In: Advances in Health and Disease. Volume 9 ISBN: 978-1-53614-793-3
Editor: Lowell T. Duncan © 2019 Nova Science Publishers, Inc.

Chapter 3

INTRATHECAL MIDAZOLAM AS AN ANALGESIC IN CHRONIC BACK PAIN

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ABSTRACT

Background. The antinociceptive effect of intrathecal midazolam is based on its affecting spinal gamma-amino butyric acid receptors.

Objective. To evaluate pain relief in patients with chronic low back pain and failed back surgery syndrome after a single-shot intrathecal administration of midazolam.

Design. A prospective, open-label study.

Outcome Measures. The analgesic effect was determined using a patient questionnaire during subsequent visits to the pain therapy service. We classified a pain reduction of 50% or more as a positive outcome with improvement in quality of life and functional condition.

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Results. Between 1995 and 2017 we performed 748 administrations: 319 administrations in 63 male patients and 429 administrations in 85 female patients. We performed 93 administrations for chronic low back pain and 655 administrations for failed back surgery syndrome. The average age of our patients was 51.8 years (range 28 to 86). The dose administered ranged from 2 to 5 mg of midazolam. The analgesic effect lasted 9 weeks on average, ranging from 1 week to 3 years; median of 5 weeks. In 65% of patients we achieved pain relief lasting 4 weeks or longer; in 11%, the administration provided no analgesic effect at all. The incidence of side effects (drowsiness, nausea, headache, or transient worsening of complaints) was rather low.

Conclusion. Intrathecal midazolam is a useful supplement to standard analgesic therapy with opioids, non-opioids, or spinal steroids.

Keywords: intrathecal midazolam, failed back surgery syndrome, chronic low back pain, spinal analgesia, off-label

1. INTRODUCTION

Spinal opioids are widely used for pain relief in acute or chronic pain. Patients indicated for spinal opioids usually require a sophisticated device for continuous administration. However, spinal opioids are not suitable for all patients. In cases of a weak analgesic effect of spinal steroids there are a very few alternatives. Intrathecal midazolam is one such alternative for spinal analgesia.

Chronic low back pain (LBP) and failed back surgery syndrome (FBSS) are serious medical conditions with a significant health, social, and economic impact. Causes of chronic LBP and FBSS are usually multifactorial. Low back pain can persist in patients who have already undergone surgery and are not indicated for another surgery due to an elevated risk of failure. Furthermore, pain can persist after spinal surgery despite the absence of any correlates found by radiographic examinations. These patients fall into the FBSS category and become candidates for comprehensive pain management in pain therapy centers, which provide various interventional therapies. Therapeutic interventions should be distinguished according to the type of pain, which can be either somatic or

radicular (Manchikanti 2009), while pain etiology can be somatic, neuropathic, or mixed, especially in the case of FBSS. Spinal steroids administered via a caudal or intervertebral approach, preferably under fluoroscopic control, are widely used in patients with chronic LBP or FBSS (Conn et al. 2009; Parr et al. 2009). However, there are only a few simple, minimally invasive and low-cost options to treat those patients in whom spinal steroids provide minimal analgesic effect. These patients are subsequently destined for spinal cord stimulation or implantable drug delivery systems – both relatively costly methods. Another option for pain treatment is intrathecal (IT) administration of midazolam (Goodchild et al. 1997).

Midazolam was the first clinically employed water soluble benzodiazepine and is commonly used in anesthesia and intensive care. Unfortunately, a preservative free, commercially available formulation is not available in the United States. This formulation is applicable for anesthesia or long-term sedation, but not for intrathecal administration and should not be used intrathecally in patients with noncancer pain unless they are at end of their life (Deer et al. 2010).

The analgesic effect of spinal midazolam has been known since 1980 and is based on influencing spinal gamma amino butyric acid ($GABA_A$) receptors (Niv et al. 1983; Munro et al. 2013). In 1986, it was demonstrated that there is a high density of $GABA_A$ receptors in lamina II of the dorsal horn of human spinal cord, possibly explaining the pain modulation effect of midazolam (Zencirci, 2014). Midazolam binds with these receptors and acts as an agonist (Ho and Ismail, 2008). It decreases excitatory synaptic transmission at the benzodiazepine/$GABA_A$ receptor in the interneuron, decreases excitability of spinal dorsal horn neurons and increases duration and amplitude of GABAergic synaptic current by acting on benzodiazepine/$GABA_A$ receptors in substantia gelatinosa neurons, subsequently involving phasic and particularly tonic neuronal plasticity. This is the main pathway for intrathecal midazolam induction of segmental analgesia. Midazolam also acts on sigma opioid receptors in the spinal cord and on kappa opioid receptors (Mody, 2005; Nishiyama, 2015).

Functional plasticity of inhibitory synapses plays an important role in adaptation of neural excitability in the central nervous system (CNS). The neurotransmitter gamma aminobutyric acid (GABA) mediates most of neural inhibition in the brain by acting through GABAA receptors. These receptors are key elements involved in establishing inhibitory tone of neurons in the brain. Activation of the $GABA_A$ receptor leads to an influx of chloride ions and to membrane hyperpolarization. Thus, 16 subunits of $GABA_A$ receptor have been identified: 6 α subunits, 3 β subunits, 3 γ subunits, and the δ, ε, θ and π subunits. Benzodiazepines interact with subunit combinations of (α1)2, (β2)2 and γ2. Other allosteric binding sites are the barbiturate site, the site of general anesthetics (both intravenous – etomidate or propofol, and inhalational – halothane) and the site for channel blocking agents such as picrotoxin. Ethanol also interacts with extra synaptic $GABA_A$ receptors depending on its concentration in the brain (Froestl, 2011; Lüscher and Keller, 2004; Munro et al. 2013; Sieghart, 2006).

The great advantage of intrathecal midazolam is the possibility of a single shot administration (Serrao et al. 1992). The purpose of this retrospective open study was to evaluate the effectiveness of single shot treatment with intrathecal midazolam in patients with chronic low back pain (LBP) and failed back surgery syndrome (FBSS).

2. MATERIAL AND METHODS

In our pain relief center, we developed a three-stage algorithm for patients with chronic LBP or FBSS (Figure 1). In the first step there are local interventions (trigger point injections, sacroiliac joint injections, or facet joint injections). In cases where the analgesic effect is not sufficient, we proceed to the second step – applying epidural steroids through a lumbar or caudal approach. If this second interventional step is not sufficient either, we proceed to the IT administration of midazolam as a third step. All these interventions are used as a supplement to oral opioids or non-opioid analgesics (Procházka et al. 2011).

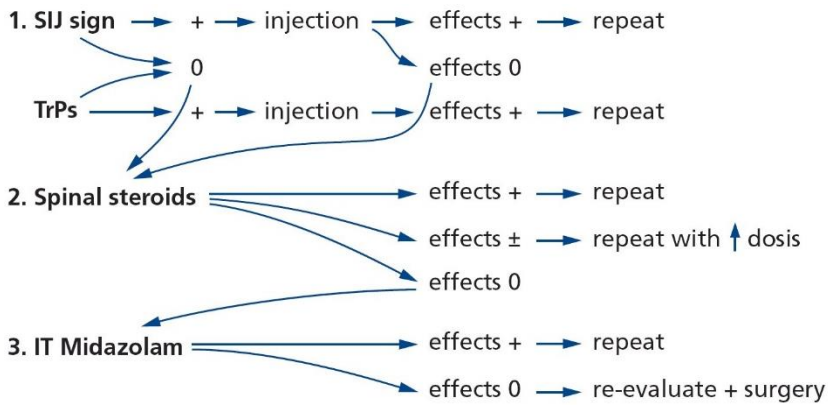


Figure 1. Our three-stage algorithm for interventional therapy in low back pain.
SIJ sign = sacroiliac joint pain; TrPs = myofascial trigger points.

After obtaining written informed consents, midazolam was administered as a single-shot injection in outpatients. We strictly used only preservative-free midazolam (Dormicum F. Hoffmann-La Roche Ltd., Basel, Switzerland, or Midazolam Torrex, Torrex Chiesi Pharma GmbH, Vienna, Austria), and the dose of midazolam was dissolved in 5% glucose or in normal saline solution up to 3 mL in volume. All administrations were performed with the patient in a recumbent position after local anesthesia of puncture site, with a small-gauge spinal needle (initially 22G, but in 1997 we switched to 25G). After administration, patients remained at bed rest for approximately 3 hours for observation before they are released. This serves as a prevention of post-dural puncture headache (PDPH) and enables monitoring of vital signs following the procedure.

The initial dose was always 2 mg of midazolam, and according to the analgesic effect achieved, we could increase the dose up to 5 mg in a single injection. These doses correspond to 0.02 – 0.06 mg/kg of midazolam. A 5 mg dose of midazolam is considered to be a ceiling single shot dose for chronic non-malignant pain. Time intervals between subsequent administrations were at least 4 weeks.

When we aspirated the cerebrospinal fluid back into the syringe filled with midazolam solution to confirm correct needle position in the subarachnoid space, we observed a slight turbidity of the solution. This

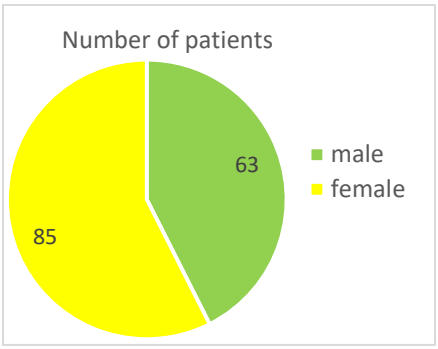
turbidity in otherwise clear solution was most likely caused by precipitation of cerebrospinal fluid (CSF) proteins due to low pH of the solution (pH = 3.3). This level of pH is necessary for lipid solubility when midazolam is exposed to physiologic pH. This lipophilicity is responsible for its rapid CNS effect (Zencirci 2014).

The analgesic effect was evaluated during subsequent patient visits, specifically analysis of subjective pain relief achieved for each patient. Intervals between administration and a follow-up visit were determined by the patient's individual needs. Follow-up visits came at intervals of 4 weeks to 9 years. In some cases, patients ceased the treatment or had their analgesic doses transiently decreased (we describe these periods as "analgesic holidays"). We considered at least a 50% pain reduction with improved quality of life (QoL) and improved functional condition with focus on the overall feeling, quality of sleep, housework, or hobbies capability, etc. to be a positive outcome (in accordance with Moore et al. 2010).

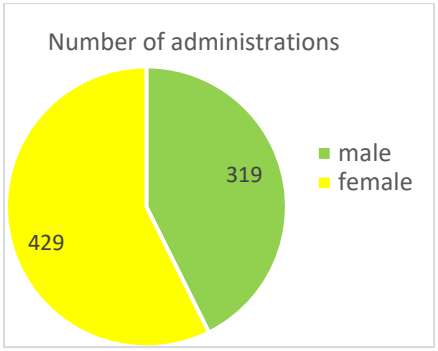
After midazolam administration, we evaluated the quality of sedation using a four-point scale as follows: 0 = wide awake and alert; 1 = at times drowsy but easily aroused; 2 = somnolent but easily aroused; and 3 = somnolent and difficult to arouse (Yegin et al. 2004). Some early side effects were registered during bedside visits; late side effects were recorded during subsequent visits of the patient to the pain therapy service.

3. RESULTS

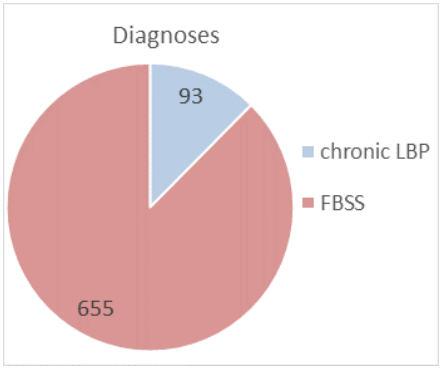
Between 1995 and 2017, we performed 748 administrations in our department: 319 administrations in 63 male patients and 429 administrations in 85 female patients. We performed 93 administrations in patients with chronic LBP and 655 administrations in cases of FBSS (for summary of the demographic data see Graph 1 – Number of patients, Graph 2 – Number of administrations and Graph 3 - Diagnoses). The average age of our patients at the time of administration was 52 years (range 28 to 86). The dose administered ranged from 2 to 5 mg of midazolam (Table 1).



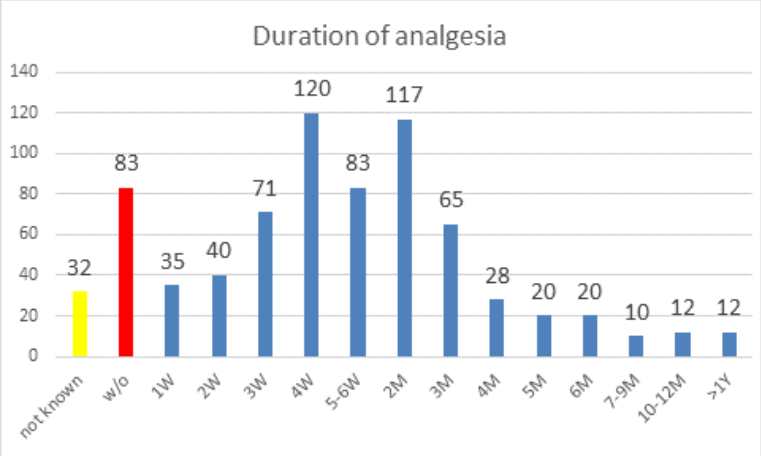
Graph 1. Number of patients.



Graph 2. Number of administrations.



Graph 3. Diagnoses indicated for IT midazolam.



Graph 4. Duration of achieved analgesia after a single intrathecal administration.

Table 1. Administered dose of midazolam

Dose of midazolam	Number of administrations
2 mg	211
3 mg	184
4 mg	154
5 mg	199

The duration of pain relief is shown in Graph 4. After 83 administrations (11%), we observed either no pain relief, only weak relief (less than 50% pain reduction), or too short duration of pain relief (only several days). In 32 cases (4%), we have no information about the extent of analgesia achieved. Average pain relief duration achieved after a single spinal injection was 9 weeks, median 5 weeks; in 65% of the cases we achieved a significant pain reduction lasting more than 4 weeks.

The incidence of side effects was low. The most common side effects were drowsiness in 1 to 3 points on a four-point scale (approximately 31% administrations), headache (4%), nausea (1%), and a transient worsening of pain (7%). We did not see any clinical signs of neurotoxicity (bladder or bowel dysfunction or new radiculopathy) following midazolam administration, even though we performed more than 10 intrathecal administra-

tions of midazolam (up to 57 for twelve years) in 16 cases. Drowsiness levels vary individually among patients; as well as in the same patient based on the dose.

4. DISCUSSION

4.1. Theoretic Background

Systemic analgesics are effective in most patients with chronic pain; however, in some cases their effect is minimal. Pain relief in these patients can be achieved via spinal analgesia. This approach usually requires continuous spinal infusion via an implantable or external pump in postoperative pain management of FBSS or chronic LBP therapy. In contrast to this tactic, we employ only a single injection administered without any catheter or pump system.

When deciding to apply spinal analgesics, we must balance between risks (neurotoxicity, side effects of the drug) and expected benefits (pain relief, quality of life) (Lavand'homme 2006). When introducing a new method for spinal analgesia, one must meet the following criteria: the analgesic efficacy must be confirmed by experimental data and clinical experience, the method must be safe and well-tolerated by patients, it must be easy to perform, and the costs of the method should be reasonable.

Local anesthetic agents and opioids commonly used in spinal anesthesia and analgesia provide only a very limited duration of effect. To maximize the duration of anesthesia or analgesia many adjuvants have been tried. However, intrathecal opioids are associated with many dose-related adverse effects, such as respiratory depression, nausea, vomiting, urinary retention, pruritus or sedation. Therefore, the use of other agents – non-opioids such as ketamine, clonidine, neostigmine, midazolam or ziconotide – have become popular adjunct for post-operative or long-term analgesia (Zencirci, 2014, Nishiyama, 2015).

Intrathecal midazolam can meet many of the requirements for an ideal spinal analgesic: its analgesic properties have been confirmed in several

studies; the method has a low incidence of side effects and the patients solicit additional administrations; it is very simple – only a single-shot administration in outpatients not requiring any catheters or pumps; and finally, the costs of this method are low.

Spinal $GABA_A$ receptors play a significant role in antinociception. Midazolam is a water-soluble benzodiazepine widely used for sedation in intensive care units or in the operating room due to its sedative, anxiolytic and amnestic effects. Its spinal antinociceptive mechanism can be explained as a reduction of excitatory synaptic transmission by acting on the gamma-amino butyric acid ($GABA_A$) receptor in interneurons, leading to a decrease in the excitability of spinal dorsal horn neurons (Yaksh et al. 2004; Kohno et al. 2006). Moreover, GABAergic modulation could be involved in antinociceptive action of opioids and cannabinoid systems in periaqueductal gray matter (PAG) and rostral ventromedial medulla (RVM) (Lau and Vaughan, 2014).

In our country, midazolam is supplied as a preservative free solution with pH value between 3.0 and 4.0 (buffered with hydrochloride acid alone or hydrochloride acid and sodium hydroxide). This level of pH is necessary for lipid solubility when exposing midazolam to physiologic pH. The lipophilicity of midazolam is responsible for its rapid CNS effect (Zencirci 2014). In 1998, Nishiyama et al. studied effects of adding midazolam and bupivacaine to human cerebrospinal fluid (CSF) and this solution was examined for any changes of pH and a reduction of transparency of the solution. Adding midazolam or bupivacaine resulted in decreased pH and cerebrospinal transparency. However, midazolam in saline solution neither decreased the pH bellow 7.0 nor reduced transparency. These results showed that therapeutic doses of intrathecal or epidural midazolam were not neurotoxic (Nishiyama et al. 1998 b). We observe a slight turbidity in otherwise clear solution of midazolam, when aspirating cerebrospinal fluid back into the syringe during midazolam administrating into intrathecal space. However, this turbidity can only be seen on the small volume syringe and may be not significant when dissolving midazolam within the entire cerebrospinal compartment. Moreover, this turbidity can be useful for us in detecting intrathecal space.

4.2. Clinical Studies

The analgesic effect of intrathecally administered midazolam has been demonstrated in several animal studies, which were later followed up by clinical studies. Intrathecal midazolam was most often used as a supplement together with an opioid and local anesthetic in postoperative analgesia. Several studies discussed analgesia after a Cesarean delivery. A dose of 2 mg of intrathecal midazolam shortens the onset of spinal analgesia, moderately extends postoperative analgesia when used as an adjunct to bupivacaine and decreases postoperative nausea and vomiting (Prakash et al. 2016; Abdollahpour et al. 2015). Intrathecal midazolam appears to be an effective analgesic technique for abdominal surgery. This technique achieved excellent analgesia with low requirements for other analgesic interventions (Duncan et al. 2007). In another study, Yegin et al. (2004) demonstrated that intrathecal midazolam combined with intrathecal bupivacaine bring about longer and more effective analgesia when compared to sole bupivacaine in patients undergoing perianal surgery. This use as a single dose is considered safe, however may result in increased sedation. Iranian authors used intrathecal midazolam in labor pain therapy as an adjunct to sufentanil with no significant adverse effects. They concluded that intrathecal midazolam could be an appropriate alternative to parenteral or epidural analgesia in small hospital settings. Improved or longer lasting analgesia was achieved using a continuous IT infusion of midazolam in combination with an opioid, local anesthetics, or clonidine, with minimal drug-related side effects (Salimi et al. 2014). Meta-analysis involving 672 patients from thirteen randomized controlled studies confirmed improving perioperative or peripartum analgesia and a reduction of nausea and vomiting during Caesarean delivery, when adding intrathecal midazolam to other spinal medications. A small dose of intrathecal midazolam (1 to 2.5 mg) does not increase the duration of motor blockade, the risk of respiratory depression or of short-term neurological deficits (Ho and Ismail, 2008).

Intrathecal midazolam administration can also be utilized in settings other than post-operative analgesia, such as pain management. Serrao et al. (1992) compared 2 mg intrathecal midazolam injection with 80 mg epidural

methyl prednisolone. Both treatments produced similar improvement in one-half to three-quarters of patients over a 2-month period in patterns of activity and sleep as well as in sensory and affective components of the pain. However, even though the improvement in the two groups was similar, all patients treated with epidural steroids were taking equal or higher amount of self-administered analgesic medications after their treatment, whereas one-third to one-half of the patients treated with midazolam were taking less rescue analgesic medication during the 2 months of a follow-up period. This data is consistent with our previous study published in recent years (Procházka et al. 2011). The study of Boussofara et al. (2006) published completely opposite findings. They concluded that adding midazolam to an intrathecal mixture of bupivacaine and clonidine does not potentiate postoperative analgesia after an elective lower-extremity surgery and prolongs the motor blockade.

Borg and Krijnen (1996) reported long-term intrathecal administration of midazolam and clonidine in patients suffering from refractory musculoskeletal pain. The treatment spanned over 2.5 years and they used intrathecal midazolam in doses up to 6mg/day, which showed promising results. They discovered that such high doses did not result in any neurological deficits.

Midazolam can also be administered into epidural space, however only a few studies have been performed for analyzing this procedure. Epidural midazolam induces a wide range of analgesic dermatomes, accelerates the onset of sensory block and time to peak effect and prolongs the duration of motor and sensory blocks of epidural lidocaine. In continuous epidural administration along with bupivacaine, midazolam potentiated the analgesic effect of epidural morphine, but inhibited the analgesic effect of fentanyl. These varying effects with morphine and fentanyl can be the result of their different lipophilicities. In clinical studies, improved pain relief or an extended duration of analgesia with good cardiovascular stability after the addition of epidural midazolam was confirmed particularly in postoperative analgesia after abdominal surgery in adults (Nishiyama 2015, Nishiyama et al. 1998 a).

Indications and contraindications for spinal injections and for an examination before injection in chronic pain patients are discussed in Landers (2008) with an emphasis on correlation between patient history, type of pain, neurologic findings, and the results of an imaging examination. We always attempt to proceed from simple interventions to sophisticated techniques. All our patients undergo comprehensive medical management (CMM) for chronic LBP or FBSS (non-opioids, opioids, anticonvulsives, antidepressants, minimally invasive interventions – trigger point injections or facet joint injections), with IT midazolam serving as a supplement to this therapy in the third stage of our algorithm when epidural steroids show little analgesic effect (see Figure 1). The initial dose of 2 mg of IT midazolam has been established based on a comparative study (Serrao et al. 1992) and one of the first clinical studies about the efficacy of spinal midazolam on somatic nociceptive pain (Goodchild et al., 1992).

Since 2007, the International Neuromodulation Society has built a group of experts to evaluate evidence and organize the Polyanalgesic Consensus Conferences (PACC) to guide the practice for intrathecal drug infusion systems. They have developed algorithms for intrathecal medication approaches to treat nociceptive and neuropathic pain, localized or diffuse, in patients with cancer and noncancer pain. The current PACC update considers midazolam to be merely an adjuvant for cancer or terminal condition-related pain with localized or diffuse nociceptive or neuropathic pain in the 6th Line (Deer et al. 2017). However, these algorithms are pertinent for continuous intrathecal infusion therapy, while our method only uses a single shot administration.

4.3. Neurotoxicity

The neurotoxicity of spinally administered drugs used in pain therapy is reviewed in Hodgson et al. (1999). Neurotoxicity of spinal midazolam specifically is still a controversial topic. We must distinguish between histopathological signs (neural injury, gliosis, damage of the myelin sheath, inflammatory changes), physiological signs (changes of spinal cord blood

flow, disruption of the blood–brain barrier, changes in electrophysiology), and clinical signs of neurotoxicity (pain, motor and sensory deficits, bowel and bladder dysfunction, behavioral changes). Furthermore, many preservatives, antioxidants, or excipients used in drugs applied spinally can cause neurotoxic changes in animal models even are considered safe when administered intravenously or intramuscularly (Hodgson et al. 1999; Abram, 1996).

The controversy of spinal midazolam stems from ambivalent outcomes of animal studies, as some of them observe its neurotoxicity, while others deny it. Those its neurotoxic effect reportedly administered much higher doses of midazolam or used spinal catheters (Nishiyama, 2015). Other animal studies found no difference in the amount of histopathologic or inflammatory changes between intrathecal midazolam and saline control group (Zencirci, 2014; Nishiyama 2015). A cohort human study investigating 1100 patients as well as meta-analysis of thirteen randomized controlled studies involving 672 patients did not show any neurological symptoms after intrathecal midazolam administration (Ho and Ismail, 2008; Tucker et al. 2004). In order to minimize the risk of neurotoxicity, the midazolam we used is a preservative-free solution.

4.4. Our Data

Our study spanning over 22 years demonstrated an average pain relief of 9 weeks (median 5 weeks) after single-shot midazolam administration. In 65% administrations we achieved analgesia for 4 weeks or more. In 11% we did not register any pain relief or registered relief for only a brief period. Intrathecal midazolam was used as an adjunct to a comprehensive medical management. Adverse effects seen in our study were only mild and transient. The most common side effects were drowsiness in 1 to 3 points on a four-point scale (approximately 31% administrations), headache (4%), nausea (1%), and a transient worsening of pain (7%). We did not observe any clinical signs of neurotoxicity (bladder or bowel dysfunction or new radiculopathy) following midazolam administration, despite performing

more than 10 intrathecal administrations of midazolam (up to 57) in 16 cases. Drowsiness levels vary individually among patients, as well as in the same patient based on the dose.

4.5. Off-Label Method

Intrathecal or epidural midazolam administration is an off-label method. Labeling contains essential scientific information needed for safe and effective use of a drug. It should be informative and accurate without being promotional, false, or misleading and should be based on data providing substantial evidence of safety and effectiveness (Chang et al. 2005). The term "unlicensed" or "off-label" should not be taken to imply disapproval, nor incorrect or improper use of drugs. There are several categories of off-label therapy: (1) unlicensed medicines used when no appropriate formulation of a drug is commercially available (for example: crushing tablets; opening capsules and suspending them into liquid formulation for children; drugs prepared in a pharmacy), (2) use reaching beyond conditions of the product license (for example: a dose lower or higher than recommended; drug used in children under a certain age; drug used in the indication not covered by the license; alternative route of administration; using drug against contraindications) (Conroy, 2002). Spinal (intrathecal or epidural) midazolam administration falls into the category of "alternative route of administration of licensed drug," because midazolam injections are designated only for intravenous or intramuscular administration.

Many drugs used in anesthesiologic practices are still considered to be off-label therapy, for example: sufentanil for intrathecal use; fentanyl for intrathecal or epidural use; ketamine in obstetrics or pediatric patients younger than 16 years; bupivacaine for use in patients younger than 12 years. US Food and Drug Administration (FDA) recommendations do not regulate medical practice based on knowledge of the medical literature, medical judgment and experience. Physicians are responsible for being well informed about the drugs they are using and for basing off-label use on firm scientific rationale or on sound medical advice (Chang et al. 2005).

Development of off-label therapies, including investigative or innovative methods, alternative routes or use outside patients' age limits offers an abundant source for medical progress.

CONCLUSION

The analgesic effect of intrathecal midazolam is caused by influencing the benzodiazepine/$GABA_A$ receptors in human spinal cord. It appears to be a suitable supplement to comprehensive medical management of patients with chronic LBP or FBSS who suffer somatic or neuropathic pain. Our study proved that analgesia for a duration of 4 weeks or more, following single shot intrathecal midazolam administration was achieved in 65% of cases, with a low incidence of side effects. This method could be useful when medical therapy alone or with epidural steroids have minimal effect. Neurotoxicity of spinal midazolam is still a controversial topic, with a strong recommendation that its use in clinical practice be performed using preservative-free drugs, due to the potential of neurotoxicity of its additives. The advantage of this therapeutic method is single-shot administration, which avoids introducing any catheters or utilizing any external or implantable pumps for continuous infusion therapy.

Intrathecal midazolam remains an off-label method; however, only wide clinical experience and laboratory research can convert it to an on-label status, following the example of opioids many years ago. Until then, intrathecal midazolam for pain relief should be used in strictly indicated cases. Further clinical studies and animal neurotoxicity studies are necessary.

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