


DECLARATION

This Dissertation is my own original work and has not previously been presented for a degree in any University.

Signed - Candidate

This Dissertation has been submitted for examination with my approval.

Signed  (DR - d)
Supervisor

MEDICAL LIBRARY
UNIVERSITY Of NAIROBI
P. O. Box iW6
NAIROBI i

T I T L E

DIAZEPAM: ITS USE IN ANAESTHESIA AND INTENSIVE CARE
THERAPY AT THE KENYATTA NATIONAL HOSPITAL, NAIROBI, FROM
JANUARY, 1980 TO DECEMBER, 1984.

B Y

DR. MILMA JOHN HENRY, MD. (DONETSK)

A DISSERTATION SUBMITTED IN PART FULFILMENT FOR
THE DEGREE OF MASTER OF MEDICINE (ANAESTHESIA) OF
THE UNIVERSITY OF NAIROBI.

ACKNOWLEDGEMENTS

I would like to record my sincere appreciation to the following:

Dr. S. K. Kahuho, FFARCS (Irel) D.A. , Senior Lecturer, Head, Anaesthetics section and Consultant Anaesthetist, Kenyatta National Hospital, Dr. P. Q Huma, FFARCS (Eng.) Lecturer and Consultant Anaesthetist, Kenyatta National Hospital, for their useful criticisms and advice during the study and preparation of this dissertation.

All the consultant anaesthetists, physicians and surgeons who managed these patients in the Intensive Care Unit and or in the operation theatres and wards of the Kenyatta National Hospital who have been my constant source of knowledge on the subject.

Senior House Officers in Medicine, Paediatrics, Surgery, Obstetrics and Gynaecology and Senior House Officers in Anaesthesia who worked in the Intensive Care Unit, the various theatres and wards of Kenyatta National Hospital during the period of study.

The Director, Kenyatta National Hospital, for allowing this study to be done.

The nursing staff in the wards, Intensive Care Unit and operation theatres for their accurate recording of the necessary information in the files of patients under study.

The staff of the records department, Kenyatta National Hospital, for making the relevant case notes readily available to me for this study.

My wife Eunice and my children for their great inspiration and co-operation during the period of study and the writing of this dissertation.

M . Mbarani for her secretarial work.

CONTENTS

	PAGE
DECLARATION	i
TITLE	ii
ACKNOWLEDGEMENTS	iii
LIST OF FIGURES AND TABLES	v
SUMMARY	1
INTRODUCTION	4
OBJECTIVES	9
MATERIALS AND METHODS	10
RESULTS	12
DISCUSSION	18
SUGGESTIONS AND CONCLUSIONS	28
REFERENCES	43-52

LIST OF FIGURES AND TABLES

			<u>PAGE</u>
FIGURE	1	Summary of possible mechanisms for the pharmacological properties of benzodiazepine drugs.	29
FIGURE	2	Age distribution in years.	30
TABLE	1	Sex distribution of the patients.	31
TABLE	2	Distribution of in-patients.	32
TABLE	3	Distribution of day cases.	33
TABLE	4	Indications for the administration of diazepam in anaesthesia.	34
TABLE	5	Parenteral/oral administration- patient relationship.	35
TABLE	6	Intravenous (Bolus/DRIP/oral- patient relationship.	36
TABLE	7	Form and amount of diazepam administered for anaesthesia and intensive therapy.	37
TABLE	8	Distribution of diazepam in gramms in anaesthesia.	38
TABLE	9	Distribution of diazepam in gramms in intensive care.	39
TABLE	10	Distribution of the mean doses of diazepam in anaesthesia.	40
TABLE	11	Distribution of the mean doses of diazepam in intensive therapy.	41
FIGURE	3	Distribution of pre-determined doses of diazepam in anaesthesia.	42

SUMMARY

A retrospective study was carried out at the Kenyatta National Hospital on 1369 patients who received diazepam for anaesthesia and for intensive therapy in the period between January, 1980 and December 1984. About 1274 of these cases approximately (93.1%) received diazepam for anaesthesia and 95 cases about (6.9%) for intensive care therapy.

Patient age distribution of the 1274 cases studied in anaesthesia ranged from 9 months to 67 years; 1121, about, (88%) of them were females and 153, about (12%) were males. In the Intensive Care Unit, of the 95 cases studied, 49, about (51.6%) were males and 46, about (48.6%) were females with an age distribution of between three weeks and 70 years (Figure 2 and Table 1).

Basing on the American Society of Anaesthesiologists' classification, which categorises the fitness of a patient for anaesthesia, 1027 cases, about (75%) of all the patients studied were of grades III and IV and were admitted to either the Intensive Care Unit or to other wards at the Kenyatta National Hospital (Table 2). These patients underwent various procedures and or operations in theatre or in the Intensive Care Unit. About 342 patients, about (25%) were of the 2nd grade by the ASA classification but they formed a special group because they came for day case surgery and were discharged home the same day after undergoing various surgical procedures and operations (Table 3).

Indications for the administration of diazepam in anaesthesia included:

- i) Premedication,
- ii) Induction of anaesthesia,
- iii) An an adjuvant to both general anaesthesia and local analgesia, and
- iv) Modifying the emergence phenomena after ketamine anaesthesia (Table 4).

In the Intensive Care Unit, indications for the administration of anaesthesia included:

- i) Sedation of patients during mechanical ventilatory support of the lungs ,
- ii) Relief of muscle rigidity and spasms in tetanus cases ,
- iii) As a tranquilizer during intensive monitoring.
and
- iv) As an anticonvulsant.

The most common clinical situations that necessitated the administration of diazepam in the Intensive Care Unit were:-

- i) Tetanus,
- ii) Postmeasles laryngotracheobronchitis
- iii) Meningitis
- iv) Post operation status , and
- v) Status asthmaticus ,severe trauma, status epilepticus and severe eclampsia.

The routes of administration of diazepam were parenteral, as an intravenous bolus dose, as the case was in anaesthesia or as intravenous divided bolus doses or through a drip as the case was in the Intensive Care Unit. The oral route of administration was used in the Intensive Care Unit only (Table 5,6).

The mean duration of administration of diazepam in anaesthesia was one day whereas in the Intensive Care Unit was about 18.3 days. The average daily dose in anaesthesia per patient was about 10.3 mg while in the Intensive Care Unit it was about 116 mg.

Predetermined doses of diazepam were usually preferred in anaesthesia and bolus single or divided doses of 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg and 40 mg were administered (Figure 3).

Complications and side effects arising from the use of diazepam in both anaesthesia and Intensive care were difficult to detect since diazepam was administered along with many other drugs. To determine the specific complications and side effects, a different study will be necessary. However, pain at injection site in anaesthesia and thrombophlebitis in the Intensive Care Unit was recorded in our study.

INTRODUCTION

The history and development of the benzo-diazepine group of drugs , of which diazepam is a member, started in the 1950's when the tranquilizers, a new class of therapeutic agents, were shown to have considerable clinical value and Roche decided to embark on a programme concerned with the synthesis of products of this type (38). By 1960 and 1963 chlordiazepoxide and diazepam had been discovered and marketed respectively (38). Despite the discovery of other members of this family of drugs eg. Flunitrazepam , 1970; Chlorazepate, 1972; Clonazepam, 1975 and Lorazepam , 1977 (38), diazepam has been and is still the most widely used drug in this group for both anaesthesia and intensive care therapy (6).

In intensive care therapy, diazepam is used because of the following of its pharmacological properties:

- 1) Amnesia.
- 2) Sedation.
- 3) Anticonvulsant
and
- 4) Muscle relaxation

McClish et al, 1968^{sig} (5) observed that patients who were subjected to post operative mechanical ventilatory support and had received their usual post-operative analgesic medication supplemented by intravenous doses of 2.5 mg to 5 mg of diazepam six times a day, had a better patient-nurse, patient doctor relationships. Because of the

sedative and amnestic properties of this drug, they (5) recommended the use of diazepam as a sedative in the Intensive Care Units (5,6). Other studies were conducted by G. M. Hall et al in 1974 (7) to determine the effects of intravenous diazepam on experimentally induced pain, and they concluded that although diazepam is not an ideal drug in that it does not consistently elevate pain thresholds, in view of its relative safety, it would seem to be one of the better drugs for producing sedation in the Intensive Care Units (8).

The anterograde amnesic effect of diazepam was reported by Clarke et al, 1970 (11), who noted that, intravenous diazepam in clinical doses, causes anterograde amnesia in the first ten minutes after administration, and that this was not accompanied by a serious reduction in the level of consciousness. A. C. McKay et al, in 1980 (9) and J. Kerr et al, (1979 (10) have confirmed this property of diazepam.

Gastant et al in 1965 (30), and Lombroso in 1966 (35) used diazepam as an anticonvulsant in non-traumatic cases of status epilepticus successfully. To date it is an established anticonvulsant agent (3), though it should not be used for long term therapy (34,36).

Shershin and Katz in 1964 (32), first used diazepam in the control of muscle rigidity and spasm in tetanus cases. Weinberg in 1964 (33), clinicians in Nigeria (6), and Nganga in Nairobi in 1981 (37), have since reported its use for the treatment of muscle rigidity and spasms in tetanus patients in Intensive Care Units.

The broad-spectrum pharmacological properties of benzodiazepines have been explained by various workers to be attributed to various theories of their mode of action at Cellular level.

Mohler et al in 1977 (42) and Squires et al in 1977 (41) , independently described specific benzodiazepine receptors. This has provided a basis for a better understanding of the effects of these drugs and a more rational approach to their future development (39). These receptors in man (40) , are found not only in the central nervous system including the spinal cord (41 , 42 , 43), but also in many other tissues including the kidney, liver and lung (45). Binding to non-nervous tissue is much weaker, where the mitochondria is the main binding site whereas in the brain and the rest of the nervous tissue the binding site is the cell membrane, hence very strong binding affinity. This theory was further developed by Braestrup and Squires in 1977 (43) , who suggested that the binding sites of benzodiazepines are membrane proteins in nerve cells and further showed that the abilities of various benzodiazepines to bind to receptors correlated well with their pharmacological potencies as anxiolytic agents (3). Snyder et al have suggested that the sedative properties of benzodiazepines could result from GABA-ergic neurotransmission possibly in the cortex. Snyder and Enna (49) pointed out that the sedative and anxiolytic properties of benzodiazepines are distinguishable from each other since they are dose-related (47). The anticonvulsant property of benzodiazepines was reported by Paul and

Skolnik (45) who observed that benzodiazepines are inhibitors of convulsants for seizures caused by interference with GABA-neurotransmission. The GABA-ergic mechanism for benzodiazepines are unique and do not extend to mechanisms of other anticonvulsant drugs (46).

Snyder and Enna (47) reviewed data and showed that benzodiazepines have an affinity for receptors in the spinal cord. This affinity for glycine receptors correlates with their potency as muscle relaxants and anxiolytic agents.

Snyder et al (47) suggested that benzodiazepines have a glycine mimetic action at the brain stem. Muscle relaxation could result from glycine-mimetic action in the spinal cord.

The mechanisms of action as proposed by Snyder et al (47, 49) and Costa and Gnidotti are shown in Figure 1.

At the Kenyatta National Hospital, diazepam has been the only benzodiazepine used because of its ready availability in both the oral (tablet) and injectable forms. It is also easy to administer and its margin of safety is wide. It is used in the Intensive Care Unit, Nganga in 1981 (37), and also in anaesthesia.

Side effects, though rare, include hypotension, allergic reactions (5), prolonged drowsiness in day-case surgery, respiratory depression (48, 49, 50, 51), pain at the injection site, and thrombophlebitis (52). At Kenyatta National Hospital, documentation of complications resulting

from the use of diazepam was poor with only 20 cases (1.6%) having been recorded in their case notes for having had pain at the injection site in anaesthesia and 5 cases (0.4%) in the Intensive Care Unit, having had thrombophlebitis as a complication resulting from the use of diazepam. These complications can however, not be blamed on diazepam alone since it was administered along with other drugs.

Overdosage of the drug has been successfully treated with aminophylline intravenously (29).

OBJECTIVES

- 1 . To determine the categories of patients to whom diazepam was administered for anaesthesia and intensive care therapy, procedures and operations carried out on these patients , indications for the administration of diazepam in these cases , the routes of administration of the drug, the duration of administration of diazepam, and the dose of diazepam administered per patient.

2. To make suggestions on a possible improvement in the rationale of using diazepam for anaesthesia and intensive care at the Kenyatta National Hospital.

3. To make conclusions on the use of diazepam for anaesthesia and intensive care therapy at the Kenyatta National Hospital during the period of study.

MATERIALS AND METHODS

Case notes of patients who received diazepam therapy for anaesthesia and intensive care therapy in the five years , between January, 1980 and December, 1984 were carefully studied. These included case notes of patients from the general wards and the casualty department at the Kenyatta National Hospital, patients transferred directly to the Intensive Care Unit from outside Kenyatta National Hospital and day-cases who underwent day surgery and were discharged home the same day.

The case notes were studied further to provide information on the categories of patients who were treated with diazepam , procedures and operations performed, indications for the administration of the drug, routes of administration of diazepam, duration of administration and dosage of diazepam, and complications encountered with diazepam therapy and how these were treated in both anaesthesia and intensive care.

A further study of the case notes was carried out with regard to the routes of administration of the drug. These routes of administration were considered separately in the study with a view of establishing the more popular ones. Individual dosages were studied to determine the mean value of diazepam administered per patient during the period of study and in any one given day.

Initially, literature on diazepam was drawn from the index medicus

series from 1960 to 1985 and the literature available was scrutinized and quoted as reference in this dissertation.

RESULTS

A total of 1369 cases were studied including 1274 cases about (93.1%) who underwent surgical, diagnostic or radiotherapeutic procedures, and 95 cases, about (6.9%) consecutively admitted into the Intensive Care Unit who received diazepam as one of the drugs used for anaesthesia and intensive care therapy.

The ages of the patients ranged from 3 weeks to 70 years. 1001 cases, about (73.1%) had their ages ranging from 31 to 60 years Figure 2. Sex distribution of the patients showed that there were 1167, about (85.3%) females and 202, about (14.7%) males, Table 1.

The total number of in-patients included in this study was 1027 cases, about (75%). This included 932 cases, about (80.7%) who were admitted into all other wards at the Kenyatta National Hospital and 95 cases, about (9.3%) who were admitted into the Intensive Care Unit and received diazepam for anaesthesia and intensive therapy during the period of study.

About 712 cases, about (69.3%) of these in-patients had cancer of the cervix and were examined under general anaesthesia with diazepam as one of the drugs administered, for staging and biopsy. This group of patients also required insertion of caecium for radiotherapy under general anaesthesia incorporating diazepam administration. About 24 cases, about (2.3%) underwent other gynaecological procedures such as

laparoscopy and or tubal ligation; 15 cases, about (1.5%) underwent caesarean section with diazepam as one of the anaesthetic drugs because they had cardiac lesions and 181 cases, about (17.6%) underwent various surgical operations such as open-heart for valve replacements , vascular surgery for coarctation of the aorta and aneurysms , thymectomy for myasthenia gravis and adrenalectomy for pheochromocytoma. In this group of patients, diagnostic procedures such as carotid angiography for diagnosis of intracranial masses was also carried out and required anaesthesia incorporating diazepam.

The remaining 95 in-patients, about (9.3%) were admitted to the Intensive Care Unit for mechanical ventilatory support, close monitoring before and or after surgery, control of muscle rigidity spasms and convulsions (Table 2).

In this study it became clear that there were 342 day cases , about (25%) who underwent minor surgery and or diagnostic procedures who were treated with diazepam as one of the anaesthetic agents and discharged home the same day. The operations and procedures carried out included minor gynaecological operations like diagnostic laparoscopy and or tubal ligation, minor surgical operations like incision and drainage of abscesses and removal of foreign bodies from the ears ,(Table 3).

Indications for the administration of diazepam in anaesthesia were found to be:-

- 1) premedication 11 cases, about (0.86%)
- 2) induction of anaesthesia 88 cases, about (6.9%)
- 3) as an adjuvant to general anaesthesia 90 cases , about (7%)
- 4) as an adjuvant to local anaesthesia 216 cases, about (16.9%)
- 5) for both induction of anaesthesia and as an adjuvant to general anaesthesia 11 cases.
- 6) modifying the emergence phenomena after ketamine anaesthesia 869 cases, about (68.2%) (Table 4).

Indications for the administration of diazepam in the Intensive Care Unit were found to be:-

- 1) Sedation of patients during mechanical ventilation of the lungs 33 cases, about (34.7%)
- 2) Relief of muscle rigidity and spasms in tetanus patients 40 cases , about (42%)
- 3) As a tranquilizer during intensive monitoring 10 cases, about (10.5%)
- 4) As an anticonvulsant in status epilepticus and meningitis patients 12 cases, about (12.8%).

In this study it was further noted that the parenteral route of administration of diazepam was preferred in all the 1274 (100%) cases who received the drug for anaesthesia. In the Intensive Care Unit, diazepam was administered parenterally to 79 cases, about (83.2%) and

orally to 6 cases, about (6.3%). 10 patients, about (10.5%) received diazepam both parenterally and orally. The parenteral route preferred in anaesthesia was intravenous. Diazepam was in this cases administered as a single intravenous bolus dose to each of 1259 cases, about (98.8%) and in two divided bolus doses to each of 15 cases, about (11.2%). For intravenous therapy divided bolus doses were administered to 49 patients, about (51.6%), continuous intravenous doses using an injection pump or through a 5% dextrose drip to 30 cases, about (31.6%). 10 patients, about (10.5%) received diazepam orally (crushed tablet) through a nasogastric tube, as an intravenous bolus dose and through a 5% dextrose drip as a continuous dose. The oral route of administration of diazepam was used only when the patient could feed by a nasogastric tube (Tables 5 and 6). The syrup form of oral diazepam was not used because it was not available during the period under study.

A total amount of 215.1 gm of diazepam was administered for anaesthesia and intensive care therapy during the period of study. Of these 35.1 gm, about (16.3%) were administered orally (as a crushed tablet), while 180 gm, about (83.7%) were given parenterally (Table 7).

The distribution of the total amount of diazepam administered in the Intensive Care Unit and for anaesthesia is shown in Tables 8 and 9.

Each patient in anaesthesia received diazepam within one day only. In the Intensive Care Unit the treatment period of the patients with diazepam ranged from one day to 89 days. The average treatment period

in this category of patients was about 18.3 days per patient.

The mean daily dose of diazepam in anaesthesia was 10.3 mg and 116 mg in the Intensive Care Unit.

The average diazepam dose over the period of study per patient in anaesthesia was distributed as follows:-

- 1) premedication, about 11.4 mg.
- 2) induction of anaesthesia, about 18.1 mg.
- 3) as an adjuvant to general anaesthesia, about 11 mg.
- 4) as an adjuvant to local anaesthesia, about 10 mg.
- 5) as an adjuvant to ketamine anaesthesia, about 9.5 mg.

(Table 10)

For intensive therapy the mean dose distribution over the period of study was as follows:-

- 1) sedation, about 0.5 gm.
- 2) control of muscle rigidity and spasms, about 4.7 gm.
- 3) as a tranquilizer, about 0.04 gm.
- 4) as an anticonvulsant, about 0.49 gm.

(Table 11)

Predetermined doses were usually given in anaesthesia. The doses which were administered included:-

5 mg dose each 103 patients, about (8.1%)

10 mg dose each 1052 patients, about (82.6%)

15 mg dose each 89 patients, about (7.0%)

20 mg dose each 22 patients, about (1.7%)

30mg, 35mg, and 40 mg doses each, 8 patients, about (0.6%)

(Figure 3)

It was not possible to draw up a distribution pattern for the use of diazepam in the Intensive Care Unit. But it was established that the 95 patients under study in the Unit received 202 gm. of diazepam during the period of study. The mean dose of diazepam per patient in the Intensive Care Unit was thus 2.1 gm.

Complications and side effects arising from the use of diazepam in anaesthesia and intensive care therapy were not recorded in most of the case notes studied. Diazepam was usually administered along with many other drugs for anaesthesia and in the Intensive Care Unit hence it was difficult to blame whatever side effects or complications that were recorded in the case notes on diazepam alone. It was, however, noted from the case notes that 20 patients (1.6%) in anaesthesia had pain at injection site and 5 cases (0.4%) in the Intensive Care Unit developed thrombophlebitis.

DISCUSSION

Like other benzodiazepines, diazepam is used in anaesthesia partly because of its wide margin of safety.

During the period of study, diazepam was used in 100% of the cases studied. This was so because it was readily available, not only in the injectable form, but also in the oral (tablet) form.

R. S. J. Clarke et al (1, 8), comparing diazepam and flunitrazepam as induction agents for cardiac surgical operations, noted that diazepam was widely used because it causes minimal cardiac and respiratory depression and is therefore suitable for poor-risk patients (1), like those who require cardioversion (58), where other forms of anaesthesia would be dangerous (64), the elderly and the shocked patients (6).

In this study, all the cases were either poor-risk, of ASA classification III and IV or they were day-cases; 95 cases, about (9.3%) were admitted to the Intensive Care Unit for intensive therapy which included mechanical ventilatory support, control of muscle rigidity and spasms in tetanus cases, control of convulsions in status epilepticus and intensive monitoring before and or after surgery. About 932 cases, about (80.7%) of the 1027 in-patients, were admitted into other wards at the Kenyatta National Hospital, and included 736 cases, about (71.6%) with gynaecological problems, 15 cases, about (1.5%) with obstetric

problems, 181 cases, about (17.6%) with cardiovascular, general surgical and diagnostic problems. Procedures performed included examination under general anaesthesia for staging and biopsy in cases of the cancer of the cervix 712 cases , about (69.3%), laparoscopy and or bilateral tubal ligation 24 cases, about (2.3%) , caeserean section in patients with cardiac lesions 15 cases, about (1.5%), open heart surgery for valve replacements , vascular surgery for coarctation of the aorta and aneurysms , thymectomy for myasthenia gravis , adrenalectomy for phaeochromocytoma and carotid angiography for diagnosis of intracranial masses 181 cases, about (17.6%).

Indications for the administration of diazepam in anaesthesia and intensive care therapy are reflected by the pharmacological properties of the drug such as:~

- 1) Antianxiety.
- 2) Sedation.
- 3) Anticonvulsant.
- 4) Muscle relaxation.
- 5) Amnesia.

Diazepam in anaesthesia has therefore been used for:-

- 1) 1) premedication in general (8, 55 , 58), in minor gynaecological surgery (56), in cardiac surgery (1), in paediatrics (62) and in otolaryngological surgery (13). In this study diazepam was used for premedication in 11 cases (0.86%) who under-

went anaesthesia at Kenyatta National Hospital.

- 2) induction of anaesthesia in general and in cardiac patients (1, 30, 58, 70). For this purpose, it was found that diazepam was used in 88 cases, about (6.9%).
- 3) as an adjuvant, to general anaesthesia (6, 12).
The study revealed that 90 cases, about (7.0%) received diazepam for this purpose.
- 4) sedation during local analgesia (6). In this study 216 cases, about (16.95%) received diazepam for augmentation to local anaesthesia
- 5) modification of the emergency phenomena during ketamine anaesthesia (12, 21, 30, 31). Diazepam was administered to 869 cases, about (68.2%) during ketamine anaesthesia in this study.
- 6) facilitation of amnesia during anaesthesia (9, 10, 11, 24).
There is no record in the case notes about this property of diazepam.

*11 patients (0.86%) received diazepam for both augmentation to general anaesthesia and induction of anaesthesia in this study.

Diazepam is extensively used in Intensive Care Units for sedation of patients (6, 7, 8). Gastaunat et al in 1965 (34), and Lombroso in 1966 (35), used diazepam as an anticonvulsant in status epilepticus.

To date diazepam is an established anticonvulsant (45). Muscle rigidity and spasms in tetanus cases are also well controlled by diazepam (6, 32, 33, 37).

About 33, about (34.7%) of the patients who received diazepam in the Intensive Care Unit required it for sedation during mechanical ventilatory support with or without curarization, 12 cases (12.8%) received diazepam to control convulsions in status asthmaticus, 40 patients, about (42%) required it for the control of muscle rigidity and spasms and 10 cases, about (10.5%) required diazepam as a tranquilizer during intensive monitoring.

The total amount of diazepam administered to each patient in the Intensive Care Unit depended on the age of the patient, diagnosis and length of stay in the Unit. In anaesthesia on the other hand the dose administered depended on what the anaesthetist wanted to achieve.

For premedication, Steen and Hahl in 1969 (67) found diazepam 10 mg intramuscularly to be a near-ideal form of premedication (6). Dundee, Loan and Morrison in 1970 (68) found diazepam 10 mg to be an adequate premedicant. Premedication with 10 mg diazepam can be combined with atropine or hyoscine when a parasympathetic action is required. The average dose of diazepam used for premedication during the period of study was 11.4 mg which is in agreement with other workers.

For induction of anaesthesia, an average dose of 18.1 mg of diazepam was administered during the period of study. The average dose of diazepam recommended for induction of anaesthesia is within the range of 0.3 - 1.0 mg/kg. Noting that most of the patients who were induced with diazepam had cardiac lesions and that they were usually premedicated with hyoscine and morphine may explain the lower induction dose in this study.

As an adjuvant to general anaesthesia, an average dose of 10.9 mg was administered per patient while modification of ketamine anaesthesia, an average dose of 9.5 mg of diazepam was administered per patient. M. A. K. Mattila et al in 1981 (31), advocated the administration of diazepam in three divided doses of 5 mg each during ketamine anaesthesia. In this study, pre-determined doses of 5 mg and 10 mg were administered, as the condition of the patient dictated during ketamine anaesthesia.

Personage and Norris in 1967 (61), employed diazepam in the treatment of status epilepticus in 9 patients. Immediate control of convulsions was obtained in 7 of these cases with an initial dose of 10 mg of diazepam intravenously, and this was followed by an intravenous infusion of 100 mg in 500 ml of normal saline and was given as required. Apart from the intravenous route of administration of diazepam as recommended by Nutter and Massumi in 1965 (6) and Kahler, Burrow and Felig in 1967 (62), and Kernohan in 1966 (63), the oral route of

administration of diazepam has been recommended in children (6). The oral route of administration has been successfully used for pre-medication of patients who were to undergo minor gynaecological surgery and the surgery of the eye (69). Whenever possible this route is preferred since the rate of absorption of diazepam is known to be as good as when diazepam is administered by the intravenous route (34).

In this study diazepam was administered intravenously for anaesthesia as there was always an already established intravenous line and the time of onset of effects would be faster than if administered intramuscularly. The oral route of administration was never used for anaesthesia.

Intramuscular administration of diazepam for premedication 1-2 hours before operation was first described by Thuries and Poncet, and Ducailler et al in France in 1964. In the United States of America it was described by Tornetta, in 1963 and in 1965 (6); the recommended dose is 10 mg (6) by deep intramuscular injection (34). The intramuscular route of administration of diazepam was not used in this study.

A total number of 1323 patients received diazepam by the intravenous bolus method, 30 cases by the continuous drip method and 6 cases by the oral route. 10 patients received diazepam by the intravenous bolus, continuous infusion drip and the oral (tablet through nasogastric tube) route.

Diazepam administered orally is known to be excreted 75% in the urine, 10% in the stool and the rest undergoes metabolism. The main

metabolite is desmethyl-diazepam which in itself is an active metabolite. Swatz et al in 1965 identified conjugated oxazepam as a major metabolite of diazepam. There are usually two peak values of plasma diazepam, one at 90 min and another after 6 to 8 hours. This is suggestive of enterohepatic circulation, Van der Klein et al, 1971 (64).

Complications arising from the use of diazepam in anaesthesia and intensive care are now well documented. Pain at injection site and thrombophlebitis are frequently reported after the administration of diazepam intravenously (28). The solvent has been thought to be responsible for these side effects, Braham, Pagano and Katz in 1977 (33), Schon Olesen and Huttel in 1980 (54). Respiratory depression as a side effect of diazepam therapy is now generally accepted (49, 50, 51).

Although hypersensitivity reactions to diazepam and other benzodiazepines are uncommon allergic reactions have been reported, Jata S. Ghosh, in 1977 (81). In most cases chlordiazepoxide alone was the offending agent followed by diazepam and flurazepam (81). In a review of cutaneous reactions to benzodiazepines, Almeyda (82) reported that allergic reactions to chlordiazepoxide consisted of urticaria, angioneurotic oedema, macular erythematous rash, photoallergy, purpura with or without thrombocytopenia, erythemamultiforme, erythema-nodosum and galactorrhoea. Immediate hypersensitivity with bronchospasm has been associated with the intramuscular and intravenous use of diazepam (83). In most cases, the abnormalities resolved after

the agent was discontinued. However, rechallenge in some instances with the aetiological agent at a later date was rapidly followed by the reappearance of the allergic reactions noted earlier (81).

Alain Forster et al in 1980(48) , concluded that Midazolam and diazepam injected intravenously in equipotent doses depress the respiratory function significantly and similarly. Their effects are due to a direct depression of the central respiratory drive, however, a simultaneous depression of respiratory muscle efficiency may be contributory.

Hypotension though transient following the administration of diazepam is likely to be due to a reflex relaxation of peripheral vessels than myocardial depression.

Researchers have up to now concentrated on finding a suitable solvent of diazepam. Though commonly used in anaesthesia and intensive care, the intravenous administration of diazepam poses some problems, mainly due to venous complications (72, 73, 74, 75, 76). Earlier cremophor was reported to have a lower incidence of thrombophlebitis when used as a solvent (72, 73, 74, 75, 76), but the risk of anaphylactoid reactions associated with it limits its clinical use (78, 79). In his paper, M.A.K. Mattila et al in 1984, two different formulations of diazepam dissolved in soya-bean oil and emulsified in water (Diazemuls-Kalsi-Vitrum) and (2) Valium Roche Micelles with its lecithin-bile acids-water solvent are mentioned. These

two preparations have been found to be as effective as the conventional diazepam formulations but have better local tissue tolerance. They have been associated with only mild pain at injection site although diazemuls have proved to be easier to inject than diazepam. Their use for intramuscular use is still under investigation (77).

When the intravenous route is to be used with any of the diazepam formulations, a slow injection in a large vein with care to avoid extravasation has been recommended. Mixing or diluting diazepam with other solutions or drugs in a syringe or infusion flask is to be discouraged. If it is not feasible to administer diazepam directly intravenously it may be injected slowly through the infusion tubing (34).

In this study some of these complications were noted and precautions against them accomplished. A basic question was the use of diazepam by the continuous drip method in the Intensive Care Unit. Many clinicians have used this method, Dundee and Wyant (4, 5) and have reported of its use (37). However, it must be borne in mind that diazepam has poor solubility in water and other solutions. In normal saline, cloudiness occurs due to the formation of an emulsion of small particulate matter, though the potency is maintained.

Other adverse effects of diazepam, drowsiness, fatigue, confusion, depression, headache, slurred speech, syncope, tremor, constipation, nausea, cardiovascular collapse, blurred vision may occur. Paradoxical reactions like acute hyperexcited states, anxiety, hallucinations and

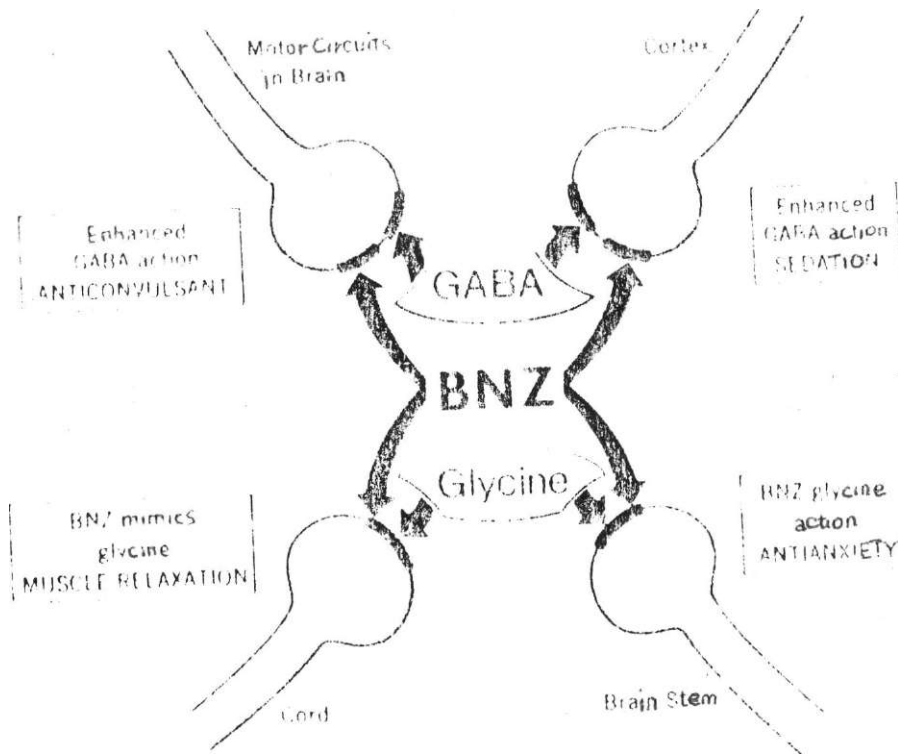
increased muscle rigidity have been reported. In addition laryngospasm, rebound insomnia, rage and sleep disturbances have also been reported(29). These side effects must be borne in mind and the patient carefully observed when diazepam is being administered. A patient who has had diazepam as one of the anaesthetic agents should not be left unattended and day cases should go home accompanied and should not handle machinery or drive for at least 24 hours. Complications and side effects though rare, related to the much advocated wide margin of safety do occur and this should always be remembered.

CONCLUSION

A report on a retrospective study on the use of diazepam in 1369 patients in five years at the Kenyatta National Hospital is made. From this study, it is quite clear that most people prefer parenteral administration of this drug. It is suggested that the oral route of administration be encouraged as well, after an exhaustive review of literature.

FIGURE 1

BNZ FACILITATES INHIBITORY ACTION OF GABA



BNZ MIMICS INHIBITORY ACTION OF GLYCINE

Summary of possible mechanisms for the pharmacological properties of Benzodiazepine drugs: (BNZ)

The Schematic diagram illustrates the actions of gammaaminobutyric acid (GABA) and glycine in pre-synaptic nerve terminals.

The mechanisms involving GABA were proposed by Costa and Guidotti (46). The actions involving glycine were proposed by Snyder et al (47, 49). The model suggests that glycinemimetic action at brains stem synapses inhibits afferent conduction to anxiety centres that are located "higher" in the brain.

FIGURES and TABLES

FIGURE 2

AGE DISTRIBUTION IN YEARS



AGE IN YEARS

TABLE 10

SEX DISTRIBUTION OF THE PATIENTS

Sex	Cases In Anaesthesia	Cases In Intensive care	Total	Percentage (%)
Females	1121	46	1167	85.3
Males	153	49	202	14.7
Total	1274	95	1369	100

TABLE 10

DISTRIBUTION OF IN-PATIENTS

Unit	Number of Cases	Percentage (%)
Gynaecological	736	71.6
Obstetric	15	1.5
Cardiovascular General surgical Diagnostic	181	17.6
Intensive Care Unit	95	9.3
Total	1027	100

TABLE 10

DISTRIBUTION OF DAY-CASES

Operation	Number of Cases	Percentage (%)
Minor Gynaecological	188	55
Minor Surgical	154	45
Total	342	100

INDICATIONS FOR THE ADMINISTRATION OF DIAZEPAM
IN ANAESTHESIA

Indications	Number of Cases	Percentage (%)
Premedication	11	0.86
Induction of Anaesthesia	88	6.91
Adjuvant to General Anaesthesia	90	7.06
Adjuvant to Local Anaesthesia	216	16.96
Adjuvant to ketamine Anaesthesia	869	68.21
Total	1274	100

* 11 patients received diazepam for both induction of anaesthesia and as an adjuvant to general anaesthesia.

TABLE 10

PARENTERAL/ORAL ADMINISTRATION - PATIENT RELATIONSHIP

Route of Administration	Anaesthesia (Number of Cases)	Intensive Care Unit Number of Cases	Total	Percentage (%)
Parenteral	1274	79	1353	98.8
Oral		6	6	0.5
Oral + Parenteral		10	10	0.7
Total	1274	95	1369	100

TABLE 10

INTRAVENOUS (BOLUS/DRIP)/ORAL - PATIENT RELATIONSHIP

Route of Administration	Anaesthesia (Number of Cases)	Intensive Care Unit Number of Cases)	Total	Percentage (%)
Intravenous Bolus	1274	49	1323	96.6
Intravenous Drip	.	30	30	3.2
Oral	.	6	6	0.5
Intravenous Bolus + Drip + Oral	.	10	10	0.7
Total	1274	95	1369	100

TABLE 10

FORM AND AMOUNT OF DIAZEPAM ADMINISTERED
FOR ANAESTHESIA AND INTENSIVE CARE THERAPY

Form of Administration	Amount of Diazepam given in Gramms for Anaesthesia	Amount of Diazepam given in Gramms for Intensive Care	Total	Percentage (%)
Parenteral	13.1	166.9	180	83.7
Oral (Tablet)		35.1	35.1	16.3
Total	13.1	202.0	215.1	100

TABLE 10

DISTRIBUTION OF DIAZEPAM IN GRAMMS IN ANAESTHESIA

Indication	Amount of Diazepam in Gramms	Percentage (%)
Premedication	0.125	1.0
Induction	1.590	12,1
Adjuvant to General Anaesthesia	0.985	7.5
Adjuvant to Local Anaesthesia	2.160	16.5
Adjuvant to ketamine Anaesthesia	8.245	62.9
Total	13.1	100

TABLE 10

DISTRIBUTION OF DIAZEPAM IN GRAMMS IN INTENSIVE CARE

Indication	Amount of Diazepam in Gramms	Percentage (%)
Sedation	8.3	4.1
Control of muscle rigidity and spasms	187.3	92.8
Tranquilizer	0.4	0.2
Anticonvulsion	6.0	2.9
Total	202.0	100

TABLE 10

DISTRIBUTION OF THE MEAN DOSES OF DIAZEPAM IN
ANAESTHESIA

Indication	Number of Cases	Amount of Diazepam Administered in Gramms	Mean Value of Diazepam per patient in Mg.
Premedication	11	125.0	11.4
Induction	88	1590.0	18.1
Adjuvant to general Anaesthesia	90	985.0	11.0
Adjuvant to Local Anaesthesia	216	2160.0	10.0
Adjuvant to Ketamine Anaesthesia	869	8245.0	9.5
Total	1274	13105.0	60.0

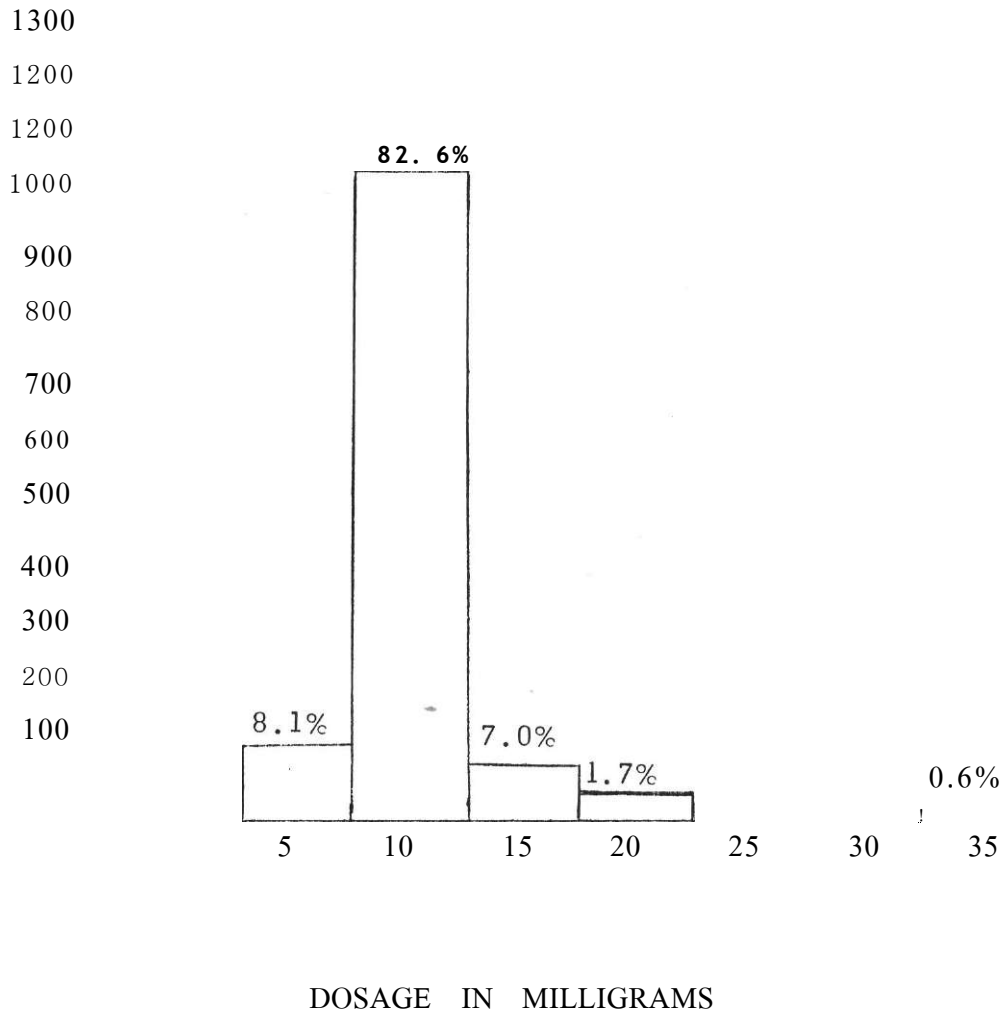
TABLE 10

DISTRIBUTION OF THE MEAN DOSES OF DIAZEPAM IN
INTENSIVE CARE THERAPY

Indication	Number of Cases	Amount of Diazepam Administered in Gramms	Mean Value of Diazepam per patient in Gramms
Sedation	33	8.295	0.25
Control of muscle rigidity and spasms	40	187.342	4.7
Tranquilizer	10	0.441	0.04
Control of Convuls ions	12	5.912	0.49
Total	95	202.0	5.48

FIGURE 3

DISTRIBUTION OF PRE-DETERMINED DOSES OF DIAZEPAM
IN ANAESTHESIA



R E F E R E N C E S

»

1. R. S. J., CLARKE AND S. M. LYONS: Diazepam and Flunitrazepam as Induction agents for cardiac surgical operations.
ACTAAnaesth. Scand. 1977, 21, 282 - 292.
2. ANDREW SMITH, M. D. RAWLINS: Community Clinics in Clinical Pharmacology. Benzodiazepines. Bri. Med.J.,
13 August, 1977 p. 447.
3. JAMES J. RICHTER: Current Theories about the Mechanisms of Benzodiazepines and Neuroleptic Drugs. Medical Intelligence. Anaesthesiology 54: 66-72, 1981.
4. DUNDEE J. W. AND WYANT G. M.,: Intravenous Anaesthesia ,
Edinburgh, London, Churchill - Livingstone, 1974.
5. McMCLISH, A. , ANDREW , D. , AND TETRAULT, L. , 1968:
Intravenous Diazepam for Psychiatric Reactions following open heart surgery. Canad. Anaesth. Soc. J. , 15, 63.
6. J. W. DUNDEE, AND W.H.K. HASLETT: The Benzodiazepines.
Bri. J. Anaesth. , 1970, 42 , 217.
7. S. STUART BROWN AND JOHN W. DUNDEE: Clinical Studies of Induction agents . XXV Diazepam.
Bri. J. Anaesth. 1968, 40, 108.
8. G. M. HALL, J.G. WHITWAM AND M. MORGAN: Effects of Diazepam on experimentally induced pain thresholds.
Bri. J. Anaesth. 1974, 46, 50.

9. A. C. McKAY AND J. W. DUNDEE: Effects of Oral Benzodiazepines on memory. *Bri. J. Anaesth.* , 1980, 52, 1247.
10. J. KERR RADCLIFFE INFIRMARY, OXFORD ENGLAND: Current Topics in Tetanus. Editorial. *Intensive Care Medicine* 5, 105-110 (1979).
11. P. R. F. CLARKE, P.S. ECCERSLEY, J. P. FRISBY AND J. A. THORNTON: The Amnestic effects of Diazepam. *Bri. J. Anaesth.* 1970, 42, 60.
12. M.A .K. MATTILA, K. SAILA, T. KOKKO AND T. KARKKAINEN: A Comparison of Diazepam and Flunitrazepam as Adjuncts to General Anaesthesia in preventing arousal followings surgical stimuli: *Bri. J. Anaesth.* 1979, 51, 329.
13. L. LINDGREN, L. SAARNIVAARA AND J. J. HIMBERG: Comparison of I. M. Pethidine, Diazepam and Flunitrazepam as Premedicants in children undergoing Otolaryngological surgery. *Bri.J. Anaesth.* 1979, 51, 321.
14. C.T . TREW, N.J. MANUS , D. M. JACKSON: Intra-Ocular Pressure and Premedication with Oral Diazepam. *Anaesthesia*, 1982 pages 339 - 340.
15. BEPKO,F . , LOWE, E. AND WAXMAN , B 1965: Relief of the emotional factor in labour with parenterally administered diazepam. *Obstet. and Gynae.* , 26, 852.
16. CAVANAGH, D. , AND CONDO, C.S. 1964: Diazepam. A Pilot study of drug concentrations in maternal blood, amniotic fluid, and cord blood. *Curr. Therap. Res.* 6, 122.

17. DESILVIA, J. A. F. , D'ARCONTE, L. , AND KAPLAN, L. , 1964:

The determination of blood levels and the placental transfer of diazepam in humans. *Curr. Therap. Res.* 6, 115.
18. W.N. CHESTNUTT, K. G. LOWRY, J. W. DUNDEE, S. K. PANDIT AND R. K. MIRAHUR: Failure of two benzodiazepines to prevent suxamethonium induced muscle pain:

Anaesthesia, 1985, Vol. 40 , pages 263 - 269.
19. VERMA R. S. , CPIATTERJIS , MATHUR, N.,: Diazepam and succinylcholine induced muscle pains: *Anaesthesia and Analgesia*, 1978, 57; 295-7.
20. EISENBERG M. , BALSLE , S. , KAT Z,; Effects of diazepam on succinylcholine induced myalgia , pottassium increase, creative phosphokinase elevation and relaxation:

Anaesthesia and Analgesia , 1979, 58:314-317.
21. FAHMY, N. R. , MALEK, N.S. , LAPPAS , D.G.: Diazepam prevents some adverse effects of suxamethonium: *Clinical Pharmacology and Therapeutics* , 1979, 26:395-8.
22. VERMA, R.S. ,: Diazepam and suxamethonium muscle pain. (A dose-response study). *Anaesthesia*, 1982; 37:688-90.
23. DAVIES , A. O. : Oral Diazepam premedication produces the incidence of post-succinylcholine muscle pains.

Canad. Anaesth. Soc. J. , 1983, 30:603-6.
24. BARKET , A.B. , : Induction of Anaesthesia with diazepam .

Anaesthesia, 1969, 24:388-94.
25. ERKOLA, O. , SALMENPERA, M. , TOMMISTO, T. ,: Does diazepam

pre-treatment prevent succinylcholine induced fasciculation, A double blind comparison of diazepam and tubocurarine pre-treatments: Anaesthesia and Analgesia, 1981, 59: 932-34.

26. NEWMAN, P.T.F. , LOUDON, J.M. ,:Muscle pain following administration of suxamethonium. The aetiological role of muscle fitness: Bri. J. Anaesth. 1966, 38:533-40.
27. BENNET, E.J. , MONTGOMERY, S. J. , DALAL, F.Y. , RAJ, P.P. ,: Pancuronium and fasciculations of succinylcholine. Anaesthesia and Analgesia , 1973, 52:892-6.
28. S. ARVIDSON, D. NIEMAND, S. MARTINELL, B. EKSTROM-JODAL: Aminophylline reversal of diazepam sedation. Anaesthesia, 1984, Vol. 39, Pages 806-809.
29. ERBGUTH, P.H. , REIMAN, B. , KLEIN, R.L. ,: The influence of chlorpromazine, diazepam and droperidol on emergence from Ketamine. Anaesthesia and Analgesia , current researches 1972; 5:693 - 8.
30. M. A. K. MATTILA, K. H. HYNYNEN, R. ERONEN, S. HEIKKINEN E. A. HYVONEN, P.O. PEKKOLA AND M. H. BACKSTROM: Diazepam dosage and timing in Ketamine. Combination anaesthesia. A double blind study. Anaesthesia, 30: 500-503, 1981.
31. P.O. CARTWRIGHT AND S. M. PINGEL: Mindazolam and diazepam in Ketamine anaesthesia. Anaesthesia, 1984, Vol. 39, pages 439 - 442.

32. SHERSHIN , P. H. , AND KATZ, S.S. 1964: Diazepam in the treatment of tetanus. Report of a case following tooth extraction. Cl. Med. 71 , 362.

33. WEINBERG, W. A. , 1964: Control of the neuromuscular and convulsive manifestations of severe systemiltetanus. Case report of a new drug, Valium (Diazepam). Clin. Paediat. , 3 , 226.

34. CORNER, J. T. , GEORGE, K.A. , DUNDEE, J. W. , AND PANDIT, S. K. , GREGG, J. M. , RYAN, D.E. , LEVIN, K. H. , : Injectable valium (diazepam/Roche). Anaesthesia and Analgesia , Vol. 64, Number 3. March, 1985, page 445.

35. LOMBAROSO, C. T., 1966: Treatment of status epilepticus with diazepam. Neurology (Minner) 16, 629.

36. GASTAUT, H. , NAGNET, R. , PIRE , R. AND TASSIMANI, C. A. , 1965: Treatment of status epilepticus with diazepam (valium). Epilepsia, 6, 167.

37. N. W. NGANGA: Intensive care in tetanus. A five year experience in the intensive care unit at the Kenyatta National Hospital, Nairobi. 1981.

38. LEO. H. STERNBACH The benzodiazepine story. Journal of medical chemistry, Vol. 22, Number 1, Jan. 1979.

39. EDITORIAL BY WHITWAM: Benzodiazepine receptors . Anaesthesia, 1983 , Vol. 38, Pages 93 - 95.

40. MOHLER, H. , OKADA, T.: The Benzodiazepine receptor in normal and pathological human brain. Bri. J. Psychiatry. 1978, 133: 216 - 18.

41. SQUIRES, R. F. , BRAESTRUP, C. , : Benzodiazepine receptors in rat brain, *Nature*, 1977, 266: 732 - 4 .
42. MOHLER, H. , OKADA, T. , : Benzodiazepine receptors: Demonstration in the central nervous system. *Science*, 1977 , 198: 49- 51.
43. BRAESTRUP, C. , SQUIRES, R.F. ,: Specific benzodiazepine receptors in rat brain characterized by high affinity (H) Diazepam binding. *Proceedings of the National Academy of Sciences. U.S.A.* 1977, 79:3805 - 9.
44. GUIDOTTI, A. , TOFFANO , G. , COSTA, E. ,: An endogenous protein modulates the affinity of GABA and benzodiazepine receptors in rat brain. *Nature*, 1978; 275: 553 - 5.
45. PAUL, S. M. , SKOLNICK, P. , : Rapid changes in brain benzodiazepine receptors after experimental seizures. *Science*, 202: 892 - 894, 1978.
46. COSTA, E. , GUIDOTTI, A. , Molecular mechanisms in the receptor action of benzodiazepines . *Annul. Rev. Pharmacology and Toxicology*, 19: 531 - 545, 1979.
47. SNYDER, S. H. , ENNA, S. J. , YOUNG, A. B.: Brain mechanisms associated with therapeutic actions of benzodiazepines: Focus on Neurotransmitters. *Am. J. Psychiatry*, p. 34: 662- 664. 1977.
48. ALAIN FORSTER, JEAN-PATRICE GORDAZ , PETER M. SUTER , MARCEL GEMPERIE: Respiratory depression by Midazolam and Diazepam: *Anaesthesiology* 53: 494-497 , 1980.

32. CATCHLOVE, R. F. H. , KAFER, E. R. , : The effects of diazepam on ventilatory response to carbondioxide and on steady-state gas exchange. *Anaesthesiology*, 34: 9-13, 1971.
50. GREENBLATT, D. J., SHADER, R. I.: Benzodiazepines, *New England Journal of Medicine*, 291: 1011 - 1015, 1974.
51. DALEN, J. E. , EVANS, G. L. , BANAS , J. S. , : The Haemodynamic and respiratory effects of diazepam (valium). *Anaesthesiology* , 30: 259 - 263, 1969.
52. S. JENSEN, M. S. FIUTTEL and A. SCHOU OLESEN: Venous complications after I.V. administration of diazemuls (diazepam) and dormincum (Midazolam). *Bri. J. Anaesth.* 1981; 53, 1083.
53. GRAHAM, C. W. , PAGANO, R.R. , and KATZ, R.L. 1977: Thrombophlebitis after intravenous diazepam. Can it be prevented? *Anaesthesia and Analgesia (Cleve)* , 56,409.
54. SCHOU OLESENA, A. , AND HUTTEL, M. S. , 1980: Local reactions to I.V. diazepam in three different formulations. *Bri. J. Anaesth.* , 52 , 609.
55. P. CHALMERS, J. N. HORTON: Oral bromazepam in premedication. A comparison with diazepam. *Anaesthesia*, 1984, Vol. 39, pages 370 - 372.
56. C. G. MALE AND H. D. JOHNSON: Oral Benzodiazepine premedication in minor gynaecological surgery. *Bri. J. Anaesth.* 1984, 56, 499.
57. F. J. RICHARDSON AND M. L. M. MANFORD: Comparison of Flunitrazepam and diazepam for oral premedication in older children. *Bri. J. Anaesth.* 1979, 51, 313.

58. D. O. NUTTER, AND R. A. MASSUMI: Diazepam in cardioversion. Brief recording. The new English Journal of Medicine Sept. 16. 1965. p. 650.
59. GROGON, A. Q. , 1963: Anaesthesia for artial defibrillation. Effects of quinidine on muscle relaxation. Lancet, 2. 1039.
60. STOCK, R. J., 1963: Cardioversion without anaesthesia . New England Journal of Medicine, 2 69 , 534.
61. PARSONAGE , M.J. AND NORRIS , J. W. , 19 67: Use of diazepam in the treatment of status epilepticus. Bri. Med. Journal 3, 85.
62. KAHLER, R. L. , BURROW, G. N. and FELIG , P. , 1967; Diazepam induced amnesia for cardioversion. J. Amer. Med. Ass. 200, 997.
63. KERNOMAN, R. S. 1963: Clinical evaluation of injectable librium in pre-anaesthetic medication. Anaesthesia and Analgesia, Current Research, 42 , 463.
64. VAN DER KLEIJN, E. , VAN ROSSUM , J. M. , MUSKENS E. T. J.M. , AND RIJNTIJE, S. N. V. M. 1971: Pharmacokinetics of diazepam in dogs, mice and humans. Acta Pharmacol. (Kbh), 29, Suppl. 3, 109.
65. MARRUBINI, M. , BOZZ, A. , and TRETOLA, L. 1965: Diazepam as a pre-operative tranquilizer in neuro-anaesthesia. A preliminary note. Bri. J. Anaesthesia, 37, 934.
66. McCLISH, A. 19 66: Diazepam as an intravenous induction agent for general anaesthesia. CAN. Anaesth. Soc. J., 13, 562.

67. STEEN, S. N. and HAHN, D. , 1969: Controlled evaluation of parenteral diazepam in pre-anaesthetic medication. *Anaesthesia and Analgesia. Current Research*, 48, 4, 549.
68. DUNDEE, J. W. , LOAN, W.B. , and M CRRISON, J. D. , 1970: Studies of drugs given before anaesthesia. XIX Opiates. *Bri. J. Anaesth. , 42, 54.*
69. HOLLOWAY, K. B. , : Control of the eye during general anaesthesia for intra-ocular surgery. *Bri. J. Anaesth. 1980, 52:671 - 9.*
70. J. W. , DUNDEE, W. H.K. HASLETT, S. R. KEILTY and S. K. PANDIT
Studies of drugs given before anaesthesia. XIX diazepam-containing mixtures. *Br. J. Anaesth. 1970, 42, 143.*
71. COMMITTEE ON THE REVIEW OF MEDICINES:
Systemic review of benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide , medazepam , chlorazepate , lorazepam , oxazepam , temazepam , triazolam, nitrazepam and rfflurazepam.
Bri. J Med. J. , 29 March, 1980.
72. LONGDON, D. E.: Thrombophlebitis following diazepam. *Journal of American medical Association , 1973, 225, 1389.*
73. LONGDON, D. E. , HAVLAN, J. R. , BAILEY, R. L.: Thrombophlebitis with diazepam used intravenously. *JAMA, 1973, 223, 184 - 5.*
74. HEGARTY, J. E. , DUNDEE, J. W. , : Sequelae after the intravenous injection of three benzodiazepines - diazepam , lorazepam and flunitrazepam. *Br. J. Anaesth. 1977, 2:1384 - 5.*

75. MATTILA, M. A. K. , ROUPPI, M. , KORHONEN , M. , IAVNI, H.M. , VALTONENT, HEKKINENT: Prevention of diazepam induced Thrombophlebitis with cremophor as a solvent. Bri. J. Anaesth. , 1979 , 51 , 891 - 4.
76. KORTILLAK, AROMAA, U. : Venous complications after I. V. injection of diazepam, flunitrazepam , thiopentone and etomidate. ACTA. Anaesth. Scand. 1980, 24, 227 - 30.
77. M. A. K. MATTILA, and M. SUISTOMAA: Intravenous premedication with diazepam. A comparison between two vehicles. Anaesthesia, 1984, Vol. 39, pages 879 - 882.
78. CLARKE , R. S. J. DUNDEE, J. W. , GARRE, R.T. , McARDLE, G. K. , SUTTON, J. A , : Adverse reactions to intravenous anaesthetics. A survey of 100 reports. Bri. J. Anaesth. 1975, 47 , 575 - 85.
79. DUNDEE, J. W. ^Hypersensitivity to I.V. anaesthetic agents. Bri. J. Anaesth. , 1976, 48 : 57 - 8.
80. R. A. DIXON, N. R. BENNET, M. J. HARRISON, C. KEYTON and J. A. THORNTON: I.V. flunitrazepam and I. V. diazepam in conservative dentistry. A cross-over trial. Bri. J. Anaesth. (1980), 52, 517.
81. JATA, S. , GHOSH: Allergy to diazepam and other benzodiazepines (letter). Bri. Med. J. 2nd April, 1977.
82. ALMEYDA, J. British Journal of Dermatology 1971, 84 , 298.
83. LUTZ, E. G. American Journal of Psychiatry, 1975, 132.