Oral Ketamine: A Four-years Experience in a Tumour Clinic in Lusaka Zambia

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Pain management is an important component in cancer management. The administration of painful injections to children in an oncology clinic can create difficulties. This study was undertaken to determine the role of oral ketamine to modify the response to pain.

Between 1996 and 1999, 6324 patients attended a tumour clinic in a developing country teaching hospital. Forty eight children required cytotoxic injections on 103 occasions. These children were subdivided into 3 groups according to the year of attendance: 1996, 1997 and 1998/8. each group was premeded differently. The first group received ketamine 4.5mg/Kg; the second received ketamine 6mg/Kg and the third had ketamine 6mg/Kg with diazepam 0.1mg/Kg. The response to pain in each group was evaluated by using an observer based scoring system. The visual analogue scale was not used.

The study showed that oral ketamine is an effective and safe drug for use in a clinic setting. However, its action was not always predictable due to a number of confounding factors. A phenothiazine should be routinely used in these children to enhance the effectiveness of ketamine and to diminish the likelihood of its well-known side effects. Further studies using less costly lower doses of ketamine is recommended.

Introduction

Children who attend oncology clinics can create difficulties that are not always predictable. A lengthy process of examination, a painful tumour, and the administration of a painful injection aggravate the situation. Analgesics and anxiolytics of adequate potency and of suitable paediatric formulation should be used as premedication in these patients, but such drugs are often in short supply in our Departments. Because of these limitations, alternatives have had to be considered. One such alternative has been ketamine, which was available in our hospital pharmacy. Ketamine is said to be a potent analgesic[1] and may also have pre-emptive analgesic properties and has a "tolerance-protective" effect[2]. It has been used as an analgesic to control chronic ischaemic pain in lower extremity atherosclerosis[3] and to control neutropathic pain[4]. Its use has been reported for change of dressing in a ward settling for burnt child[5].

Ketamine has also been used successfully for treatment of status asthmaticus[6] and if used correctly it does not cause respiratory depression[6]. Furthermore, of particular relevance in cancer therapy, ketamine in combination with an opioid is said to have the potential to reduce the adverse effects of opioids, namely nausea and vomiting[7]; these symptoms also occur with cytotoxic therapy. Ketamine has moreover a liquid formulation and was therefore suitable for oral use.

Not withstanding its psychotomomimetic side effects it continues to be a popular drug; it is easy to use, versatile and safe. This prospective study was undertaken to evaluate the use of oral ketamine as premedication in children attending a Tumour Clinic.

Patients and Methods

The Tumour Clinic in the Department of Surgery, University Teaching Hospital, Lusaka was established

two decades ago. Patients with various attend for counselling, surgery, therapy and long term follow up. The clinic accepts referrals from within and outside the city as well as from our inpatients. Patients are referred from General Surgical and various subspecialty units including Ophthalmology, Otorhinolaryngology, Orodental, paediatric surgery and urology. Occasional consultations were received from the Gynaecology and Paediatric Departments. However, the Paediatric Department had its own Oncology Unit, which deals mainly with haematological malignancies. A few of their patients requiring surgery are occasionally referred to our adult Tumour clinic for management. Some examples of the variety of Paediatric malignancies managed in the Tumour Clinic included retinoblastoma, lymphoma, Burkitt's lymphoma, neuroblastoma, rhabdomyosarcoma and nephroblastoma.

Between the years 1996 and 1999, 6324 patients attended the Tumour Clinic. Of these, forty-eight were children who required cytotoxic injections. Ages ranged two years to fourteen years. Children who came to the clinic but did not receive injections have been excluded from this study. All patients were weighed on arrival at the clinic by the nursing stuff. Drug dosage was calculated according to the weight of the patient, surface area was not used. The author prior to receiving premedication saw all patients. Children who were due to receive parenteral cytotoxics were premedicated half to three quarters of an hour before the injection. In the years 1996

Table 1

Year	Number Of patients	Age in Years	Gender	Weight Kg (Average)	Ketamine Average Dose (mg)	Diazepam Average Dose (Mg)	Dosage
1996	37	-	-	17	77.3	-	Ketamine 4.5mg/Kg
1997	39	5.4	F=15 M=24	19.4 (38 Patients)	120	-	Ketamine 6mg/Kg
1998/9	32	6.8	F=10 M=22	20.5	123.5	2	Ketamine (6mg/Kg) Diazepam (0.1mg/Kg)

Table 2

Year	Awake	Sleep/ Drowsy	Crying With Inj.	Crying All the Time	Disturbed	Comments
1996 Ketamine 4.5mg/Kg	17	7	* 12 #	-	1	* 2 incidences reported in same pt. # 2 incidences reported in same pt. (Different categories)
1997 Ketamine 6mg/kg	6	18	* * 10 #	3 #		*4 separate incidents in one patient. *2 separate incidents in one patient. # 2 different Categories in one Other patient. (Separate occasions)
1998 Ketamine 6mg/Kg + Diazepam 0.1mg/Kg	7	15	* * 9 #	1 #	-	*2 separate incidents in one patient. *2 children received half the dose prescribed. # 2 different categories in one other patient. (Separate occasions)

Table 3. M.K. file No. 63749, 7 years, Female.

Weight	Dose in Mgs	Dose in mls	Response
21	94.5 mg	2 ml	Drowsy
23	103.5 mg	2 ml	Awake
20.3	91.3 mg	2 ml	Awake / crying with injection
24	108.0 mg	2 ml	Awake
23.8	107.1 mg	2 ml	Crying with injection
23	103.5 mg	2 ml	Awake
24	144.0 mg	3 ml	Drowsy, asleep
21	126.0 mg	3 ml	Drowsy, asleep
22	132.0 mg	3 ml	Crying with injection
24	144.0 mg	3 ml	Crying all the time

and 1997, the premedication consisted of ketamine only. In1998 and 1999, diazepam was added. This step was taken with the expectation that it would control the well-known occasional troublesome side effects of ketamine [8]. After the premedication had been given, the junior doctor in the clinic gave the cytotoxic injection and the clinic nurse recorded the child's response in a register. The register was also used to record details such as the name of the child, the weight and drug dosage. Age and gender details were recorded from 1997 onwards.

The visual analogue scale[9] which is commonly used for assessing pain in adults was not used in this study. Instead, a pain scoring system based on an observer was devised which was considered to be more suitable for the unique conditions of our Tumour Clinic. This pain scoring system was documented in the register, which became known as the Ketamine Book. These details are seen in table 2.

The injections were given by a junior doctor in a separate area of the Tumour clinic out of sight of the consultant. And in order to avoid bias, the response to the injection was recorded by the tumour clinic nurse without the supervision of the consultant who prescribed the drugs.

Results.

Forty-eight children were given intravenous cytotoxic drugs on 103 occasions. The data collected on these patients is tabulated in tables 1 and 2. What is not obvious in these figures is the number of instances where the "Crying" category (Table 2) showed spuriously high numbers because the same patient on different visits had an unchanged response. An example is a child that in 1997, during four visits to the Tumour clinic, had on all four occasions an unfavourable outcome; and at each visit was therefore correctly categorized as "crying with injections". Thus the numbers in that category appear to be high.

Table III shows that the response to the drug was not always predictable in the individual patient. It is possible that a number of factors such as the clinic environment, minor errors in dosage and weighing could have accounted for these differences. Another possibility is that there may be predetermined, perhaps tumour related individual differences or pain threshold differences in patients, to explain the unpredictable[6] manner in which some patients responded to ketamine.

There were no serious complications noted during the four-year study period. In particular there were no episodes recorded in the register or patient's file, of respiratory depression or vomiting following successful swallowing of the drug.

Discussion

Ketamine has been in clinical use for 34 years. It is an anaesthetic agent, but in sub anaesthetic doses it can act as an analgesic[6]. It was popular in paediatric anaesthesia in the seventies[10] and remains so in our own institution currently. It has been used parenterally as an adjuvant to local anaesthesia in an office operating room by a surgeon and his nurse assistants[11]. It has also been used parenterally by a General Practitioner as an analgesic and even as an anaesthetic agent in the pre-hospital environment[12].

The drug has been administered by various routes including intramuscularly, intravenously, intrathecally[6], extradurally[6], and in trials, intraperitoneally[13]. There is paucity of information

on the oral route of administration of this drug. To the best knowledge of the author, the first Reference that appeared on this subject was in the form of a letter published in 1983[5].

An Editorial in the British Journal of Anaesthesia discussed the action and unusual clinical uses of Ketamine but made no mention of oral administration of this drug in clinical practice[6].

In keeping with all psychotropic drugs there is the danger of potential misuse of Ketamine[14] but such morbidity was not encountered in our Tumour clinic patients.

The response to pain in an adult can be evaluated using a Visual Analogues Scale[9]. However, this method would have been unsuitable in a young child attending our cancer clinic. A frightened uncooperative young child is not in a position to complete a scale, which is incomprehensible at that age. Furthermore, the child's mother tongue was often different from the commonly spoken language, and this created difficulties in communication. For the aforementioned reasons a different pain scale had to be devised. The scale had to be simple to document, easily understood by the nursing staff, and relatively objective in its evaluation. The pain scoring system used in this study appears to have achieved these aims.

There were a number of unforeseen problems observed as the study progressed. The apparently unpalatable nature of the drug on occasion caused the child not to swallow the medication. This however, was a rare occurrence, which did not influence the overall conclusions of the study. Psychotropic symptoms including perceptual and cognitive disturbances are well known side effects if ketamine[3] and were occasionally noted in some children. These tended to occur during the recovery phase in the crowded and busy clinic, an area where it was not always possible to offer a quiet and calm environment. Some of the more overt psychotomimetic manifestations took the form of excessive vocalisation and purposeless movements. Nonetheless, if by error such a possibility was documented, it is unlikely to have influenced the results significantly, as only 3 out of the 103 results were categorized as disturbed.

An appropriate paediatric weighing machine was not available and the accuracy of the clinic weighing machine varied and it required calibration on a number of occasions. The practice of weighing a very sick clothed child in the mother's arms followed by the subtracting of the mother's weight from the combined figures, further increased the likelihood f inaccuracies.

The drug dosage was written in milligrams and needed conversion to millilitres in order to draw the appropriate volume from the 50mg/ml ketamine vial. The busy nurse dealing with the subdivisions of a millilitre in the two ml or five ml syringe could have introduced minor errors during the collection (See Table III). Thus, the reason for the dosages being rounded off to the nearest millilitre (See Table IV).

Recommendations

In contrast to adults, ketamine induced psychotropic side effects are said to be less likely in young children. Nevertheless, this study suggests that a sedative should be routinely given to these children preferably before arrival to the clinic. The ketamine however will need to be given in the clinic to permit observation. Nursing staff should be familiarise themselves with the various concentrations of ketamine which are marketed by the manufacturers and should be also standardise the two or five ml syringes to avoid errors in converting the milligrams to millilitres. A calibrated pipette would be simpler and a more suitable alternative. The diazepam should have the manufacturer's liquid formulation. The ketamine should be diluted with milk or a soft drink to improve palatability. Following the administration the child should rest in a quiet place in the clinic and at least half an hour should elapse before the cytotoxic drugs are injected.

Further studies are required to determine if the lower dose of 1 mg/kg ketamine[5,8] given orally would be as efficacious as 6 mg/kg when administered with diazepam. Such an aim would be worthwhile, as a lower dose of ketamine is said to be less likely to produce undesirable side effects[2] and would be less costly over the long term. In 1996 a 10 ml vial of ketamine at the concentration of 50 mg/ml cost pond sterling 7.31[15].

To optimise the future role of premedication in cancer patients who attend similar oncology clinics, research should include not only ketamine but also other compounds[8]. The aim should be to find a drug, or a combination of drugs, which has a wide safety margin and which can be used in the unique environment of a developing country hospital oncology clinic. The drug(s) should offer analgesia, sedation and amnesia, and should have antisialogogue and antiemetic properties without over

Sedation or respiratory depression. Such drugs should be in a liquid form, palatable, not costly and

easily procured in the developing world hospital pharmacy. In the absence of a single drug with such a wide spectrum of activity, a Tumour Clinic such as ours will need to continue to use sedatives such as largactil or diazepam[16] combined with the non-opioid analgesic ketamine. The alternative is to oral pethidine or oral morphine[16], which currently are not available.

The role of local anaesthetic gels for desensitising venepuncture sites in children is limited at it does not address the overall management of these patients. Such tropical analgesics are currently not available in our hospital but could be included in future studies.

The drawbacks of using ketamine which became apparent as the study progressed can be addressed by the introducing greater attention to the accuracy and logistics of its administration; by pre-emptive dosing with a phenothiazine or similar drug; and recommending to the manufacturers to market a liquid oral formulation.

The study has shown that ketamine can be given orally and has been safely used in a Tumour Clinic. Side effects to oral ketamine appear to be less likely if it is administered with a phenothiazine[3,8] .

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