DECLARATION

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

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

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SUM MARY

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 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 (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 Braestrum 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).

Synder 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
laparascopy 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 adrenectomy for phaeochromocytoma. 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 laparascopy 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%), continous 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 continous 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%), laparascopy 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, adrenectomy for phaeochromocytoma and casotid 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 mis 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 Ducailer 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 nasogstric 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, erythemat multiniforme, 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 acide-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 continous 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.
BNZ FACILITATES INHIBITORY ACTION OF GABA

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

The Schematic diagram illustrates the actions of gamma-aminobutyric 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
### SEX DISTRIBUTION OF THE PATIENTS

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases In Anaesthesia</th>
<th>Cases In Intensive care</th>
<th>Total</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>1121</td>
<td>46</td>
<td>1167</td>
<td>85.3</td>
</tr>
<tr>
<td>Males</td>
<td>153</td>
<td>49</td>
<td>202</td>
<td>14.7</td>
</tr>
<tr>
<td>Total</td>
<td>1274</td>
<td>95</td>
<td>1369</td>
<td>100</td>
</tr>
</tbody>
</table>
### DISTRIBUTION OF IN-PATIENTS

<table>
<thead>
<tr>
<th>Unit</th>
<th>Number of Cases</th>
<th>Percentage (%)</th>
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</thead>
<tbody>
<tr>
<td>Gynaecological</td>
<td>736</td>
<td>71.6</td>
</tr>
<tr>
<td>Obstetric</td>
<td>15</td>
<td>1.5</td>
</tr>
<tr>
<td>Cardiovascular General surgical Diagnostic</td>
<td>18 1</td>
<td>17.6</td>
</tr>
<tr>
<td>Intensive Care Unit</td>
<td>95</td>
<td>9.3</td>
</tr>
<tr>
<td>Total</td>
<td>1027</td>
<td>100</td>
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</tbody>
</table>
### DISTRIBUTION OF DAY-CASES

<table>
<thead>
<tr>
<th>Operation</th>
<th>Number of Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Gynaecological</td>
<td>188</td>
<td>55</td>
</tr>
<tr>
<td>Minor Surgical</td>
<td>154</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>342</td>
<td>100</td>
</tr>
</tbody>
</table>
**TABLE 10**

**INDICATIONS FOR THE ADMINISTRATION OF DIAZEPAM IN ANAESTHESIA**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Number of Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication</td>
<td>11</td>
<td>0.86</td>
</tr>
<tr>
<td>Induction of Anaesthesia</td>
<td>88</td>
<td>6.91</td>
</tr>
<tr>
<td>Adjuvant to General Anaesthesia</td>
<td>90</td>
<td>7.06</td>
</tr>
<tr>
<td>Adjuvant to Local Anaesthesia</td>
<td>216</td>
<td>16.96</td>
</tr>
<tr>
<td>Adjuvant to ketamine Anaesthesia</td>
<td>869</td>
<td>68.21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1274</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

* 11 patients received diazepam for both induction of anaesthesia and as an adjuvant to general anaesthesia.
TABLE 10

PARENTERAL/ORAL ADMINISTRATION - PATIENT RELATIONSHIP

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Anaesthesia (Number of Cases)</th>
<th>Intensive Care Unit Number of Cases</th>
<th>Total</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>1274</td>
<td>79</td>
<td>1353</td>
<td>98.8</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>6</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>Oral + Parenteral</td>
<td></td>
<td>10</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>1274</td>
<td>95</td>
<td>1369</td>
<td>100</td>
</tr>
</tbody>
</table>
### INTRAVENOUS (BOLUS/DRIP)/ORAL - PATIENT RELATIONSHIP

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Anaesthesia (Number of Cases)</th>
<th>Intensive Care Unit Number of Cases</th>
<th>Total</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Bolus</td>
<td>1274</td>
<td>49</td>
<td>1323</td>
<td>96.6</td>
</tr>
<tr>
<td>Intravenous Drip</td>
<td></td>
<td>30</td>
<td>30</td>
<td>3.2</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>6</td>
<td>6</td>
<td>0.5</td>
</tr>
<tr>
<td>Intravenous Bolus + Drip + Oral</td>
<td></td>
<td>10</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>1274</td>
<td>95</td>
<td>1369</td>
<td>100</td>
</tr>
<tr>
<td>Form of Administration</td>
<td>Amount of Diazepam given in Gramms for Anaesthesia</td>
<td>Amount of Diazepam given in Gramms for Intensive Care</td>
<td>Total</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>Parenteral</td>
<td>13.1</td>
<td>166.9</td>
<td>180</td>
<td>83.7</td>
</tr>
<tr>
<td>Oral (Tablet)</td>
<td>.</td>
<td>35.1</td>
<td>35.1</td>
<td>16.3</td>
</tr>
<tr>
<td>Total</td>
<td>13.1</td>
<td>202.0</td>
<td>215.1</td>
<td>100</td>
</tr>
</tbody>
</table>
### DISTRIBUTION OF DIAZEPAM IN GRAMMS IN ANAESTHESIA

<table>
<thead>
<tr>
<th>Indication</th>
<th>Amount of Diazepam in Gramms</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication</td>
<td>0.125</td>
<td>1.0</td>
</tr>
<tr>
<td>Induction</td>
<td>1.590</td>
<td>12.1</td>
</tr>
<tr>
<td>Adjuvant to General Anaesthesia</td>
<td>0.985</td>
<td>7.5</td>
</tr>
<tr>
<td>Adjuvant to Local Anaesthesia</td>
<td>2.160</td>
<td>16.5</td>
</tr>
<tr>
<td>Adjuvant to Ketamine Anaesthesia</td>
<td>8.245</td>
<td>62.9</td>
</tr>
<tr>
<td>Total</td>
<td>13.1</td>
<td>100</td>
</tr>
</tbody>
</table>
TABLE 10

DISTRIBUTION OF DIAZEPAM IN GRAMMS IN INTENSIVE CARE

<table>
<thead>
<tr>
<th>Indication</th>
<th>Amount of Diazepam in Gramms</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>8.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Control of muscle rigidity and spasms</td>
<td>187.3</td>
<td>92.8</td>
</tr>
<tr>
<td>Tranquilizer</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Anticonvulsion</td>
<td>6.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>202.0</td>
<td>100</td>
</tr>
</tbody>
</table>
**TABLE 10**

**DISTRIBUTION OF THE MEAN DOSES OF DIAZEPAM IN ANAESTHESIA**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Cases</th>
<th>Amount of Diazepam Administered in Gramms</th>
<th>Mean Value of Diazepam per patient in Mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication</td>
<td>11</td>
<td>125.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Induction</td>
<td>88</td>
<td>1590.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Adjuvant to general Anaesthesia</td>
<td>90</td>
<td>985.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Adjuvant to Local Anaesthesia</td>
<td>216</td>
<td>2160.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Adjuvant to Ketamine Anaesthesia</td>
<td>869</td>
<td>8245.0</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1274</strong></td>
<td><strong>13105.0</strong></td>
<td><strong>60.0</strong></td>
</tr>
</tbody>
</table>
### DISTRIBUTION OF THE MEAN DOSES OF DIAZEPAM IN INTENSIVE CARE THERAPY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Cases</th>
<th>Amount of Diazepam Administered in Gramms</th>
<th>Mean Value of Diazepam per patient in Gramms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>33</td>
<td>8.295</td>
<td>0.25</td>
</tr>
<tr>
<td>Control of muscle rigidity and spasms</td>
<td>40</td>
<td>187.342</td>
<td>4.7</td>
</tr>
<tr>
<td>Tranquilizer</td>
<td>10</td>
<td>0.441</td>
<td>0.04</td>
</tr>
<tr>
<td>Control of Convuls ions</td>
<td>12</td>
<td>5.912</td>
<td>0.49</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>202.0</td>
<td>5.48</td>
</tr>
</tbody>
</table>
FIGURE 3

DISTRIBUTION OF PRE-DETERMINED DOSES OF DIAZEPAM IN ANAESTHESIA

DOSAGE IN MILLIGRAMS
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