Submitted: 16 November, 2022 Accepted: 07 March, 2023 Published: 08 January, 2024 DOI:10.22514/sv.2024.011

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Signa Vitae

CASE REPORT

Management of severe delirium with dexmedetomidine in a palliative care patient—a case report

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Abstract

Dexmedetomidine is used as an adjunct to anaesthesia or as a stand-alone agent for conscious sedation. It is a potent α2-adrenergic receptor agonist, with a fast onset of action and peak effects in 30 minutes to 1 hour after application, depending on the route of administration. It is metabolized in the liver and excreted in urine as a glucuronide. It potentiates analgesia and is effective in opioid sparing. Clinical trials show its efficacy in the treatment of Intensive Care Unit (ICU) delirium with an effect comparable to antipsychotics and benzodiazepines. It has also been used at the Eye Clinic of the University Medical Centre Ljubljana to sedate patients undergoing intraocular surgery. It proved to be an excellent alternative to other sedatives and analgesics, such as midazolam and remifentanil. The aim of this paper is to review the pharmacokinetics and pharmacodynamics of dexmedetomidine and to investigate its potential use in the palliative care population, particularly in the management of delirium. This area of application is still largely unexplored and opens up a new field of application. At the Institute of Oncology (IO) Ljubljana, we have used it with success in several palliative patients with delirium, when all other modalities were failing. At the IO Ljubljana, anaesthesiologists are involved in the palliative management of patients, especially in pain management, but also in sedation and delirium treatment. Given its favourable pharmacokinetic and pharmacodynamic effects, dexmedetomidine could be used more frequently and perhaps alternative and less complex routes of administration, such as intranasal administration, could be explored. In this paper, we present a case of a palliative care patient in whom dexmedetomidine was used successfully.

Keywords

Sedation; Delirium; Palliative care; Dying patient

1. Introduction

In contrast to benzodiazepines or propofol, which act on gamma-aminobutyric acid (GABA) receptors, dexmedetomidine (Dexdor; Orion Corporation, Espoo, Finland) provides sedation by acting on alpha-2 presynaptic receptors. Compared to benzodiazepines or propofol, it causes less delirium associated with the use of the drug. Its desired effects are related to the fact that it does not act on GABA receptors (*vs.* midazolam or propofol), it is not anticholinergic, it induces a natural sleep rhythm, it is an analgesic (reduces the pain that may otherwise exacerbate delirium) and it allows for less opioid consumption [1] not only in the ICU, but in surgical patients also, as various studies have demonstrated [2].

Dexmedetomidine has been used for many years as an adjunct to anaesthetics, in conscious sedation, for sedation in intensive care units and as a treatment for delirium. It is mainly used as an intravenous infusion because it can cause complications such as bradycardia and circulatory instability if injected as a bolus too rapidly. Infusion achieves the desired effect only after one hour, which is too time-consuming for certain surgical procedures. Other routes of administration have not yet been studied well, with individual case reports published, mostly with favourable results without serious complications. They include intramuscular or intranasal applications, where pharmacokinetics could be more favourable. The onset of action is achieved more rapidly, with less haemodynamic effects, as seen in intravenous bolus application. A study, performed at the Eye Clinic of the University Medical Centre Ljubljana, demonstrated its advantage over previously used remifentanil technique in conscious sedation [3].

Dexmedetomidine is also proving to be useful in palliative medicine, as complications could be less frequent with its use than with the usual medications so far, mainly benzodiazepines and antipsychotics. Sedation of patients in the late palliative phase aims to reduce worry, anxiety and agitation in the dying patient [3, 4].

Sedation should be shallow, scored 0 to −2 on the Richmond Agitation Sedation Scale (RASS), but effective. It should en-

able the patient and relatives to have a dignified goodbye. Too deep sedation or anaesthesia, which is rarely used, prevents communication with the patient [4].

Delirium is common in the terminal patient and, among other things, prevents a dignified farewell. It increases discomfort for the patient and relatives. The risk factors for the development of delirium are benzodiazepine use, advanced age, comorbidities, sepsis, previous coma, emergency surgery, and high APACHE (Acute Physiology and Chronic Health Evaluation) score. Delirium can be reduced and treated by appropriate pharmacological measures. The agents used to treat delirium are various antipsychotics, most of which are not available (except haloperidol) in parenteral form. Dexmedetomidine is very effective in the treatment of delirium [3]. It has been used for many years in ICUs [5].

Adequate analgesia should always be provided before sedation is started. A multimodal approach is most often used, with dexmedetomidine playing an important role. When added to opioids, it reduces their consumption and adverse effects. This improves the patient's cognitive function and reduces the unwanted side effects of opioids (constipation, dizziness, nausea, vomiting) [6].

Dexmedetomidine can be chosen and administered by an anaesthesiologist or a palliative physician with appropriate expertise. Palliative physicians of other disciplines should consult an anaesthesiologist if necessary [3].

2. Case report

A 42-year-old patient was seen in the emergency ENT (Ear, nose and throat) outpatient clinic in early June 2021, because of a left neck mass, which was already painful and fist-sized at that time. Mild dysphagia was also present. Physical examination revealed trismus, with a 2 cm mouth opening and a hard, cauliflower-shaped tumour on the left side of the alveolar ridge and in the tonsillar region, on the lateral pharyngeal wall of the oropharynx with a slightly firmer left half of the root of the tongue. A big lump was observed on the neck. The diagnosis was grade II squamous cell carcinoma, which was p16 negative. No metastases were found. His WHO (World Health Organization) performance status (WHO PS) was assessed as 0.

The otorhinolaryngology council suggested non-operative treatment with radical chemotherapy with cisplatin and radiotherapy. The disease progressed very rapidly, so the treatment was changed to palliative. He developed large subcutaneous infiltrates on the left side of his neck. There was also a significant deterioration in his performance status (WHO PS 2–3). Due to severe breathing and swallowing difficulties, a tracheostomy and a nasogastric tube (NGT) were inserted. He could only eat soft food and developed signs of cachexia.

Initially, he had moderate pain in the left neck, rated 5 out of 10 on the visual analogue scale (VAS), initially helped by a combination of metamizole drops (Metamizo Stada, Stada Arzneimittel AG, Bad Vilbel, Germany) (1 g/6 h) and non-steroidal anti-inflammatory drugs (naproxen (Nalgesin S, Krka d.d., Novo mesto, Slovenia) 275 mg up to 4×/day) as needed, for pain rated >3 on the VAS. He reported an allergy to pantoprazole, so no proton pump inhibitors were prescribed at this time. His pain soon worsened and did not respond adequately to peripheral analgesics. Opioids were introduced, namely fentanyl patch (Epufen, Lek d.d., Ljubljana, Slovenia) 25 μg/72 h and morphine pills (Sevredol, Mundipharma Gesselschaft mbH, Frankfurt am Main, Germany) 10 mg as needed (at VAS >4). Due to intermittent restlessness, he was given clomethiazole (Distraneurin, Cheplapharm Arzneimittel, GmbH, Greifswald, Germany)192 mg 3×/day and additionally as needed. For sleep, he received quetiapine (Kventiax, Krka d.d., Novo mesto, Slovenia) 25 mg in the evening. He became pain-free and without signs of delirium.

At the beginning of August, he was admitted to the radiotherapy department of the IO LJ for palliative radiation therapy, where signs of hyperactive delirium were already observed on admission, but the condition was not quantitatively assessed. Morphine 10 mg was administered subcutaneously instead of perorally for pain treatment at VAS >4. He became increasingly restless and occasionally confused, yet the delirium was not assessed. At the physician's discretion, midazolam 2.5 mg was administered subcutaneously. He was started on subcutaneous elastomeric analgesic pump with morphine 20 mg, haloperidol 5 mg, metamizole 5 g, midazolam 5 mg, dexamethasone 8 mg in combined volume of 48 mL of saline, with 2 mL/h flow rate. He continued to receive morphine 10 mg subcutaneously as needed at VAS >4.

As he became increasingly restless and unmanageable, he was examined by a psychiatrist who noted that communication with the patient was difficult due to the tracheostomy. The patient did not engage in conversation and responded mainly with monosyllables. He was situationally oriented, his attention was divergent. Delusional symptomatology was present, he was anxious, his day-night rhythm was disturbed, he was difficult to manage. Psychomotor restless was observed, he was tearing up his diaper and pulling on vascular lines, his risk of falling from the bed was high. The psychiatrist prescribed the following therapy: quetiapine (3 × 25 mg and 50 mg as needed), clomethiazole 192 mg for restlessness, midazolam for severe restlessness 2.5 mg subcutaneously and haloperidol 2.5 mg 3×/day. As his condition did not improve in the following days, the psychiatrist increased the doses, as following: quetiapine 3 × 50 mg, haloperidol 2.5 mg for restlessness up to 3×/day, lorazepam 3 × 1 mg plus 2.5 mg as needed for restlessness and midazolam 2.5 mg for restlessness up to 5×/day.

Delirium did not subside with the use of any of the listed medications. On the 16th of August, after consultation with the anaesthesiologist, dexmedetomidine infusion was introduced at the rate of 0.2 μg/kg/h, which, since the patient weighed 73 kg, equalled 15 μg/h. The dose was increased very gradually every 15 min, until we reached the rate of 0.33 μg/kg/h, which equalled 24 μg/h. Dexmedetomidine administration instructions were followed. Within one hour, the patient was completely calm and his previous neuroleptic and sedation therapy could be withdrawn. In the following days, he reacted sensibly and responded to instructions, his day-night rhythm was restored. He answered questions meaningfully by nodding. The CAM-ICU (Confusion Assessment Method for the ICU) questionnaire was used to rule out the presence of delirium. Pain, which was monitored as a vital parameter

several times a day, was also adequately controlled, never exceeding VAS >3. He was able to undergo palliative irradiation. He became slightly restless on the 20th of August, and the dose was increased to 32 μL/h, consequently, the patient was again completely calm. During the entire administration of dexmedetomidine, the patient did not have any side effects.

A family meeting was held with the relatives. The patient expectedly died on the 24th of August, peacefully, without delirium, surrounded by his family.

3. Discussion

In recent years, dexmedetomidine has become increasingly popular for treating delirium in surgical patients. It has not yet been established in other fields of medicine, but individual reports of its successful use for the treatment of delirium in palliative wards have been described [4]. Nevertheless, more and higher quality studies are necessary to clarify its potential use in palliative care [7]. According to the published literature, it can also be used in the palliative care department, if all other forms of treatment for the listed conditions have been exhausted [8, 9].

Indications for its use include: a restless and/or anxious patient, the presence of delirium, which can be hyperactive, hypoactive and mixed delirium, sleep and circadian rhythm disturbances, and it is also used as an adjunct to analgesia. It is most often introduced when all other forms of therapy for the above conditions have been exhausted [9, 10]. It enables shallow sedation, treatment of delirium and multimodal pain management [9]. Currently, it is only registered for intravenous use, in the form of a continuous infusion. Other forms of application such as intranasal, intramuscular or subcutaneous are not yet routinely used, because they have not yet been sufficiently researched. Even in analgesic mixtures for subcutaneous infusion with elastomeric pumps, which are often used in cancer palliative patients and repeatedly administered with off-label active ingredients, we do not use it for the time being.

Dexmedetomidine is very suitable for patient sedation. The goals of sedation should be clearly defined before use and regularly adjusted according to the current clinical situation. The actual depth of sedation should be monitored and compared to the planned one. Standardized Richmond Agitation Sedation Scale (RASS) is used for this purpose [5].

In the palliative patient, shallow sedation with RASS score from 0 to −2 is usually wanted, which can be well achieved with dexmedetomidine [4, 10]. For deeper sedation or when sedation with dexmedetomidine is insufficient, other agents (benzodiazepines, opioids, antipsychotics) are used [3].

Most often, the desired state is when the patient is calm, awake and cooperative. It is important that he is able to communicate with relatives and medical staff. During sedation, RASS is assessed for the first two hours, or until the desired level of sedation is reached for 15 min, then every 3 hours [11].

Our patient had a disrupted circadian rhythm and was restless from the beginning. We did not regularly monitor the patient's sedation in the ward with the help of RASS, so we introduced and dosed the drugs according to the clinical effect. Initially, we decided on antipsychotics, benzodiazepines and opioids, and only finally on dexmedetomidine.

In patients expected to develop delirium (intensive care, palliative care unit), regular testing (once per shift) to detect it is recommended. Hypoactive delirium, in particular, is very often overlooked, when the patient appears calm, but is in fact in distress. A simple tool is recommended: "Confusion Assessment Method for the Intensive Care Unit" (CAM-ICU) (Fig. 1), which is useful for rapid assessment of delirium, also outside of intensive care units [9, 11]. Unfortunately, we only observed and described the clinical condition of our patient, but did not diagnose delirium with the appropriate tools. Once delirium is recognized, it is necessary to start treatment immediately. If we had followed the written advice, we would have approached the treatment of delirium earlier and more systematically and would possibly have saved the patient and his family a lot of suffering. In addition to other established drugs such as antipsychotics (haloperidol, risperidone, quetiapine and olanzapine), guidelines recommend the use of dexmedetomidine. Other drugs, such as benzodiazepines have undesirable effects, may exacerbate delirium and are mostly not available in the intravenous form [1, 11–13].

Contraindications for dexmedetomidine use are rare. They include hypersensitivity and allergy [5]. Our patient reported an allergy to pantoprazole, after taking it he allegedly developed an urticarial rash, which is not a contraindication for the use of dexmedetomidine. Because it can cause bradycardia, it is not given to patients with advanced second or third-degree atrioventricular block [5]. It can cause a moderate drop in blood pressure and thus reduce cerebral perfusion, thus aggravating delirium. It should not be given, when uncontrolled hypotension and acute cerebrovascular symptoms are present [5], which in our patient, despite infection and probable sepsis (Leukocytes 17.09 $\times$ 10^9/L, immature granulocytes 3%, C reactive protein 342 mg/L, PCT (procalcitonin) 0.96 mcg/L) was not present, as his vital parameters were regularly measured and recorded, and were always within normal limits, nor did he need vasoactive support with adequate hydration. Furthermore, in palliative medicine, all contraindications (except hypersensitivity) are relative. Thus, our patient could have received dexmedetomidine without concern, even in the early deliriant period.

Before using dexmedetomidine, we should perform a laboratory examination of blood liver enzymes, since it is metabolized in the liver, and record an ECG (electrocardiogram), because it can worsen bradycardic heart rhythm disorders [1, 6, 9]. In our patient, we performed these tests. Transaminases were slightly elevated (AST (aspartate aminotransferase) 0.95 microkat/L, ALT (alanin transaminase) 0.69 microkat/L), gamma GT (gamma-glutamyl transerase) 1.28 microkat/L and LDH (lactate dehydrogenase) 4.73 microkat/L, and the ECG was within normal limits (Sinus rhythm, 80/ min, normal cardiac axis, no signs of impaired conduction, no signs of ischemia). In general, there were no concerns about the use of dexmedetomidine.

When introducing dexmedetomidine outside the ICU, first, a low dose of 0.2 μg/kg/h should be administered and then gradually increased (by 0.2 μg/kg/h) every 15 minutes, until the desired effect is achieved. The dose should be reduced appropriately in case of hepatic insufficiency. The drug effect

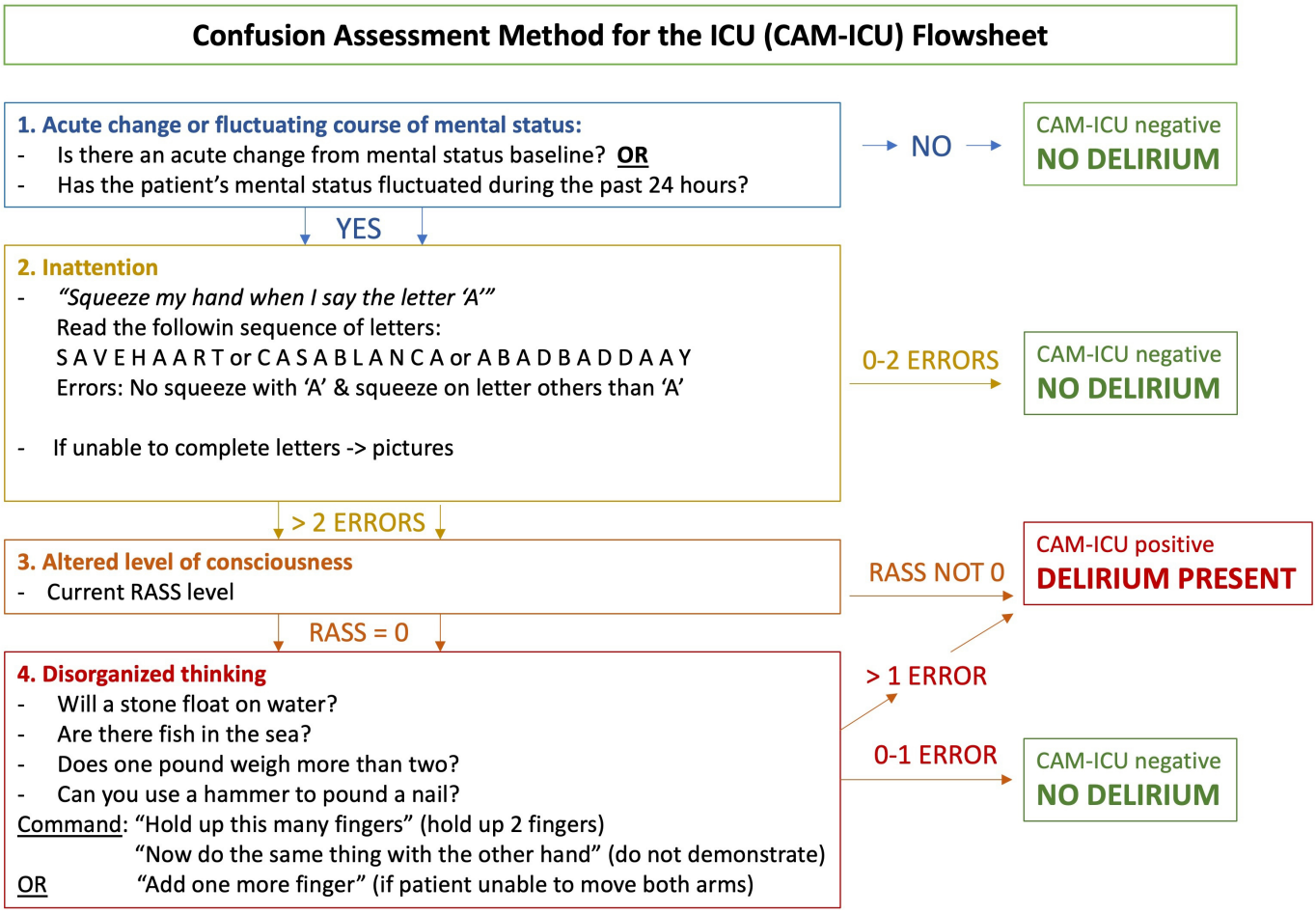

FIGURE 1. "Confusion Assessment Method for the Intensive Care Unit" (CAM-ICU) tool. ICU: Intensive Care Unit.

occurs after 5–10 minutes, $t_{1/2}$ is 1.8–3.1 hours. The drug is administered intravenously, in a continuous infusion. A concentration of 200 μg/50 mL should be used. Dose titration is guided by the RASS scale, where the goal is −1 to −2, and when this is achieved, the infusion rate can be reduced. The maximum dose of the drug is 0.7 μg/kg/h (upper limit for a non-intubated patient) [3, 6]. In our patient, we followed the recommendations described above and administered small doses. There is still a fear of using the drug outside the ICU, because of a lack of experience and not enough relevant research and scientific recommendations that have not yet been published.

Off-label use intranasally or intramuscularly is performed with a dose of 1–2 μg/kg. For intranasal application, special intranasal applicators are used, so that it spreads evenly over the nasal mucosa and the patient does not swallow it, preventing the desired effects due to first-pass hepatic metabolism [10, 14].

In patients receiving dexmedetomidine, bradycardia and hypotension can be expected at higher doses. At the initial dose, loss of the airway reflex can be observed. Even more care should be taken when co-administering drugs that affect the heart rhythm and cause bradycardia (antidepressants, antipsychotics, metoclopramide, neostigmine). We do not need to monitor vital signs in dying patients. When caring for such a patient, his clinical condition, the appropriate level of sedation and the presence of delirium should be monitored. This was also taken into account in our patient.

Dexmedetomidine, which is usually administered starting with a loading dose in the ICU, can be given safely and effectively in the palliative care unit without an initial loading dose. Dexmedetomidine can be administered to patients without venous access and in nursing environments (intranasal, intramuscular, subcutaneous) where intensive monitoring of the patient is not reasonable and necessary [6].

Our case suggests that dexmedetomidine may be a useful adjunct to palliative treatment. Future research and guidelines will be needed to compare dexmedetomidine infusion with standard midazolam infusion therapy. At OI LJ, we have developed internal guidelines for its use, which have been approved by the OI LJ Expert Council. For the time being, dexmedetomidine can only be used in the Palliative Care Unit, if all other treatments have been exhausted, in intravenous form. Its use is not allowed in the wards for the time being.

4. Conclusions

Palliative care is becoming an important area of medicine in where also anaesthesiologists participate. With our knowledge and experience, we can contribute a lot to better treatment of pain, as well as other conditions such as delirium and the need for patient sedation. Anaesthesiologists are also involved in palliative care at IO LJ. Recently, we have also been involved in mobile palliative teams. In order to treat patients well, it is

important to be familiar with medications and techniques, so it is important to apply our knowledge from operating theatres and ICUs to palliative care. Dexmedetomidine is a potentially useful drug for the targeted treatment of pain and delirium in the tertiary palliative care setting. When used for sedation and delirium treatment, dexmedetomidine fits with the patient's, family's and physician's goals of care when patient alertness and participation in conversations with loved ones and health care personnel are important at the end of life.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

IP—treated the patient. AH, TZ and IP—wrote the manuscript. TZ—created the figure. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institute of Oncology Ljubljana Ethics Committee approved this case report (approval number ERIDEK-0107/2022). The patient's relatives approved this case report *via* phone call.

ACKNOWLEDGMENT

We are thankful to all the nursing staff for providing support in treating our patient.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Andrej Hostnik, Teodora Zupanc, Iztok Potočnik. Management of severe delirium with dexmedetomidine in a palliative care patient—a case report. Signa Vitae. 2024; 20(1): 145-149. doi: 10.22514/sv.2024.011.