

Seminars on Controversial Issues

Introduction

As promised in our last issue, we present here the first in what is intended to be an occasional series of seminars on controversial issues. It is intended that each should have a central paper or papers and a series of shorter invited commentaries that add to the theme. This first one addresses the subject of sedation. The central paper is a short review written by authors in Nigeria. The short commentaries from Sweden and from Israel taken together with the UK National Clinical Guidelines that are also published here are published with the intention of improving understanding of how sedation is currently used in different parts of the world. Sedation is used in many countries and the editor would welcome correspondence and papers for publication that would add to debate on this important topic.

A review of the pharmacological approach to the management of dental anxiety in children

M. O. FOLAYAN¹, A. FAPONLE² & A. LAMIKANRA³

¹*Department of Preventive Dentistry, ²Department of Anaesthesia, and ³Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria*

Summary. This paper aims to review the existing literature on the pharmacology of a number of sedative drugs used in the management of dental anxiety in the conscious child patient. Pharmacological agents may be used as a complement to behavioural techniques to assist in the management of anxiety in some paediatric dental patients. Their use may also be especially indicated in children with disabilities. These agents are usually sedative in action and do not, in themselves, eliminate anxiety but merely enhance patient acceptance by reducing arousal and modifying anticipation of danger. The agents used are varied and diverse and include nitrous oxide, benzodiazepines and narcotics. Nitrous oxide has proved to be of particular value but carries a degree of risk for the operating staff. Amongst the benzodiazepines, Midazolam has been used more frequently in recent years. It may be given by a variety of routes, including intra-nasally. Dentists who employ sedative agents and techniques should be familiar with the pharmacology of the agents selected, be cognisant of the risks and benefits of the technique employed and be able to manage any adverse events that may arise through their use.

Introduction

Methods adopted by dentists to manage dental anxiety are primarily aimed at avoiding unpleasant

and unproductive confrontations with the child. The intention is to create an environment that will facilitate development of the child's confidence and allow the dentist to carry out procedures with minimal disruption. Ideally, behavioural management techniques should be used alone to achieve treatment goals and to guide the child to develop more appropriate behaviour, but this is not always possible. This may

Correspondence: Dr M. O. Folayan, Department of Preventive Dentistry, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria. E-mail: mukpong2@yahoo.com

be especially true when managing children who are particularly fearful or anxious or for whom a disability prevents their being able to co-operate. Either conscious sedation or pre-medication with pharmacological agents is often recommended when such children need dental treatment [1].

There appears to be no consensus amongst paediatric dentists as to when behavioural techniques alone are no longer sufficient [2]. The child's level of resistance, the extensiveness of treatment required and the proficiency and experience of the clinicians carrying out treatment are all known to play a role in determining the need for sedation. It is important for the dentist however, to be aware of these considerations before employing any form of sedation, as the agents and techniques available do not eliminate anxiety but merely enhance patient acceptance by reducing arousal and modifying anticipation of danger. Sedation only short circuits the occurrence of non-coping behaviour [2,3]. Thus, sedation is advised only when behavioural strategies alone have failed or are contra-indicated. Techniques and agents vary and dentists who employ them should be familiar with the pharmacology of the agents selected, be cognisant of the risks and benefits of the technique employed, and be able to manage any adverse events that may arise as a result of their use [4]. This paper aims to review, from previously published literature, some of the drugs currently used in conscious sedation for the management of dental anxiety in the child patient and outline their advantages and disadvantages.

Sedation techniques

Sedation, simply defined, is the production of a depressed state involving a lack of total consciousness but short of anaesthetic sleep [5]. In sedation, the protective pharyngeal and laryngeal reflexes are not dulled, so the patient can maintain his or her own airway. In this sedated state, the functional activity of the higher centres of the central nervous system is reduced without distortion of the vital functions.

In dentistry, the objective of sedative management is often to achieve mild to moderate levels of sedation. Pain relief is not a major goal, rather, the sedation is used as an adjunctive means of controlling the psychological component of discomfort and resistance to treatment [5]. Sedation becomes optimally effective only when there is some rapport between the dentist and patient.

The ideal sedative produces somnolence with euphoria and muscular relaxation, but not anaesthetic sleep [5]. The agents used should be rapidly and reliably effective with absorption and uptake fast enough to allow treatment to begin within a very short time of administration. It should have an adequate duration of effect as well as rapid recovery. This means that the reflexes should return quickly enough to obviate the need for prolonged professionally supervised recovery (as with general anaesthesia) and allow discharge from the office in the company of a reasonable adult soon after completion of treatment. In addition, an ideal agent would have pharmacokinetics with minimal physiological effects, a high degree of specificity and a high therapeutic safety margin [6]. It is important that agents used are not only sedative but also anxiolytic, as anxiety tends to reduce the pain threshold. Ideally, a sedative drug should also produce amnesia. For practical and planning purposes cost benefit would also be a consideration if an agent or technique is to be widely used, although this is not a pharmacological characteristic.

In discussing the various pharmacological agents used for sedative management in dentistry, it will become apparent that none of the agents and techniques presently in use possess all of these ideal attributes.

Pharmacological agents used

Many drugs are available for use as sedatives. Apart from the inhalational agent, nitrous oxide, all others are suitable for oral, intra-muscular, rectal and intra-vascular administration; each of which routes has indications and limitations. Drugs can be administered via these routes either singly or in combination.

Nitrous oxide

Nitrous oxide, which is widely used in general anaesthesia, is also a popular gaseous sedative agent used to produce moderate sedation. Its effects on dental anxiety have been studied by several authors [7–10]. Nitrous oxide has analgesic, sedative and hypnotic properties [11]. One major advantage of the agent is the lack of prolonged effects after the treatment session. Its other advantages includes its wide range of safety for the patient, rapid onset of action and rapid elimination. Also, it does not significantly impair higher cognitive tasks and thus

patients who have had treatment with nitrous oxide sedation are able to resume normal activities in the immediate postoperative period [12].

The value of nitrous oxide can be enhanced by using it primarily as an adjunct to other forms of sedation. When initial doses of non-titratable agents fail to produce adequate sedation, its use may be preferable to administering additional doses of medication [2]. It can also be used as an adjunct at the end stage of a treatment procedure to prolong the working time available so that treatment can be completed before the effects of oral or parenteral medications wear off [2,8,13,14]. However, some studies have reported haemoglobin desaturation when nitrous oxide was used in combination with sedatives. This complication is of importance in children because of their reduced body size, decreased oxygen reserve, higher basal oxygen consumption and lower residual lung capacity when compared to adults [15].

Its use as an analgesic and sedative agent is limited to patients with mild to moderate levels of anxiety for nitrous oxide but does not work well in highly anxious patients [8]. Nitrous oxide is administered in varying concentrations up to a level where the child becomes sedated, but with an upper limit of 40% to 50%.

Nitrous oxide has the disadvantage that it may give rise to haematological and reproductive difficulties in dental surgery staff [16,17]. Effective scavenging systems are essential and staff should not be exposed to nitrous oxide for prolonged periods [18].

Tranquillizers

Many tranquillizers can be used effectively to produce light sedation for dental patients. Promethazine is one example. The drug affects behaviour and the autonomous nervous system. Phenothiazine is least likely to produce untoward effects although even when these occur they are less severe than the effects produced by other agents [5]. Phenothiazine is antihistaminic (making it a good choice for atopic patients), and antiemetic (good choice for use with nitrous oxide). Less favourably, the drug is also capable of producing an extrapyramidal reaction complicated by restlessness, tendon movement, muscle spasm, anxiety and/or sweating. These effects are however, rarely seen after a single dose. Phenothiazine is usually given orally.

Benzodiazepines are a particular group of tranquilizers. They function by binding with benzodiazepine receptors thereby activating GABA (gamma aminobutyric acid), an inhibitory CNS transmitter. Activation of the GABA receptor sites allows for the rapid entry of the chloride ion into the neurone resulting in a hyperpolarization with an inhibition or attenuation of the nerve impulse [19].

A large number of drugs classified in this group can be used effectively to produce sedative hypnotic effects for dental treatment. As well as acting as sedatives, benzodiazepines produce mild muscle relaxation and have anticonvulsant properties. These agents also produce dose related anterograde amnesia as a result of effects on the early phase of memory processing [19,20]. Amnesia does not result however, when benzodiazepines are given as a single dose [21,22]. One such agent is diazepam, a drug that is relatively lipid soluble and water insoluble. Given intramuscularly, its absorption is however, slow, erratic and incomplete [6] and it should therefore only be administered orally, rectally or by the intravascular route. Diazepam is available for intravascular administration as an emulsion in soya bean oil (Diazemols) or as a viscous solution containing organic solvents (propylene glycol, ethanol and sodium benzoate in benzoic acid); both preparations contain 5 mg/mL diazepam. When taken orally, its availability is 100%.

Diazepam is effective within 30–45 min of oral administration and has a duration of action of at least 4–6 h. However, when administered in the dental clinic prior to treatment, it may take up to 60 min before sedation is effected and with low doses, fear and tension may not be abated [20–22]. Diazepam induces sedation within 1–2 min after bolus intravenous administration but it has a long elimination half-life (20–90 h). This results partly from enterohepatic recirculation. In addition, one of its metabolites, N-desmethyl diazepam is pharmacologically active and has a long half-life. It thus takes a long while for full alertness to be recovered following drug administration.

Randall [26] as well as Gallardo *et al.* [24] reported negative results with 5 mg dose of oral diazepam. Yanase [25] however, reported that a dose of 0.3 mg/kg body weight diazepam would induce a sedative level 30 min after administration with the deepest sedative effects occurring after 60–90 min. Oral diazepam could be administered at home to fearful child patients prior to dental treatment [28].

This would allow the deepest sedative effect to be attained by the time of treatment and the accumulated anxiety-inducing effect of having to wait in the clinic for the drug to take effect would be eliminated. Diazepam is known to make some children excitable, so its effects are not entirely predictable [29]. However, despite its disadvantages, this agent has a wide safety margin with relatively few side-effects [26].

Midazolam, a water soluble imidazobenzodiazepine derivative, has almost replaced diazepam as an intravascular sedative. It is commonly available as both 2 mL ampoules containing 5 mg/mL and 5 mL ampoules containing 2 mg/mL [6]. It has a slightly more rapid onset of action than diazepam after intravenous injection because of its lipid solubility at physiological PH and is therefore able to cross the blood-brain-barrier with relative ease. It also has a stable sedative effect and minimal residual effects [30,31]. It has a shorter duration of action, with an elimination half-life of 1.5–2.5 h because its metabolites are inactive.

It can be administered via the oral, intra-muscular, intravenous, nasal, sublingual or rectal routes. However, because of its rapid hepatic clearance, the nasal, intra-muscular and intravenous routes of administrations ensure higher systemic availability than the other routes [33]. Although, the nasal route is known to cause a burning sensation in the nasal mucosa and is less well tolerated by children [33], it is still less traumatic than the intra-muscular or intravenous routes. It also has the advantage of rapid absorption directly into the systemic circulation from an area rich in blood supply without the disadvantage of passing through the portal circulation [34]. The sedative effect when given intra-nasally appears within 5–10 min, with a stable level attained by 10 min, compared to the 30 min which occurs with the oral, rectal or intra-muscular routes [35]. For these reasons, the nasal route has been suggested as the administration route of choice [32,36]. It may however, only be tolerated where one is able to get close to a child and successfully and safely administer it into the nose. This can be difficult to achieve clinically and a nasal insufflator may prove invaluable.

Midazolam is available as a tablet, lolly or syrup for oral use and as a lozenge for sublingual use. In addition to the other disadvantages associated with use of drugs orally, oral and sublingual routes, like the nasal route, also require the child's cooperation.

Its use and dose control may be difficult as the child may spit or regurgitate the oral medication because of its bitter taste [37], which is a result of the acid base of the drug [6]. In a bid to promote the oral use of this drug, efforts have been made to mask the bitter taste, leading to the production of formulations of different flavours although the taste is still difficult to mask. There is still a generally low acceptance of the oral route as an alternative route of administration for midazolam despite its potential advantages over the more common and more invasive intravenous route. This may be due to its presently low commercial availability.

The rectal route also has disadvantages. This includes interruption of absorption by defecation and the lack of patients' (and parents') acceptance [37].

The recommended dosage varies for each route of administration. Intravenous administration is carried out at 0.25–1.5 µg/kg/min in children. It must be administered slowly. However, the onset of its clinical effect may be delayed and there is the danger of overdose if the drug is given rapidly without waiting to assess its effects [6]. There have been reports of respiratory depression [6] (sometimes associated with severe hypotension [6]) following intravenous administration. For intra-nasal midazolam use, the optimum concentration is 0.2 mg/kg body weight [35,37–39]. Oral dose concentration usually has to be twice as high as the equivalent intravenous dose to achieve a comparable effect because of its first-pass hepatic extraction [6].

Paradoxical reactions of midazolam have been recorded in children, and this is a major drawback. These include hallucinations, agitation, inconsolable crying, restlessness and disorientation. A minority of patients using diazepam also manifest these reactions. The incidence of these reactions in association with midazolam use is however, low [40]. Massanari *et al.* [40] recorded an incidence of only 1.4% over a four year study period. When they do occur, the reactions can be reversed through the use of Flumazenil [40–42].

Narcotics

In addition to being anxiolytic, narcotics also have analgesic properties through depression of the cerebral response to pain. They also produce euphoria and deep sedation. Different preparations are available which are effective as intravenous sedative and analgesic for outpatient dentistry. However, these

agents often need to be used in combination with another drug to potentiate their action.

One narcotic agent used in dentistry is ketamine, a phencyclidine derivative. Ketamine may be used in combination with a benzodiazepine such as midazolam to achieve sedation for a painful procedure. This is believed to be a safe, effective and cost effective technique that may be used as an alternative to general anaesthesia for children requiring minor dental procedures under local anaesthesia. Ketamine inhibits pain by interrupting nerve pathways connecting different cortical areas within the thalamo-neocortical system causing disorganized neural transmission [43]. It inhibits re-uptake of catecholamines and can thus produce a mild to moderate increase in blood pressure, heart rate and cardiac output [44]. This latter effect is less noticeable in children than in adults [45]. Ketamine also stimulates salivary and tracheobronchial secretions and concurrent administration of an anticholinergic drug is therefore recommended [46]. Even without these however, the risk of aspiration after administration is minimal probably because of the preservation of laryngeal reflexes.

A further disadvantage is that ketamine tends to cause perceptual and psychic disturbances in a dose-related manner [47,48]. Irrespective of its disadvantages, the use of ketamine in combination with midazolam seems appropriate because of the following:

- 1 Both drugs have sedative and amnesic properties
- 2 Ketamine adds an analgesic component
- 3 Midazolam counteracts the psychic side-effects of ketamine and
- 4 Ketamine counteracts the depressive effect of midazolam (which is the reduction of average blood oxygen level) on vital body function [49].

Ketamine is extremely lipid soluble. After intravenous injection, it induces deep sedation bordering on anaesthesia within 30–60 s, which lasts for 10–15 min. After intramuscular injection, the agent is effective within 3–4 min with a duration of 15–25 min. It is administered slowly at a dose of 2 mg/kg when given intravenously. Used in this way, ketamine has proved to be very useful in developing countries where anaesthetic equipment and trained staff are in short supply [50,51].

In all circumstances however, it is important to monitor for unwanted cardiovascular and respiratory side-effects of this drug as respiratory depression and oxygen desaturation may occur. This is because of the difficulty in titrating doses effectively to

provide a satisfactory level of sedation without tilting the patient into deeper levels of sedation and general anaesthesia.

Another narcotic agent used in sedation is meperidine. This drug induces deep sedation although its duration of action is short and the patient can usually be easily aroused. Absorption is rapid following either oral or parenteral administration. The liver metabolizes 90% of the drug and the rest is excreted in urine along with degradation products [5].

Tolerance, habituation and addiction are uncommon following the use of narcotics in sedative management as a consequence of the limited maintenance dose used [5]. Respiratory depression often occurs if the recommended clinical dose is exceeded, and especially following intravenous administration. Use of narcotic agents in outpatient dental practice is often limited because of the need for an anaesthetist to administer the agent(s) and monitor the patient.

Other pharmacological agents

Other pharmacological agents used in the past which are though no longer popular, include Chloral hydrate, an agent which is an oral sedative. The adverse effects of Chloral hydrate now makes it very unpopular. These include excessive central nervous system depression, gastrointestinal disturbances, central nervous system excitation, cutaneous reactions [52] and, when it is used in high doses, cardiac dysrhythmias [53]. Comparative studies with midazolam, a more readily available anxiolytic agent with fewer side-effects, have shown an increased level of sedation prior to the administration of local anaesthetic in patients compared with those given chloral hydrate [54].

Another intravenous agent used in the past was Propofol, a 2,6-diisopropylphenol, which has a good sedative effect together with additional antiemetic properties and a short recovery time of approximately 15 min [6]. It is only slightly soluble in water and is formulated for clinical use in a soya bean oil-egg yolk-lecithin emulsion [6]. An intravenous dose of 2–2.5 mg/kg produces loss of consciousness in less than a minute [6] which lasts for approximately 5 min. However, when propofol infusion is used along with Diprifuor (Zeneca Pharma, Wilmslow, UK), a sedative rather than a general anaesthetic state may be achieved and maintained. Its hypotensive effects and the systemic

bacteraemia that has been associated with its use have made it unpopular, especially as a sedative agent [19].

Conclusion

Although use of pharmacological agents in the management of a dentally anxious child may help to achieve the treatment plan, the overall goal of the dentist should be to help the child to be comfortable and happy in the dental environment. The dental surgery and the methods of management used should be designed to this end so that the child willingly returns to the clinic for regular check ups throughout the childhood years and into adult life with no reluctance. Wherever possible, in the longer term, this should entail helping all patients to receive any necessary treatment on subsequent dental visits without sedation and by using behavioural management strategies alone. Pharmacological approaches should never be seen as an alternative way to manage the uncooperative child patient because of time constraint on the part of the dentist and should only be employed when absolutely indicated. Only then can the risk of complications associated with drug use be justified. Finally, whatever the drug of choice, the goal of sedative management should be the amelioration of mild to moderate anxiety. Where the patient is extremely agitated and/or simply unable to offer the necessary co-operation for administration of a sedative agent, general anaesthesia may be indicated.

Résumé. Cet article a pour objectif de passer en revue la littérature existant sur la pharmacologie de certaines substances de sédation consciente utilisées dans la gestion de l'anxiété dentaire chez l'enfant. Les agents pharmacologiques peuvent être utilisés en complément de techniques comportementales pour aider à la prise en charge de l'anxiété chez certains jeunes patients. Leur utilisation peut également être particulièrement indiquée chez les enfants présentant des déficiences. Ces agents ont habituellement une action sédative, et n'éliminent pas par eux-mêmes l'anxiété. Ils améliorent l'acceptation par le patient en réduisant l'attention suspicieuse et modifiant l'anticipation du danger. Les agents utilisés sont variés et divers et comprennent le protoxyde d'azote, les benzodiazépines et les narcotiques. L'efficacité du protoxyde d'azote est reconnue, mais présente un certain niveau de risque pour l'équipe soignante.

Parmi les benzodiazépines, le midazolam a été plus utilisé ces dernières années. Il peut être administré par différentes voies, incluant la voie nasale. Les dentistes employant des agents et techniques de sédation devraient connaître la pharmacologie des agents retenus, les risques et avantages des techniques employées, et être capables de gérer tout événement indésirable en rapport avec leur utilisation.

Zusammenfassung. Ziel dieser Arbeit ist es, eine Übersicht über die Literatur zum Thema der Pharmakologie einer Reihe von sedierenden Arzneimitteln für die Prämedikation ängstlicher Kinder bei der Zahnbehandlung zu vermitteln. Pharmakologische Substanzen können bei manchen Patienten dazu benutzt werden, um verhaltenstherapeutische Techniken im Management von Behandlungsangst zu ergänzen. Sie können insbesondere indiziert sein bei Kindern mit Behinderungen. Meist sind die verwendeten Substanzen weniger anxiolytisch als sedierend, erhöhen aber indirekt die Kooperation durch Dämpfung von Aufgeregtheit und Modifikation der Gefahreinschätzung. Die Substanzen sind vielfältig und unterschiedlich, sie schließen u.a. ein: Lachgas, Benzodiazepine, Narkotika. Lachgas hat sich bewährt, es besteht allerdings ein gewisses Risiko für die an der Behandlung beteiligten Personen. Unter den Benzodiazepinen hat Midazolam in den letzten Jahren eine zunehmende Verbreitung erfahren. Es existieren verschiedene Darreichungsformen, unter anderem auch die intranasale Applikation. Zahnärzte, die Prämedikation einsetzen, sollten vertraut sein mit der Pharmakologie der ausgewählten Medikamente, sie sollten Nutzen und Risiken der eingesetzten Techniken kennen und in der Lage sein, eventuelle unerwünschte Reaktionen zu beherrschen.

Resumen. Este artículo tiene el objetivo de revisar la literatura existente sobre la farmacología de una serie de medicamentos que causan sedación consciente, usados en el manejo de la ansiedad dental en el paciente infantil. Los agentes farmacológicos pueden usarse como un complemento de las técnicas de conducta para ayudar en el tratamiento de la ansiedad de algunos pacientes odontopediátricos. Su uso puede estar también especialmente indicado en niños con discapacidades. Estos agentes generalmente tienen efecto sedante y no eliminan la ansiedad en si mismos, simplemente mejoran la aceptación del paciente, reduciendo el dintel y modificando la anticipación de peligro. Los agentes usados son

varios y diversos e incluyen óxido nítrico, benzodiazepinas y narcóticos. El óxido nítrico ha demostrado ser especialmente valioso pero conlleva un cierto grado de riesgo para el equipo de trabajo. De entre las benzodiazepinas, recientemente el midazolam se ha venido usando con más frecuencia. Puede ser administrado por varias vías, incluyendo la intranasal. Los odontólogos que emplean agentes y técnicas de sedación deberían familiarizarse con la farmacología de los agentes seleccionados, ser conscientes de los riesgos y beneficios de la técnica empleada y ser capaces de tratar cualquier efecto adverso que pueda producirse con su uso.

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