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Midazolam as an anti-emetic

F. RODOLÀ

Istituto di Anestesiologia e Rianimazione, Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore – Rome (Italy)

Abstract. – Benzodiazepines have been involved during the years in the prevention and treatment of Post-Operative Nausea and Vomiting (PONV).

Midazolam, a short acting benzodiazepine widely used as a premedicant before surgery, for induction of anaesthesia, and for conscious sedation, has been particularly studied, sometimes with conflicting results.

This paper will discuss the possible mechanisms of action of midazolam in PONV management and its fields of application (adults and children undergoing surgery, treatment of persistent postoperative emesis), as far as potentialities of other non-traditional anti-emetics, maybe ready to get out the arena of case reports, and the need of further studies on postoperative anti-emetics in their efficacy in treating established PONV.

Key Words:

Benzodiazepines, Midazolam, Post-Operative Nausea and Vomiting (PONV), Anti-emetics.

Introduction

Post-Operative Nausea and Vomiting (PONV), well defined by Knapp and Beecher[1] since 1956, is an undesired and unpleasant side effect of anaesthesia, both general and regional. Although it may induce serious complications[2], it is most often a minor problem after surgery: it does not become chronic, and almost never kills; however, it may be very distressing for patients[3]. A great variety of drugs with different mechanisms of action, used alone or in combination, more or less expensive, have been used through the years with the intent to prevent and treat it. Nevertheless, its incidence seems to remain quite constant: according to Kovac[4] up to 20-30% of patients undergoing general anaesthesia still experience PONV, despite all prophylactic measures.

Benzodiazepines have been involved during the years in the prevention and/or treatment of PONV: e.g., lorazepam proved an anti-emetic effect in younger patients after strabismus surgery[5], as, more recently, diazepam-atropine sulfate premedication[6].

Midazolam has been studied in the last 15-20 years both for prevention and, less frequently, for treatment of established and persistent PONV, sometimes with conflicting results.

Aim of this paper is to shortly report the last researches on this subject, discussing possible mechanisms of the anti-emetic effect of midazolam, its fields of application, and controversy on its use in preventing and treating PONV.

Midazolam

Midazolam hydrochloride is a short-acting benzodiazepine CNS depressant. It may be administered before surgery as a premedicant to relieve apprehension and impair memory, for induction of anaesthesia (although in comparison with barbiturates its use is associated with a slower onset of action and a more prolonged recovery time), and for conscious sedation[7].

Midazolam may be administered by mouth, parenterally, or via the intranasal or endorectal route in children; preservative free intrathecal midazolam has been used for postoperative analgesia in caesarean section delivery[8].

It has been postulated that a possible mechanism for the anti-emetic effect of benzodiazepines could be an action at the chemoreceptor trigger zone reducing synthesis, release and postsynaptic effect of dopamine[9]. Whether benzodiazepines reduce dopamine release centrally, or by blocking the re-uptake of adenosine, causing an adenosine-mediated reduction of dopamine release, has been matter of debate[10-14].

Corresponding Author: Ferdinando Rodolà, MD; e-mail: rodofam81@hotmail.com

Dopaminergic neuronal activity and 5-hydroxytryptamine release may also be reduced by binding of midazolam to the GABA benzodiazepine complex[9,12,15]: thus, anxiolysis as a secondary effect may also contribute to antiemesis. However, Wang and Klein[16], in a cross-sectional study exploring a possible association between preoperative anxiety and PONV in a group of children undergoing outpatient surgery did not find any predictive value of children's anxiety for the occurrence of PONV.

Midazolam in preventing and treating PONV

Midazolam has been used as an anti-emetic in adults and children, both as a preventive medicine and a rescue medication. Up to the turn of century almost only case reports have been published, but in the last few years the first randomised controlled studies started to appear, although dosage, route and modality of administration are still far to be standardized, and almost every group of Authors used midazolam in a different way.

Adult Surgical Population

Studies reporting postoperative emetic symptoms in adults have been performed in various surgical settings. Midazolam has been used for monitored sedation in adult patients scheduled for central venous access[17], for breast biopsy[18], for plastic surgery under high-volume tumescent local anaesthesia[19] or other kind of local anaesthesia[20]. All but one of these studies[20] were not specifically designed to investigate PONV occurrence, and reported it at a variable rate, whereas more specific comparative, prospective and controlled investigations on anti-emetic effect of midazolam have been recently carried out in patients undergoing general anaesthesia.

Midazolam has been used for premedication in patients undergoing orthopaedic[21], outpatient[22] and abdominal surgery[23], and as a preventive drug instituted as a continuous infusion after tracheal extubation in patients undergoing cardiac surgery involving cardiopulmonary bypass[24]. Its effectiveness for the treatment of established PONV has been studied in gynaecological and abdominal surgery[25].

All but one of these studies[21] showed at least the same beneficial effect of midazolam on PONV if compared with other premedicants, traditional anti-emetic medications, or placebo; the institution of a continuous infusion of midazolam after cardiac surgery[24] has been found to be more effective than the administration of ondansetron by I.V. boluses.

Paediatric Surgery

Midazolam has been studied as an anti-emetic mostly in small patients undergoing strabismus surgery[26] or ear-nose-throat (ENT) operations: actually, it is reported that up to 80% of children not receiving an anti-emetic and undergoing adenotonsillectomy may suffer PONV[27,28]. Avoiding intra- and peri-operative emetic agents as nitrous oxide and morphine based opioids[29], using non-steroidal anti-inflammatory drugs (NSAIDs) or codeine as premedicants[30], and administering systematically anti-emetics[31] may reduce PONV rate down to less than 20%.

Safety and effectiveness of midazolam as oral premedication, after assessment of sedation, quality of induction and effects on gastric contents (residual volume and pH) have been demonstrated by Riva et al[32]; nevertheless, papers investigating its ability in preventing PONV, even when not specifically designed, report conflicting results.

Splinter et al[33] found a lower incidence of PONV than a placebo group: 42% vs 57%, still a quite high rate, but used for anaesthesia nitrous oxide and halothane, both known to be emetic.

Zedie et al[34] used the same kind of anaesthesia for paediatric outpatient surgery, but reported a very low 6% of PONV. The Bergendahl group[35] did not find, in a prospective, randomized, controlled clinical trial in children undergoing ENT surgery any particular advantage in administering midazolam as a premedication. Results of another recent study[36] showed that steroids significantly reduce the incidence of PONV, but usual anti-emetic agents, as well as drugs known to possess antiemetic properties such as midazolam lack any significant protective effect against emesis.

Persistent Emesis

Persistent (not only postoperative) emesis may rise to a priority to deal with both for patients and physicians, and lead to unanticipat-

ed admissions of up to 1% ambulatory surgery patients[37]. Three cases of persistent PONV treated with low dose midazolam given by I.V. infusion have been reported by Di Florio in 1992[9]; the same Author[38] later compared midazolam to placebo in patients resistant to standard anti-emetic medications, achieving statistically significant good results, although with a limited number of patients.

A case of a female patient presenting, according to a widely used simplified PONV risk score[39], two or maybe more predictive characteristics, has been quite recently reported[40]. She received a subarachnoid block for orthopaedic surgery, and developed in the recovery room a severe emetic status resistant to all class of available anti-emetics. Only midazolam, actually administered primarily to reduce anxiety and prevent bad memories of the event, stopped all emetic symptoms. In this case the Authors suspected that a timely coincidence with a delayed onset of action of one or more of the anti-emetics the patient received could not be excluded.

A curious case of severe postoperative nausea (but not vomiting), successfully treated with I.V. midazolam, has been described in a known epileptic female patient[41]. Actually, reviewed by the anaesthesiological team, she admitted that she had a severe feeling of nausea prior to her fits; the Authors of the case report concluded that is worth bearing in mind that in epileptic patients, warning signs of impending seizures may manifest as a postoperative problem, in this case emesis.

Interestingly, midazolam and parenteral nutrition have proven their effectiveness in a non surgical case of persistent and life threatening *hyperemesis gravidarum*[42], while, more recently, a case of a teenage boy affected by CVS (Cyclical Vomiting Syndrome: a condition that recent literature suggests to be linked with migraine and adrenergic autonomic dysfunction) successfully treated with a combination of I.V. midazolam and clonidine has been reported[43]. Midazolam has been also found to be an effective anti-emetic during chemotherapy[44].

Side Effects

A number of drug interactions, side effects and complications could be associated with the use of midazolam. According to the commercial product labelling adverse effects may include hypotension, tachycardia, anterograde amnesia (actually in most perioperative situations a beneficial effect), psychomotory excitation, respiratory depression, and even nausea and vomiting.

All but amnesia are rare on the whole and midazolam may be considered as a quite safe drug; nevertheless, literature reports some conditions that is worth mentioning.

One minor trouble of intranasal administration of midazolam in paediatric patients is irritation, and children are likely to cry, more than after the administration of other drugs by the same route[34].

A further problem in children may be represented by paradoxical reactions following I.V. administration of midazolam: they include restlessness, violent behaviour against relatives and medics, and acts of self-injury, sometimes needing for restraints. Rescue medications may be needed: recently, a controlled trial has shown that paradoxical reactions can be aborted by ketamine, with a not yet clear mechanism[45].

One more concern is the administration of midazolam as treatment of persistent PONV. Midazolam is normally given by I.V. infusion at subhypnotic doses (a 0.5-1 mg bolus as starter, followed by a 1 mg per hour infusion). Low dose midazolam is safe to use perioperatively, and respiratory depression usually does not occur, even in combination with opioids[46,47]; however oxygen supplementation and pulse oximetry monitoring are recommended[48]. Elderly people are especially sensitive to such effect of midazolam.

Discussion

Although case reports and controlled trials are now numerous, it has been observed that midazolam does not have still widely earned acceptance as an anti-emetic medication[49]; it looks to be popular in the Australasian area[9,13,38,48,50], where postoperative services seem to have reached a good experience with low-dose midazolam as a therapy for severe PONV recalcitrant to anti-emetics[43].

Nevertheless, there is a general agreement that low dose midazolam is one of the drugs that can form part of the combination for difficult patients. Other non-traditional anti-

emetics, as propofol[51], clonidine[52], dexamethasone[53] and even thiopentone[54] may be successfully used to stop emesis, and may deserve more attention, as well: the use is not included in the labelling, but, once a drug has been approved for a certain use, experience may show its usefulness for other problems.

It may be worth to lay stress on that most of these drugs fulfil the need to cut down costs of PONV treatment[55]; more, there is not a clear evidence that prophylaxis actually decreases the likelihood of unanticipated admissions[56]. Furthermore, patients might be put at risk of suffering from unnecessary adverse drug reactions, e.g. headache related to 5-HT3 receptor antagonists administration[4,57], if a widespread prophylaxis policy is adopted. Postoperative emesis is a difficult multifactorial problem involving both patient's aptitude, type of surgery and perioperative administration of drugs, mostly given for anaesthesia and analgesia after surgery. In patients at high risk of PONV a multimodal approach should be adopted[58], avoiding all avoidable risk factors depending on the anaesthesia technique itself (e.g. opiates, volatile agents, and nitrous oxide), administering intravenous anaesthetic agents with a recognized anti-emetic action, assuring anxiolysis and effective postoperative analgesia, and adopting combination prophylaxis with drugs working via different receptors[50,59]. Unfortunately, both in controlled trials and case reports, it is not uncommon that heterogeneity in dosage, route and timing in administration of anti-emetics, and the goal of the study itself, compromise the reliability of data to allow meaningful conclusion; furthermore, there is still debate about a possible "hard core" of patients suffering PONV whatever anaesthetic technique is adopted[60]. In the last few years reliable and validated simplified PONV risk scores, operation independent, instead of endless listing of often doubtful risk factors have been elaborated[39,61,62]. The simplified risk score by Apfel and colleagues[39] allows to assess the probability of PONV by the small number of the most relevant risk factors, i.e. female gender, non-smoking status, history of motion sickness and/or PONV, administration of opioids for postoperative analgesia. According to the Authors, if none or all four risk factors are present, PONV risk may increase from 10% (no risk factors) to 80% (all four risk factors). Predictive characteristics of simplified scores appear, according to Apfel and colleagues[63] and Pierre and colleagues[64] to be as good as more complex models, and easier to handle.

One more concern may be represented by the discrepancy between the great number of trials on prevention of PONV and a much lesser number of papers on its treatment. According to some Authors[65] the whole thing is not so surprising: therapeutic trials are logistically more difficult to perform, and manufacturers may have not any commercial interest in the treatment of established emesis, since a preventive strategy may be worthwhile, assuming that all patients will receive the anti-emetic drug, and not only who needs it: that is, treatment of established symptoms is likely to be in many cases more cost-effective than prevention[66]. More, manufacturers seem sometimes not to be keen to compare their drugs with new and old comparators, and data on nausea occurrence are often disregarded or underreported.

Valid data on the actual efficacy of anti-emetics, classic, new, and even non-traditional as midazolam and others, are still needed, as far as their ability for established PONV treatment is not completely investigated and understood.

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