazepam, numerous studies have been made in attempt to control or eliminate the problem (24). Until recently the

drug has only been available only in such solvents as propylene glycol diazepam is insoluble in water. Propylene glycol has been shown to produce motor incoordination, depression of most synaptic reflexes and ataxia (25). A new solvent for lipid soluble drugs was developed in the 1970's. The active substance was dissolved in soya bean oil and then emulsified in water. In 1981 KabiVitrum introduced the diazepam emulsion (DIAZEMULS TM) in the United Kingdom. Comparative pharmacokinetic and pharmacodynamic studies showed this diazepam emulsion to have a higher margin of safety than an aqueous preparation of diazepam, while plasma concentrations and elimination kinetics for both were similar. The major differences were the greatly decreased incidence of adverse effects such as pain, and thrombophlebitis. An interesting feature of this formulation has been seen to occur on accidental infusion of the solution extravenously, in that the tissue changes differ from those seen under similar circumstances with diazepam (VALIUM). The tissue is not raised significantly at the injection site, widespread bruising does not occur, and pain on injection is less with (DIAZEMULS) than with (VALIUM). The tissue also seems to return to normal more quickly under circumstances of extravasation with (DIAZEMULS) than with diazepam. This study was carried out using veins in the anti-cubital fossa, as it is highly likely to have thrombotic phenomena occur during administration of (VALIUM) through a vein in the dorsum of the hand (48).

Clinically, because of the decreased viscosity of (DIAZEMULS), it is necessary to inject more slowly, as the solution enters the vein

with considerably less resistance than (VALIUM) (25) (27).

While one of the major problems of i.v. diazepam, has been the problem of thrombophlebotic phenomena, and the introduction of (DIAZEMULS) has shown to be a viable alternative, much recent research has centred upon the use of water soluble benzodiazepines.

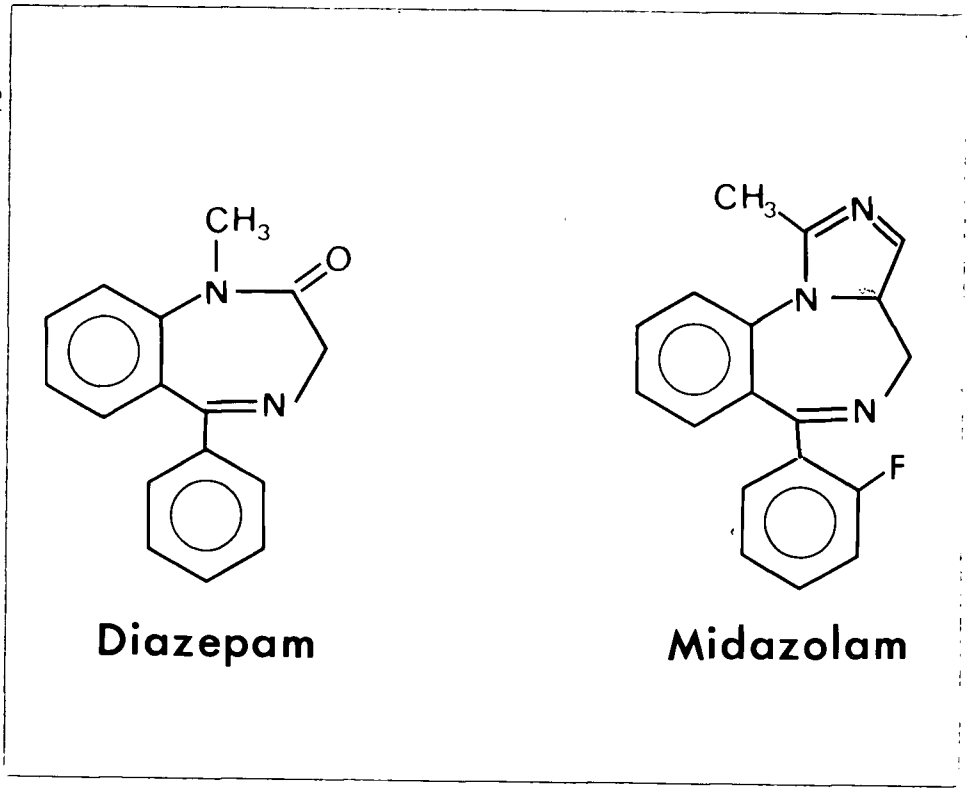
As was mentioned earlier, flunitrazepam (ROHYPNOL) has shown less incidence of local sequlae than diazepam (VALIUM). Another approach has been to study a "short acting drug which can be reinjected in measured increments as required, without increasing recovery time, and still avoid the incidence of local effects (28)." Unfortunatley, while proving successful in the latter factor, flunitrazepam has a prolonged recovery time. In cases where longer duration of effects is desireable, e.g. in the preparation of teeth for full mouth reconstruction where appointments may last several hours, then this would be a viable alternative to diazepam. Intravenously flunitrazepam appears to be 15 times as potent a sedative as diazepam, so careful titration would be of utmost importance.

Another water soluble benzodiazepine, midazolam maleate (HYPNOVAL) is receiving considerable attention. Like the other water soluble benzodiazepines, this also shows excellent local tolerance when injection intravenously. Of perhaps more interest in dentistry, is its shorter duration of action and shorter recovery time.

Chemically, when compared to diazepam, the salient differences in structure, are an imidazole ring substitution, in midazolam,

which accounts for its increased water solubility. A fluoride substitution is responsible for the increased potency. In solution, it is buffered to a pH of 3.3 to maintain the benzodiazepine ring in the open position (29).

DIAGRAMME 2



Midazolam is still largely in the experimental stage. Because of the acidic pH of midazolam solutions, alkaline solutions should not be administered concomitantly. Since midazolam is water soluble, the burning sensation experienced with diazepam (VALIUM) is not present during intravenous injection.

Biotransformation of midazolam, first by hydroxylation, takes place in the liver. Three metabolites have been identified, none of which are active. Midazolam therefore fails to exhibit the 'second peak' effect noted with diazepam, because of its lack

of active metabolites and enterohepatic circulation (30). The plasma half life of midazolam is in the range 1.7-2.4 hours, as compared to diazepam which is over 24 hours. While midazolam is approximately 94% plasma protein bound, the volume of distribution is so great that no significant displacement of oral anticoagulants nor of hypoglycemic agents has been demonstrated. Both these qualities indicate the drug should have a wide margin of safety.

In studies using midazolam for the induction of general anaesthesia, induction times range from one to two minutes. In tests to determine the duration of sleep after single intravenous doses, it was found that there was little difference in the dose-response effects between doses of 10 mg and 15 mg. This would account for its safety margin in clinical use. Generally speaking, for benzodiazepines this is a common dose-response situation.

Amnesic effects are desirable in the treatment of anxious patients, and midazolam is effective in producing these. In one study 96% of patients showed amnesia at two minutes, and 57% at 43 minutes. This would indicate it is superior to diazepam and lorazepam, for anterograde amnesia (31).

Having similar cardiovascular effects to diazepam, it may possibly prove useful in patients with ischemic heart disease "because of its rapid action and modest effects on haemodynamic parameters" (29). High induction doses may result in transient hypotension. The hypotension, a potential problem with hypovolemic patients may be

related to the pooling of blood in the splanchnic vascular bed.

When used as a general anaesthetic induction agent, transient episodes of apnea occur but these are not dose related. However such episodes are significantly shorter than those known to take place with the use of thiopental (29).

Another study, which compared midazolam and hydroxyzine (ATARAX) as intramuscular sedative premedicants, concluded that midazolam produced a faster onset and superior anxiolytic effects over the first hour of treatment. More amnesic effects, less local irritation, and wider patient acceptance was reported with midazolam than with hydroxyzine (32). The addition of hyoscine, but not atropine, was found to enhance the sedative capabilities of both drugs.

It would appear therefore, that midazolam with its increased water solubility, short half life, and low incidence of local and systemic effects, may in the future become an important drug for dental sedative treatment.

In the continuing effort to classify these drugs according to their elimination half lives, Greenblatt, Divoll, Abernathy et al. (33) have labelled midazolam, triazolam, and brotizolam as ultra-short acting agents. Their pathways of metabolism involve oxidation and hydroxylation to a glucuronide, and no active substances remain in the blood. While with the highly lipid soluble drugs such as diazepam, half

life of elimination may be almost inconsequential to the duration of action due to the rapid redistribution to peripheral tissues, in short acting agents elimination may be as important as redistribution in the termination of drug action.

It is this lack of active metabolites that is believed to be responsible for the short duration of action in these new drugs. Triazolam (HALCION), has been used mainly for its hypnotic effects in the treatment of insomnia. Administered orally in 0.25 mg or 0.5 mg tablets it has been shown to be superior to flunitrazepam in induction, duration and quality of sleep. Triazolam is little better than placebo in these effects in the non-insomniac.

Long term use of triazolam in insomniacs has shown that no tendancy for habituation or tolerance occur over a twelve month period (34). Monitoring of insomniacs' cognitive and psychomotor performances the day after using triazolam has shown the least residual effects when compared with other benzodiazepines used for insomnia. It seems reasonable to believe that the low end of the usual hypnotic dose would produce sedative effects in the anxiety prone patient, and have minimal after effects normally seen with the longer-acting agents, due to the lack of active metabolites. When taken orally triazolam reaches peak plasma concentration in 1-2 hours. Elimination in the healthy individual occurs in 2-4 hours (33). In the elderly an exagerated response has been noted. Greenblatt et al feel this is due to a reduced oxidizing capacity in elderly individuals together with reduced hepatic blood flow (33). This would manifest as an increase in systemic

availability and subsequently an increase in half-life. Similarly an increase in systemic availability has been noted when taken in combination with cimetidine or isoniazid. In patients with cirrhosis or other hepatic disease, it is reasonable to expect an increase in bio-availability due to incomplete first-pass hepatic extraction.

At present the drug has been marketed only for the treatment of insomnia and only in the oral form. It would be interesting to explore the possibility of using the shortened half life effect and lack of accumulation property, while utilizing the sedative and anxiolytic effects for the dental patient.

Considering the non-accumulating effects, and the lack of carried over day-time sedation, these ultra-short acting agents should be acceptable drugs for sedative use prior to dental procedures. It has been demonstrated that patients in hospital when given triazolam the night prior to surgery, had reduced sleep latency and work less often than those taking flurazepam or a placebo (36). The conclusion drawn was that a single dose taken the night prior to an elective operation improved the patients' sleep. The effects were more pronounced with triazolam than with lorazepam. For the nervous dental patient the administration of triazolam the night prior to dental treatment would seem to be suitable treatment.

VI CONCLUSION

The ideal dental sedative then, is one which will almost put the patient to sleep yet leave him arousable, cooperative and will maintain protective reflexes. It will not interfere to any great extent with day to day activities after the appointment is over. Obviously the ideal has yet to be found, since long term impairment is still a factor with any drug employed.

It may be seen therefore, that the benzodiazepines offer the dentist a considerable number of benefits over previously popular sedative agents when treating anxious patients.

Due to benzodiazepine receptor specificity, overall effects are generally more predictable than when sedative such as barbiturates are used. Less 'drug hangover' is seen with benzodiazepines than with the barbiturates. Motor impairment varies with both the drug employed and the individual patient, and continues to be a problem. In this respect, the benzodiazepines in sedative doses demonstrate the least problem. Even in the respiratory compromised patient the benzodiazepines are superior to the barbiturates as sedatives since the benzodiazepines are less likely to produce respiratory depression. This is not to be interpreted as a recommendation that one use benzodiazepines in the patient with chronic lung disease. However, with caution, there may be indications for benzodiazepine sedative use e.g. when the patient is breathing due to hypoxic drive not due to hypercarbia. Pharmacokinetically, the most useful sedative in dentistry is one with

rapid onset. Oral diazepam and sublingual lorazepam, both with an onset of 20 minutes are quite acceptable in the dental practice. Diazepam formulations, administered intravenously with an onset of 3-4 minutes, are also presently accepted. However (VALIUM) i.v. is still by far the most popular in North America, in spite of good reports of (DIAZEMULS) and (ATIVAN) as alternatives producing fewer thrombotic phenomena than (VALIUM).

Since a major goal in dental sedation is to minimize the long term effects of the sedative, a benzodiazepine which is biotransformed to numerous active agents should be avoided. For example medazepam is metabolized to diazepam and oxazepam, both of which in turn are metabolized to compounds with long half lives. Lorazepam is effective in minimizing long term effects since it does not alter the treatment of older patients and in those with liver disease where most sedatives tend to produce exaggerated effects, even in recommended doses.

It is accepted that benzodiazepines are effective in the treatment of anxiety in the short term. It follows that drug tolerance should not occur in dental treatment since these agents should only be for short term use. Drugs such as chlorazepate (TRANXENE) should be avoided in dentistry since there is considerable residual motor impairment, due to the active metabolites. Its use is indicated in the long term treatment of anxiety.

Regarding intravenous use of benzodiazepines; newer water soluble agents such as flunitrazepam and midazolam have been shown to be effective for sedation of patients prior to surgery, and to produce fewer local complications than diazepam. There is a slightly greater incidence of post-operative ataxia with flunitrazepam than with diazepam. This should not be a major deterring factor in its use as a dental sedative since all sedated patients should be escorted from the dental office after the appointment.

Midazolam, with its lack of enterhepatic circulation, lack of active metabolites and lack of second peak effect, has yet to be investigated for use in dentistry, but its qualities demonstrated to date appear to indicate it would be a good candidate for dental use.

While dental fear may be extremely common, it can be reduced in a number of ways. If anxiety cannot be allayed by non-pharmacological methods, the patient may be treated with anxiolytic agents usually of the benzodiazepine group, unless the patients' medical history contraindicates the use of these drugs.

NEUROLEPTANALGESIA

HISTORY - In 1949, the concept of an anaesthetic technique which blocked the cerebral cortical, some endocrine, and autonomic responses normally activated by surgery was proposed by Laborit (43). This was achieved by the administration of promethazine, chlorpromazine, and meperidine. He later added a butyrophenone, usually droperidol,, and an opioid analgesic such as fentanyl. The clinical state he achieved with his patients became known as neuroleptanalgesia. It is characterized by analgesia,absence of clinically apparent motor activity and suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in some but not all patients (44).

DROPERIDOL - (INAPSINE)

While classified as a neuroleptic and antiemetic drug, droperidol is also used for its sedative properties. Clinically it produces a mental state of detachment and indifference in patients during anaesthetic induction and maintenance of surgical procedures. It does not cause loss of protective reflexes in healthy patients being treated with recommended doses during regional anaesthesia procedures.

In man, neuroleptic drugs cause a striking lack of initiative, disinterest in the environment, little display of emotion and a limited range of affect. Subjects tend to be easily aroused and cooperative, and seem to have intellectual functions intact; there is no ataxia, incoordination, or dysarthria (6).

Chemically, droperidol is a butyrophenone derivative. Pharmacologically, in addition to inducing neurolepsis, it has α-adrenergic blocking, anti-emetic, anti-fibrillatory and anticonvulsant actions. It also enhances other CNS depressants. Under normal circumstances, droperidol has little if any affect on the cardiovascular system. In hypovolemic patients, a considerable drop in blood pressure will occur due to profound vasodilatation. Its α-adrenergic blocking effect may result in moderate hypotension, therefore rapid changes in posture should be avoided.

While transient bradycardia may be observed, other cardiac effects are rare. The heart is not sensitized to epinephrine, and adverse renal, haematological or hepatic effects have not been demonstrated (49). Respiratory effects may be profound. Depressed respiration is a predictable and real possibility, and assisted ventilation during anaesthetic procedures is necessary. The time required for the onset of clinical signs is relatively short, usually three to ten minutes, and duration of action is usually two to four hours. Since droperidol is usually combined with fentanyl for anaesthetic procedures, and since fentanyl has a relatively shorter duration of about 20-30 minutes, additional increments of fentanyl are usually indicated. Clinical signs for the need of supplemental doses may manifest themselves as an increased pulse rate (marking an increase in sympathetic activity), an increased blood pressure, diaphoresis and limb movements. Because of additive or potentiating

effects it is recommended that the usual doses be reduced by 50% when used in combination with barbiturates, narcotics or anti-psychotic agents (46).

After bolus intravenous injection, hypotension and tachycardia may occur. This is of short duration and may be avoided by slow administration of the drug. A small percentage of patients have reported having a 'big tongue' and difficulty swallowing. Dental patients should be less likely to complain of these effects since they usually expect to encounter these problems after dental procedures where regional anaesthesia is customary.

ADVERSE REACTIONS - In addition to the uncommonly occurring extrapyramidal effects of oculogyria, dystonia, and akathisia, an emergence syndrome may occur on rare occasions. This syndrome consists of unusual restlessness and excitement. With careful titration, this syndrome, the extrapyramidal reactions, or oversedation occur only in about 1% of the patients. Since droperidol has no specific antidote, the treatment of overdose is chiefly supportive; oxygen, restoration of fluid levels, and in the case of extrapyramidal symptoms, an anti-parkinsonian drug may be indicated (49).

The manufacturer recommends a dose of 2.5-5.0 mg be given intravenously as an adjunct to regional anaesthesia. Reductions in doses for debilitated or elderly patients are indicated. While benefits are derived with the combination of droperidol and fentanyl for both the clinician and patient, there is a potential problem when

this combination is used on an outpatient basis. Due to the possible duration of action of 24 hours of droperidol and the short duration of action of fentanyl there is a distinct possibility that the patient could be dismissed only to have the analgesic effect wear off and the "tranquilizer" effect remain, i.e. the patient could appear calm yet be suffering from mental agitation and restlessness (45).

When judiciously used droperidol is a safe drug, provided the patient is properly monitored, is not hypovolemic, and is not suffering from Parkinson's disease.

FENTANYL-(SUBLIMAZE)

Fentanyl citrate is a synthetic narcotic analgesic with anaesthetic actions similar to morphine, and some sedative properties. While it is considered a 'short' acting narcotic, this term refers to its analgesic effects; it respiratory depressant effects may last considerably longer (45). While most narcotics demonstrate emetic effects, fentanyl shows this less than other opioids. Fentanyl shows little effect on the cardiovascular system and only minor changes in pulse and blood pressure have been noted (46). Interestingly, after the addition of 10 mg diazepam, several patients demonstrated a significant decrease in stroke volume, cardiac output and blood pressure, and an increase in central venous pressure (46).

Chemically, fentanyl is grouped with the narcotics such as meperidine, alphaprodine, anileridine and diphenoxylate. Though all drugs in this group differ structurally from morphine, they all demonstrate similar pharmacological effects to morphine.

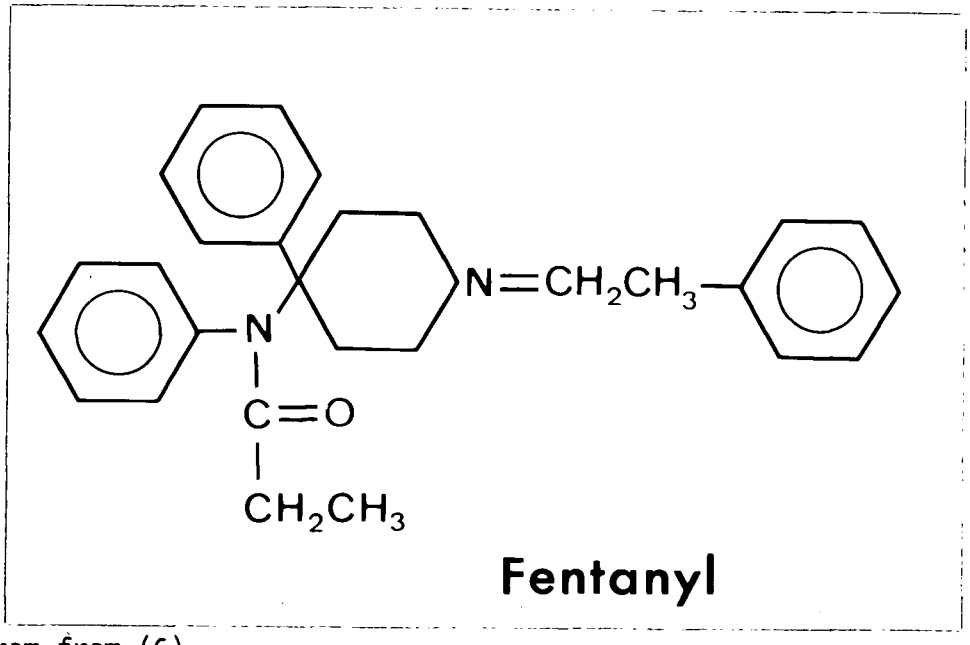


Diagram from (6).

Pharmacologically, fentanyl binds to the opioid receptors, and produces effects chiefly on the CNS. Clinically this manifests as analgesia and respiratory depression. Gastro-intestinal effects are similar to morphine but less pronounced. Absorption and onset of clinical symptoms is rapid, as is drug redistribution. Therefore plasma levels decrease rapidly. Older patients often demonstrate higher than average plasma concentrations, and decreased plasma protein binding. These phenomena may account for an increased response to the 'average' therapeutic doses.

INTRODUCTION TO THE STUDY

In consideration of the aforementioned drugs, benzodiazepines and butyrophonones, it was reasonable to study these drugs in combination with fentanyl. Specifically the combinations diazepam + fentanyl, and droperidol + fentanyl, were chosen. Reasons for the choice of these specific drugs as being representative of the drug group were many; both diazepam and droperidol are readily available in intravenous solutions, both are employed as conventional sedatives for surgical procedures, and both drugs are used on a regular basis at the University of British Columbia Acute Care Unit.

In addition, anaesthetists use these drugs on a regular and approximately equal frequency when providing sedative services for the patients undergoing surgical procedures at this centre. Each of these drugs is usually combined with a narcotic such as fentanyl in such procedures.

In dentistry, diazepam is often used for sedation. It would be be interesting to study the anaesthetic, psychological, and pharmacological aspects of diazepam in relation to those of droperidol, a drug which is not commonly used in dentistry, and see if the use of these drug combinations are suitable for use in dentistry.

OBJECTIVES OF THE STUDY

To compare two conventional sedative combinations; Diazepam/Fentanyl and Droperidol/Fentanyl, in patients underoing cataract extraction and intraocular lens replacement for the following effects.

1. CNS DEPRESSION - to observe and compare the depression intra-operatively and post-operatively and check for major differences in magnitude.

2. CVS EFFECTS - to observe patients for occurrence of bradycardia and hypotension, intra-operatively and immediately post-operatively and compare differences in occurrence.

3. ALLEVIATION OF ANXIETY - to note inherent differences in the drug regimens in the relief of the patients' anxiety, and note adverse side-effects if any.

4. TO ASSESS SURGEON AND ANAESTHETIST OPINIONS -for any preference between the two combinations.

5. TO ASSESS FOR PSYCHOMOTOR IMPAIRMENT - to assess if either combination left the patient impaired considerably longer than did the other.

6. TO ESTABLISH A UNIFORM PROTOCOL - for assessing sedative methods for the judicious treatment of dental out-patients for the future use of drugs as they become available for clinical use.

RATIONALE FOR STUDYING EYE PATIENTS

Due to the significant numbers of patients being treated for cataract extraction at the University of British Columbia Health Sciences Centre, different drug regimens for these patients being treated with regional anaesthesia and conscious sedation techniques can be compared.

These patients are similar to dental surgical patients in that both need surgical procedures which usually may be treated without a general anaesthetic, and both may be treated on an out-patient basis. Considering the uniformity of the operating conditions, and the access to the relatively large numbers of patients undergoing cataract extraction as compared to relatively small numbers of dental surgical patients, it was decided to use cataract patients as subjects for the following experiment.

RATIONALE FOR THE DRUG REGIMEN

Since the drugs of choice in North America today for use as sedative adjuncts to regional anaesthesia/analgesia in surgery are benzodiazepines or butyrophenones in combination with short acting narcotics, and since at this time few benzodiazepines are licenced for intravenous use in Canada, it was considered reasonable to study the two most commonly used combinations in use at this centre. These are diazepam/fentanyl (VALIUM/SUBLIMAZE) and droperidol/fentanyl

(INAPSINE/SUBLIMAZE).

While both of these combinations have proven successful as adjuncts to anaesthesia with patients undergoing short surgical procedures where intense muscle relaxation is not a requirement, there are still numerous patients treated with general anaesthetics where regional anaesthesia and sedative adjunct would suffice. Specifically, dental procedures such as periodontal, endodontic and oral surgical procedures; ophthalmologic procedures such as cataract extraction and intraocular lens replacement; and certain gynecological and urological procedures, are suitable for non general anaesthetic methods.

METHODS AND MATERIALS -

The acceptance of this experimental protocol was obtained from the University of British Columbia Human Experimentation Committee, and the Acute Care Hospital Experimentation Committee (Appendix 1).

The Ophthalmology Anaesthesia and Nursing Department were approached to explain the experiment and to seek their cooperation.

Three senior undergraduate Psychology students offered their time to do the psychological testing involved.

Patients undergoing cataract extraction and intraocular lens replacement were approached to request their participation in the

study. Those who agreed were given informed consent documentation to sign (Appendix 2). Patients were permitted to leave the study at any point during the study if they so wished with no effect on their subsequent treatment.

Experimental Design - Experimentally a between group, single treatment design where patient, psychologist, ophthalmologist and nursing staff were not cognizant of the drug group assignment was chosen. This double-blind design was achieved by allowing only the anaesthetists assigned to the patient the experimental protocol and asking their cooperation in not talking to the other staff members. Due to the delicate nature of the treatment of the patients it would not have been ethical for anaesthetists to have been unaware to which drug treatment individual patients had been assigned. Neither would it have been practical since the different viscosities of the drugs in the experiment would have immediately alerted the anaesthetist to which drug had been assigned. Analysis of data later showed an absence of bias by the anaesthetists in spite of their knowledge.

Sample - One hundred patients were assigned to groups R1=50 or R2=50 by random assignment. All patients were 45 years or older, male or female, had the ability to communicate well in English and did not have serious hearing impairments. Measurement for systematic bias regarding random assignment by sex to different drug groups showed that the patients were randomly assigned by sex. All patients needed cataract extraction and intraocular lens replacement in at least one eye.

Exclusions - Before random assignment, as noted from the medical history, all patients being treated for insomnia, anxiety neuroses, depression, or for chronic pain were excluded from the study. Patients with myasthenia gravis, Parkinson's Disease or with allergies to the drugs being tested were eliminated from the study.

Drug Treatment -R1=Fentanyl + Droperidol

-R2=Fentanyl + Diazepam

TREATMENT SETTING - All patients were admitted as in-patients to the Acute Care Centre at the University of British Columbia Hospital.

VARIATION OF TREATMENT FROM NORMAL - All patients were treated as patients are normally treated at this centre. Patients were not given anything by mouth for at least six hours pre-operatively. No pre-medication (sedatives) was administered.

TESTING METHODOLOGY - The psychology students administered the pre-operative state portion (in order to establish the base-line for anxiety) of the State Trait Anxiety Inventory STAI (39) (Appendix 3) in the patient's room on the ward the evening prior to the surgery. In the case of ten 'day-surgery' patients, the patients were administered the state portion of the STAI in the day-surgery holding room. None of the patients was tested in the ante-room to the operating room. Neither the patient nor the psychology student was cognizant of the patient assignment to drug group R1 or R2.

Patients were brought to the operating room approximately 20 minutes before surgery was to begin, for verication of physical status, and surgical preparation. When the patient was brought into the operating room he was transferred to the surgical table with the assistance of the nurses. The intravenous line was established in the dorsum of the left hand or the left wrist with a 'Jelco-intracath #22' and an intravenous solution of 0.9% saline was begun. In a few cases the intravenous line had been established on the ward with a solution of dextrose 5.0% solution. This was changed to a saline solution when the bag was empty.

Sedation was administered, depending on whether the patient was to receive droperidol/fentanyl or diazepam/fentanyl. Patients were titrated according to acceptable standards of conscious sedation at the University of British Columbia Health Sciences Centre, i.e. calm, yet able to respond to commands, and having protective reflexes intact. The ophthalmologist administered the local anaesthetic (retro-bulbar block and "O'Brian" partial facial nerve block). The anaesthetic was bupivicaine 1.5%, or lidocaine 2.0%, both without epinephrine. The choice depended on the preference of the surgeon. No significant drug interactions have been demonstrated when either of these anaesthetics is combined with the drug combinations being tested. All patients received a constant flow of oxygen by mask. Patients were then surgically draped from head to toe, in the customary manner at this centre. An additional plastic drape was placed over the face with a hole for the eye. The only physical contact with the patient was by anaesthetist hand holding.

All patients were monitored for vital signs every ten minutes. The blood pressure cuff was placed on the right arm prior to draping and remained there during the procedure. A Honeywell E+M electrocardiograph running lead II was attached to each patient via left and right shoulder and ground leads. Pulse was monitored concurrently with blood pressure.

In all cases the ability to convert to a general anaesthetic was available if necessary, however this was not called for.

The surgery was begun and during that time, other than the monitoring of vital signs and occasionally reassuring the patient that the surgery was proceeding well, there was little verbal contact. If it became obvious because of patient movement, restlessness, or because of signs of increasing sympathetic stimulation, that either the procedure was painful or the patient was anxious, additional increments of fentanyl were administered. In no case was there any attempt to give additional local anaesthetic. The last part of the surgical procedure consisted of the subconjunctival administration of either Cefalozin sodium (ANCEF), or Gentamicin Sulfate (GARAMYCIN), if the patient had penicillin related allergies. The indication for this cephalosporin antibiotic, was as a prophylactic to reduce the incidence of post-operative infections in patients at high risk, e.g. those over 70 years of age. Neither of these drugs reacts significantly with the sedatives being tested.

The drapes were removed and the patient was transferred with the assistance of the nurses and orderlies to post anaesthetic recovery (PAR). There the oxygen by mask was usually discontinued if the patient showed no signs of having respiratory distress. Lead II was monitored, along with blood pressure and pulse for the duration of time in PAR, until the anaesthetist considered the patient to be of status suitable for returning to the ward. In most cases this time was about an hour and a half. The patients were permitted to have fluids by mouth after arrival at PAR.

The psychology student returned to administer the state/trait portion of the STAI approximately five hours post operatively with some variation due to the standard ward routines.

ASSESSMENT

1 - PSYCHOLOGICAL

The patients were administered the STAI the evening prior to surgery. The state portion was repeated five hours post-operatively except in the case of two patients who were dismissed two hours after the surgical procedure and they were tested just prior to being dismissed.

Raw scores were tabulated, normalized, and compared to the date provided by the authors for general medical surgical (GMS) patients (39).

Post-operatively the Sensory/Affect Pain testing scale (40) was applied by the same psychology student who had administered the STAI.

Examples of the questionaires for (39) and (40) are (Appendix 3) and (Appendix 4).

2 - ANAESTHETIC

Trends for blood pressure and pulse changes for both groups were analysed. Any occurrence of respiratory obstruction (stridor) or depression was monitored until the patient was deemed healthy to return to the ward.

Mean doses and standard deviation for drug groups were analysed. Opinions of degree of sedation of the patient during the surgery were made according to the scale of Berggren, Erriksson (41), and drug groups were analysed for differences in sedation produced. Anaesthetist ratings of the overall procedure were also analysed and scaled according to the different drug groups. In keeping with anaesthesia procedure, the anaesthetists were rotated on different days to different surgeons and their patients. Assignment of anaesthetists to patients in different drug groups is shown below. An attempt was made to have the anaesthetists do approximately half their case load in each drug group.

Anaesthetists	Droperidol/Fentanyl	Diazepam/Fentanyl
A	4	3
B	9	12
C	6	7
D	3	2
E	4	7
F	5	7
G	6	7
H	0	2

OVERALL OPINION OF THE SEDATION OF THE PATIENT

0-unable to proceed with the surgery due to the lack of sedation
1-awake but cooperative
2-drowsy but responds readily to stimuli
3-asleep between recordings of bp and pulse
4-asleep - but aroused with difficulty
5-reaction to painful stimuli, but no verbal contact

ANAESTHETIST OPINION OF THE PROCEDURE

0 - unable to proceed as planned (poor)

1 - sedation just sufficient, patient restless, required numerous additional increments

2 - good

3 - excellent

Regarding the endpoint of sedation, the majority of patient (67%) were titrated anaesthetically to endpoint sedation of being drowsy, but responding well to stimuli such as blood pressure measurements, and maintaining the ability to answer questions.

THE ANAESTHETIC RECORD USED FOR EACH PATIENT - (APPENDIX 5)

3 - SURGICAL ASSESSMENT - The surgeon was asked to rate the ease of performance of the overall procedure and the opinions were analysed according to drug group.

OVERALL EASE OF PERFORMANCE OF SURGERY

0 - unable to proceed as planned

1 - able to proceed with some difficulty (fair)

2 - good

3 - excellent

STATISTICAL ANALYSIS

FOR SURGICAL, ANAESTHETIC, AND PSYCHOLOGICAL DATA - The Hotelling's T-Square Analysis, an omnibus multivariate analysis was carried out. Subsequent testing using chi-square, and ANOVA (or 2-way Bystrata ANOVAS) were carried out where the mutivariate results were significant.

PSYCHOLOGICAL-STATE TRAIT ANXIETY INVENTORY (STAI) - Normative data have been reported by the authors for general medical and surgical patients. The information provided by the authors made it possible to compare scores obtained in this selected experimental group. Raw scores ontained in this experiment were normalized and compared by drug group. The experimental scores were compared by taking the means and standard deviations for the different drug groups and comparing them to those supplied by the authors.

SENSORY/AFFECT RATIO DESCRIPTORS - The patients' description of each descriptor was graphed by grouping the data and plotting it. The mean rank versus ratio descriptor magnitudes were also plotted.

ANAESTHETIC - Opinions of the anaesthetists were analysed by ANOVA technique and then scores were graphed. The chi-square test was used for drug group comparisons for this sedation opinion and for the opinion regarding the overall ease of performance of the procedure.

SURGICAL - Surgeons opinions were analyzed by ANOVA technique then the opinions were tabulated and graphed. Chi-square test was applied for drug comparisons.

RESULTS

One hundred cases were completed, however any that did not follow the standardized anaesthetic, surgical or psychological format established at the outset were not included in the data analysis. Those cases include two patients who had originally agreed to participate in the study but requested a general anaesthetic at the time of surgery as they did not want to know "what was going on." Three patients were treated with general anaesthetics at the request of the anaesthetist due to the patients' previous history of epilepsy. Although these patients had been stabilized for two years without a seizure, the use of general anaesthetic is understandable considering the delicate nature of the procedure. Cataract extraction is carried out under microscopic conditions and any unexpected movement by the patient could have disastrous consequences. Five other patients had agreed to participate. However upon psychological testing it was believed the patients' had some misunderstanding of the questions and the patients' results were thus excluded. Two patients agreed to participate but after surgery was completed felt too tired to answer any questions and did not wish to continue. Each of these two patients was from a different treatment group. Four patients were dismissed prior to completion of the psychological testing. It was felt psychological post-operative testing outside the treatment setting would introduce error. A total of 47 patients from the diazepam/fentanyl group and 37 patients from the droperidol/fentanyl group had their results analysed. While the dropout rate

for droperidol/fentanyl group was greater than the diazepam/ fentanyl group this difference in rate may be due to inherent differences in the drug combination or to chance differences in the groups despite random sampling.

PSYCHOLOGICAL RESULTS - Administration of the STAI indicated that the patient data obtained in this study correlated well with the data from the general medical surgical patient (GMS) data for which the norms were established (39).

	ANXIETY-TRAIT		ANXIETY-STATE (PRE-OP)	
	MEAN	SD	MEAN	SD
GMS	41.33	12.55	42.68	13.76
EXPERIMENT RESULTS	42.26	10.49	42.27	10.10

A comparison of the means and standard deviations obtained in this experiment correlates well with those for general medical surgical patients of Spielburger et al. Therefore, using a two-tailed ANOVA with $\alpha \leq .01$, since $n > 25$, and the Central Limit Theorum holds, it was found that there was not a significant difference in scores for GMS patients and experimental patients for scores on the anxiety-trait, and the anxiety state pre-op. Spielburger et al do not offer socres for post-op GMS patients. By these standards, the experimental

patients were considered to be typical in their overall state/trait conditions of anxiety for both state and trait testing.

A 2-way Bystrata ANOVA was carriedout between drug groups versus pre-operative and post-operative normalized scores on the state portion of the STAI, $p \leq .01$. A significant difference was found in this respect for both drugs over time, with both groups demonstrating lower immediate post-operative anxiety - than pre-operative anxiety. This is consistant with the findings of Spielburger et al.

An ANOVA was carried ot to test for between drug variability versus within subject variability for both pre-operative and post-operative scores on the STAI in order to determine if there was some difference over time. For pre-op scores a significant difference was found with $p \leq .02$, and $F=5.5304$. However in post-op scores ANOVA statistics results in $p \leq .09$ and $F-2.7850$. Thus some change in scores over time resulted, depending on the drug treatment, though not a considerable amount. For both drug groups, state anxiety increased only slightly post-operatively. This is consistant with the findings of Auerbach (42), who elaborated on the findings of Spielburger's STAI in evaluating the effects of surgery-induced stress on anxiety and the relationship between pre-op state and post-op state adjustment to this stress.

	ANXIETY-TRAIT		ANXIETY-STATE			
	MEAN	SD	MEAN	SD	MEAN	SD
			pre-operative		post-operative	
DRUG GROUP Drop/Fent	44.91	10.18	44.34	10.07	46.12	8.71
Diaz/Fent	39.60	10.80	40.19	10.14	42.46	10.00

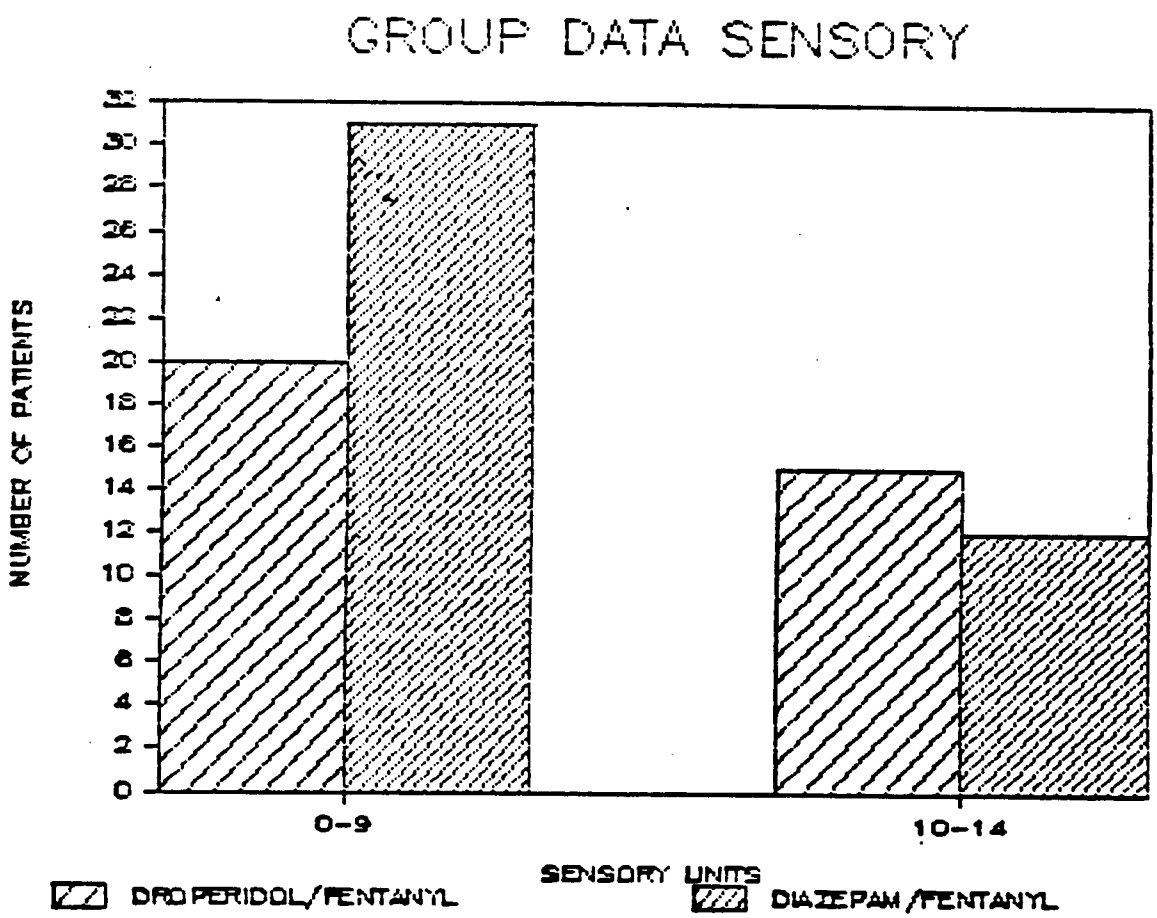
In spite of random assignment there was a significant difference found in trait anxiety scores for patients between drug groups, with the droperidol/fentanyl patients scoring slightly higher. The statistics reported take this difference into consideration. Consistent with the trait statistics showing the diazepam/fentanyl patients to have scored lower than the droperidol/fentanyl patients the state scores yielded similar findings.

While both drug combinations proved to be good sedatives for use in this procedure, some subtle differences were noted.

Regarding the scores of the patients on the Sensory/Affect Descriptors, it was found that although patients may have found the maximum sensation extreme or considerable, they did not necessarily describe the effective qualities the same. Of the droperidol/ fentanyl patients (44%), and (30%) of diazepam/fentanyl patients described the sensation at the most intense time during surgery as 9 or greater on the scale of Graceley, Dubner and McGrath (graph 1).

GRAPH 1

PATIENTS' OPINION - SENSORY DESCRIPTORS



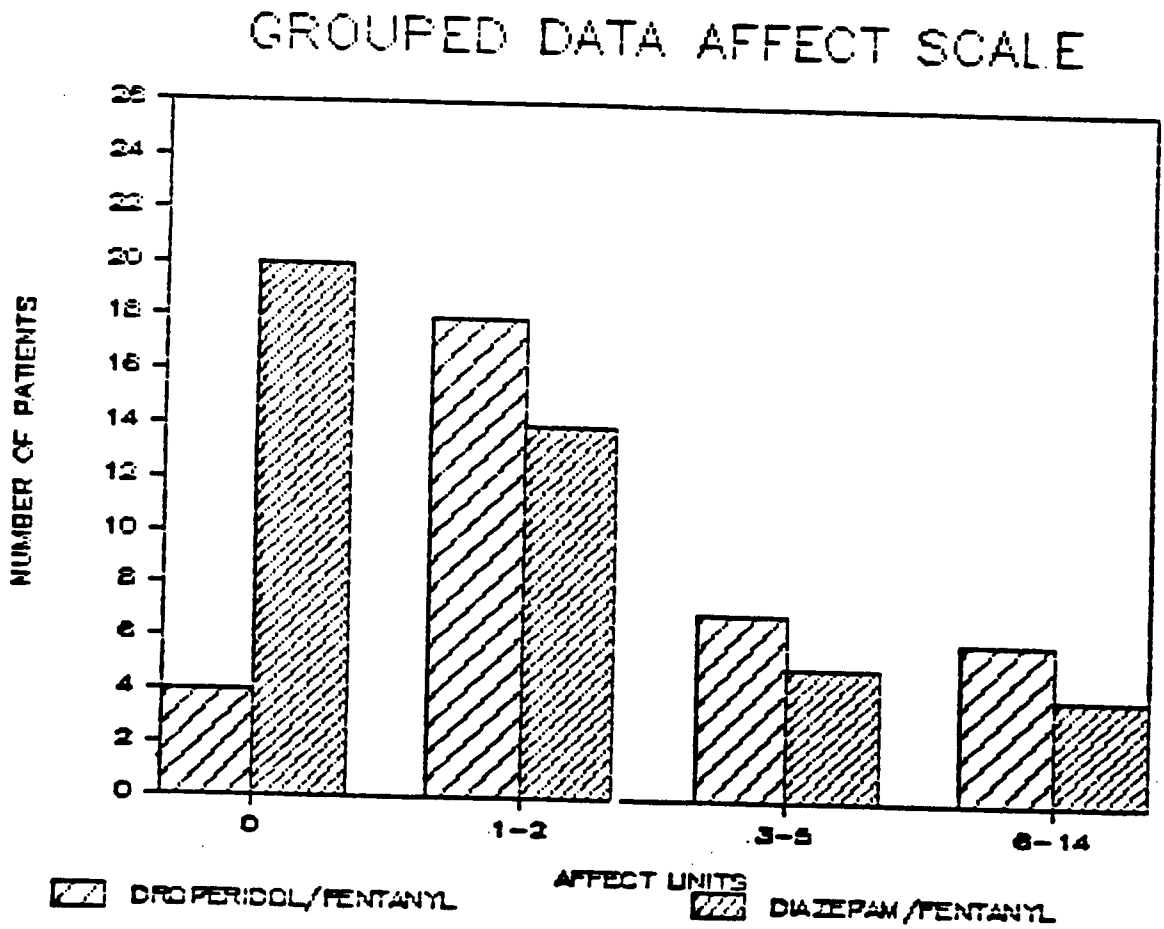
Analysis of these data using chi-square technique, at $\alpha \leq .01$ showed there was a significant number of patients rating the procedure as intense or greater depending on which drug combination was used. In other words, a significant number of patients rated the procedure as more intense when the droperidol/fentanyl combination was used, than when the diazepam/fentanyl combination was used. When plotted, ratio magnitude values versus mean rank for sensory and affective descriptors show a generalized increase for both drug combinations, with the diazepam/fentanyl group generally ranking lower for both descriptors (Graph 1A).

Regarding the affective scale, there was also a difference of opinion amongst patients in different drug group. The most common opinions of patients (49%) in the droperidol/fentanyl group was in the annoying to uncomfortable range, while the most common opinion of patients (44%) in the diazepam/fentanyl group was less than any of the choices offered (graph 2). Many offered the opinion that the experience was quite pleasant and that they would be happy to have the other eye 'done' in the same manner if it were necessary. None of the patients in the droperidol/fentanyl group volunteered this comment.

Analysis of data by Hotelling's T-Square test shoed there was no significant bias, $F(10,64)=1.5944$, $p \leq .1286$ between drug groups regarding sex.

GRAPH 2

PATIENT'S OPINION-AFFECT DESCRIPTORS



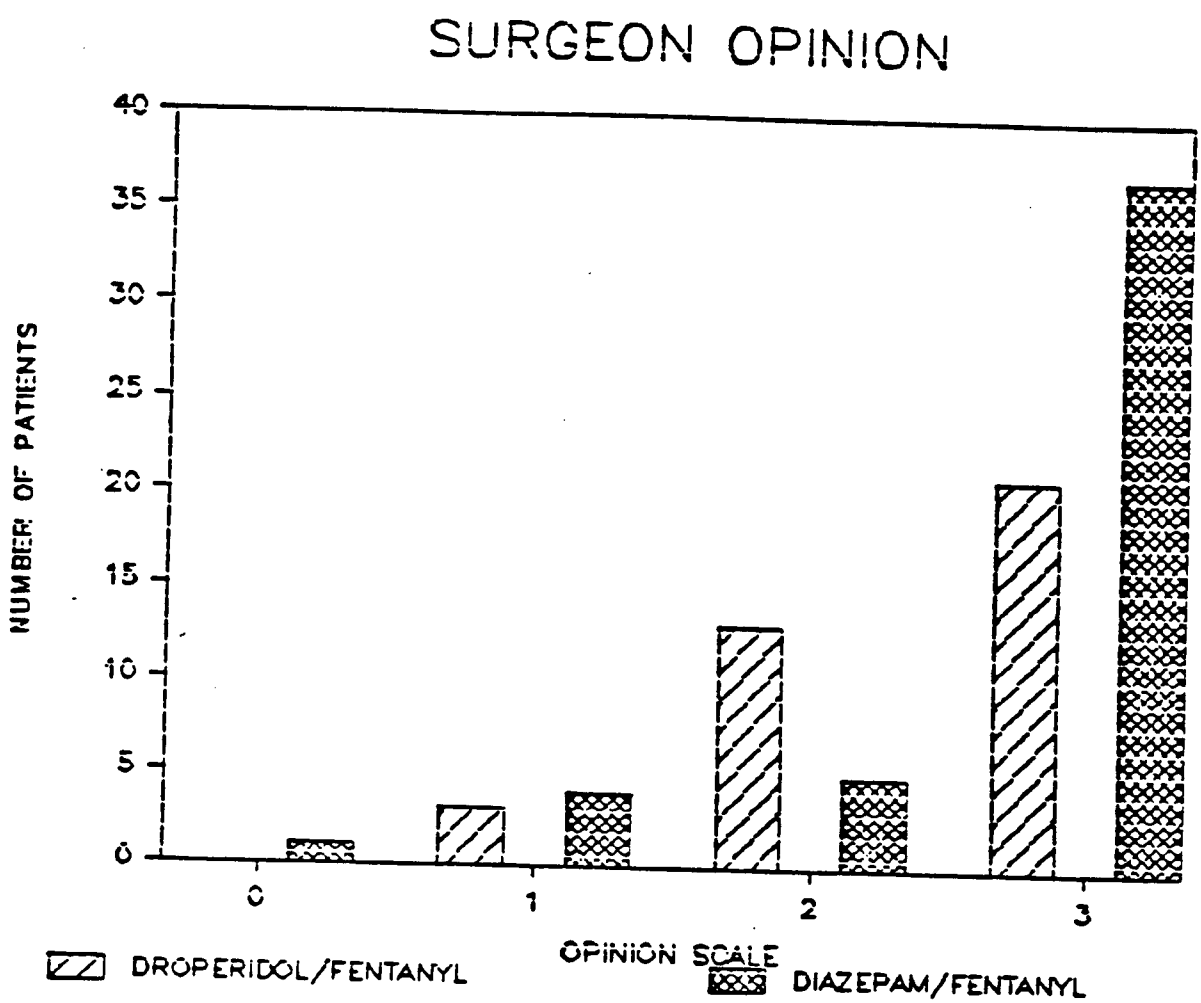
SURGICAL RESULTS - The surgeons rated (89%) of the procedures as excellent or good regarding ease of performance of the surgery. As stated in the methods section, the surgeons were not cognizant of the group to which the patients had been assigned. Composites of opinions are shown below.

SURGEON OPINION

	0	1	2	3
DROP/FENT	0 (0 %)	3 (8 %)	13 (35%)	21 (57%)
DIAZ/FENT	1 (2 %)	4 (8 %)	5 (11%)	37 (79%)

It was found that there was a significant difference in the surgeons' opinions of ease of performance of surgery at $p \leq .001$. Diazepam/Fentanyl was significantly better than droperidol/fentanyl for patients undergoing this procedure at this facility from the point of view of the surgeon (Graph 3). Multivariate analysis for ungrouped data upheld this result $F(10,64)=7.257$, $p \leq .001$.

GRAPH 3


SURGEON OPINION
NUMBER OF PATIENTS
40
35
30
25
20
15
10
5
0
0
1
2
3
OPINION SCALE
DROPERIDOL/FENTANYL
DIAZEPAM/FENTANYL

ANAESTHETIC RESULTS -

In keeping with ethical practices necessary in conducting surgery, the anaesthetists conducted the sedation in keeping with normal hospital procedures and anaesthesia practices. Therefore, the patients were titrated to safe levels of sedation in keeping with the surgeon's need for a calm, cooperative yet awake patient. For this reason it was decided that a fixed dose regimen was not indicated. In order to titrate a drug to a patient's need, numerous considerations as to the age, physical status, and possible drug reactions must be made. In keeping with the drug manufacturers recommendations, the drug doses were reduced from full therapeutic doses when combined with fentanyl. Comparison of doses for each drug when combined with fentanyl are shown below.

	Diazepam	Droperidol	Fentanyl
Recommended dose	5.0-10.0 mg	2.3-5.0 mg	50-100 µg
Experimental dose	5.4mg 502.4	-	53µg SD28
		1.7mg 50.8	66µg SD57

It may be seen that when patients were titrated to sedated levels that the mean drug doses used were within the manufacturers' recommendations. Significantly more fentanyl was used when combined with droperidol than with diazepam, $F(10,64)=7.257$, $p \leq .0001$. Additional increments of fentanyl were more commonly given when droperidol was used than when diazepam was used.

SCORE - Overall sedation (from p.61)

DRUG TREATMENT	0	1	(%)	2	(%)	3	(%)	4	(%)	5	(%)
Droperidol/Fentanyl	0	11	(30)	25	(68)	1	(2)	0		0	
Diazepam/Fentanyl	0	10	(22)	34	(72)	1	(2)	1	(2)	1	(2)

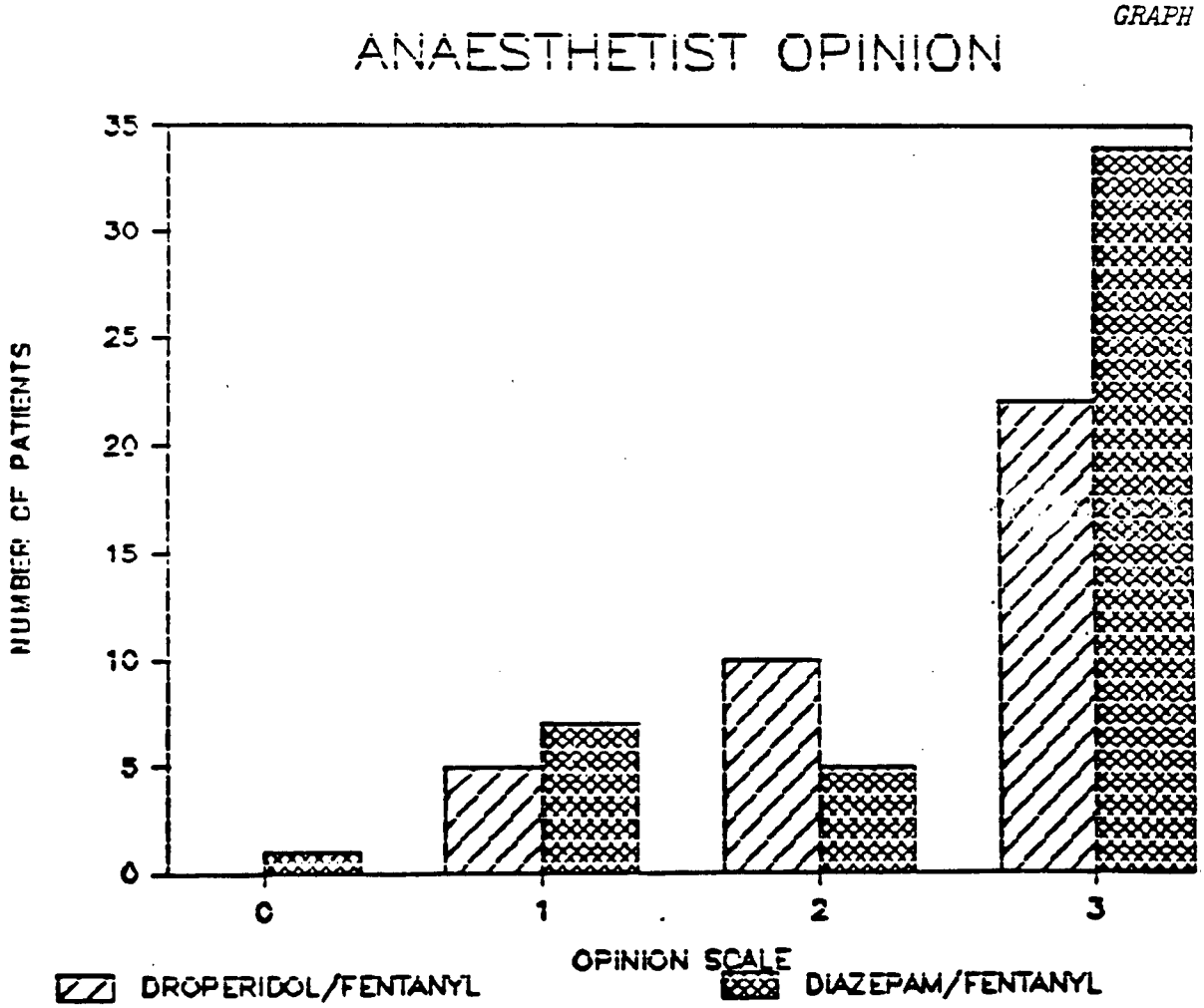
There was no significant difference between drug groups as to overall sedation achieved during the procedure i.e. patients in both drug groups appeared to have been sedated to the same level according to the above scale. While it is apparent that the majority of patients (67%) were sedated to category 2, only (26%) were sedated to the awake but cooperative category. As it is the intention of conscious sedation to maintain patients with reflexes intact, yet cooperative and anxiety free, it is significant that only (6%) of the patients were sedated beyond the drowsy stage. Considering the difficulty of viewing the patient due to the surgical drapes (the patient is completely covered except for the eye) the obvious preference for the anaesthetist is to sedate on the 'light' side. The only physical contact was via anaesthetist-patient hand holding. For many patients this appeared to be a powerful and positive aid during the procedure.

Results for the anaesthetist rating of the overall procedure are:
(from p. 62)

ANAESTHETIST OPINION

DRUG TREATMENT	0	1(%)	2(%)	3(%)
DROPERIDOL/FENTANYL	0	5(14%)	10 (27%)	22 (59%)
DIAZEPAM/FENTANYL	1	7(15%)	5 (11%)	34 (74%)

GRAPH 4



Chi-square analysis at $\alpha \leq .01$ showed there was a significantly greater number of cases rated as good or excellent for grouped data, in the diazepam/fentanyl group than in the droperidol/fentanyl group. Since the eight anaesthetists were not aware of each others' opinions it is unlikely that observer bias entered into the opinions of the anaesthetists. Systematic error can be ruled out since the number of cases by each anaesthetist was evenly distributed between drug groups.

Regarding hemodynamic/respiratory results of the experiment;

With both drug group combinations a transient fall in blood pressure was noted shortly after drug administration, in most cases. This is not an unexpected occurrence and there were no serious consequences for any patients in either drug group. One patient in the droperidol/fentanyl group exhibited premature ventricular contractions (PVC's) approximately five minutes after drug injection. As the frequency was increasing over the next two minutes, cardiac lidocaine was administered, and the episodes of PVC's were terminated within a minute. There were no recurrences of these episodes.

Signs of increased sympathetic response, such as increases in pulse rate, restlessness, and expressions of discomfort by the patient were treated by giving additional increments of fentanyl. No additional doses of local anaesthetic were given. In only one case was respiratory distress noted. This occurred in a patient from the diazepam/fentanyl group. He was trembling severely upon arrival

at post anaesthetic recovery (PAR) and had considerable difficulty breathing for approximately ten minutes after arrival at PAR. Humidified oxygen by mask was administered and the condition self corrected. There were no recurring episodes for this patient.

The trends of blood pressure and pulse rates for patients in the two different treatment groups are shown below:

	Droperidol/ Fentanyl		Diazepam/ Fentanyl	
	Pulse	BP	Pulse	BP
remained constant	53%	53%	63%	46%
transient increase	0%	3%	2%	6%
transient decrease	32%	21%	22%	26%
general increase	3%	5%	0%	11%
general decrease	12%	18%	13%	11%

For both drug combinations the tendancy was for the pulse rate and blood pressure to remain constant, or show only a transient decrease.

ADDITIONAL PATIENT COMMENTS -

As the experiment proceeded, any unsolicited comments regarding the procedure were noted. Specifically, four patients from the droperidol/fentanyl group commented they had felt quite irritated in PAR,yet outwardly had appeared calm. The best description from one patient was that he felt as if he was trying to escape but did not know why, nor was he able to express his anxiety. He commented this feeling did not come on immediately but he noticed it beginning toward the end of the procedure and continuing for some hours afterward. None of the patients from the diazepam/fentanyl group made similar comments.

Six other patients commented they felt the 'needles' at the end of the procedure. Five of these patients were from the droperidol/fentanyl group. They were referring to the injection subconjuntivally of cefalozin (ANCEF) or gentamicin (GARAMYCIN), a routine practice for surgical procedures of this nature.

TIME REQUIRED FOR PERFORMANCE OF THE SURGICAL PROCEDURE

A wide range of anaesthetic times occured, ranging from a minimum of 20 minutes from the start of the administration of the drug intravenously, to a maximum of 90 minutes to the arrival of the patient in PAR. Where the anaesthetists most often rated the overall procedure as only fair, the procedures took over an hour, and additional increments of fentanyl had been administered. Generally the longer the procedure, the more restless the patient tended to

become. This would be an expected result, as the operating table is narrow and hard, the drapes totally cover the patient, the drugs lose their maximum sedative effects over 20-30 minutes, and the local anaesthetic effect would also decrease as the procedure progressed.

For anaesthetic time less than 45 minutes there was a significant difference in patients' scores in both sensory and especially affect scores, for both drug combinations, $F(10,12)=7.8358, p \leq .0007$. While the patients scored much lower when total time was less than 45 minutes, both surgeons and anaesthetists found no significant difference in opinion for the overall procedure when the procedure lasted less than or greater than 45 minutes. The mean anaesthetic time for patients in the droperidol/fentanyl group was 48 minutes, and for the diazepam/fentanyl group was 37 minutes.

DISCUSSION

Psychological testing showed the patients were typical in their levels of anxiety for general medical surgical patients with both pre-operative and post-operative anxiety as to the tests carried out. While both drug combinations proved to be successful for the surgical procedure, patients tended to find the procedure more intense if the droperidol/fentanyl combination was used. Regarding opinion of affect, many patients in the diazepam/fentanyl group rated the procedure as being less than any of the choices offered. Many were happy to have the procedure repeated, for the other eye if it became necessary. The strong effect of diazepam on memory storage may be responsible for this patient response. Since diazepam has an amnesic effect, and droperidol has also, but only on some, not all patients, it is possible, that the difference in opinion is due to the fact the patient simply could not remember, or that the difference was due to the drug itself. However it is not possible to prove either of these possibilities.

Surgical opinion showed there was a significantly better opinion of diazepam/fentanyl for this surgical procedure, when rated at the good versus excellent standard. Numerous possibilities exist for the difference in degree of sedation noted in the patient and thus the ease of performance of the surgical procedure.

It is interesting to note that while the anaesthetists titrated the anaesthetic doses so patients would remain conscious

yet cooperative, the doses administered to patients in the droperidol group were well below the recommended dose of the manufacturer; however the doses for the diazepam group were within the recommended dose of the manufacturer. Other than wanting to avoid possible respiratory depression or excessive sedative effects, since these are possible complications with both droperidol and diazepam, the opinion amongst all the anaesthetists was that the manufacturer recommended dose was too high. One drug combination of droperidol and fentanyl called INNOVAR had become quite popular several years ago. However the amount of droperidol relative to the amount of fentanyl present in the drug ratio was such that one had to administer a considerable amount of the drug to obtain the benefit of the fentanyl. The result was that the patients received too much droperidol, and adverse effects of droperidol were observed relatively often, i.e. respiratory depression, extrapyramidal symptoms, and excessive sedation. INNOVAR is not commonly used in major centres now, yet the combination is popular, when the anaesthetist combines the two drugs himself. Perhaps the sacrifice in dosage to minimize complications also decreases the sedative effect. The therapeutic index for droperidol regarding sedative effects is narrower than that of diazepam.

As expected, both drugs caused hemodynamic changes in keeping with drug manufacturer warnings. Generally pulse rate and blood pressure remained constant, though some patients showed transient decreases. None of the changes was significant.

There was a significant difference between drug group combinations as to the amount of time needed to carry out the procedure, $p \leq .008$. The average time for droperidol/fentanyl was 48 minutes, and for diazepam/fentanyl was 37 minutes. Although both combinations were considered equally effective by the anaesthetists and surgeons in this aspect, the patients considered that the sensation felt during the procedure increased in severity as time for the procedure exceeded 45 minutes, and found the effective qualities to be considerably greater as well.

There was no significant difference in the amount of CNS. depression observed intra-operatively nor post-operatively. Therefore both drugs were considered to be clinically equivalent in this aspect.

Due to the age of the patients and the fact that patients do not gain full vision immediately after the procedure, it was difficult to evaluate psychomotor impairment, as a reliable base-line could not be obtained. Judging from the amount of time patients were kept in PAR prior to returning to the ward, there did not appear to be a difference between the two drug combinations. When patients were able to sit up unsupported and drink fluids, they were returned to the ward. The significant factor here seemed to be the patient's age and general condition. Those who were physically well usually remained about an hour in PAR regardless of the drug. Those who were frail were kept about two hours. Interestingly, no patients who had received droperidol were dismissed the same day, while five of the diazepam/fentanyl patients were dismissed within a few hours of the surgery.

Regarding the establishment of a uniform protocol for the use of intravenous sedative procedures, considering the lack of complications, good patient acceptance, and uniformity of anaesthetic and surgical handling of the procedure, the protocol outlined in the methods is a good outline for the handling of out-patient or short duration in-patient surgical procedures.

An interesting alternative to diazepam might be the use of midazolam, a water soluble benzodiazepine with short onset and duration of effects. Unfortunatley this drug is not yet available in Canada. Not only would the patient have less residual drowsiness the following day, the amnesic effects are reported to be similar to those of diazepam, and the local irritant effects of diazepam are missing with midazolam, due to its water solubility.

Due to the delicate nature of the surgery, certain problems could have arisen regarding the depth of sedation necessary to carry out the surgery. The major problem is to sedate the patient sufficiently so the procedure will be painless yet not over-sedate the patient thus risking respiratory depression or other adverse effects.

While some might advocate a fixed dose regimen, this would have created the problem in that the dose may have been sufficient in some but not all patients, or might have produced over sedation in some patients. The added fact that most of the patients were elderly and debilitated also would be a contraindication for a fixed dose,

since these patients all metabolize drugs at different rates, and react in different magnitudes. The best technique, albeit a subjective one, is to titrate the patient to a safe level given uniform qualities.

SUMMARY

The comparison of two conventional sedatives droperidol and diazepam, when combined with fentanyl was carried out. A safe protocol for the administration of these drug combinations was outlined.

Both combinations proved to be successful for providing the sedation of the patients that was needed for the surgical procedure of cataract extraction and intra-ocular lens replacement. When used judiciously few complications were noted systemically for either drug combination.

A significant difference was found between the two drug combinations regarding surgeons' opinion of ease of carrying out the procedure. Diazepam/fentanyl proved superiod to droperidol/fentanyl in their opinion.

The patients also found there was a difference in alleviation of anxiety between the two drug groups. Patients in the diazepam/fentanyl group found both sensory and affective qualities of the procedure to be less than did the patients in the droperidol/fentanyl group.

For both drug groups, when the anaesthetic time exceeded 45 minutes the procedure was rated more severe by patient indicators. Since the anaesthetic outcome for both procedures was equivalent, and both the patient and the surgeon found the diazepam/fentanyl combination superior to the droperidol/fentanyl combination, the use

of diazepam or another benzodiazepine should be used when possible for such surgical procedures. In addition, the lack of the possibility of extrapyramidal effects with benzodiazepines is another reason for their use whenever possible.

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THANK YOU

APPENDIX 2

The following is representative of the approach to the patient requesting he or she participate in the experiment.

We are currently conducting a study to compare two of the drugs we use for patients who are having eye procedures such as yours. Only normal procedures will be followed. We are asking patients to answer some questions about how they feel before the procedure, and then some other questions when the procedure is finished. This will take about 10-15 minutes of your time. You are not under any deligation to participate, and if you agree to participate and later change your mind that will be fine. It will not effect the procedure or your treatment in any way.

I have a consent form I am going to read to you and if you are willing to participate then I will ask you to sign. Do you have any questions?

Patient #----

I, ----------agree to participate in this study.

I understand the treatment will not vary from any normal procedures which are usually followed for patients undergoing cataract removal.

I understand the purpose is to compare the effects of drugs normally used in patients undergoing cataract removal.

I understand those who will be involved in the study are myself, the Anaesthesiologist, the ophthalmologist, and an observer who will ask me the questions before and after the surgery. My name will not appear anywhere except as normally it would appear on medical records.

Time involved to answer the questions will be about 10-15 minutes in total.

I understand I may refuse to enter the study or withdraw from it at any time if I so choose without it effecting my treatment in any way.

Patient Signature ----------
Witness ----------
Date ----------

APPENDIX - 3-STATE

SELF-EVALUATION QUESTIONNAIRE

Developed by C. D. Spielberger, R. L. Gorsuch and R. Lushene

STAI FORM X-1

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *feel* right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	①	②	③	④
2. I feel secure	①	②	③	④
3. I am tense	①	②	③	④
4. I am regretful	①	②	③	④
5. I feel at ease	①	②	③	④
6. I feel upset	①	②	③	④
7. I am presently worrying over possible misfortunes	①	②	③	④
8. I feel rested	①	②	③	④
9. I feel anxious	①	②	③	④
10. I feel comfortable	①	②	③	④
11. I feel self-confident	①	②	③	④
12. I feel nervous	①	②	③	④
13. I am jittery	①	②	③	④
14. I feel "high strung"	①	②	③	④
15. I am relaxed	①	②	③	④
16. I feel content	①	②	③	④
17. I am worried	①	②	③	④
18. I feel over-excited and "rattled"	①	②	③	④
19. I feel joyful	①	②	③	④
20. I feel pleasant	①	②	③	④

APPENDIX - 3 TRAIT

SELF-EVALUATION QUESTIONNAIRE

STAI FORM X-2

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	①	②	③	④
22. I tire quickly	①	②	③	④
23. I feel like crying	①	②	③	④
24. I wish I could be as happy as others seem to be	①	②	③	④
25. I am losing out on things because I can't make up my mind soon enough	①	②	③	④
26. I feel rested	①	②	③	④
27. I am "calm, cool, and collected"	①	②	③	④
28. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29. I worry too much over something that really doesn't matter	①	②	③	④
30. I am happy	①	②	③	④
31. I am inclined to take things hard	①	②	③	④
32. I lack self-confidence	①	②	③	④
33. I feel secure	①	②	③	④
34. I try to avoid facing a crisis or difficulty	①	②	③	④
35. I feel blue	①	②	③	④
36. I am content	①	②	③	④
37. Some unimportant thought runs through my mind and bothers me	①	②	③	④
38. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39. I am a steady person	①	②	③	④
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

APPENDIX 4

9-I am going to ask you some questions about the eye surgery that you have just had. When the surgery was taking place how would you describe the sensation you felt at the most intense time?

00-Extremely weak
01-Faint
02-Very weak
03-Very mild
04-Mild
05-Very moderate
06-Slightly moderate
07-Moderate
08-Barely strong
09-Clear cut
10-Slightly intense
11-Strong
12-Intense
13-Very intense
14-Extremely intense

10-I am going to ask you how you would rate the overall surgery in general. Which of the following best describes your feelings for the surgery you have just had?

00-Distracting
01-Annoying
02-Uncomfortable
03-Unpleasant
04-Irritating
05-Upsetting
06-Distressing
07-Miserable
08-Frightful
09-Dreadful
10-Horrible
11-Agonizing
12-Intolerable
13-Unbearable
14-Excruciating

APPENDIX 5

UBC HEALTH SCIENCES CENTRE HOSPITAL

ANAESTHESIA RECORD

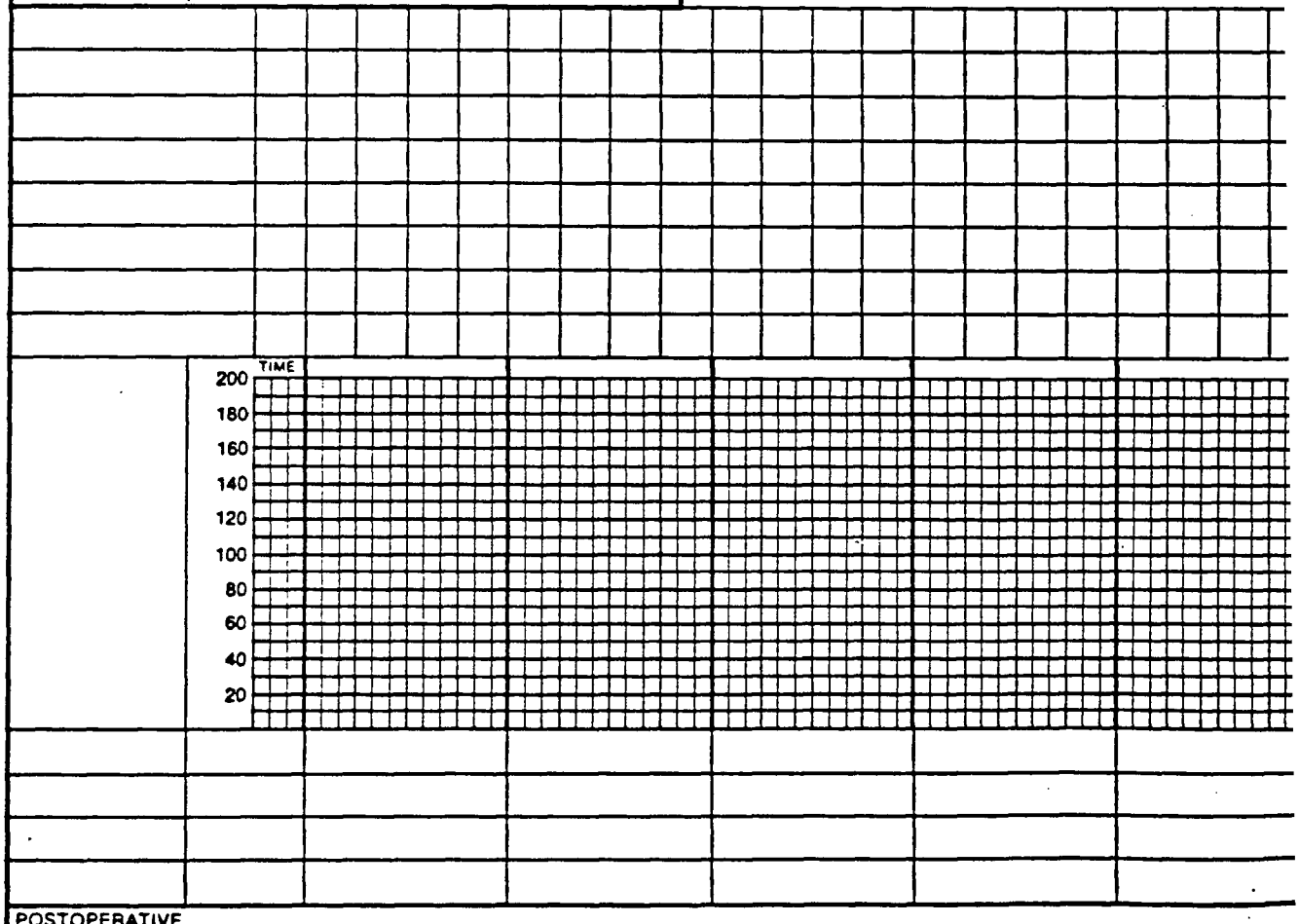
PREOPERATIVE

ANAESTHETIST DATE

OPERATION

SURGEON

ANAESTHETIC MANAGEMENT



POSTOPERATIVE

11-12-82 Rev. 2

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                    MEANS FOR SEX

     VARIABLE       M              F
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    5.POST          44.394         43.905
    6.TRAIT         42.242         45.119
    7.SENS          6.0909         7.8333
    8.AFF           1.4545         2.7619
    9.OPIN          2.6364         2.5714
   10.SED           2.5152         2.5000
   11.TIME          38.333         45.000
   12.TOTF          43.485         59.286
   13.TD            .27576 -1      .29048 -1
N                     33             42


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EQUALITY OF STRATUM MEANS:  DF= 10, 12  F= 7.8358  SIG= .0007

                    MEANS FOR TIME

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    7.SENS          6.8095         8.5000
    8.AFF           1.1429         6.0000
    9.OPIN          2.6190         2.5000
   10.SED           2.2857         2.5000
   11.TIME          29.524         90.000
   12.TOTF          40.000         65.000
   13.TD            .28571 -1      .15000 -1
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UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 4.V4  N= 75 OUT OF 75

SOURCE              DF SUM OF SQRS  MEAN SQR  F-STATISTIC SIGNIF

BETWEEN              1    418.67     418.67     5.5304      .0214
WITHIN              73    5526.3     75.703
TOTAL               74    5945.0     (RANDOM EFFECTS STATISTICS)

ETA= .2654  ETA-SQR= .0704  (VAR COMP= 9.2260  %VAR AMONG= 10.86)

V3           N    MEAN     VARIANCE   STD DEV

(1)         34  43.941      74.784     8.6478
(2)         41  39.195      76.461     8.7442

GRAND       75  41.347      80.338     8.9631

 CONTRAST        MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 OBSERVED    PREDICTED    F-STAT    SIGNIF LEV=.9000

 -34.449      1.0000      130.73     .0000

 PAIRWISE        MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 STRATA        DIFF       F-STAT    SIGNIF LEV=.9000

(1)
   (2)        4.7461      5.5304     .0214 3.3622

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 5.V5  N= 75 OUT OF 75

SOURCE              DF SUM OF SQRS  MEAN SQR  F-STATISTIC SIGNIF

BETWEEN              1    248.20     248.20     2.7850      .0994
WITHIN              73    6505.7     89.120
TOTAL               74    6753.9     (RANDOM EFFECTS STATISTICS)

ETA= .1917  ETA-SQR= .0367  (VAR COMP= 4.2793  %VAR AMONG= 4.58)

V3           N    MEAN     VARIANCE   STD DEV

(1)         34  46.118      75.925     8.7135
(2)         41  42.463      100.00     10.000

GRAND       75  44.120      91.269     9.5535

 CONTRAST        MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 OBSERVED    PREDICTED    F-STAT    SIGNIF LEV=.9000
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UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 4.V4  N= 75 OUT OF 75

SOURCE              DF SUM OF SQRS  MEAN SQR  F-STATISTIC SIGNIF

BETWEEN              1    418.67     418.67     5.5304      .0214
WITHIN              73    5526.3     75.703
TOTAL               74    5945.0     (RANDOM EFFECTS STATISTICS)

ETA= .2654  ETA-SQR= .0704  (VAR COMP= 9.2260  %VAR AMONG= 10.86)

V3           N    MEAN     VARIANCE   STD DEV

(1)         34  43.941      74.784     8.6478
(2)         41  39.195      76.461     8.7442

GRAND       75  41.347      80.338     8.9631

 CONTRAST       MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 OBSERVED   PREDICTED   F-STAT    SIGNIF LEV=.9000

 -34.449     1.0000     130.73     .0000

 PAIRWISE       MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 STRATA      DIFF       F-STAT    SIGNIF LEV=.9000

(1)
   (2)      4.7461      5.5304     .0214 3.3622

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 5.V5  N= 75 OUT OF 75

SOURCE              DF SUM OF SQRS  MEAN SQR  F-STATISTIC SIGNIF

BETWEEN              1    248.20     248.20     2.7850      .0994
WITHIN              73    6505.7     89.120
TOTAL               74    6753.9     (RANDOM EFFECTS STATISTICS)

ETA= .1917  ETA-SQR= .0367  (VAR COMP= 4.2793  %VAR AMONG= 4.58)

V3           N    MEAN     VARIANCE   STD DEV

(1)         34  46.118      75.925     8.7135
(2)         41  42.463      100.00     10.000

GRAND       75  44.120      91.269     9.5535

 CONTRAST       MULTIPLE COMPARISON      SCHEFFE ALLOWANCES
 OBSERVED   PREDICTED   F-STAT    SIGNIF LEV=.9000
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(1)	34	46.235	43.882	6.6244
(2)	41	41.878	41.110	6.4117
GRAND	75	43.853	46.559	6.8234

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 7.V7 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	25.413	25.413	1.5392	.2187
WITHIN	73	1205.3	16.510		
TOTAL	74	1230.7	(RANDOM EFFECTS STATISTICS)		

ETA= .1437 ETA-SQR= .0206 (VAR COMP= .23948 %VAR AMONG= 1.43)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	7.7059	17.365	4.1672
(2)	41	6.5366	15.805	3.9755
GRAND	75	7.0667	16.631	4.0781

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 8.V8 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	27.610	27.610	4.6897	.0336
WITHIN	73	429.78	5.8874		
TOTAL	74	457.39	(RANDOM EFFECTS STATISTICS)		

ETA= .2457 ETA-SQR= .0604 (VAR COMP= .58435 %VAR AMONG= 9.03)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	2.8529	6.6747	2.5835
(2)	41	1.6341	5.2378	2.2886
GRAND	75	2.1867	6.1809	2.4861

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 9.V9 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	.62195	.62195	1.4469	.2329
WITHIN	73	31.378	.42984		
TOTAL	74	32.000	(RANDOM EFFECTS STATISTICS)		

ETA= .1394 ETA-SQR= .0194 (VAR COMP= .51681 -2 %VAR AMONG= 1.19)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	2.5000	.43939	.66287
(2)	41	2.6829	.42195	.64958
GRAND	75	2.6000	.43243	.65760

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 10.V10 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	.80956 -1	.80956 -1	.14533	.7041
WITHIN	73	40.666	.55706		
TOTAL	74	40.747	(RANDOM EFFECTS STATISTICS)		

ETA= .0446 ETA-SQR= .0020 (VAR COMP= -.12808 -1 %VAR AMONG= -0.)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	2.4706	.49911	.70648
(2)	41	2.5366	.60488	.77774
GRAND	75	2.5067	.55063	.74204

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 11.V11 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	2255.2	2255.2	7.4493	.0079
WITHIN	73	22100.	302.73		
TOTAL	74	24355.	(RANDOM EFFECTS STATISTICS)		

ETA= .3043 ETA-SQR= .0926 (VAR COMP= 52.522 %VAR AMONG= 14.78)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	48.088	389.42	19.734
(2)	41	37.073	231.22	15.206
GRAND	75	42.067	329.12	18.142

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 12.V12 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	4390.5	4390.5	3.7431	.0569
WITHIN	73	85626.	1173.0		
TOTAL	74	90017.	(RANDOM EFFECTS STATISTICS)		

ETA= .2208 ETA-SQR= .0488 (VAR COMP= 86.556 %VAR AMONG= 6.87)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	60.735	1724.4	41.526
(2)	41	45.366	717.99	26.795
GRAND	75	52.333	1216.4	34.878

UNIVARIATE 1-WAY ANOVA

ANALYSIS OF VARIANCE OF 13.V13 N= 75 OUT OF 75

SOURCE	DF	SUM OF SQRS	MEAN SQR	F-STATISTIC	SIGNIF
BETWEEN	1	296.50	296.50	81.690	.0000
WITHIN	73	264.96	3.6295		
TOTAL	74	561.45	(RANDOM EFFECTS STATISTICS)		

ETA= .7267 ETA-SQR= .5281 (VAR COMP= 7.8784 %VAR AMONG= 68.46)

V3	N	MEAN	VARIANCE	STD DEV
(1)	34	1.6279	.65351	.80840
(2)	41	5.6220	6.0848	2.4667
GRAND	75	3.8113	7.5872	2.7545